Royal College of
Obstetricians and Gynaecologists

Bringing to life the best in women's health care

Fertility:
assessment and treatment for people with fertility problems

February 2013

NICE Clinical Guideline

National Collaborating Centre for Women's and Children's Health

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Fertility: assessment and treatment for people with fertility problems

National Collaborating Centre for Women's and Children's Health

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This guideline has been fully funded by NICE. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient.

Implementation of this guidance is the responsibility of local commissioners and/or providers

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1 Guideline summary

1.1 Original guideline development group (GDG) membership (2004), NCC-WCH staff and acknowledgements

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1.2 Updated (2013) guideline: guideline development group (GDG) membership, NCC-WCH staff and acknowledgements

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1.3 Foreword

This guidance is a partial update of the National Institute for Health and Clinical Excellence (NICE) clinical guideline 11 (published February 2004) and will replace it. For further information refer to Appendices A and D.

New and updated recommendations have been included on:

- How accurate are tests of ovarian reserve in predicting pregnancy and its outcomes?
- How accurate are clinical scoring systems in predicting the outcome of IVF treatment?
- What is the effectiveness and safety of different embryo/blastocyst transfer strategies?
    - number of embryos (comparing single vs. double)
    - timing of transfer (comparing cleavage vs. blastocyst stage).
- What is the effectiveness and safety of ovarian stimulating agents in women with unexplained infertility?
- What is the effectiveness and safety of ovulation induction strategies in women with World Health Organization (WHO) Group I Ovulation Disorders?
- What is the effectiveness and safety of ovulation induction strategies in women with WHO Group II Ovulation Disorders?
- What is the long-term safety of ovulation induction and ovarian stimulation strategies in women with infertility and their children?
- What is the effectiveness of intrauterine insemination (IUI)?
- What is the effectiveness of cryopreservation (including vitrification) in fertility preservation strategies?
- What is the effectiveness and safety of sperm washing to reduce the risk of viral transmission?

  The original purpose of this section was to investigate the effectiveness and safety of sperm washing. However, the question was further broadened in the context of HIV. This resulted in three additional questions:

    - What is the risk of transmission by vaginal intercourse when HIV positive male partners are on treatment?
    - What is the risk of transmission by vaginal intercourse when HIV positive male partners have a low viral load? and;
    - What is the risk of transmission by vaginal intercourse when HIV negative women with HIV positive male partners use pre-exposure anti-retroviral prophylaxis?

- What is the effectiveness of pre-treatment as part of an ovarian stimulation strategy for women undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatment?
- What is the effectiveness of down regulation as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?
- What is the effectiveness of the following strategies as part of an ovarian stimulation protocol in women undergoing IVF or ICSI treatment?
    - stimulation with gonadotrophins
    - 'milder' stimulation
    - adjuvant growth hormone and di-hydro-epi-androsterone (DHEA) treatment for women with a previous poor response.
- Which is the most effective ovulation trigger to use as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?
- What is the effectiveness of luteal phase support as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?

Recommendations are marked to indicate the year and type of review:

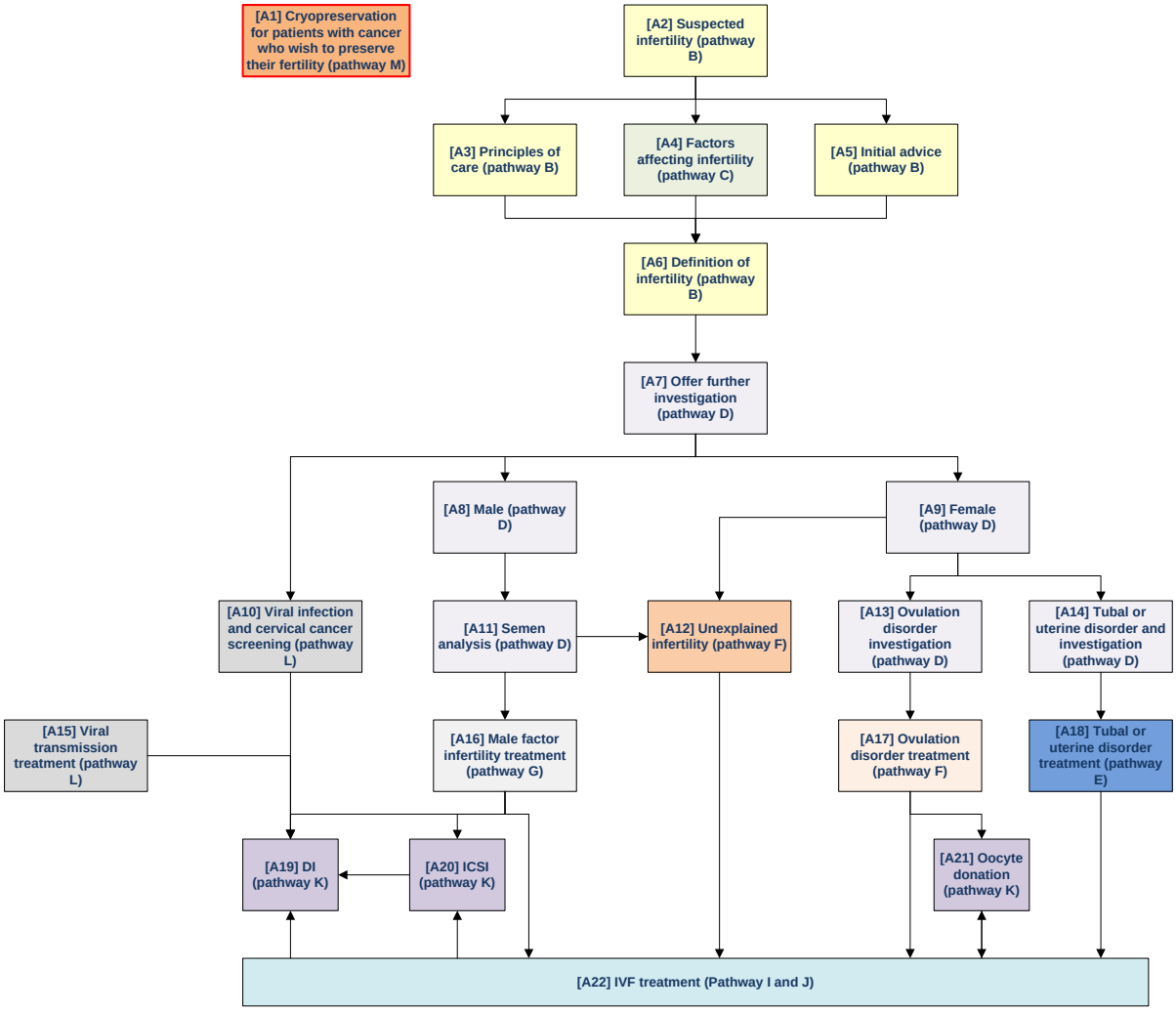
- **[2004]** if the evidence has not been reviewed since the original guideline.
- **[2004**, amended **2013]** if the evidence has not been reviewed, but an essential change has been made that affects the meaning of the recommendation.
- **[2013]** if the evidence has been reviewed but no change has been made to the recommendation.
- **[new 2013]** if the evidence has been reviewed and the recommendation has been updated or added.

Appendix L contains recommendations from the 2004 guideline that GDG has deleted in the 2013 update. This is because the evidence has been reviewed and the recommendation has been updated or because NICE has updated other relevant guidance and has replaced the original recommendations. Where recommendations have been replaced, details are provided. Where there is no replacement recommendation, an explanation for the proposed deletion is given.

A grey bar down the side of the page indicates sections of the guideline which are new or have been updated. Material from the original guideline which has been deleted can be found in Appendix I.

1.4 Care pathway

A. Overall care pathway



2013 Update

B. General considerations

[B1] Principles of care

- Couples who experience problems in conceiving should be seen together because both partners are affected by decisions surrounding investigation and treatment.
- People should have the opportunity to make informed decisions regarding their care and treatment via access to evidence-based information. These choices should be recognised as an integral part of the decision-making process. Verbal information should be supplemented with written information or audio-visual media.
- Information regarding care and treatment options should be provided in a form that is accessible to people who have additional needs, such as people with physical, cognitive or sensory disabilities, and people who do not speak or read English.
- People who experience fertility problems should be informed that they may find it helpful to contact a fertility support group.
- People who experience fertility problems should be offered counselling because fertility problems themselves, and the investigation and treatment of fertility problems, can cause psychological stress.
- Counselling should be offered before, during and after investigation and treatment, irrespective of the outcome of these procedures.
- Counselling should be provided by someone who is not directly involved in the management of the individual's and/or couple's fertility problems.
- People who experience fertility problems should be treated by a specialist team because this is likely to improve the effectiveness and efficiency of treatment and is known to improve people's satisfaction with treatment.
- The environment in which investigation of fertility problems takes place should enable people to discuss sensitive issues such as sexual abuse.

[B2] Initial advice to couples seeking infertility treatment

- People who are concerned about their fertility should be informed that over 80% of couples in the general population will conceive within 1 year if:
  - the woman is aged under 40 years **and**
  - they do not use contraception and have regular sexual intercourse.

  Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%).
- Inform people who are using artificial insemination to conceive and who are concerned about their fertility that:
  - over 50% of women aged under 40 years will conceive within 6 cycles of intrauterine insemination (IUI)
  - of those who do not conceive within 6 cycles of intrauterine insemination, about half will do so with a further 6 cycles (cumulative pregnancy rate over 75%).
- Inform people who are using artificial insemination to conceive and who are concerned about their fertility that using fresh sperm is associated with higher conception rates than frozen-thawed sperm. However, intrauterine insemination, even using frozen-thawed sperm, is associated with higher conception rates than intracervical insemination.
- When couples have fertility problems, both partners should be informed that stress in the male and/or female partner can affect the couple's relationship and is likely to reduce libido and frequency of intercourse which can contribute to the fertility problems.
- Inform people who are concerned about their fertility that female fertility and (to a lesser extent) male fertility decline with age.
- Discuss chances of conception with people concerned about their fertility who are:
  - having sexual intercourse (see table 5.1), **or**
  - using artificial insemination (see table 5.2).

[B3] Initial assessment

- People who are concerned about delays in conception should be offered an initial assessment. A specific enquiry about lifestyle and sexual history should be taken to identify people who are less likely to conceive.
- Offer an initial consultation to discuss the options for attempting conception to people who are unable to, or would find it very difficult to, have vaginal intercourse.
- The environment in which investigation of fertility problems takes place should enable people to discuss sensitive issues such as sexual abuse.

[B4] Referral for specialist consultation

- Healthcare professionals should define infertility in practice as the period of time people have been trying to conceive without success after which formal investigation is justified and possible treatment implemented.
- A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner.
- A woman of reproductive age who is using artificial insemination to conceive (with either partner or donor sperm) should be offered further clinical assessment and investigation if she has not conceived after 6 cycles of treatment, in the absence of any known cause of infertility. Where this is using partner sperm, the referral for clinical assessment and investigation should include her partner.
- Offer an earlier referral for specialist consultation to discuss the options for attempting conception, further assessment and appropriate treatment where:
  - the woman is aged 36 years or over
  - there is a known clinical cause of infertility or a history of predisposing factors for infertility.
- Where treatment is planned that may result in infertility (such as treatment for cancer), early fertility specialist referral should be offered.
- People who are concerned about their fertility and who are known to have chronic viral infections such as hepatitis B, hepatitis C or HIV should be referred to centres that have appropriate expertise and facilities to provide safe risk-reduction investigation and treatment.

2013 Update

C. Factors affecting fertility

[C1] Alcohol

- Women who are trying to become pregnant should be informed that drinking no more than 1 or 2 units of alcohol once or twice per week and avoiding episodes of intoxication reduces the risk of harming a developing fetus.
- Men should be informed that alcohol consumption within the Department of Health's recommendations of 3 to 4 units per day for men is unlikely to affect their semen quality.
- Men should be informed that excessive alcohol intake is detrimental to semen quality.

[C2] Smoking

- Women who smoke should be informed that this is likely to reduce their fertility.
- Women who smoke should be offered referral to a smoking cessation programme to support their efforts in stopping smoking.
- Women should be informed that passive smoking is likely to affect their chance of conceiving.
- Men who smoke should be informed that there is an association between smoking and reduced semen quality (although the impact of this on male fertility is uncertain), and that stopping smoking will improve their general health.

[C3] Folic acid supplementation

- Women intending to become pregnant should be informed that dietary supplementation with folic acid before conception and up to 12 weeks' gestation reduces the risk of having a baby with neural tube defects. The recommended dose is 0.4 mg per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication or who have diabetes (see Diabetes in pregnancy, NICE clinical guideline 63), a higher dose of 5 mg per day is recommended.

[C4] Obesity

- Women who have a body mass index (BMI) of 30 or over should be informed that they are likely to take longer to conceive.
- Women who have a BMI of 30 or over and who are not ovulating should be informed that losing weight is likely to increase their chance of conception.
- Women should be informed that participating in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone.
- Men who have a BMI of 30 or over should be informed that they are likely to have reduced fertility.

[C5] Low body weight

- Women who have a BMI of less than 19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception.

[C6] Tight underwear

- Men should be informed that there is an association between elevated scrotal temperature and reduced semen quality, but that it is uncertain whether wearing loose-fitting underwear improves fertility.

[C7] Occupation

- Some occupations involve exposure to hazards that can reduce male or female fertility and therefore a specific enquiry about occupation should be made to people who are concerned about their fertility and appropriate advice should be offered.

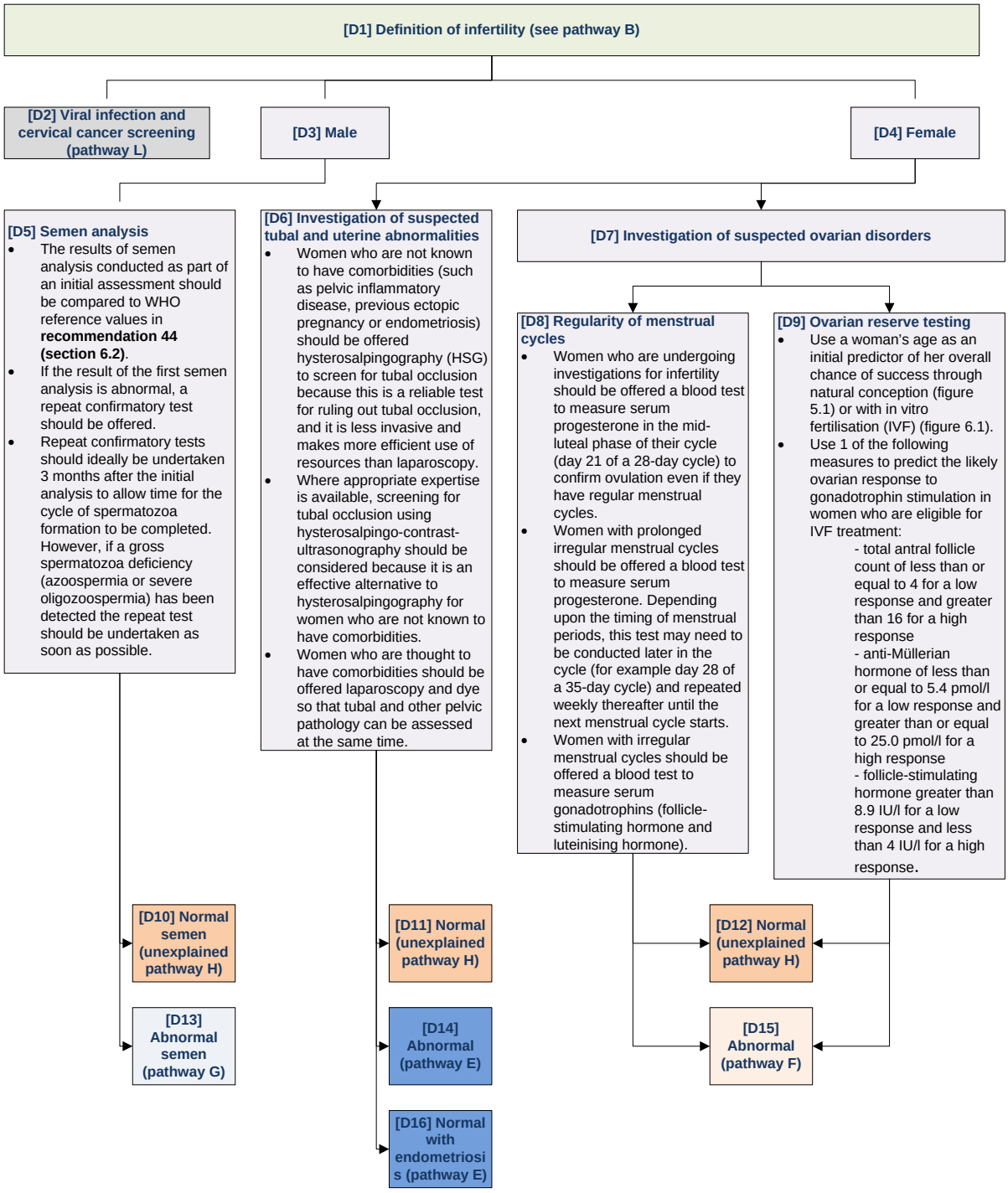
[C8] Prescribed, over-the-counter and recreational drug use

- A number of prescription, over-the-counter and recreational drugs interfere with male and female fertility, and therefore a specific enquiry about these should be made to people who are concerned about their fertility and appropriate advice should be offered.

[C9] Frequency and timing of sexual intercourse or artificial insemination

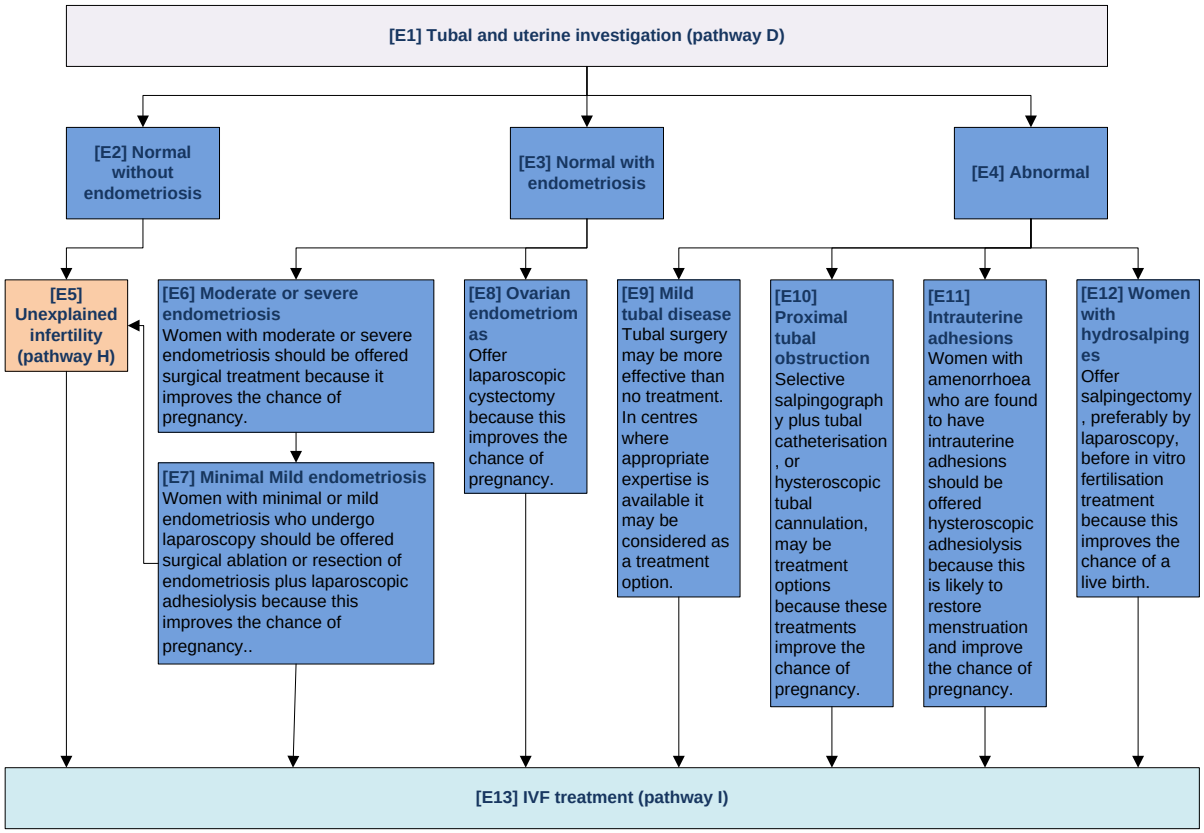
- People who are concerned about their fertility should be informed that vaginal sexual intercourse every 2 to 3 days optimises the chance of pregnancy.
- People who are using artificial insemination to conceive should have their insemination timed around ovulation.

D. Investigations of infertility



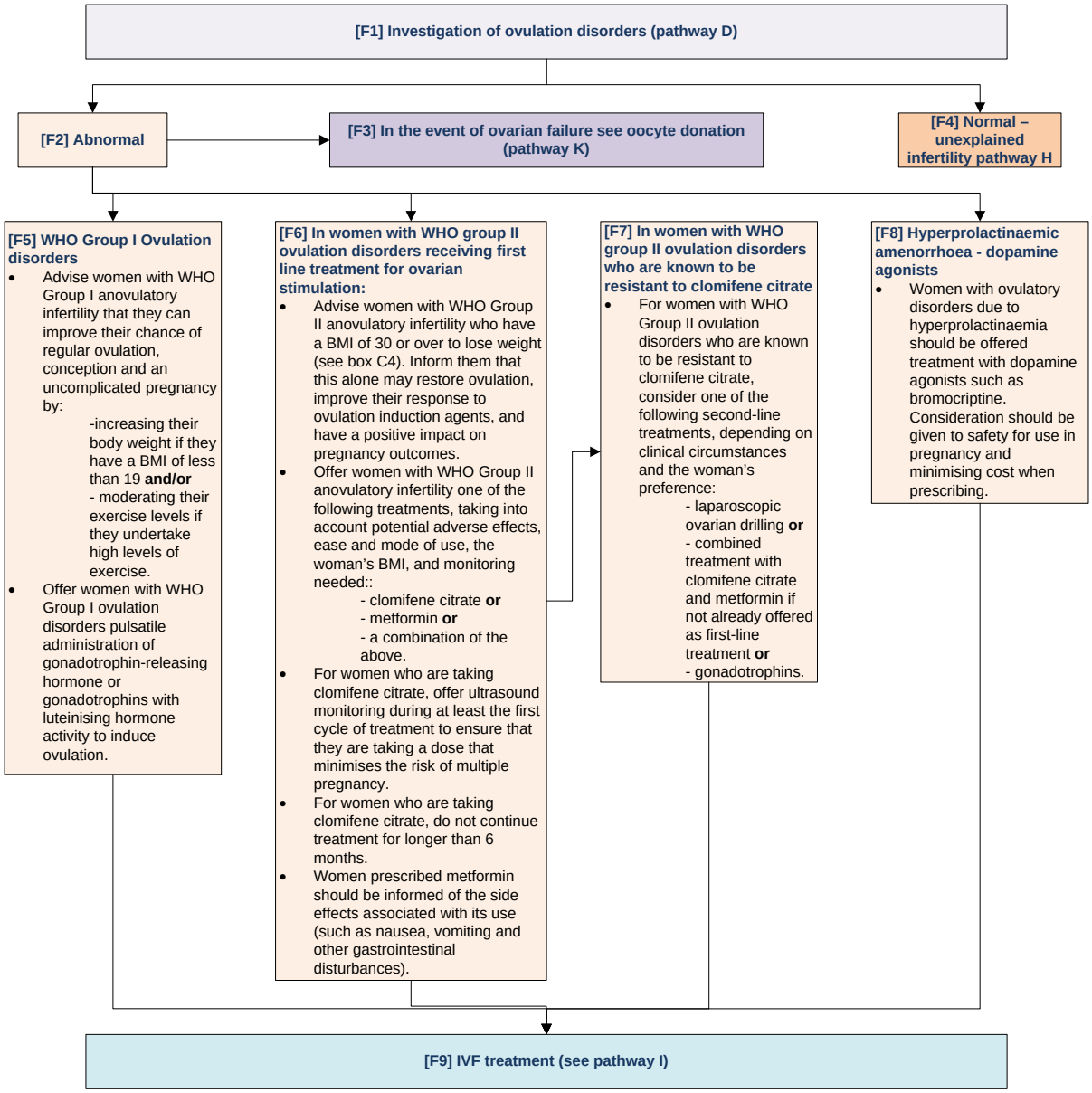
2013 Update

E. Suspected tubal and uterine disorders



2013 Update

F. Suspected ovarian disorders



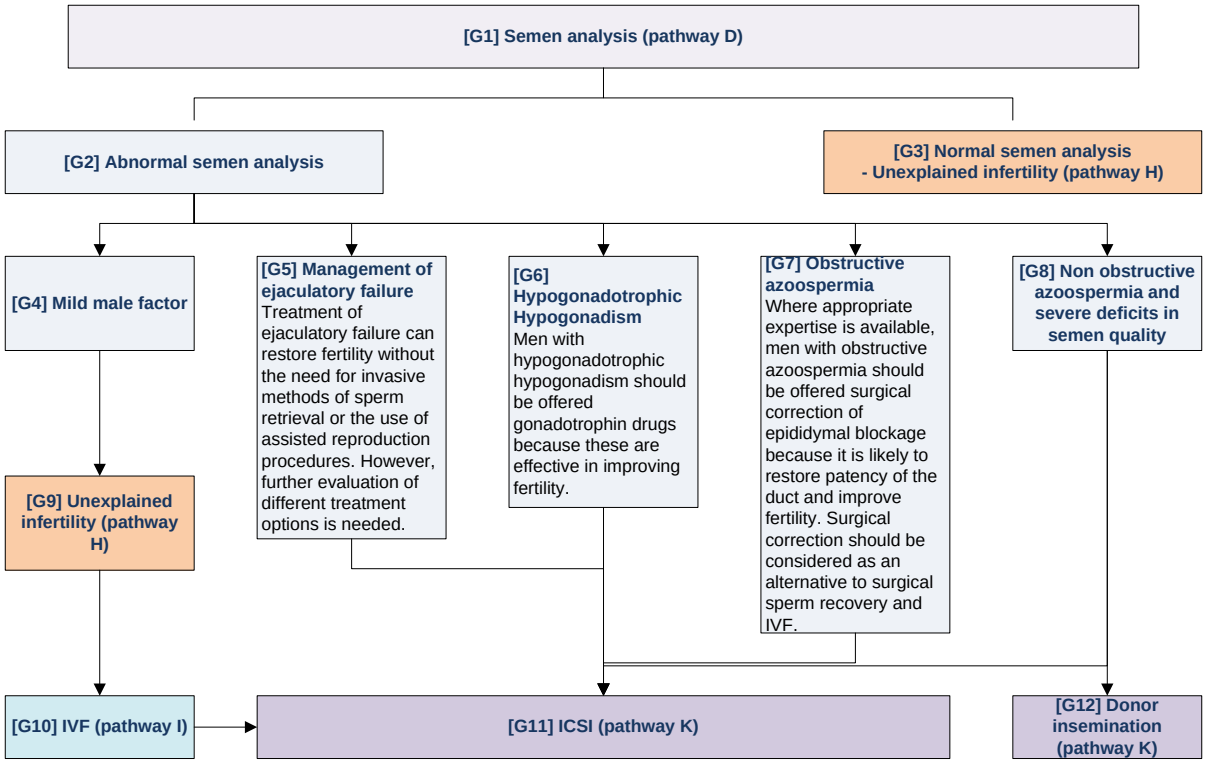
[F10] Ovulation induction

- Women who are offered ovulation induction with gonadotrophins should be informed about the risk of multiple pregnancy and ovarian hyperstimulation before starting treatment.
- Ovarian ultrasound monitoring to measure follicular size and number should be an integral part of gonadotrophin therapy to reduce the risk of multiple pregnancy and ovarian hyperstimulation.

[F11] Long term health outcomes of ovulation induction and ovarian stimulation

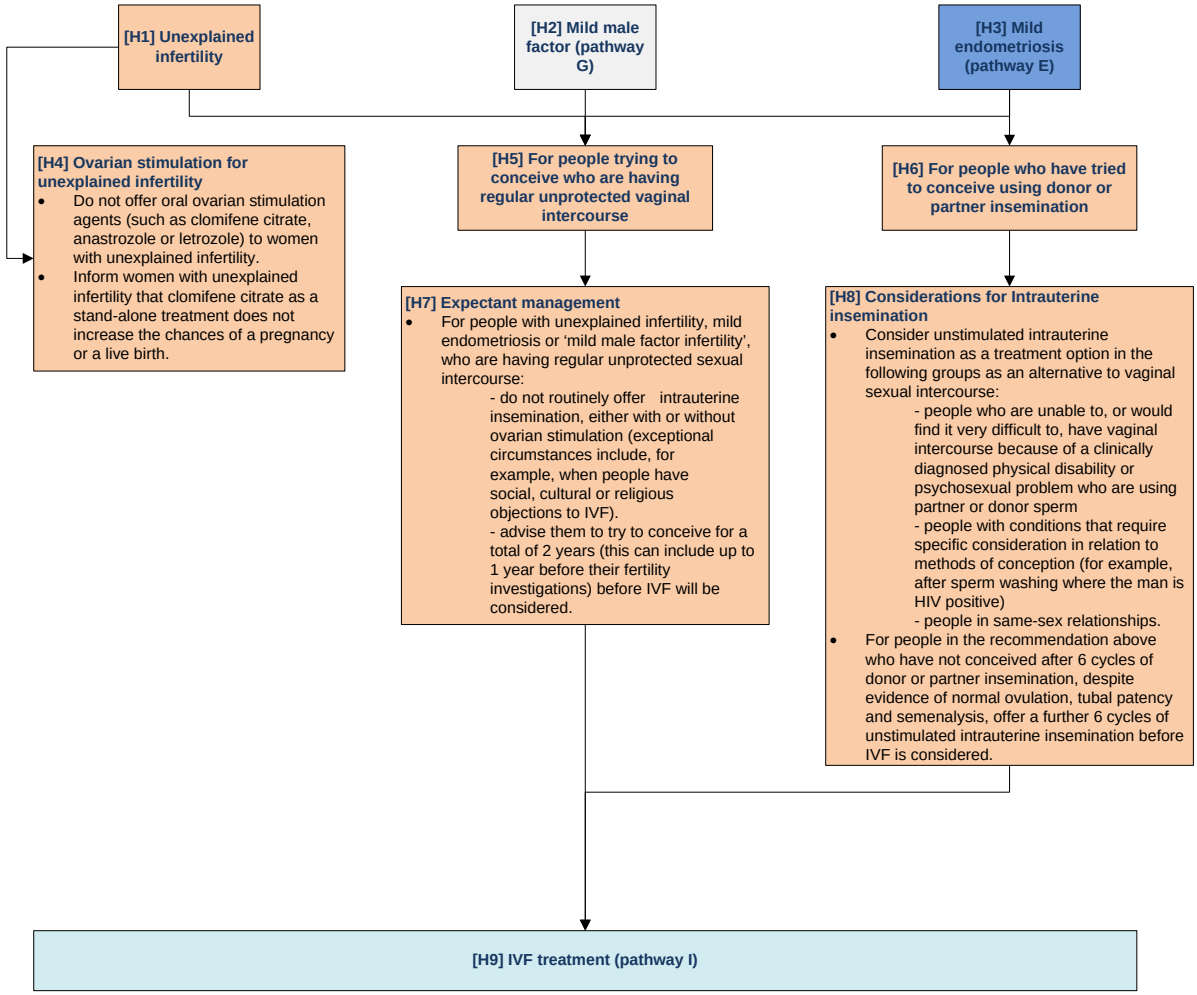
- Give people who are considering ovulation induction or ovarian stimulation up-to-date information about the long-term health outcomes of these treatments.
- Inform women who are offered ovulation induction or ovarian stimulation that:
  - no direct association has been found between these treatments and invasive cancer **and**
  - no association has been found in the short- to medium-term between these treatments and adverse outcomes (including cancer) in children born from ovulation induction **and**
  - information about long-term health outcomes in women and children is still awaited.
- Limit the use of ovulation induction or ovarian stimulation agents to the lowest effective dose and duration of use..

G. Suspected male factor infertility



2013 Update

H. Unexplained infertility



2013 Update

I. Prediction of IVF success and IVF procedure

[I1] Prediction of IVF success

- Inform women that the chance of a live birth following IVF treatment falls with rising female age (see figure 6.1).
- Inform people that the overall chance of a live birth following IVF treatment falls as the number of unsuccessful cycles increases.
- People should be informed that IVF treatment is more effective in women who have previously been pregnant and/or had a live birth.
- People should be informed that the consumption of more than 1 unit of alcohol per day reduces the effectiveness of assisted reproduction procedures, including IVF.
- People should be informed that maternal and paternal smoking can adversely affect the success rates of assisted reproduction procedures, including IVF treatment.
- People should be informed that maternal caffeine consumption has adverse effects on the success rates of assisted reproduction procedures, including IVF treatment.
- Women should be informed that female BMI should ideally be in the range 19–30 before commencing assisted reproduction, and that a female BMI outside this range is likely to reduce the success of assisted reproduction procedures.

[I2] IVF procedure

- When considering IVF as a treatment option for people with fertility problems, discuss the risks and benefits of IVF in accordance with the current Human Fertilisation and Embryology Authority (HFEA) code of practice.
- Inform people that normally a full cycle of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), should comprise 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s).
- In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles.
- In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:
  - they have never previously had IVF treatment
  - there is no evidence of low ovarian reserve (see box D10)
  - there has been a discussion of the additional implications of IVF and pregnancy at this age.
- Where investigations show there is no chance of pregnancy with expectant management and where IVF is the only effective treatment, refer the woman directly to a specialist team for IVF treatment.
- In women aged under 40 years any previous full IVF cycle, whether self- or NHS-funded, should count towards the total of 3 full cycles that should be offered by the NHS.
- Take into account the outcome of previous IVF treatment when assessing the likely effectiveness and safety of any further IVF treatment.
- Healthcare providers should define a cancelled IVF cycle as one where an egg collection procedure is not undertaken. However, cancelled cycles due to low ovarian reserve should be taken into account when considering suitability for further IVF treatment.

[I3] Pre-treatment for IVF

- Advise women that using pre-treatment (with either the oral contraceptive pill or a progestogen) as part of IVF does not affect the chances of having a live birth.
- Consider pre-treatment in order to schedule IVF treatment for women who are not undergoing long down-regulation protocols.

[I4] Down regulation and other regimens to avoid premature luteinising hormone surges in IVF

- Use regimens to avoid premature luteinising hormone surges in gonadotrophin-stimulated IVF treatment cycles.
- Use either gonadotrophin-releasing hormone agonist down-regulation or gonadotrophin-releasing hormone antagonists as part of gonadotrophin-stimulated IVF treatment cycles.
- Only offer gonadotrophin-releasing hormone agonists to women who have a low risk of ovarian hyperstimulation syndrome.
- When using gonadotrophin-releasing hormone agonists as part of IVF treatment, use a long down-regulation protocol.

[I5] Controlled ovarian stimulation in IVF

- Use ovarian stimulation as part of IVF treatment.
- Use either urinary or recombinant gonadotrophins for ovarian stimulation as part of IVF treatment.
- When using gonadotrophins for ovarian stimulation in IVF treatment use an individualised starting dose of follicle-stimulating hormone, based on factors that predict success, such as: age, BMI, presence of polycystic ovaries and ovarian reserve. Do not use a dose of FSH of more than 450 IU/day
- Offer women ultrasound monitoring (with or without oestradiol levels) for efficacy and safety throughout ovarian stimulation.

[I6] Triggering ovulation in IVF

- Offer women human chorionic gonadotrophin (urinary or recombinant) to trigger ovulation in IVF treatment.
- Offer ultrasound monitoring of ovarian response as an integral part of the IVF treatment cycle.
- Clinics providing ovarian stimulation with gonadotrophins should have protocols in place for preventing, diagnosing and managing ovarian hyperstimulation syndrome.

[I7] Oocyte and sperm retrieval in IVF

- Women undergoing transvaginal retrieval of oocytes should be offered conscious sedation because it is a safe and acceptable method of providing analgesia.
- The safe practice of administering sedative drugs published by the Academy of Medical Royal Colleges should be followed.
- Surgical sperm recovery before ICSI may be performed using several different techniques depending on the pathology and wishes of the man. In all cases, facilities for cryopreservation of spermatozoa should be available.

[I8] Embryo transfer strategies (see pathway J)

[I9] Luteal phase support

- Offer women progesterone for luteal phase support after IVF treatment.
- Do not routinely offer women human chorionic gonadotrophin for luteal phase support after IVF treatment because of the increased likelihood of ovarian hyperstimulation syndrome.
- Inform women undergoing IVF treatment that the evidence does not support continuing any form of treatment for luteal phase support beyond 8 weeks' gestation.

[I10] Long term adverse outcomes safety of IVF

- Give people who are considering IVF treatment, with or without ICSI, up-to-date information about the long-term health outcomes (including the consequences of multiple pregnancy) of these treatments.
- Inform women that while the absolute risks of long-term adverse outcomes of IVF treatment, with or without ICSI, are low, a small increased risk of borderline ovarian tumours cannot be excluded.
- Inform people who are considering IVF treatment that the absolute risks of long-term adverse outcomes in children born as result of IVF are low.
- Limit drugs used for controlled ovarian stimulation in IVF treatment to the lowest effective dose and duration of use.

J. IVF Embryo transfer strategies

[J1] Embryo transfer strategies – procedural

- Women undergoing IVF treatment should be offered ultrasound-guided embryo transfer because this improves pregnancy rates.
- Replacement of embryos into a uterine cavity with an endometrium of less than 5 mm thickness is unlikely to result in a pregnancy and is therefore not recommended.
- Women should be informed that bed rest of more than 20 minutes' duration following embryo transfer does not improve the outcome of IVF treatment.

[J2] Embryo transfer strategy – embryo number

- Evaluate embryo quality, at both cleavage and blastocyst stages, according to the Association of Clinical Embryologists (ACE) and UK National External Quality Assessment Service (UK NEQAS) for Reproductive Science Embryo and Blastocyst Grading schematic (see appendix O).
- Where a top-quality blastocyst is available, use single embryo transfer.
- No more than 2 embryos should be transferred during any one cycle of IVF treatment.
- When considering double embryo transfer, advise people of the risks of multiple pregnancy associated with this strategy.
- Offer cryopreservation to store any remaining good-quality embryos after embryo transfer.
- Advise women who have regular ovulatory cycles that the likelihood of a live birth after replacement of frozen–thawed embryos is similar for embryos replaced during natural cycles and hormone-supplemented cycles.
- For women undergoing IVF treatment with donor eggs, use an embryo transfer strategy that is based on the age of the donor.

[J3] For women aged under 37 years

[J6] 1st full cycle
Use single embryo transfer

[J7] 2nd full IVF cycle
Use single embryo transfer if 1 or more top-quality embryos are available. Consider using 2 embryos if no top-quality embryos are available.

[J8] 3rd full IVF cycle
Use no more than 2 embryos

[J4] For women aged 37–39 years

[J9] 1st full IVF cycle
use single embryo transfer if there are 1 or more top-quality embryos. Consider double embryo transfer if there are no top-quality embryos.

[J10] 2nd full IVF cycle
use single embryo transfer if there are 1 or more top-quality embryos. Consider double embryo transfer if there are no top-quality embryos.

[J11] 3rd full IVF cycle
Use no more than 2 embryos

[J5] For women aged 40–42 years

[J12] Full IVF cycle
Use no more than 2 embryos

2013 Update

K. Special procedures (ooctye donation, donor insemination and ICSI)

[K1] Indications for donor insemination

- The use of donor insemination is considered effective in managing fertility problems associated with the following conditions:
  - obstructive azoospermia
  - nonobstructive azoospermia
  - severe deficits in semen quality in couples who do not wish to undergo ICSI.
- Donor insemination should be considered in conditions such as:
  - where there is a high risk of transmitting a genetic disorder to the offspring
  - where there is a high risk of transmitting infectious disease to the offspring or woman from the man
  - severe rhesus isoimmunisation

[K2] Information and counselling

- Couples should be offered information about the relative merits of ICSI and donor insemination in a context that allows equal access to both treatment options.
- Couples considering donor insemination should be offered counselling from someone who is independent of the treatment unit regarding all the physical and psychological implications of treatment for themselves and potential children.

[K3] Screening of sperm donors

- Units undertaking semen donor recruitment and the cryopreservation of donor spermatozoa for treatment purposes should follow the 'UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors' (2008) describing the selection and screening of donors.
- All potential semen donors should be offered counselling from someone who is independent of the treatment unit regarding the implications for themselves and their genetic children, including any potential children resulting from donated semen.

[K4] Assessment of the female partner

- Before starting treatment by donor insemination (for conditions listed in box K1) it is important to confirm that the woman is ovulating. Women with a history that is suggestive of tubal damage should be offered tubal assessment before treatment.
- Women with no risk factors in their history should be offered tubal assessment after 3 cycles if treatment by donor insemination (for conditions listed in box K1) has been unsuccessful.

[K5] Intrauterine insemination

- Women who are ovulating regularly should be offered a minimum of 6 cycles of donor insemination (for conditions listed in box K1) without ovarian stimulation to reduce the risk of multiple pregnancy and its consequences.

[K6] Indications for oocyte donation

- The use of donor oocytes is considered effective in managing fertility problems associated with the following conditions:
  - premature ovarian failure
  - gonadal dysgenesis including Turner syndrome
  - bilateral oophorectomy
  - ovarian failure following chemotherapy or radiotherapy
  - certain cases of IVF treatment failure.

oocyte donation should also be considered in certain cases where there is a high risk of transmitting a genetic disorder to the offspring.

[K7] Oocyte donation and 'egg sharing'

- Before donation is undertaken, oocyte donors should be screened for both infectious and genetic diseases in accordance with the 'UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors' (2008).
- Oocyte donors should be offered information regarding the potential risks of ovarian stimulation and oocyte collection.
- Oocyte recipients and donors should be offered counselling from someone who is independent of the treatment unit regarding the physical and psychological implications of treatment for themselves and their genetic children, including any potential children resulting from donated oocytes.
- All people considering participation in an 'egg-sharing' scheme should be counselled about its particular implications.

[K8] Indications for intracytoplasmic sperm injection

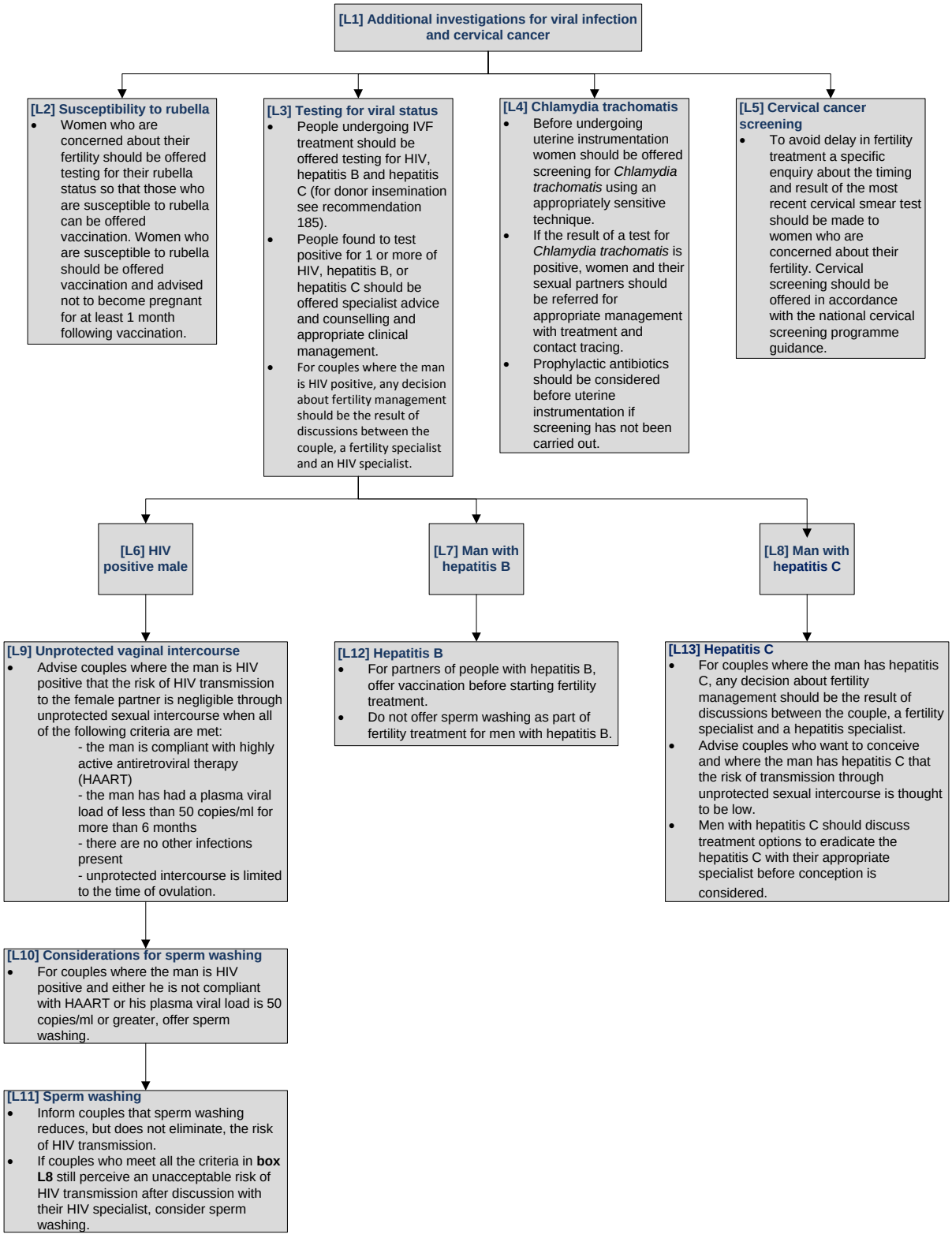
- The recognised indications for treatment by ICSI include:
  - severe deficits in semen quality
  - obstructive azoospermia
  - non-obstructive azoospermia

In addition, treatment by ICSI should be considered for couples in whom a previous IVF treatment cycle has resulted in failed or very poor fertilisation.

[K9] Genetic issues and counselling

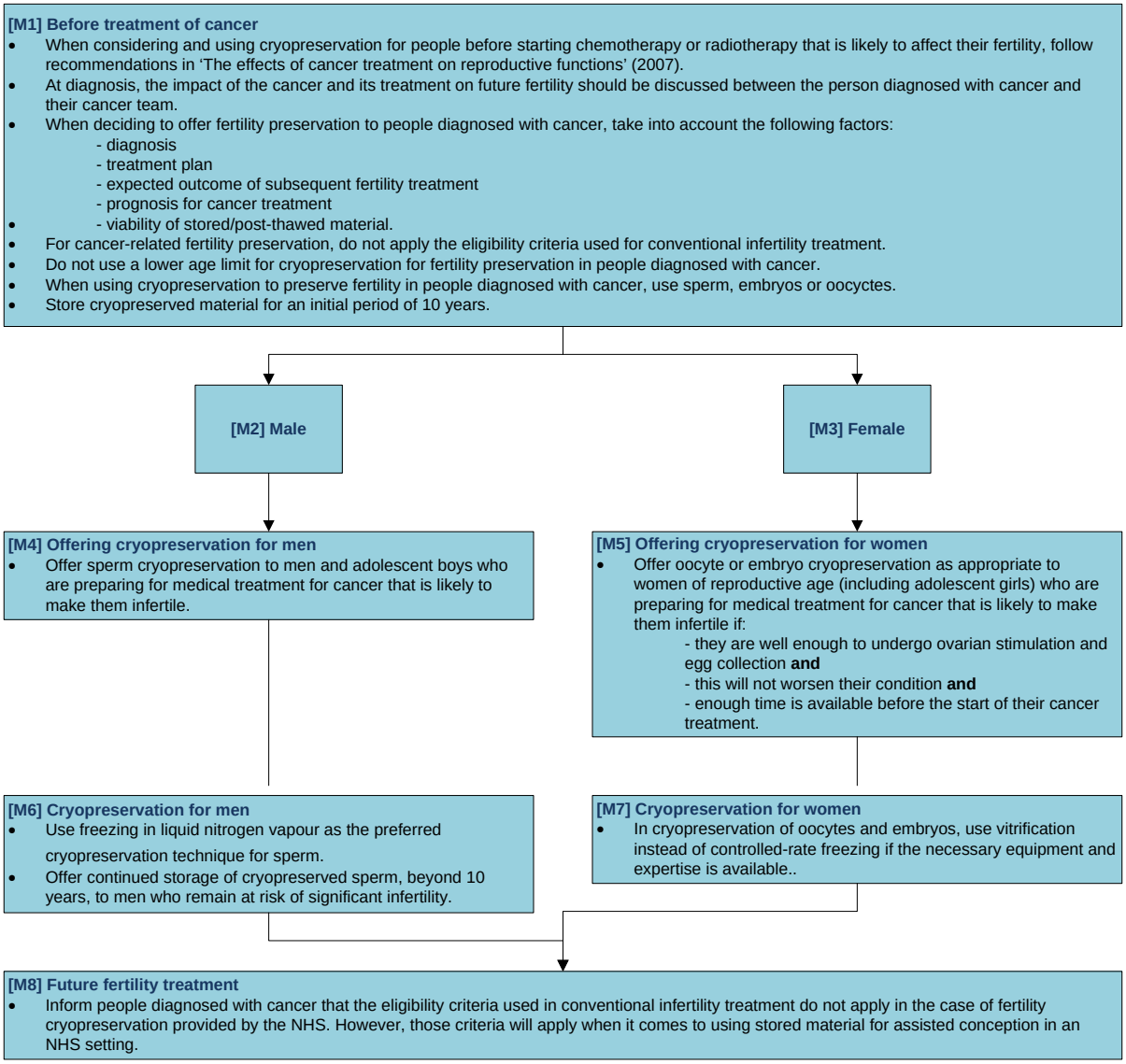
- Before considering treatment by ICSI, people should undergo appropriate investigations, both to establish a diagnosis and to enable informed discussion about the implications of treatment.
- Before treatment by ICSI consideration should be given to relevant genetic issues.
- Where a specific genetic defect associated with male infertility is known or suspected couples should be offered appropriate genetic counselling and testing.
- Where the indication for ICSI is a severe deficit of semen quality or non-obstructive azoospermia, the man's karyotype should be established.
- Men who are undergoing karyotype testing should be offered genetic counselling regarding the genetic abnormalities that may be detected.
- Testing for Y chromosome microdeletions should not be regarded as a routine investigation before ICSI. However, it is likely that a significant proportion of male infertility results from abnormalities of genes on the Y chromosome involved in the regulation of spermatogenesis, and couples should be informed of this.

L. Viral transmission and cancer screening



2013 Update

M. Cryopreservation for patients with cancer who wish to preserve their fertility



1.5 Key priorities for implementation

Number	Recommendation	See section
39	A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner. **[new 2013]**	5.13
41	Offer an earlier referral for specialist consultation to discuss the options for attempting conception, further assessment and appropriate treatment where: • the woman is aged 36 years or over • there is a known clinical cause of infertility or a history of predisposing factors for infertility. **[new 2013]**	5.13
113	Do not offer oral ovarian stimulation agents (such as clomifene citrate, anastrozole or letrozole) to women with unexplained infertility. **[new 2013]**	11.2
116	Offer IVF treatment (see recommendations 129-130) to women with unexplained infertility who have not conceived after 2 years (this can include up to 1 year before their fertility investigations) of regular unprotected sexual intercourse. **[new 2013]**	11.2
119	For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse: • do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF) • advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**.	12.2
128	Inform people that normally a full cycle of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), should comprise 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s). **[new 2013]**	14.5
129	In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles. **[new 2013]**	14.5
130	In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled: • they have never previously had IVF treatment • there is no evidence of low ovarian reserve (see recommendation 50) • there has been a discussion of the additional implications of IVF and pregnancy at this age. **[new 2013]**	

Number	Recommendation	See section
162	When considering the number of fresh or frozen embryos to transfer in IVF treatment: • For women aged under 37 years: o In the first full IVF cycle use single embryo transfer. o In the second full IVF cycle use single embryo transfer if 1 or more top-quality embryos are available. Consider using 2 embryos if no top-quality embryos are available. o In the third full IVF cycle transfer no more than 2 embryos. • For women aged 37–39 years: o In the first and second full IVF cycles use single embryo transfer if there are 1 or more top-quality embryos. Consider double embryo transfer if there are no top-quality embryos. o In the third full IVF cycle transfer no more than 2 embryos. • For women aged 40–42 years consider double embryo transfer. **[new 2013]**	15.7
165	Where a top-quality blastocyst is available, use single embryo transfer. **[new 2013]**	15.7

2013 Update

1.6 Recommendations

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, but only if there is good evidence to support that use.

Number	Recommendation	See section
	Providing information	
1	Couples who experience problems in conceiving should be seen together because both partners are affected by decisions surrounding investigation and treatment. **[2004]**	4.2
2	People should have the opportunity to make informed decisions regarding their care and treatment via access to evidence-based information. These choices should be recognised as an integral part of the decision-making process. Verbal information should be supplemented with written information or audio-visual media. **[2004]**	4.2
3	Information regarding care and treatment options should be provided in a form that is accessible to people who have additional needs, such as people with physical, cognitive or sensory disabilities, and people who do not speak or read English. **[2004]**	4.2

Number	Recommendation	See section
	Psychological effects of fertility problems	
4	When couples have fertility problems, both partners should be informed that stress in the male and/or female partner can affect the couple's relationship and is likely to reduce libido and frequency of intercourse which can contribute to the fertility problems. **[2004, amended 2013]**	4.3
5	People who experience fertility problems should be informed that they may find it helpful to contact a fertility support group. **[2004]**	4.3
6	People who experience fertility problems should be offered counselling because fertility problems themselves, and the investigation and treatment of fertility problems, can cause psychological stress. **[2004]**	4.3
7	Counselling should be offered before, during and after investigation and treatment, irrespective of the outcome of these procedures. **[2004]**	4.3
8	Counselling should be provided by someone who is not directly involved in the management of the individual's and/or couple's fertility problems. **[2004, amended 2013]**	4.3
	Generalist and specialist care	4.4
9	People who experience fertility problems should be treated by a specialist team because this is likely to improve the effectiveness and efficiency of treatment and is known to improve people's satisfaction with treatment. **[2004, amended 2013]**	
	Chance of conception	
10	People who are concerned about their fertility should be informed that over 80% of couples in the general population will conceive within 1 year if: • the woman is aged under 40 years **and** • they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%). **[2004, amended 2013]**	5.2
11	Inform people who are using artificial insemination to conceive and who are concerned about their fertility that: • over 50% of women aged under 40 years will conceive within 6 cycles of intrauterine insemination (IUI) • of those who do not conceive within 6 cycles of intrauterine insemination, about half will do so with a further 6 cycles (cumulative pregnancy rate over 75%). **[new 2013]**	5.2
12	Inform people who are using artificial insemination to conceive and who are concerned about their fertility that using fresh sperm is associated with higher conception rates than frozen-thawed sperm. However, intrauterine insemination, even using frozen-thawed sperm, is associated with higher conception rates than intracervical insemination. **[new 2013]**	5.2

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Number	Recommendation	See section
13	Inform people who are concerned about their fertility that female fertility and (to a lesser extent) male fertility decline with age. **[new 2013]**	5.2
14	Discuss chances of conception with people concerned about their fertility who are: • having sexual intercourse (see table 5.1) **or** • using artificial insemination (see table 5.2). **[new 2013]**	5.2
	Frequency and timing of sexual intercourse or artificial insemination	
15	People who are concerned about their fertility should be informed that vaginal sexual intercourse every 2 to 3 days optimises the chance of pregnancy. **[2004, amended 2013]**	5.3
16	People who are using artificial insemination to conceive should have their insemination timed around ovulation. **[new 2013]**	5.3
	Alcohol	
17	Women who are trying to become pregnant should be informed that drinking no more than 1 or 2 units of alcohol once or twice per week and avoiding episodes of intoxication reduces the risk of harming a developing fetus. **[2004]**	5.4
18	Men should be informed that alcohol consumption within the Department of Health's recommendations of 3 to 4 units per day for men is unlikely to affect their semen quality. **[2004, amended 2013]**	5.4
19	Men should be informed that excessive alcohol intake is detrimental to semen quality. **[2004]**	5.4
	Smoking	
20	Women who smoke should be informed that this is likely to reduce their fertility. **[2004]**	5.5
21	Women who smoke should be offered referral to a smoking cessation programme to support their efforts in stopping smoking. **[2004]**	5.5
22	Women should be informed that passive smoking is likely to affect their chance of conceiving. **[2004]**	5.5
23	Men who smoke should be informed that there is an association between smoking and reduced semen quality (although the impact of this on male fertility is uncertain), and that stopping smoking will improve their general health. **[2004]**	5.5
	Caffeinated beverages	
24	People who are concerned about their fertility should be informed that there is no consistent evidence of an association between consumption of caffeinated beverages (tea, coffee and colas) and fertility problems*. **[2004]**	5.6

*See recommendation 127 for a recommendation about caffeine intake and IVF treatment.

Number	Recommendation	See section
	Obesity	
25	Women who have a body mass index (BMI) of 30 or over should be informed that they are likely to take longer to conceive. **[2004, amended 2013]**	5.7
26	Women who have a BMI of 30 or over and who are not ovulating should be informed that losing weight is likely to increase their chance of conception. **[2004, amended 2013]**	5.7
27	Women should be informed that participating in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone. **[2004]**	5.7
28	Men who have a BMI of 30 or over should be informed that they are likely to have reduced fertility. **[2004, amended 2013]**	5.7
	Low body weight	
29	Women who have a BMI of less than 19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception. **[2004]**	5.7
	Tight underwear	
30	Men should be informed that there is an association between elevated scrotal temperature and reduced semen quality, but that it is uncertain whether wearing loose-fitting underwear improves fertility. **[2004]**	5.8
	Occupation	
31	Some occupations involve exposure to hazards that can reduce male or female fertility and therefore a specific enquiry about occupation should be made to people who are concerned about their fertility and appropriate advice should be offered. **[2004]**	5.9
	Prescribed, over-the-counter and recreational drug use	
32	A number of prescription, over-the-counter and recreational drugs interfere with male and female fertility, and therefore a specific enquiry about these should be made to people who are concerned about their fertility and appropriate advice should be offered. **[2004]**	5.10
	Complementary therapy	
33	People who are concerned about their fertility should be informed that the effectiveness of complementary therapies for fertility problems has not been properly evaluated and that further research is needed before such interventions can be recommended. **[2004]**	5.11

Number	Recommendation	See section
	Folic acid supplementation	
34	Women intending to become pregnant should be informed that dietary supplementation with folic acid before conception and up to 12 weeks' gestation reduces the risk of having a baby with neural tube defects. The recommended dose is 0.4 mg per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication or who have diabetes (see Diabetes in pregnancy, NICE clinical guideline 63), a higher dose of 5 mg per day is recommended. **[2004, amended 2013]**	5.12
	Defining infertility	
35	People who are concerned about delays in conception should be offered an initial assessment. A specific enquiry about lifestyle and sexual history should be taken to identify people who are less likely to conceive. **[2004]**	5.13
36	Offer an initial consultation to discuss the options for attempting conception to people who are unable to, or would find it very difficult to, have vaginal intercourse. **[new 2013]**	5.13
37	The environment in which investigation of fertility problems takes place should enable people to discuss sensitive issues such as sexual abuse. **[2004]**	5.13
38	Healthcare professionals should define infertility in practice as the period of time people have been trying to conceive without success after which formal investigation is justified and possible treatment implemented. **[new 2013]**	5.13
39	A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner. **[new 2013]**	5.13
40	A woman of reproductive age who is using artificial insemination to conceive (with either partner or donor sperm) should be offered further clinical assessment and investigation if she has not conceived after 6 cycles of treatment, in the absence of any known cause of infertility. Where this is using partner sperm, the referral for clinical assessment and investigation should include her partner. **[new 2013]**	5.13
41	Offer an earlier referral for specialist consultation to discuss the options for attempting conception, further assessment and appropriate treatment where: • the woman is aged 36 years or over • there is a known clinical cause of infertility or a history of predisposing factors for infertility. **[new 2013]**	5.13
42	Where treatment is planned that may result in infertility (such as treatment for cancer), early fertility specialist referral should be offered. **[2004, amended 2013]**	5.13

Number	Recommendation	See section
43	People who are concerned about their fertility and who are known to have chronic viral infections such as hepatitis B, hepatitis C or HIV should be referred to centres that have appropriate expertise and facilities to provide safe risk-reduction investigation and treatment. **[2004]**	5.13
	Semen analysis	
44	The results of semen analysis conducted as part of an initial assessment should be compared with the following World Health Organization reference values*: • semen volume: 1.5 ml or more • pH: 7.2 or more • sperm concentration: 15 million spermatozoa per ml or more • total sperm number: 39 million spermatozoa per ejaculate or more • total motility (percentage of progressive motility and non-progressive motility): 40% or more motile or 32% or more with progressive motility • vitality: 58% or more live spermatozoa • sperm morphology (percentage of normal forms): 4% or more. **[2004, amended 2013]**	6.2
45	Screening for antisperm antibodies should not be offered because there is no evidence of effective treatment to improve fertility. **[2004]**	6.2
46	If the result of the first semen analysis is abnormal, a repeat confirmatory test should be offered. **[2004]**	6.2
47	Repeat confirmatory tests should ideally be undertaken 3 months after the initial analysis to allow time for the cycle of spermatozoa formation to be completed. However, if a gross spermatozoa deficiency (azoospermia or severe oligozoospermia) has been detected the repeat test should be undertaken as soon as possible. **[2004]**	6.2
	Post-coital testing of cervical mucus	
48	The routine use of post-coital testing of cervical mucus in the investigation of fertility problems is not recommended because it has no predictive value on pregnancy rate. **[2004]**	6.2
	Ovarian reserve testing	
49	Use a woman's age as an initial predictor of her overall chance of success through natural conception (figure 5.1) or with in vitro fertilisation (IVF) (figure 6.1). **[new 2013]**	6.3

2013

* Please note the reference ranges are only valid for the semen analysis tests outlined by the World Health Organization

Number	Recommendation	See section
50	Use one of the following measures to predict the likely ovarian response to gonadotrophin stimulation in IVF: • total antral follicle count of less than or equal to 4 for a low response[*] and greater than 16 for a high response[†] • anti-Müllerian hormone of less than or equal to 5.4 pmol/l for a low response[‡] and greater than or equal to 25.0 pmol/l for a high response[§] • follicle-stimulating hormone greater than 8.9 IU/l for a low response and less than 4 IU/l for a high response[**]. **[new 2013]**	6.3
51	Do not use any of the following tests individually to predict any outcome of fertility treatment: • ovarian volume • ovarian blood flow • inhibin B • oestradiol (E2). **[new 2013]**	6.3
	Regularity of menstrual cycles	
52	Women who are concerned about their fertility should be asked about the frequency and regularity of their menstrual cycles. Women with regular monthly menstrual cycles should be informed that they are likely to be ovulating. **[2004]**	6.3
53	Women who are undergoing investigations for infertility should be offered a blood test to measure serum progesterone in the mid-luteal phase of their cycle (day 21 of a 28-day cycle) to confirm ovulation even if they have regular menstrual cycles. **[2004, amended 2013]**	6.3
54	Women with prolonged irregular menstrual cycles should be offered a blood test to measure serum progesterone. Depending upon the timing of menstrual periods, this test may need to be conducted later in the cycle (for example day 28 of a 35-day cycle) and repeated weekly thereafter until the next menstrual cycle starts. **[2004]**	6.3
55	The use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and is not recommended. **[2004]**	6.3
56	Women with irregular menstrual cycles should be offered a blood test to measure serum gonadotrophins (follicle-stimulating hormone and luteinising hormone). **[2004]**	6.3

[*] Follicles of ≤5 mm measured by transvaginal ultrasound on day 3 of cycle: low response was <4 oocytes.
[†] Follicles of 2–10 mm measured by transvaginal ultrasound on day 3 of cycle: high response was ≥15 oocytes or ≥20 oocytes.
[‡] Beckman Coulter assay: poor response defined as <4 oocytes or cancellation.
[§] Beckman Coulter or DSL assays: defined high response as ≥15 oocytes to >21 oocytes.
[**] Long protocol of down-regulation: low response defined as <4 oocytes or cancellation; high response defined as >20 oocytes.

Number	Recommendation	See section
	Prolactin measurement	
57	Women who are concerned about their fertility should not be offered a blood test to measure prolactin. This test should only be offered to women who have an ovulatory disorder, galactorrhoea or a pituitary tumour. **[2004]**	6.3
	Thyroid function tests	
58	Women with possible fertility problems are no more likely than the general population to have thyroid disease and the routine measurement of thyroid function should not be offered. Estimation of thyroid function should be confined to women with symptoms of thyroid disease. **[2004]**	6.3
	Endometrial biopsy	
59	Women should not be offered an endometrial biopsy to evaluate the luteal phase as part of the investigation of fertility problems because there is no evidence that medical treatment of luteal phase defect improves pregnancy rates. **[2004]**	6.3
	Investigation of suspected tubal and uterine abnormalities	
60	Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography (HSG) to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion, and it is less invasive and makes more efficient use of resources than laparoscopy. **[2004]**	6.4
61	Where appropriate expertise is available, screening for tubal occlusion using hysterosalpingo-contrast-ultrasonography should be considered because it is an effective alternative to hysterosalpingography for women who are not known to have comorbidities. **[2004]**	6.4
62	Women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pelvic pathology can be assessed at the same time. **[2004]**	6.4
63	Women should not be offered hysteroscopy on its own as part of the initial investigation unless clinically indicated because the effectiveness of surgical treatment of uterine abnormalities on improving pregnancy rates has not been established. **[2004]**	6.4
	Testing for viral status	
64	People undergoing IVF treatment should be offered testing for HIV, hepatitis B and hepatitis C (for donor insemination see recommendation 185). **[2004, amended 2013]**	6.5
65	People found to test positive for one or more of HIV, hepatitis B, or hepatitis C should be offered specialist advice and counselling and appropriate clinical management. **[2004, amended 2013]**	6.5

Number	Recommendation	See section
	Viral transmission	
66	For couples where the man is HIV positive, any decision about fertility management should be the result of discussions between the couple, a fertility specialist and an HIV specialist. **[new 2013]**	6.5
67	Advise couples where the man is HIV positive that the risk of HIV transmission to the female partner is negligible through unprotected sexual intercourse when all of the following criteria are met: • the man is compliant with highly active antiretroviral therapy (HAART) • the man has had a plasma viral load of less than 50 copies/ml for more than 6 months • there are no other infections present • unprotected intercourse is limited to the time of ovulation. **[new 2013]**	6.5
68	Advise couples that if all the criteria in recommendation 67 are met, sperm washing may not further reduce the risk of infection and may reduce the likelihood of pregnancy. **[new 2013]**	6.5
69	For couples where the man is HIV positive and either he is not compliant with HAART or his plasma viral load is 50 copies/ml or greater, offer sperm washing. **[new 2013]**	6.5
70	Inform couples that sperm washing reduces, but does not eliminate, the risk of HIV transmission. **[new 2013]**	6.5
71	If couples who meet all the criteria in recommendation 67 still perceive an unacceptable risk of HIV transmission after discussion with their HIV specialist, consider sperm washing. **[new 2013]**	6.5
72	Inform couples that there is insufficient evidence to recommend that HIV negative women use pre-exposure prophylaxis, when all the criteria in recommendation 67 are met. **[new 2013]**	6.5
73	For partners of people with hepatitis B, offer vaccination before starting fertility treatment. **[new 2013]**	6.5
74	Do not offer sperm washing as part of fertility treatment for men with hepatitis B. **[new 2013]**	6.5
75	For couples where the man has hepatitis C, any decision about fertility management should be the result of discussions between the couple, a fertility specialist and a hepatitis specialist. **[new 2013]**	6.5
76	Advise couples who want to conceive and where the man has hepatitis C that the risk of transmission through unprotected sexual intercourse is thought to be low. **[new 2013]**	6.5
77	Men with hepatitis C should discuss treatment options to eradicate the hepatitis C with their appropriate specialist before conception is considered. **[new 2013]**	6.5

Number	Recommendation	See section
	Susceptibility to rubella	
78	Women who are concerned about their fertility should be offered testing for their rubella status so that those who are susceptible to rubella can be offered vaccination. Women who are susceptible to rubella should be offered vaccination and advised not to become pregnant for at least 1 month following vaccination. **[2004, amended 2013]**	6.5
	Cervical cancer screening	
79	To avoid delay in fertility treatment a specific enquiry about the timing and result of the most recent cervical smear test should be made to women who are concerned about their fertility. Cervical screening should be offered in accordance with the national cervical screening programme guidance. **[2004]**	6.5
	Screening for *Chlamydia* trachomatis	
80	Before undergoing uterine instrumentation women should be offered screening for *Chlamydia trachomatis* using an appropriately sensitive technique. **[2004]**	6.5
81	If the result of a test for *Chlamydia trachomatis* is positive, women and their sexual partners should be referred for appropriate management with treatment and contact tracing. **[2004]**	6.5
82	Prophylactic antibiotics should be considered before uterine instrumentation if screening has not been carried out. **[2004]**	6.5
	Medical management (male factor infertility)	
83	Men with hypogonadotrophic hypogonadism should be offered gonadotrophin drugs because these are effective in improving fertility. **[2004]**	7.2
84	Men with idiopathic semen abnormalities should not be offered antio-estrogens, gonadotrophins, androgens, bromocriptine or kinin-enhancing drugs because they have not been shown to be effective. **[2004]**	7.2
85	Men should be informed that the significance of antisperm antibodies is unclear and the effectiveness of systemic corticosteroids is uncertain. **[2004]**	7.2
86	Men with leucocytes in their semen should not be offered antibiotic treatment unless there is an identified infection because there is no evidence that this improves pregnancy rates. **[2004]**	7.2
	Surgical management (male factor infertility)	
87	Where appropriate expertise is available, men with obstructive azoospermia should be offered surgical correction of epididymal blockage because it is likely to restore patency of the duct and improve fertility. Surgical correction should be considered as an alternative to surgical sperm recovery and IVF. **[2004]**	7.3
88	Men should not be offered surgery for varicoceles as a form of fertility treatment because it does not improve pregnancy rates. **[2004]**	7.3

Number	Recommendation	See section
	Management of ejaculatory failure	
89	Treatment of ejaculatory failure can restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction procedures. However, further evaluation of different treatment options is needed. **[2004]**	7.4
	WHO Group I ovulation disorders	
90	Advise women with WHO Group I anovulatory infertility that they can improve their chance of regular ovulation, conception and an uncomplicated pregnancy by: • increasing their body weight if they have a BMI of less than 19 **and/or** • moderating their exercise levels if they undertake high levels of exercise. **[new 2013]**	8.2
91	Offer women with WHO Group I ovulation disorders pulsatile administration of gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity to induce ovulation. **[2013]**	8.2
	WHO Group II ovulation disorders	
	In women with WHO Group II ovulation disorders receiving first-line treatment for ovarian stimulation:	
92	Advise women with WHO Group II anovulatory infertility who have a BMI of 30 or over to lose weight (see recommendation 26). Inform them that this alone may restore ovulation, improve their response to ovulation induction agents, and have a positive impact on pregnancy outcomes. **[new 2013]**	8.3
93	Offer women with WHO Group II anovulatory infertility one of the following treatments, taking into account potential adverse effects, ease and mode of use, the woman's BMI, and monitoring needed: • clomifene citrate **or** • metformin* **or** • a combination of the above. **[new 2013]**	8.3
94	For women who are taking clomifene citrate, offer ultrasound monitoring during at least the first cycle of treatment to ensure that they are taking a dose that minimises the risk of multiple pregnancy. **[2013]**	8.3
95	For women who are taking clomifene citrate, do not continue treatment for longer than 6 months. **[2013]**	8.3
96	Women prescribed metformin* should be informed of the side effects associated with its use (such as nausea, vomiting and other gastrointestinal disturbances). **[2004]**	8.3

2013 Update

* At the time of publication (February 2013), metformin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Number	Recommendation	See section
	In women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate:	
97	For women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate, consider one of the following second-line treatments, depending on clinical circumstances and the woman's preference: • laparoscopic ovarian drilling **or** • combined treatment with clomifene citrate and metformin* if not already offered as first-line treatment **or** • gonadotrophins. **[new 2013]**	8.4
98	Women with polycystic ovary syndrome who are being treated with gonadotrophins should not be offered treatment with gonadotrophin-releasing hormone agonist concomitantly because it does not improve pregnancy rates, and it is associated with an increased risk of ovarian hyperstimulation. **[2004]**	8.3
99	The use of adjuvant growth hormone treatment with gonadotrophin-releasing hormone agonist and/or human menopausal gonadotrophin during ovulation induction in women with polycystic ovary syndrome who do not respond to clomifene citrate is not recommended because it does not improve pregnancy rates. **[2004]**	8.3
100	The effectiveness of pulsatile gonadotrophin-releasing hormone in women with clomifene citrate-resistant polycystic ovary syndrome is uncertain and is therefore not recommended outside a research context. **[2004]**	8.3
	Hyperprolactinaemic amenorrhoea – dopamine agonists	
101	Women with ovulatory disorders due to hyperprolactinaemia should be offered treatment with dopamine agonists such as bromocriptine. Consideration should be given to safety for use in pregnancy and minimising cost when prescribing. **[2004]**	8.4
	Monitoring ovulation induction during gonadotrophin therapy	
102	Women who are offered ovulation induction with gonadotrophins should be informed about the risk of multiple pregnancy and ovarian hyperstimulation before starting treatment. **[2004]**	8.5
103	Ovarian ultrasound monitoring to measure follicular size and number should be an integral part of gonadotrophin therapy to reduce the risk of multiple pregnancy and ovarian hyperstimulation. **[2004]**	8.5
	Tubal microsurgery and laparoscopic tubal surgery	
104	For women with mild tubal disease, tubal surgery may be more effective than no treatment. In centres where appropriate expertise is available it may be considered as a treatment option. **[2004]**	9.2

2013 Update

* At the time of publication (February 2013), metformin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Number	Recommendation	See section
	Tubal catheterisation or cannulation	
105	For women with proximal tubal obstruction, selective salpingography plus tubal catheterisation, or hysteroscopic tubal cannulation, may be treatment options because these treatments improve the chance of pregnancy. **[2004]**	9.3
	Surgery for hydrosalpinges before in vitro fertilisation treatment	
106	Women with hydrosalpinges should be offered salpingectomy, preferably by laparoscopy, before IVF treatment because this improves the chance of a live birth. **[2004]**	9.4
	Uterine surgery	
107	Women with amenorrhoea who are found to have intrauterine adhesions should be offered hysteroscopic adhesiolysis because this is likely to restore menstruation and improve the chance of pregnancy. **[2004]**	9.5
	Medical management (ovarian suppression) of endometriosis	
108	Medical treatment of minimal and mild endometriosis diagnosed as the cause of infertility in women does not enhance fertility and should not be offered. **[2004, amended 2013]**	10.2
	Surgical ablation	
109	Women with minimal or mild endometriosis who undergo laparoscopy should be offered surgical ablation or resection of endometriosis plus laparoscopic adhesiolysis because this improves the chance of pregnancy. **[2004]**	10.3
110	Women with ovarian endometriomas should be offered laparoscopic cystectomy because this improves the chance of pregnancy. **[2004]**	10.3
111	Women with moderate or severe endometriosis should be offered surgical treatment because it improves the chance of pregnancy. **[2004]**	10.3
112	Post-operative medical treatment does not improve pregnancy rates in women with moderate to severe endometriosis and is not recommended. **[2004]**	10.3
	Ovarian stimulation for unexplained infertility	
113	Do not offer oral ovarian stimulation agents (such as clomifene citrate, anastrozole or letrozole) to women with unexplained infertility. **[new 2013]**	11.2
114	Inform women with unexplained infertility that clomifene citrate as a stand-alone treatment does not increase the chances of a pregnancy or a live birth. **[new 2013]**	11.2
115	Advise women with unexplained infertility who are having regular unprotected sexual intercourse to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**	11.2

Number	Recommendation	See section
116	Offer IVF treatment (see recommendations 129-130) to women with unexplained infertility who have not conceived after 2 years (this can include up to 1 year before their fertility investigations) of regular unprotected sexual intercourse. **[new 2013]**	11.2
	Intrauterine insemination	
117	Consider unstimulated intrauterine insemination as a treatment option in the following groups as an alternative to vaginal sexual intercourse: • people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem who are using partner or donor sperm • people with conditions that require specific consideration in relation to methods of conception (for example, after sperm washing where the man is HIV positive) • people in same-sex relationships. **[new 2013]**.	12.2
118	For people in recommendation 117 who have not conceived after 6 cycles of donor or partner insemination, despite evidence of normal ovulation, tubal patency and semenalysis, offer a further 6 cycles of unstimulated intrauterine insemination before IVF is considered. **[new 2013]**	12.2
119	For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse: • do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF) • advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**	12.2
	Prediction of IVF success	
120	Inform women that the chance of a live birth following IVF treatment falls with rising female age (see figure 6.1). **[2013]**	13.2
	Number of previous treatment cycles	
121	Inform people that the overall chance of a live birth following IVF treatment falls as the number of unsuccessful cycles increases. **[new 2013]**	13.2
	Previous pregnancy history	
122	People should be informed that IVF treatment is more effective in women who have previously been pregnant and/or had a live birth. **[2004, amended 2013]**	13.2
	Body mass index	
123	Women should be informed that female BMI should ideally be in the range 19–30 before commencing assisted reproduction, and that a female BMI outside this range is likely to reduce the success of assisted reproduction procedures. **[2004]**	13.2

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Number	Recommendation	See section
	Lifestyle factors	
124	People should be informed that the consumption of more than 1 unit of alcohol per day reduces the effectiveness of assisted reproduction procedures, including IVF. **[2004, amended 2013]**	13.2
125	People should be informed that maternal and paternal smoking can adversely affect the success rates of assisted reproduction procedures, including IVF treatment. **[2004, amended 2013]**	13.2
126	People should be informed that maternal caffeine consumption has adverse effects on the success rates of assisted reproduction procedures, including IVF treatment. **[2004, amended 2013]**	13.2
	Access criteria for IVF	
127	When considering IVF as a treatment option for people with fertility problems, discuss the risks and benefits of IVF in accordance with the current Human Fertilisation and Embryology Authority (HFEA) code of practice. **[new 2013]**	14.5
128	Inform people that normally a full cycle of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), should comprise 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s). **[new 2013]**	14.5
129	In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles. **[new 2013]**	14.5
130	In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled: • they have never previously had IVF treatment • there is no evidence of low ovarian reserve (see recommendation 50) • there has been a discussion of the additional implications of IVF and pregnancy at this age. **[new 2013]**	14.5
131	Where investigations show there is no chance of pregnancy with expectant management and where IVF is the only effective treatment, refer the woman directly to a specialist team for IVF treatment. **[new 2013]**	14.5
132	In women aged under 40 years any previous full IVF cycle, whether self- or NHS-funded, should count towards the total of 3 full cycles that should be offered by the NHS. **[new 2013]**	14.5
133	Take into account the outcome of previous IVF treatment when assessing the likely effectiveness and safety of any further IVF treatment. **[new 2013]**	14.5

Number	Recommendation	See section
134	Healthcare providers should define a cancelled IVF cycle as one where an egg collection procedure is not undertaken. However, cancelled cycles due to low ovarian reserve should be taken into account when considering suitability for further IVF treatment. **[new 2013]**	14.5
	Pre-treatment for IVF	
135	Advise women that using pre-treatment (with either the oral contraceptive pill or a progestogen) as part of IVF does not affect the chances of having a live birth. **[new 2013]**	15.2
136	Consider pre-treatment in order to schedule IVF treatment for women who are not undergoing long down-regulation protocols. **[new 2013]**	15.2
	Down regulation and other regimens to avoid premature luteinising hormone surges in IVF	
137	Use regimens to avoid premature luteinising hormone surges in gonadotrophin-stimulated IVF treatment cycles. **[new 2013]**	15.3
138	Use either gonadotrophin-releasing hormone agonist down-regulation or gonadotrophin-releasing hormone antagonists as part of gonadotrophin-stimulated IVF treatment cycles. **[new 2013]**	15.3
139	Only offer gonadotrophin-releasing hormone agonists to women who have a low risk of ovarian hyperstimulation syndrome. **[new 2013]**	15.3
140	When using gonadotrophin-releasing hormone agonists as part of IVF treatment, use a long down-regulation protocol. **[new 2013]**	15.3
	Controlled ovarian stimulation in IVF	
141	Use ovarian stimulation as part of IVF treatment. **[new 2013]**	15.4
142	Use either urinary or recombinant gonadotrophins for ovarian stimulation as part of IVF treatment. **[new 2013]**	15.4

143	When using gonadotrophins for ovarian stimulation in IVF treatment:
	• use an individualised starting dose of follicle-stimulating hormone, based on factors that predict success, such as:
	  o age
	  o BMI
	  o presence of polycystic ovaries
	  o ovarian reserve
	• do not use a dosage of follicle-stimulating hormone of more than 450 IU/day. **[new 2013]**
		15.4

144	Offer women ultrasound monitoring (with or without oestradiol levels) for efficacy and safety throughout ovarian stimulation. **[new 2013]**	15.4
145	Inform women that clomifene citrate-stimulated and gonadotrophin-stimulated IVF cycles have higher pregnancy rates per cycle than 'natural cycle' IVF. **[2013]**	15.4
146	Do not offer women 'natural cycle' IVF treatment. **[2013]**	

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Number	Recommendation	See section
147	Do not use growth hormone or dehydroepiandrosterone (DHEA) as adjuvant treatment in IVF protocols. **[new 2013]**	15.4
	Triggering ovulation in IVF	
148	Offer women human chorionic gonadotrophin (urinary or recombinant) to trigger ovulation in IVF treatment. **[new 2013]**	15.5
149	Offer ultrasound monitoring of ovarian response as an integral part of the IVF treatment cycle. **[2013]**	15.5
150	Clinics providing ovarian stimulation with gonadotrophins should have protocols in place for preventing, diagnosing and managing ovarian hyperstimulation syndrome. **[2004]**	15.5
	Oocyte and sperm retrieval in IVF	
151	Women undergoing transvaginal retrieval of oocytes should be offered conscious sedation because it is a safe and acceptable method of providing analgesia. **[2004]**	15.6
152	The safe practice of administering sedative drugs published by the Academy of Medical Royal Colleges should be followed. **[2004]**	15.6
153	Women who have developed at least 3 follicles before oocyte retrieval should not be offered follicle flushing because this procedure does not increase the numbers of oocytes retrieved or pregnancy rates, and it increases the duration of oocyte retrieval and associated pain. **[2004]**	15.6
154	Surgical sperm recovery before ICSI may be performed using several different techniques depending on the pathology and wishes of the man. In all cases, facilities for cryopreservation of spermatozoa should be available. **[2004]**	15.6
155	Assisted hatching is not recommended because it has not been shown to improve pregnancy rates. **[2004]**	15.6
	Embryo transfer strategies in IVF	
156	Women undergoing IVF treatment should be offered ultrasound-guided embryo transfer because this improves pregnancy rates. **[2004]**	15.7
157	Replacement of embryos into a uterine cavity with an endometrium of less than 5 mm thickness is unlikely to result in a pregnancy and is therefore not recommended. **[2004]**	15.7
158	Women should be informed that bed rest of more than 20 minutes' duration following embryo transfer does not improve the outcome of IVF treatment. **[2004]**	15.7
159	Evaluate embryo quality, at both cleavage and blastocyst stages, according to the Association of Clinical Embryologists (ACE) and UK National External Quality Assessment Service (UK NEQAS) for Reproductive Science Embryo and Blastocyst Grading schematic (see appendix O). **[new 2013]**	15.7

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Number	Recommendation	See section
160	When considering the number of fresh or frozen embryos to transfer in IVF treatment: • For women aged under 37 years: o In the first full IVF cycle use single embryo transfer. o In the second full IVF cycle use single embryo transfer if 1 or more top-quality embryos are available. Consider using 2 embryos if no top-quality embryos are available. o In the third full IVF cycle transfer no more than 2 embryos. • For women aged 37–39 years: o In the first and second full IVF cycles use single embryo transfer if there are 1 or more top-quality embryos. Consider double embryo transfer if there are no top-quality embryos. o In the third full IVF cycle transfer no more than 2 embryos. • For women aged 40–42 years consider double embryo transfer. **[new 2013]**	15.7
161	For women undergoing IVF treatment with donor eggs, use an embryo transfer strategy that is based on the age of the donor. **[new 2013]**	15.7
162	No more than 2 embryos should be transferred during any one cycle of IVF treatment. **[2013]**	15.7
163	Where a top-quality blastocyst is available, use single embryo transfer. **[new 2013]**	15.7
164	When considering double embryo transfer, advise people of the risks of multiple pregnancy associated with this strategy. **[new 2013]**	15.7
165	Offer cryopreservation to store any remaining good-quality embryos after embryo transfer. **[new 2013]**	15.7
166	Advise women who have regular ovulatory cycles that the likelihood of a live birth after replacement of frozen–thawed embryos is similar for embryos replaced during natural cycles and hormone-supplemented cycles. **[2013]**	15.7
	Luteal phase support after IVF	
167	Offer women progesterone for luteal phase support after IVF treatment. **[new 2013]**	15.8
168	Do not routinely offer women human chorionic gonadotrophin for luteal phase support after IVF treatment because of the increased likelihood of ovarian hyperstimulation syndrome. **[new 2013]**	15.8
169	Inform women undergoing IVF treatment that the evidence does not support continuing any form of treatment for luteal phase support beyond 8 weeks' gestation. **[new 2013]**	15.8

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Number	Recommendation	See section
	Gamete intrafallopian transfer and zygote intrafallopian transfer	
170	There is insufficient evidence to recommend the use of gamete intrafallopian transfer or zygote intrafallopian transfer in preference to IVF in couples with unexplained fertility problems or male factor fertility problems. **[2004]**	15.9
	Indications for intracytoplasmic sperm injection	
171	The recognised indications for treatment by ICSI include: • severe deficits in semen quality • obstructive azoospermia • non-obstructive azoospermia. In addition, treatment by ICSI should be considered for couples in whom a previous IVF treatment cycle has resulted in failed or very poor fertilisation. **[2004]**	16.2
	Genetic issues and counselling	
172	Before considering treatment by ICSI, people should undergo appropriate investigations, both to establish a diagnosis and to enable informed discussion about the implications of treatment. **[2004, amended 2013]**	16.3
173	Before treatment by ICSI consideration should be given to relevant genetic issues. **[2004]**	16.3
174	Where a specific genetic defect associated with male infertility is known or suspected couples should be offered appropriate genetic counselling and testing. **[2004]**	16.3
175	Where the indication for ICSI is a severe deficit of semen quality or non-obstructive azoospermia, the man's karyotype should be established. **[2004]**	16.3
176	Men who are undergoing karyotype testing should be offered genetic counselling regarding the genetic abnormalities that may be detected. **[2004]**	16.3
177	Testing for Y chromosome microdeletions should not be regarded as a routine investigation before ICSI. However, it is likely that a significant proportion of male infertility results from abnormalities of genes on the Y chromosome involved in the regulation of spermatogenesis, and couples should be informed of this. **[2004]**	16.3
	Intracytoplasmic sperm injection versus IVF	
178	Couples should be informed that ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF. **[2004]**	16.4

Number	Recommendation	See section
	Indications for donor insemination	
179	The use of donor insemination is considered effective in managing fertility problems associated with the following conditions: • obstructive azoospermia • non-obstructive azoospermia • severe deficits in semen quality in couples who do not wish to undergo ICSI. **[2004, amended 2013]**	17.2
180	Donor insemination should be considered in conditions such as: • where there is a high risk of transmitting a genetic disorder to the offspring • where there is a high risk of transmitting infectious disease to the offspring or woman from the man • severe rhesus isoimmunisation. **[2004, amended 2013]**	17.2
	Information and counselling	
181	Couples should be offered information about the relative merits of ICSI and donor insemination in a context that allows equal access to both treatment options. **[2004]**	17.3
182	Couples considering donor insemination should be offered counselling from someone who is independent of the treatment unit regarding all the physical and psychological implications of treatment for themselves and potential children. **[2004]**	17.3
	Screening of sperm donors	
183	Units undertaking semen donor recruitment and the cryopreservation of donor spermatozoa for treatment purposes should follow the 'UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors' (2008)* describing the selection and screening of donors. **[2004, amended 2013]**	17.4
184	All potential semen donors should be offered counselling from someone who is independent of the treatment unit regarding the implications for themselves and their genetic children, including any potential children resulting from donated semen. **[2004]**	17.4
	Assessments to offer the woman	
185	Before starting treatment by donor insemination (for conditions listed in recommendations 179 and 180) it is important to confirm that the woman is ovulating. Women with a history that is suggestive of tubal damage should be offered tubal assessment before treatment. **[2004, amended 2013]**	17.5
186	Women with no risk factors in their history should be offered tubal assessment after 3 cycles if treatment by donor insemination (for conditions listed in recommendations 179 and 180) has been unsuccessful. **[2004, amended 2013]**	17.5

* This recommendation has been updated to reflect a new guideline issued by the joint working party of Association of Biomedical Andrologists (ABA), Association of Clinical Embryologists (ACE), British Andrology Society (BAS), British Fertility Society (BFS) and Royal College of Obstetricians and Gynaecologists (RCOG).

Number	Recommendation	See section
	Intrauterine insemination versus intracervical insemination	
187	Couples using donor sperm should be offered intrauterine insemination in preference to intracervical insemination because it improves pregnancy rates. **[2004]**	17.6
	Unstimulated versus stimulated donor insemination	
188	Women who are ovulating regularly should be offered a minimum of 6 cycles of donor insemination (for conditions listed in recommendations 179 and 180) without ovarian stimulation to reduce the risk of multiple pregnancy and its consequences. **[2004, amended 2013]**	17.7
	Indications for oocyte donation	
189	The use of donor oocytes is considered effective in managing fertility problems associated with the following conditions: • premature ovarian failure • gonadal dysgenesis including Turner syndrome • bilateral oophorectomy • ovarian failure following chemotherapy or radiotherapy • certain cases of IVF treatment failure. Oocyte donation should also be considered in certain cases where there is a high risk of transmitting a genetic disorder to the offspring. **[2004]**	18.2
	Screening of oocyte donors	
190	Before donation is undertaken, oocyte donors should be screened for both infectious and genetic diseases in accordance with the 'UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors' (2008)*. **[2004, amended 2013]**	18.3
	Oocyte donation and 'egg sharing'	
191	Oocyte donors should be offered information regarding the potential risks of ovarian stimulation and oocyte collection. **[2004]**	18.4
192	Oocyte recipients and donors should be offered counselling from someone who is independent of the treatment unit regarding the physical and psychological implications of treatment for themselves and their genetic children, including any potential children resulting from donated oocytes. **[2004]**	18.4
193	All people considering participation in an 'egg-sharing' scheme should be counselled about its particular implications. **[2004]**	18.4

* This recommendation has been updated to reflect a new guideline issued by the joint working party of Association of Biomedical Andrologists (ABA), Association of Clinical Embryologists (ACE), British Andrology Society (BAS), British Fertility Society (BFS) and Royal College of Obstetricians and Gynaecologists (RCOG).

Number	Recommendation	See section
	Cryopreservation of semen, oocytes, embryos and ovarian tissue	
194	When considering and using cryopreservation for people before starting chemotherapy or radiotherapy that is likely to affect their fertility, follow recommendations in 'The effects of cancer treatment on reproductive functions' (2007)[*]. **[2013]**	19.2
195	At diagnosis, the impact of the cancer and its treatment on future fertility should be discussed between the person diagnosed with cancer and their cancer team. **[new 2013]**	19.2
196	When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors: • diagnosis • treatment plan • expected outcome of subsequent fertility treatment • prognosis of the cancer treatment • viability of stored/post-thawed material. **[new 2013]**	19.2
197	For cancer-related fertility preservation, do not apply the eligibility criteria used for conventional infertility treatment. **[new 2013]**	
198	Do not use a lower age limit for cryopreservation for fertility preservation in people diagnosed with cancer. **[new 2013]**	19.2
199	Inform people diagnosed with cancer that the eligibility criteria used in conventional infertility treatment do not apply in the case of fertility cryopreservation provided by the NHS. However, those criteria will apply when it comes to using stored material for assisted conception in an NHS setting. **[new 2013]**	19.2
200	When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos or oocyctes. **[new 2013]**	19.2
201	Offer sperm cryopreservation to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile. **[new 2013]**	19.2
202	Use freezing in liquid nitrogen vapour as the preferred cryopreservation technique for sperm. **[new 2013]**	19.2
203	Offer oocyte or embryo cryopreservation as appropriate to women of reproductive age (including adolescent girls) who are preparing for medical treatment for cancer that is likely to make them infertile if: • they are well enough to undergo ovarian stimulation and egg collection **and** • this will not worsen their condition **and** • enough time is available before the start of their cancer treatment. **[new 2013]**	19.2

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[*] Royal College of Physicians, The Royal College of Radiologists, Royal College of Obstetricians and Gynaecologists. The effects of cancer treatment on reproductive functions: Guidance on management. Report of a Working Party. London: RCP, 2007.

Number	Recommendation	See section
204	In cryopreservation of oocytes and embryos, use vitrification instead of controlled-rate freezing if the necessary equipment and expertise is available. **[new 2013]**	19.2
205	Store cryopreserved material for an initial period of 10 years. **[new 2013]**	19.2
206	Offer continued storage of cryopreserved sperm, beyond 10 years, to men who remain at risk of significant infertility. **[new 2013]**	19.2
	Long-term health outcomes of ovulation induction and ovarian stimulation	
207	Give people who are considering ovulation induction or ovarian stimulation up-to-date information about the long-term health outcomes of these treatments. **[new 2013].**	20.2
208	Inform women who are offered ovulation induction or ovarian stimulation that: • no direct association has been found between these treatments and invasive cancer **and** • no association has been found in the short- to medium-term between these treatments and adverse outcomes (including cancer) in children born from ovulation induction **and** • information about long-term health outcomes in women and children is still awaited. **[new 2013]**	20.2
209	Limit the use of ovulation induction or ovarian stimulation agents to the lowest effective dose and duration of use. **[new 2013]**	20.2
	Long term health outcomes and safety of IVF	
210	Give people who are considering IVF treatment, with or without ICSI, up-to-date information about the long-term health outcomes (including the consequences of multiple pregnancy) of these treatments. **[new 2013]**	20.3
211	Inform women that while the absolute risks of long-term adverse outcomes of IVF treatment, with or without ICSI, are low, a small increased risk of borderline ovarian tumours cannot be excluded. **[new 2013]**	20.3
212	Inform people who are considering IVF treatment that the absolute risks of long-term adverse outcomes in children born as result of IVF are low. **[new 2013]**	20.3
213	Limit drugs used for controlled ovarian stimulation in IVF treatment to the lowest effective dose and duration of use. **[new 2013]**	20.3

1.7 Key research recommendations

Number	Research recommendation	See section
RR 21	What is the optimum period of expectant management for women of different age groups before invasive treatment such as IVF is considered? **Why this is important** Where there is no known cause for infertility, expectant management increases the cumulative chances of successful conception.However, the chances of a live birth both by natural conception and by using assisted reproductive technology decline with advancing age because of a woman's decreasing ovarian reserve.The guideline currently recommends a shorter period of expectant management for women who are 36 years or older. This is a very crude cut-off. If there were better evidence it might be possible to customise the period of expectant management based on a woman's age, including longer periods of expectant management for younger women.	11.2
RR 33	Further research is needed to improve embryo selection to facilitate single embryo transfers. **Why this is important** In current IVF practice it is common to transfer more than one embryo in order to maximise the chance of pregnancy. As detailed in the guideline, this practice has inherent risks, especially of multiple pregnancy. Embryo selection is based on the assessment of developmental stage and morphological grading criteria in the laboratory. These features are indicative of implantation potential, though the predictive accuracy is relatively poor. However, if prediction of implantation potential could be improved, this would facilitate embryo selection for single rather than double embryo transfer.	14.6
RR 36	Further research is needed to assess the efficacy of adjuvant luteal phase support treatments such as low-dose aspirin, heparin, prednisolone, immunoglobulins and/or fat emulsions. **Why this is important** These interventions are starting to be used in clinical practice in the absence of any RCT evidence of benefit, and even where there is RCT evidence of no benefit. Their use has potential dangers to the treated women. In cases where women are advised to continue taking the preparations until the end of the first trimester there is the additional potential for teratogenicity. Immunoglobulins are also very expensive. It is important that the clinical efficacy of these agents is formally established so that clear statements about whether they should be recommended or are contraindicated can be made.	14.7
RR 44	Is there an association between ovulation induction or ovarian	19.2

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Number	Research recommendation	See section
	stimulation and adverse long-term (over 20 years) effects in women in the UK? Why this is important Women need to be reassured that it is safe to undergo ovulation induction and ovarian stimulation and that these interventions will not lead to significant long-term health issues, especially ovarian malignancy. Both treatments are common in the management of infertile women. The use of ovarian stimulation in IVF is particularly important as IVF is the final treatment option for most causes of infertility. During the course of the review for this guideline update the GDG commented on the paucity of long-term research on the subject, despite the fact that the treatments have been established practice for over 30 years. The longest length of follow-up in the studies reviewed was 20 years, and the larger studies had shorter follow-up periods.	
RR 45	What are the long-term (over 20 years) effects of IVF with or without intracytoplasmic sperm injection in children in the UK? Why this is important This topic is important in informing patients, service providers and society at large about the potential long-term safety of assisted reproduction. Both IVF and intracytoplasmic sperm injection involve manipulation of egg and sperm in the laboratory, with impacts on the development of the subsequent embryo. However, while the first successful live birth following IVF was over 30 years ago, there is relatively little long-term research on the subject. In the review undertaken in this guideline update, the longest length of follow-up in the studies reviewed was 20 years,and the larger studies had shorter follow-up periods.	

1.8 Research recommendations

Number	Research recommendation	See section
RR 1	Further research is needed to evaluate the access for people from ethnic minority groups to investigation and treatment of fertility problems.	4.2
RR 2	Further research is needed to assess the long-term psychological impact of investigation and treatment of people who perceive problems with their fertility, both in people who subsequently achieve a live birth and people who do not.	4.3
RR 3	Larger well-designed studies are needed to further define test thresholds for prediction of all outcomes, especially live birth	6.3
RR 4	What is the value of these tests in the prediction of spontaneous pregnancy in the general population?	6.3

Number	Research recommendation	See section
RR 5	Further research is needed to determine whether women with raised serum prolactin should have macroprolactin excluded.	6.3
RR 6	Further research is needed to ascertain the value of fertiloscopy and falloposcopy in the investigation of couples who experience problems with fertility.	6.4
RR 7	Further randomised controlled trials are needed to evaluate the potentially therapeutic effects of tubal flushing with water-soluble media.	6.4
RR 8	The role of pelvic ultrasound in women who are not suspected to have pelvic pathology requires further evaluation.	6.4
RR 9	What is the clinical and cost effectiveness of pre-exposure prophylaxis in HIV negative women in discordant couples?	6.5
RR 10	What is the relationship between seminal and plasma HIV viral load?	6.5
RR 11	What is the effectiveness of sperm washing in reducing the transmission of hepatitis C from men to their partner?	6.5
RR 12	Is seminal HIV viral load a better predictor of the risk of transmission than plasma HIV viral load?	6.5
RR 13	Alpha blockers and mast-cell blockers [*]need further evaluation before they can be considered in the treatment of men with semen abnormalities.	7.2
RR 14	Research into the optimum dose and duration of alpha blockers to improve semen parameters in infertile men is needed.	7.2
RR 15	Randomised controlled trials are needed to compare the effectiveness of surgery for varicocele and in vitro fertilisation treatment in men with abnormal semen quality.	7.3
RR 16	What is the cost effectiveness and safety of using clomifene citrate or metformin or a combination of the two to induce ovulation in women with WHO group II ovulation disorders?	8.3
RR 17	Further research is needed to evaluate the clinical and cost effectiveness of tubal surgery compared with no treatment and other treatment options, particularly in vitro fertilisation. This research should include consideration of any adverse consequences of treatment, such as ectopic pregnancy.	9.2
RR 18	For women who have hydrosalpinges, the effectiveness of draining of hydrosalpinges or performing salpingostomy on improving live birth rate during in vitro fertilisation needs further evaluation.	9.4
RR 19	Randomised controlled trials are needed to evaluate any benefits of surgical treatment of leiomyoma on improving the chance of live birth.	9.5
RR 20	Further research is needed to evaluate any benefit on live birth rates of surgical resection of uterine septum in women with fertility problems.	9.5

[*] Since 2004 a Cochrane review (Showell et al., 2011) has shown a benefit in pregnancy rates with use of antioxidants therefore antioxidants has been removed from this research recommendation in the 2013 update.

Number	Research recommendation	See section
RR 21	What is the optimum period of expectant management for women of different age groups before invasive treatment such as IVF is considered?	11.2
RR 22	What is the effectiveness of IUI (with and without stimulation) compared to expectant management for couples with endometriosis?	12.2
RR 23	What is the effectiveness of IUI (with and without stimulation) compared to expectant management for couples with mild male factor infertility?	12.2
RR 24	Research is needed to define semen quality criteria for assisted reproduction to be effective in the management of male infertility.	12.2
RR 25	Research is needed to determine the relative effectiveness of oral (anti-oestrogen) and injectable (gonadotrophin) drugs in stimulated intrauterine insemination in couples with unexplained fertility problems.	12.2
RR 26	Further randomised controlled trials are needed to evaluate the effectiveness of assisted reproduction procedures in relation to female body mass index.	13.2
RR 27	What is the cost effectiveness of pre-treatment when used to schedule IVF treatment?	15.2
RR 28	What is the effectiveness of short down-regulation protocols in poor responders?	15.3
RR 29	What is the clinical and cost effectiveness of ovarian stimulation with clomifene citrate compared to GnRH agonist and gonadotrophins?	15.4
RR 30	Is the use of adjuvant DHEA in poor responders clinically effective?	15.4
RR 31	What is the clinical and cost effectiveness of highly purified gonadotrophins compared to other gonadotrophins?	15.4
RR 32	Further research is needed to determine whether interventions, such as prophylactic albumin treatment, administered at the time of egg collection are effective in reducing the risk of OHSS. This research should include issues related to timing and dose?	15.5
RR 33	Further research is needed to improve embryo selection to facilitate single embryo transfers.	15.7
RR 34	Further research is needed to evaluate the effects of assisted hatching on live birth rates and long-term consequences for children born as a result of assisted hatching.	15.6
RR 35	Further research is needed to compare the effectiveness (including patient satisfaction) of different drugs and routes of administration for luteal support during in vitro fertilisation	15.8
RR 36	Further research is needed to assess the efficacy of adjuvant luteal phase support treatments such as low dose aspirin, heparin, prednisolone, immunoglobulins and/or fat emulsions.	15.8
RR 37	Further research is needed to evaluate the effect of intracytoplasmic sperm injection on live birth or pregnancy rates in	16.4

2013 Update

2013 Update

2013 Update

Number	Research recommendation	See section
	couples where the male partner has poor semen quality	
RR 38	Research is needed to evaluate the effectiveness of counselling in relation to oocyte donation and egg sharing in terms of the long-term psychological and social implications of these practices.	18.4
RR 39	What is the efficacy of vitrification of sperm?	19.2
RR 40	What is the long term outcome of babies resulting from the use of vitrified embryos or eggs?	19.2
RR 41	Is there a difference in the effectiveness of open vitrification systems compared to closed vitrification systems?	19.2
RR 42	What is the efficacy of cryopreservation of ovarian and testicular tissue?	19.2
RR 43	Is there an association between ovulation induction or ovarian stimulation and adverse long term (over 20 years) effects in children born as a result, in the UK population?	20.2
RR 44	Is there an association between ovulation induction or ovarian stimulation and adverse long-term (over 20 years) effects in women in the UK?	20.2
RR 45	What are the long-term (over 20 years) effects of IVF with or without intracytoplasmic sperm injection in children in the UK?	20.3

1.9 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 3 years from the date of publication. Reviewing may begin before 3 years have elapsed if significant evidence that affects guideline recommendations is identified sooner.

2 Introduction

2.1 Fertility

This guideline offers best practice advice on assisting people of reproductive age who have problems conceiving.

It is estimated that infertility affects about one in seven heterosexual couples in the UK. Since the original NICE guideline on fertility was published in 2004 there has been a small increase in the prevalence of fertility problems and a greater proportion of people now seeking help for such problems.

The main causes of infertility in the UK are (percentage figures indicate approximate prevalence)[1,2,3]:

- ovulatory disorders (25%)
- tubal damage (20%)
- factors in the male causing infertility (30%)
- uterine or peritoneal disorders (10%).

In about 25% of cases infertility is unexplained, with no identified male or female cause.

In about 40% of cases disorders are found in both the man and the woman. Uterine or endometrial factors, gamete or embryo defects, and pelvic conditions such as endometriosis may also play a role.

Given the range of causes of fertility problems, the provision of appropriate investigations is critical. These investigations include semen analysis; assessment of ovulation, tubal damage and uterine abnormalities; and screening for infections such as *Chlamydia trachomatis* and susceptibility to rubella.

Once a diagnosis has been established, treatment falls into three main types:

- medical treatment to restore fertility (for example the use of drugs for ovulation induction)
- surgical treatment to restore fertility (for example laparoscopy for ablation of endometriosis)
- assisted reproduction technology (ART) – any treatment that deals with means of conception other than vaginal coitus; frequently involving the handling of gametes or embryos.

2.2 Update of Fertility guideline

The original 2004 guideline on Fertility provided comprehensive coverage of the subject and allowed for an evidence-based approach to the investigation and management of infertility. The aim of this update is to revise recommendations on selected topics (see below) in the light of new evidence and, where appropriate, make new recommendations. The guideline development process is described in detail in Chapter 3. The guideline applies to all UK healthcare settings which are funded by the National Health Service (NHS).

The guideline applies to people with either explained or unexplained infertility, but for the update additional consideration was given to the following groups:

- people in same-sex relationships who remain infertile after donor insemination

- people who are unable to, or would find it very difficult, to have vaginal intercourse (such as people with a clinically diagnosed disability or psychosexual problem)
- people with conditions that require specific consideration in relation to methods of conception (such as couples where the male is HIV positive)
- people who are preparing for cancer treatment who may wish to preserve their fertility.

As this is a partial update of the original guideline only specific topics are addressed, which are:

- tests for ovarian reserve
- effectiveness of ovulation induction agents used in treatment programmes for infertility
- effectiveness of intrauterine insemination, with or without ovulation induction agents
- multifactorial prediction of success to determine clinical and cost effectiveness criteria for in vitro fertilisation (IVF) treatment
- effectiveness of the following IVF treatment strategies:
    - pretreatment
    - down-regulation and other regimens to avoid premature luteinising hormone surges in IVF
    - ovarian stimulation (including mild versus conventional stimulation)
    - triggering
    - timing and number of embryo transfer
    - luteal phase support
- cryopreservation and vitrification to preserve fertility for patients with impending cancer treatment
- appropriate management of couples where the male partner is HIV positive and female is HIV negative (including sperm washing)
- long-term safety of ovulation induction and ovarian stimulation agents in women and children
- the long-term safety of IVF in women with infertility and their children.

In addition, a considerable amount of relevant guidance has been published since 2004, and this update will cross-reference this (including the World Health Organization [WHO] reference values for semen analysis and the Human Fertilisation and Embryology Authority Code of Practice), where appropriate.

2.3 For whom is this guideline intended

This guidance is of relevance to those who work in or use the NHS in England and Wales, in particular:

- professional groups who share in caring for couples seeking advice and treatment for fertility problems, such as gynaecologists, andrologists, GPs, counsellors and nurses
- those with responsibilities for commissioning and planning fertility services in primary care trusts and Health Commission Wales
- people seeking advice and treatment for possible infertility.

2.4 Related NICE guidance

- Antenatal and postnatal mental health. NICE clinical guideline 45 (2007).
- Antenatal care. NICE clinical guideline 62 (2008).
- Diabetes in pregnancy. NICE clinical guideline 63 (2008).
- Intrapartum care. NICE clinical guideline 55 (2007).
- Multiple pregnancy. NICE clinical guideline 129 (2011).
- Postnatal care. NICE clinical guideline 37 (2006).
- Weight management before, during and after pregnancy. NICE public health guideline 27 (2010).

3 Guideline development methodology

3.1 Introduction

The guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups (2009) available from the NICE website.

3.2 Methodology for 2004 guideline

Literature search strategy

The aim of the literature review was to identify and synthesise relevant evidence within the published literature, in order to answer specific clinical questions. Searches were performed using generic and specially developed filters, relevant medical subject heading terms and free-text terms. Details of all literature searches are available on application to the NCC-WCH.

The National Guidelines Clearinghouse database, the Turning Research into Practice database, and the Organising Medical Networked Information service on the Internet were searched for guidelines produced by other development groups. The reference lists in these guidelines were checked against our searches to identify any missing evidence.

Searches were carried out for each topic of interest. The Cochrane Library (up to Issue 3, 2003) was searched to identify systematic reviews (with or without meta-analyses) of randomised controlled (clinical) trials (RCTs) and individual RCTs. The electronic databases MEDLINE (Ovid version for the period January 1966 to October 2003), EMBASE (Ovid version for the period between 1988 to October 2003), the Cumulative Index to Nursing and Allied Health Literature, the British Nursing Index and PsychInfo were also searched, as was the Database of Abstracts and Reviews of Effectiveness.

There was no systematic attempt to search the 'grey literature' (conferences, abstracts, theses and unpublished trials). A preliminary scrutiny of titles and abstracts was undertaken and full papers were obtained if the research question addressed the guideline development group's question relevant to the topic. Following a further review of the full version of the study, articles that did not address the group's question were excluded. Studies that did not report relevant outcomes were also excluded. Submitted evidence from stakeholders was included where the evidence was relevant to the group's clinical question and was of equivalent or better quality than the research identified in the literature searches.

The economic evidence presented in this guideline is not a systematic review of all the economic evidence around fertility treatment, but a review of evidence relating to specific aspects of treatment (see below). In addition to the databases listed above, the Health Economic Evaluations Database and the NHS Economic Evaluations Database were searched for relevant economic studies.

The search strategies were designed to find any economic study related to infertility. Abstracts and database reviews of papers found were reviewed by the health economists and were discarded if they appeared not to contain any cost data relevant to the UK setting or did not relate to the precise topic or question being considered in the algorithm. Relevant references in the bibliographies of reviewed papers were also identified and assessed against standard criteria.

The topic had to focus on the appropriate alternatives (the appropriate clinical question) and preferably be able to be generalised to the England and Wales setting. The review of the evidence included cost-effectiveness studies, cost-consequence studies (cost of present and future costs only) and high quality systematic reviews of the evidence (see below).

Outcome measures

For this guideline, the management of fertility problems has been assessed against a variety of reproductive and pregnancy outcomes. The justification for using these outcomes is based on their relevance to women and consensus among members of the guideline development droup. These outcomes were also informed by the Cochrane Menstruation Disorders and Subfertility Group. The outcomes were grouped to reflect their importance to women, healthcare professionals and the health service. Outcomes include those that were felt to be desirable (for example, a live birth) and those unwanted effects of treatment that it would be important to reduce to a minimum (for example, ectopic pregnancy or fetal abnormality). When assessing the effectiveness of a particular treatment, information about the effect of that treatment on one or more primary outcomes was sought. Where such information was not available secondary outcomes were used. If neither primary nor secondary outcomes were available surrogate outcomes (indirect measures of effectiveness) were considered.

Primary outcomes considered in the guideline include:

- live birth
- patient satisfaction
- anxiety/depression
- multiple births
- fetal abnormalities
- ectopic pregnancy
- ovarian hyperstimulation syndrome (OHSS).

Secondary outcomes considered in the guideline include:

- clinical pregnancy (confirmed by presence of fetal heart rate)
- miscarriage
- cycle cancellation
- low birth weight
- perinatal mortality.

Surrogate outcomes considered in the guideline include:

- tubal patency
- ovulation
- fertilisation
- implantation (number of gestational sacs identified by ultrasound)
- number of embryos transferred
- embryo quality
- improved semen parameters
- improved sexual function.

Clinical effectiveness

For all subject areas, evidence from the study designs least subject to bias was included. Where possible, the highest levels of evidence were used, but all papers were reviewed using established

guides.[5–11] Published systematic reviews or meta-analyses were used where available. For subject areas where neither was available, other appropriate experimental or observational studies were sought.

Identified articles were assessed methodologically and the best available evidence was used to form and support the recommendations. The highest level of evidence was selected for each clinical question. The retrieved evidence was graded according to the evidence-level structure shown in Table 3.1.

Each clinical question dictated the highest level of evidence that could be sought. For issues of therapy or treatment the highest possible level of evidence was a meta-analysis of RCTs or an individual RCT.

For issues of prognosis, a cohort study was the best possible level of evidence. This equates to a grade B recommendation (see below). However, this should not be interpreted as an inferior grade of recommendation because it represents the highest level of evidence attainable for that type of clinical question.

Table 3.1 Hierarchy of evidence

Level	Evidence
1a	Systematic review and meta-analysis of randomised controlled trials
1b	At least one randomised controlled trial
2a	At least one well-designed controlled study without randomisation
2b	At least one other type of well-designed quasi-experimental study
3	Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies or case studies
4	Expert committee reports or opinions and/or clinical experience of respected authorities

For diagnostic tests, test evaluation studies examining the performance of the test were used if the efficacy of the test was required, but where an evaluation of the effectiveness of the test in the management and outcome was required, evidence from RCTs or cohort studies was sought.

All retrieved articles were appraised methodologically using established guides. Where appropriate, if a systematic review, meta-analysis or RCT existed in relation to a topic, studies of a weaker design were excluded.

The evidence was synthesised using qualitative methods. These involved summarising the content of identified papers in the form of evidence tables and agreeing brief statements that accurately reflected the relevant evidence. Quantitative synthesis (meta-analysis) was performed where appropriate. Meta-analyses based on dichotomous aoutcomes are presented as relative risks with 95% confidence intervals.

For the purposes of this guideline, data are presented as absolute risks, relative risks or odds ratios where relevant (i.e. in RCTs and cohort studies). Where the data are statistically significant they are also presented as numbers needed to treat (for beneficial outcomes) or numbers need to harm (for adverse effects of treatment) if relevant.

Health economics

Aim of the economic analysis

The inclusion of economic evidence in guidelines is a fairly recent phenomenon. The purpose of including economic evidence in a clinical guideline is to allow recommendations to be made not just on the clinical effectiveness of different forms of care, but also on their cost effectiveness. The aim is to produce guidance that uses scarce health service resources efficiently, that is providing the best possible care within resource constraints.

Cost effectiveness of assisted reproduction

The approach to presenting the economic evidence on assisted reproduction was to model the cost effectiveness of assisted reproduction under different assumptions and conditions. There were several reasons for adopting this approach. First, decision analysis is an important step towards understanding the cost effectiveness of different treatment pathways that a couple may be offered. Second, the approach allows for the synthesis of clinical effectiveness evidence, alongside the estimated costs of diagnosis and treatment and the consequences of treatment that relate to the UK setting. Third, it clearly shows where gaps exist in the published literature and research evidence.

Two recent systematic reviews of economic evaluations of infertility treatment have been undertaken.[12,13] The most recent review[12] identified 2547 studies. From these, 30 economic evaluations, 22 cost studies and five economic benefit studies met the selection criteria and were reported. This was a high-quality systematic review with a transparent methodology and the results were summarised in tables showing the synthesis of cost and clinical effectiveness data where available. The authors of the systematic reviews reported high levels of variability in the costs of treatment, largely due to the variation in definitions of cost and whether costs associated with the consequences of assisted reproduction or wider social costs (to other services or to women and their families) were incorporated.

The earlier review[13] was undertaken to complement the RCOG clinical guidelines for infertility services in the UK. A high proportion of studies were not relevant to the UK setting and did not reflect the true cost of treatment in the UK.[13]

The models developed in this guideline were based on clinical and cost effectiveness data for assisted reproduction treatments. Since robust trial data on the effectiveness of different options for assisted reproduction were not available, the models used probabilities derived from a combination of sources (see Appendix M).

Key topics for the economic analysis in the guideline were determined by the guideline development group as the process of developing the guideline and reviewing the evidence evolved. The key economic questions to be considered in the guideline were:

- the cost effectiveness of in vitro fertilisation (IVF) and other forms of assisted reproduction
- the cost effectiveness of urinary versus recombinant gonadotrophins in IVF treatment
- the cost effectiveness of stimulated and unstimulated intrauterine insemination (IUI)
- a review of the current literature on the cost impact of reducing the number of embryos transferred during IVF treatment.

Valuing the cost of assisted reproduction

Alongside the review of the research evidence, data were gathered from other UK sources to obtain estimates of the costs for specific cost elements in each model. Historically, many of the services offered as part of an infertility diagnosis and treatment package have not been provided by the NHS but rather by private clinics. However, the market prices of these services were assumed to be likely to be close to 'opportunity costs' for the services.

Although the value of the resources used in assisted reproduction is an important question, the overall cost effectiveness of assisted reproduction will also be determined by important differences in clinical effectiveness of assisted reproduction treatments. The clinical and cost data that were available were not appropriate for making detailed forecasts of future expenditure on assisted reproduction. This would require a detailed costing exercise based on current and future levels of demand for the service, current capacity and future resources available. However, the data did indicate the magnitudes of costs that would be likely to be needed if specific policies were adopted. This analysis also indicates whether specific parameters (such as, the live birth rate, the number of cycles offered and the rate at which couples choose to discontinue treatment) are more important than others, and where future research effort should be directed.

Representation of the consequences of assisted reproduction: quality-adjusted life years

Ethical and moral arguments relating to the value of live births resulting from assisted reproduction are not addressed in the economic analysis because they go beyond the issues that can be addressed in a clinical guideline. The primary outcome considered in the economic models is a live birth and not a measure of life years. There is an important debate about whether the outputs of assisted reproduction can be incorporated into a measure than can be compared with other uses of the same resources. It is not logical to try to derive a quality adjusted life year (QALY) measure from live births arising from IVF. It has been argued that:[14]

"QALYs are intended to capture improvements in health among patients. They are not appropriate for placing a value on additional lives. Additional lives are not improvements in health; preventing someone's death is not the same as creating their life and it is not possible to improve the quality of life of someone who has not been conceived by conceiving them."

Another review[15] stated that:

"Cost-utility analysis has little relevance to the management of infertility where lives are produced and not saved".

This is a valid argument, so QALYs cannot be reported in the context of assisted reproduction unless they are related only to the couple seeking treatment.

Forming and grading recommendations

The guideline development group was presented with the summaries (text and evidence tables) of the best available research evidence to answer its questions. Recommendations were based on, and explicitly linked to, the evidence that supported them. Where possible, the group worked on an informal consensus basis. Formal consensus methods (the nominal group technique) were employed when required (e.g. grading recommendations and agreeing audit criteria).

The strength of evidence corresponding to each level of recommendation is shown in Table 3.2. The grading of recommendations follows that outlined in the Health Technology Assessment 'How to develop cost conscious guidelines'.[16]

Summary results are presented in the guideline text. More detailed results and other data are presented in the relevant evidence tables.

Table 3.2 Strength of evidence corresponding to each level of recommendation

Grade	Strength of evidence
A	Directly based on level 1 evidence
B	Directly based on level 2 evidence or extrapolated recommendation from level 1 evidence
C	Directly based on level 3 evidence or extrapolated recommendation from either level 1 or 2 evidence
D	Directly based on level 4 evidence or extrapolated recommendation from either level 1, 2 or 3 evidence
Good practice point (GPP)	The view of the guideline development group
NICE Technology Appraisal	Recommendation taken from a NICE Technology Appraisal

External review

The guideline has been developed in accordance with the NICE guideline development process. This has included the opportunity for registered stakeholders to comment on the scope of the guideline, the first draft of the full and summary guidelines and the second draft of all versions of the guideline.

In addition the drafts were reviewed by an independent Guideline Review Panel established by NICE and by the NICE Executive and the Patient Involvement Unit for NICE.

The comments made by the stakeholders, peer reviewers and the Guideline Review Panel were collated and presented anonymously for consideration by the guideline development group. All comments were considered systematically by the guideline development group and the resulting actions and responses were recorded.

3.3 Methodology for 2013 update

This guidance was commissioned by NICE and developed in accordance with the guideline development process outlined in the 2009 edition of The Guidelines Manual.

As part of NICE's quality assurance process, the guideline documentation and responses to stakeholders undergo final editorial checks and review by the quality assurance panel. At this point the response to a particular set of stakeholder comments, and the related removal of a recommendation, was queried. The NCC-WCH and guideline development group (GDG) provided a detailed explanation of the reasons for the response. It was not possible to resolve the issue with written communication. Therefore, taking into account the stakeholder comments and quality assurance feedback, NICE convened a meeting of the GDG to further review the wording of the recommendation. These steps are consistent with the guidance provided by the NICE Guiudelines Manual.

In accordance with NICE's Equality Scheme, ethnic and cultural considerations and factors relating to disabilities have been considered by the GDG throughout the development process and specifically addressed in individual recommendations where relevant.

Developing review questions and protocols and identifying evidence

The GDG formulated review questions based on the scope (see Appendix A) and prepared a protocol for each review question (see Appendix D). These formed the starting point for systematic reviews of relevant evidence. Published evidence was identified by applying systematic search strategies (see Appendix E) to the following databases: Medline (1950 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards) and three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects). Searches to identify economic studies were undertaken using the above databases, the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database. None of the searches were limited by date. Searches in Embase were limited to English language and searches in Medline were limited to English language and studies in humans. None of the other searches were limited by language of publication (although publications in languages other than English were not reviewed). Validated search filters were used to identify particular study designs, such as RCTs. There was no systematic attempt to search grey literature (conference abstracts, theses or unpublished trials), nor was hand searching of journals not indexed on the databases undertaken.

Towards the end of the guideline development process, the searches were updated and re-executed to include evidence published and indexed in the databases by 30 November 2011.

Reviewing and synthesising evidence

Evidence relating to clinical effectiveness was reviewed and synthesised according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. In the GRADE approach, the quality of the evidence identified for each outcome listed in the review protocol is assessed according to the factors listed below, and an overall quality rating (high, moderate, low or very low) is assigned by combining the ratings for the individual factors.

- Study design (as an indicator of intrinsic bias; this determines the initial quality rating)
- Limitations in the design or execution of the study including concealment of allocation, blinding, loss to follow up (these can reduce the quality rating)
- Inconsistency of effects across studies (this can reduce the quality rating)

- Indirectness: the extent to which the available evidence fails to address the specific review question (this can reduce the quality rating)
- Imprecision: reflects the confidence in the estimate of effect (this can reduce the quality rating)
- Other considerations including large magnitude of effect, evidence of a dose-response relationship, or confounding variables likely to have reduced the magnitude of an effect (these can increase the quality rating in observational studies, provided no downgrading for other features has occurred).

The type of review question determines the highest level of evidence that may be sought. For issues of therapy or treatment, the highest possible evidence level is a well-conducted systematic review or meta-analysis of RCTs, or an individual RCT. In the GRADE approach, a body of evidence based entirely on such studies has an initial quality rating of high, and this may be downgraded to moderate, low or very low if factors listed above are not addressed adequately. For issues of prognosis, the highest possible level of evidence is a controlled observational study (a cohort study or case–control study), and a body of evidence based on such studies would have an initial quality rating of low, which might be downgraded to very low or upgraded to moderate or high, depending on the factors listed above.

For each review question the highest available level of evidence was sought. Where appropriate, for example, if a systematic review, meta-analysis or RCT was identified to answer a question directly, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs were not identified, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the accuracy of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of the condition was required, evidence from RCTs or cohort studies was considered optimal. For studies evaluating the accuracy of a diagnostic test, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratios for positive and negative test results (LR+ and LR–, respectively) were calculated or quoted where possible (see Table 3.3). The only additional approach was used in the section on ovarian reserve testing where there were two parts to the review (see Section 6.3). The first part was to assess all available tests for ovarian reserve against pre-specified quality criteria for specified outcomes determined by the GDG. The quality criterion was a receiver operator characteristic 'area under the curve' (ROC-AUC) of 0.8 or more (based on Hosmer and Lemeshow test). Tests that met this criterion were then included in the second part of the review where more detailed assessment was undertaken and likelihood ratios were calculated for each test and the specified outcomes.

The GRADE system described above covers studies of treatment effectiveness. However, it is less well established for studies reporting accuracy of diagnostic tests. For such studies, NICE recommends using the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) methodology checklist to assess study quality (see the NICE guidelines manual, 2009).

Some studies were excluded from the guideline reviews after obtaining copies of the publications because they did not meet inclusion criteria specified by the GDG (see Appendix G). The characteristics of each included study were summarised in evidence tables for each review question (see Appendix H). Where possible, dichotomous outcomes were presented as relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs), and continuous outcomes were presented as mean differences with 95% CIs or standard deviations (SDs).

The body of evidence identified for each therapy or treatment review question (or part of a review question) was presented in the form of a GRADE evidence profile summarising the quality of the evidence and the findings (pooled relative and absolute effect sizes and associated CIs). Where possible, the body of evidence corresponding to each outcome specified in the review protocol was subjected to quantitative meta-analysis. In such cases, pooled effect sizes were presented as pooled RRs, pooled ORs or weighted mean differences. By default, meta-analyses were conducted by fitting fixed effects models, but where statistically significant heterogeneity was identified, random effects models were used to investigate the impact of the heterogeneity. Where quantitative meta-analysis could not be undertaken (for example because of heterogeneity in the included studies) the range of effect sizes reported in the included studies was presented.The GRADE evidence profiles are not

directly applicable to epidemiological studies or non-comparative cohort studies. Where these studies are presented, they are done so in descriptive paragraphs and/or tables as appropriate.

Table 3.3 '2 x 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	**Reference standard negative**	**Total**
Index test result positive	a (true positive)	b (false positive)	a+b
Index test result negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d = N (total number of tests in study)

Outcome measures

For this guideline update, the management of fertility problems has been assessed against a variety of reproductive and pregnancy outcomes. The justification for using these outcomes is based on their relevance to people covered by the guideline and consensus among members of the GDG. Outcomes include those that were felt to be desirable (for example a live birth) and unwanted effects of treatment that it would be important to reduce to a minimum (for example ovarian hyperstimulation syndrome). When assessing the effectiveness of a particular treatment, information about the effect of that treatment on one or more primary outcomes was sought.

Primary outcomes considered in the guideline include:

- live full-term singleton birth
- clinical pregnancy
- adverse pregnancy outcomes (including miscarriage, ectopic pregnancy)
- multiple pregnancy
- multiple births
- ovarian hyperstimulation syndrome (OHSS)
- congenital abnormalities
- patient satisfaction
- health related quality of life
- anxiety and/or depression
- long term effects of infertility treatment in women and their children (including premature mortality, future fertility, future gynaecological health, future malignant disease).

When considering the evidence, the GDG judged 'live full-term singleton birth' to be the most important outcome as the group believes it to be the best indicator of a healthy mother and of a 'healthy baby', and therefore the best indicator of successful IVF treatment. 'Full term' was included in the outcome as babies born at term are more likely to survive without disability than babies born pre-term. As many studies did not report live full-term singleton births, the number of live births or the number of singleton births were often used instead of live full-term singleton birth, with the data accordingly downgraded for indirectness in the GRADE profiles.

'Clinical pregnancy' was also identified as an important outcome and was used in conjunction with the live full-term singleton birth data. Clinical pregnancy was also used when a study did not report live birth data, although the GDG acknowledged that not all clinical pregnancies result in a live birth. If a study did not define clinical pregnancy, its data was also downgraded for indirectness.

Incorporating health economics

The aims of the health economic input to the guideline were to inform the GDG of potential economic issues relating to fertility, and to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits (ideally in terms of quality adjusted life years [QALYs]), harms and costs of different care options.

The GDG prioritised a number of review questions where it was thought that economic considerations would be particularly important in formulating recommendations. Systematic searches for published economic evidence were undertaken for these questions. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation. Reviews of the relevant published health economic literature are presented alongside the clinical effectiveness reviews.

Health economic considerations were aided by original economic analysis undertaken as part of the development process. For this guideline the areas prioritised for economic analysis were:

- the effectiveness of IUI (see Chapter 12)
- the cost effectiveness of IVF treatment (see Chapter 14)
- the effectiveness and safety of different embryo/blastocyst transfer strategies (see Section 15.7).

Evidence to recommendations

For each review question recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree short clinical and, where appropriate, cost effectiveness evidence statements which were presented alongside the evidence profiles. In the case of the topic on the number of embryos to be transferred during IVF a formal consensus approach was used (see 'Specific considerations for this guideline' below and Section 15.7). Statements summarising the GDG's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process. The criteria used in moving from evidence to recommendations were:

- Relative value placed on the outcomes considered
- Consideration of clinical benefits and harms
- Consideration of net health benefits and resource use
- Quality of the evidence
- Other considerations (including equalities issues).

In areas where no substantial clinical research evidence was identified, the GDG members considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions) was considered was based on GDG consensus in relation to the likely cost effectiveness implications of the recommendations. The GDG also identified areas where evidence to answer its review questions was lacking and used this information to formulate recommendations for future research.

Towards the end of the guideline development process formal consensus methods were used to identify nine key priorities for implementation (key recommendations) and five high priority research recommendations. The key priorities for implementation were those recommendations thought likely to have the biggest impact on clinical care and outcomes in the NHS as a whole. The priority research recommendations were selected in a similar way.

Where no agreement could be reached on a recommendation by the GDG, a formal vote was undertaken and a majority decision was taken forward in the recommendations.

Stakeholder involvement

Registered stakeholder organisations were invited to comment on the draft scope and the draft guideline. Stakeholder organisations were also invited to undertake a pre-publication check of the final guideline to identify factual inaccuracies. The GDG carefully considered and responded to all comments received from stakeholder organisations. The comments and responses, which were reviewed independently by NICE, are published on the NICE website.

Specific considerations for this guideline

Formal consensus survey

A formal consensus survey was used to define embryo transfer strategies, as it was agreed that a recommendation was needed but the GDG was unable to reach a conclusion using discussion alone.

Methods

The formal consensus approach involved a series of action statements relating to management or treatment under review being drafted by the NCC-WCH technical team. These were collated into a consensus questionnaire. The GDG members were asked to independently complete the questionnaire stating their level of agreement (ranging from 'Strongly agree' to 'Strongly disagree') with each statement and provide comments on where statements should be amended. The results of the voting were collated by the technical team. If 70% or more of the GDG members agreed or disagreed with a statement then it was concluded that consensus had been reached. If there was no consensus the statement could be adapted based on comments and presented for a second round of voting, applying the same majority threshold. Statements where consensus was reached were then used to draft recommendations. These were discussed and ratified at a subsequent GDG meeting.

4 Principles of care

4.1 Introduction

Infertility can be very stressful. The psychological and physical trauma associated with investigation and treatment can often be exacerbated by the length of treatment and the multi-disciplinary approach that is involved. This chapter defines what constitutes good clinical practice and recommends the principles of care that people should expect throughout treatment.

4.2 Providing information

People seeking fertility treatment often do so with a partner. In such circumstances both the World Health Organization (WHO) and the Human Fertilisation and Embryology Authority (HFEA) strongly suggest that, where possible, couples should be seen together.[207,218] Two surveys have reported that women were more satisfied when seen with their partners at their infertility consultation.[219,220] A further survey reported that couples were seen together in only 35% of clinics.[221] However, there was strong agreement among GPs that couples should be seen together as part of infertility management.[222]

Individuals and couples want information about their conditions, their treatment and outcomes.[223] Verbal as well as written information can improve understanding.[229] Patients have reported that videos and booklets of information about the practical and psychological aspects of in vitro fertilisation (IVF) improved knowledge and passage through the IVF cycle.[230] Verbal information should be supported by written evidence-based guidance sensitive to the needs of individual patients.[231] A clear protocol that sets out the purpose of investigation and the proposed care plan should be followed.

For assisted reproduction, the HFEA Code of Practice stipulates that individuals seeking treatment should be given verbal explanations, supported by relevant written materials, about the 'medical, scientific, legal and psychological implications of their decision'. Individuals should be 'encouraged to seek any further information that they may need, and all questions should be answered in as straightforward and comprehensive a way as possible'.[218] (HFEA, 2009) [Evidence level 4] Information leaflets about various aspects of assisted reproduction are available from the HFEA website.

Information and advice given in a manner that is culturally sensitive to the individuals concerned may improve acceptability of infertility management and care.[243–245] [Evidence level 3]

Recommendations

Number	Recommendation
1	Couples who experience problems in conceiving should be seen together because both partners are affected by decisions surrounding investigation and treatment. **[2004]**
2	People should have the opportunity to make informed decisions regarding their care and treatment via access to evidence-based information. These choices should be recognised as an integral part of the decision-making process. Verbal information should be supplemented with written information or audio-visual media. **[2004]**
3	Information regarding care and treatment options should be provided in a form that is accessible to people who have additional needs, such as people with physical, cognitive or sensory disabilities, and people who do not speak or read English. **[2004]**

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Number	Research recommendation
RR 1	Further research is needed to evaluate the access for people from ethnic minority groups to investigation and treatment of fertility problems.

4.3 Psychological effects of fertility problems

The relationship between psychological stress and fertility problems is complex.[246] [Evidence level 3] Individual response to stress situations will vary. Three cohort studies have reported an association between work-related stress and a lower probability of conception in women.[247–249] [Evidence level 2b] However, the association in men is less clear.[250,251] [Evidence level 2b] Psychological stress can affect a couple's relationship and libido, which may impact upon their chance of conception. A higher frequency of male sexual disturbances including loss of libido and a decrease in the frequency of sexual intercourse has been observed in couples undergoing fertility diagnostic and treatment procedures.[252–254] [Evidence level 3–4]

Infertility is regarded as an upsetting and difficult life experience for some women,[255,256] with a subpopulation of women reporting elevated levels of anxiety and depression in some studies;[255,257–265] however, another study[266] did not find such an association. In one study, the psychological symptoms of anxiety and depression associated with infertility were found to be similar to those associated with other serious medical conditions such as heart disease, cancer, hypertension and infection with HIV.[267] A study in Sweden reported that almost 50% of women said they needed professional help and support to deal with their anxiety and problems in their marital relationship two years after tubal reconstructive surgery.[268] [Evidence level 3]

Two RCTs have shown that group psychological interventions such as cognitive behavioural therapy and support prevent distress[269,270] and improve pregnancy rates (55% in a cognitive behavioural therapy group versus 54% in a support group versus 20% in a routine care group)[270] in women with less than two years' duration of infertility. [Evidence level 1b]

Psychiatric morbidity was reported to be positively associated with the experience of infertility and the number of treatment cycles, affecting more women than men.[265] [Evidence level 3] The psychological state of couples undergoing IVF may vary at different stages of treatment, the most stressful stages being waiting for the outcome of treatment and finding out that IVF has been unsuccessful.[271]

An RCT that evaluated the use of information and information combined with counselling for couples undergoing IVF treatment showed no significant differences between the two groups in terms of psychological symptoms and satisfaction.[272] [Evidence level 1b]

Four surveys have reported that most patients feel that access to a support group and counselling would be beneficial.[226,263,273,274] Some felt that psychological support should be available at all stages of infertility treatment and investigation.[230] An unpublished survey[274] found that few GPs offered counselling or identified methods of support, but two-thirds of couples attending an infertility clinic said they would accept psychological assistance if offered.[263] [Evidence level 3] In another study, 70% of patients said they would request counselling if it were available free of charge.[228] [Evidence level 3] Despite this, overall uptake of counselling is low at between 18% and 25%.[226,230,275] It has been suggested that less distressed patients may not wish to receive counselling, and some may cope well with support from their spouses and family.[276] Two-thirds of patients undergoing IVF treatment reported reading newspaper or magazine articles and watching television programmes about the psychological aspects of infertility, even though few participated in a support group or sought counselling before treatment.[277] This suggests that, for some patients, information about local and national support groups and booklets on the psychological aspects of treatment, in addition to medical information, may be beneficial. [Evidence level 3]

The emotional consequences of anxiety and stress can be reduced by adequate provision of clear information about all aspects of investigations and treatment, involving both partners as an integral part of the management plan. The impact of psychological stress should be acknowledged throughout the care of the couple with fertility problems with offers of counselling. Counselling involves a

professional relationship between a qualified counsellor and a patient, who may be an individual, a couple or a group of people. This relationship is contained within a formal counselling contract agreed and understood by both parties. The counsellor has no other relationship with the client. Nurses, doctors and scientists in fertility clinics offer support and emotional help to couples as part of their professional role, but it is necessary to recognise this as using counselling skills within an existing role.[278]

In considering the counselling needs of their patients, health professionals need to take account of evidence that suggests that couples may deny experiencing difficulties in their relationship, which may prevent them seeking help.[279] People who experience problems with fertility are often very vulnerable.[280] This may lead them to be overly compliant with suggestions made by their clinical team, for example, going ahead with treatments despite having reservations or simply requiring more time to reflect on all the implications.[280] [Evidence level 3]

The HFEA Code of Practice[218] (HFEA 2008) identifies three distinct types of counselling, all of which should be clearly distinguished from information exchange.

Implication counselling aims to enable the client to understand the implications of proposed treatments and consequent actions for themselves, their families and for any children born as a result and anyone else affected by the donation or treatment.

Support counselling aims to give emotional support at times of particular stress, for example, when there is a failure to achieve a pregnancy. This may occur at any stage before, during and after donation or treatment.

Therapeutic counselling aims to help people cope with the consequences of infertility and treatment, to resolve problems which these may cause, and to adjust their expectations so that they can cope with the outcome of treatment, whatever that may be.

The HFEA Code of Practice states that people seeking licensed treatment or consenting to the use or storage of embryos, or the donation or storage of gametes, or the use of gametes or embryos posthumously, must be given 'a suitable opportunity to receive proper counselling about the implications of taking the proposed steps' before they consent.[218] (HFEA, 2008) [Evidence level 4]

Counsellors should have professional counselling qualifications and the ability to work in accordance with the Human Fertility and Embryology Act*. They should abide by a professional code of practice, such as the Ethical Framework for Good Practice in Counselling and Psychotherapy used by the British Association for Counselling and Psychotherapy, with a commitment to regular supervision.

If there is need for genetic counselling an appropriate referral should be made to a qualified genetic counsellor. Genetic counsellors should have recognised training, either through a Masters Programme in Genetic Counselling or a nursing qualification with additional relevant academic qualifications.

Recommendations

Number	Recommendation
4	When couples have fertility problems, both partners should be informed that stress in the male and/or female partner can affect the couple's relationship and is likely to reduce libido and frequency of intercourse which can contribute to the fertility problems. **[2004, amended 2013]**
5	People who experience fertility problems should be informed that they may find it helpful to contact a fertility support group. **[2004]**
6	People who experience fertility problems should be offered counselling because fertility problems themselves, and the investigation and treatment of fertility problems, can cause psychological stress. **[2004]**

*1990, as amended in 2008

7	Counselling should be offered before, during and after investigation and treatment, irrespective of the outcome of these procedures. **[2004]**
8	Counselling should be provided by someone who is not directly involved in the management of the individual's and/or couple's fertility problems. **[2004, amended 2013]**

Number	Research recommendation
RR 2	Further research is needed to assess the long-term psychological impact of investigation and treatment of people who perceive problems with their fertility, both in people who subsequently achieve a live birth and people who do not.

4.4 Specialist and generalist care

The impact of specialist as compared to non-specialist care on the management of fertility problems has not been evaluated. In studies reviewing care of patients by specialists and generalists across many conditions (including cancer, heart disease and psychiatric illness), specialists were reported to be more knowledgeable about their area of expertise and quicker to adopt new and effective treatment than generalists, resulting in improved patient satisfaction, patterns of care and clinical outcomes.[281–283] [Evidence level 2b–3] Training and expertise have been suggested as reasons for women achieving higher pregnancy rates after tubal surgery carried out by specialists rather than general gynaecologists.[284] [Evidence level 3]

In a survey, patients seeking fertility treatment were reported to be more satisfied with services provided in a specialist clinic than those provided in a general gynaecological clinic.[220] [Evidence level 3] Patients were dissatisfied with attending an infertility clinic which shared a waiting room with users of antenatal classes or was located in a place where parent craft classes took place.[274]

A review of treatments and services in the management of people with fertility problems recommended that the management of fertility services should be carried out in specialist units with access to a wider range of skills than a general hospital because this is expected to improve the efficiency and effectiveness of treatment.[2] [Evidence level 4]

Recommendations

Number	Recommendation
9	People who experience fertility problems should be treated by a specialist team because this is likely to improve the effectiveness and efficiency of treatment and is known to improve people's satisfaction with treatment. **[2004, amended 2013]**

5 Initial advice to people concerned about delays in conception

5.1 Introduction

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People wishing to conceive are faced with many sources of advice of varying quality and often conflicting in content. Therefore, it is important that the information they receive at an initial consultation is based on the best available evidence. This chapter outlines the minimum information that people should be aware of before starting fertility investigation and treatment.

5.2 Chance of conception

The natural process of human reproduction begins when spermatozoa are ejaculated into the vagina during sexual intercourse. The spermatozoa travel through the cervix and uterine cavity to the fallopian tubes where they meet the ovum (egg) and fertilisation takes place. The embryo then travels back down the fallopian tube and enters the uterine cavity where implantation takes place.

This process is reliant upon the chance of satisfactory ovulation and transport of viable sperm and ova in the reproductive tract. It is influenced by endocrine control, timing and frequency of sexual intercourse, and the general health status of the man and the woman. The length of a menstrual cycle varies between 26 days and 36 days. Ovulation usually takes place 12 to 16 days before the start of the next period. For a woman with a 28-day menstrual cycle (the first day of menstruation being day 1), ovulation takes place around day 14. After ovulation, the egg usually lives for up to 24 hours. After ejaculation, sperm can survive for up to 7 days in the genital tract and sometimes even longer (see Section 5.3).[17]

In the general population (which covers all ages and includes people with fertility problems), it is estimated that 84% of women would conceive within 1 year of regular unprotected sexual intercourse. This rises cumulatively to 92% after 2 years and 93% after 3 years (te Velde et al., 2000) [18,19]

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Fertility may be measured as conception rate per menstrual cycle. This is known as fecundability. Female fertility declines with age. Figure 5.1 shows the effect of maternal age on the average rate of pregnancy, calculated on the basis of studies in 10 different populations that did not use contraceptives. (Heffner, 2004, based on two reviews by Menken et al, 1986, and Anderson et al, 2000).[21] However, in general, data on fecundability rates of specific age groups in fertile populations are limited. One study, using a modelling approach in a population with normal fertility who chose to delay child-bearing, reported that after 2 years of trying, women who were age 35 years had a 87% chance of conceiving and 67% of those who were age 38 years became pregnant.[25] That study also reported that the decline with age in rates of conception is seen mostly after age 30 years and is more marked after age 35 years. [25,] A prospective cohort from the European Fecundability Study reported even more favourable conception rates in women aged 35 to 39 years after 2 years follow-up (see Table 5.1 and Figure 5.2) (Dunson et al., 2004).

Figure 5.1 The effect of maternal age on the average rate of pregnancy, calculated on the basis of studies in10 different populations that did not use contraceptives (adapted from Heffner, 2004, based on two reviews by Menken et al, 1986, and Anderson et al, 2000)

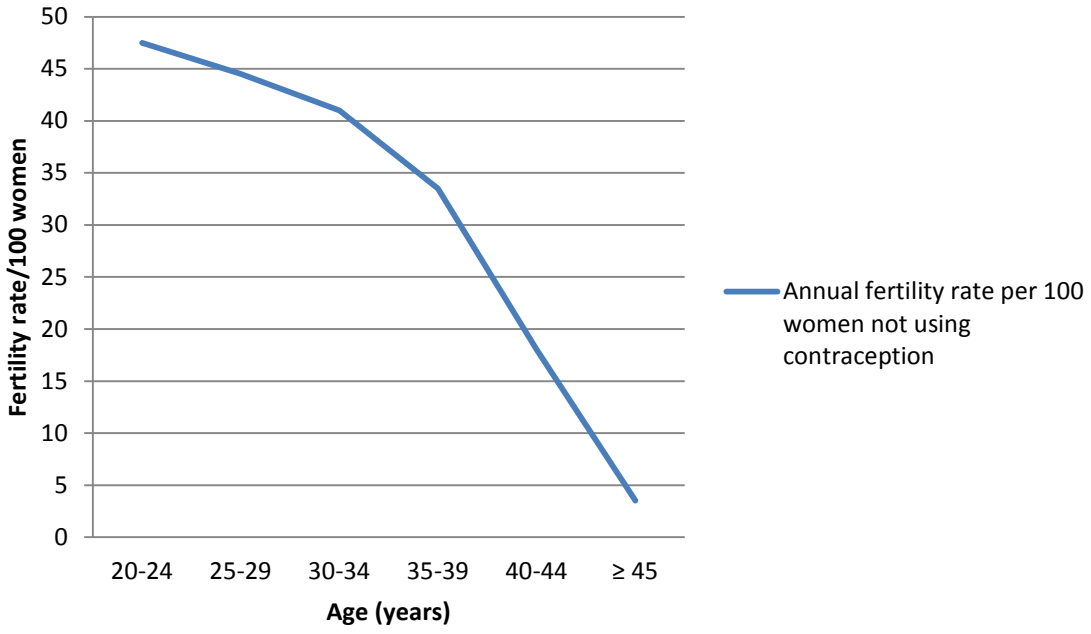
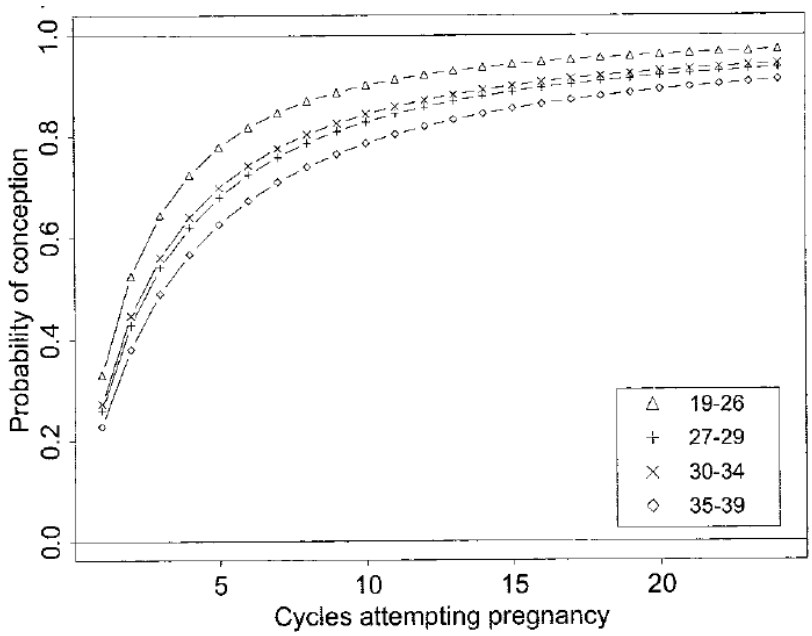


Table 5.1 Cumulative probability of conceiving a clinical pregnancy by number of menstrual cycles in women in four different age categories attempting to conceive (assuming vaginal intercourse occurs twice per week) (adapted from Dunson et al., 2004)

Age (years)	Pregnant after 1 year (12 cycles) (%)	Pregnant after 2 years (24 cycles) (%)
19–26	92	98
27–29	87	95
30–34	86	94
35–39	82	90

Figure 5.2 Cumulative probability of conceiving a clinical pregnancy by number of menstrual cycles in women in four different age categories attempting to conceive (assuming intercourse occurs twice per week) (reproduced with permission, Dunson et al., 2004)



There are very few sources of data to provide similar guidance for people who are using some form of artificial insemination to conceive. The evidence that does exist demonstrates that the chances of success with artificial insemination, with semen from either their partner or donor, are influenced by whether the insemination is intra-uterine or intra-cervical (with the former having higher rates of successful conception) and whether the sperm is fresh or thawed (with fresh sperm being associated with higher rates of successful conception; see Table 5.2) (Schwartz et al., 1982; van Noord-Zaadstra et al., 1991; HFEA data [http://www.hfea.gov.uk/1270.html#1299]). The data from these three sources reflect results using insemination with donor semen and not partner semen. In addition, in clinical practice use of fresh donor sperm is not an option since the appropriate screening and safety checks mandate the use of thawed frozen sperm for artificial insemination. If a partner's sperm is to be used then the screening is not necessary and fresh sperm would be preferable.

Table 5.2 Probability of conceiving a clinical pregnancy by the number of cycles of insemination in different age categories and according to the method and sperm status where assistaed reproduction technology (ART) is being used

Woman's age (years)	ICI using thawed semen (Schwartz et al., 1982)		Woman's age (years)	ICI using fresh semen (van Noord-Zaadstra, 1991)		Woman's age (years)	IUI using thawed semen (HFEA)[a]	
	6 cycles	12 cycles		6 cycles	12 cycles		6 cycles	12 cycles
<30y	50%	70%	<31y	58%	76%	-	-	-
30-34y	43%	62%	31-35y	50%	71%	<35y	63%	86%
>34y	33%	54%	>35y	39%	55%	35-39y	50%	75%

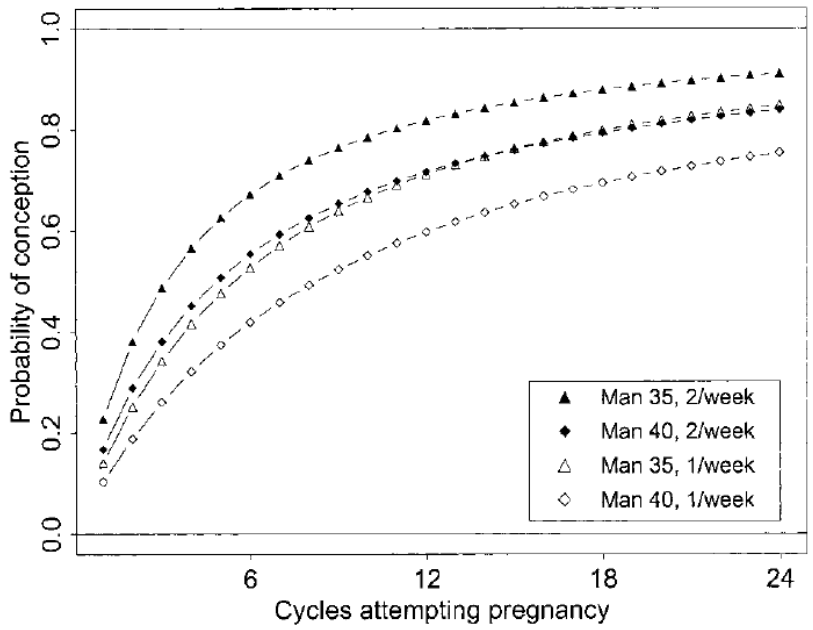
ICI intra-cervical insemination, IUI intra-uterine insemination

a (HFEA data http://www.hfea.gov.uk/1270.html#1299)

In the original guideline it was stated that the effect of age on male fertility was unclear (Wood, 1989, van Noord-Zaadstra et al., 1991). However, there now is evidence of declining male fertility with

increasing age which is independent of coital frequency (Dunson et al., 2004). That study showed that men aged 40 years having intercourse twice per week will have approximately 10% lower cumulative success rates compared with men aged 35 years over a period up to 24 months (see Figure 5.3) (Dunson et al., 2004).

Figure 5.3 Cumulative probability of conceiving a clinical pregnancy for a woman aged 35 years with either a partner the same age or 5 years older and with intercourse frequency of once or twice per week (reproduced with permission, Dunson et al., 2004)



Another important factor that can influence conception rates in the general population is coital frequency. Estimates suggest that fecundability rises sharply with frequency of intercourse (te Velde, 1992) (see Section 5.3). With regular intercourse, commonly meaning intercourse two or three times per week, at least 94% and 77% of fertile women aged 35 years and 38 years respectively conceive after three years of trying (te Velde, 1992). These findings have been confirmed in the European Fecundability Study reported above (Dunson et al., 2004). In that study the conception rates within 12 months for couples having intercourse twice per week were 92% for women aged 19 to 26 years, 86% for women aged 27 to 34 years, and 82% for women aged 35 to 39 years (see Table 5.1 and Figure 5.1). For couples having intercourse once per week the figures fell to 85%, 76% and 71%, respectively. Conception rates for those couples having intercourse three times per week were about the same as those having intercourse twice per week (Dunson et al., 2004).

Psychological stress can affect libido and coital frequency and hence fertility (see Section 5.3). Understandably, some couples are concerned about their failure to conceive within a timeframe they consider is reasonable. However, this is often not long enough to have allowed natural conception to occur. In such circumstances, immediate investigation and treatment is not appropriate. Couples who have not conceived but have been trying for less than the recommended time to qualify for fertility assessment and treatment (see Section 5.13) should be advised that they may successfully conceive during a period of 'expectant management'. This involves supportively offering them information and advice about the regularity and timing of intercourse and any lifestyle changes which might improve their chances of conceiving. This approach does not involve any active clinical or therapeutic interventions. However, part of this care will involve the initiation of assessment and possible treatment after an agreed period of 'expectant management'. This chapter covers many of these issues.

Recommendations

Number	Recommendation
10	People who are concerned about their fertility should be informed that over 80% of couples in the general population will conceive within 1 year if: • the woman is aged under 40 years **and** • they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%). **[2004, amended 2013]**
11	Inform people who are using artificial insemination to conceive and who are concerned about their fertility that: • over 50% of women aged under 40 years will conceive within 6 cycles of intrauterine insemination (IUI) • of those who do not conceive within 6 cycles of intrauterine insemination, about half will do so with a further 6 cycles (cumulative pregnancy rate over 75%). **[new 2013]**
12	Inform people who are using artificial insemination to conceive and who are concerned about their fertility that using fresh sperm is associated with higher conception rates than frozen-thawed sperm. However, intrauterine insemination, even using frozen-thawed sperm, is associated with higher conception rates than intracervical insemination. **[new 2013]**
13	Inform people who are concerned about their fertility that female fertility and (to a lesser extent) male fertility decline with age. **[new 2013]**
14	Discuss chances of conception with people concerned about their fertility who are: • having sexual intercourse (see table 5.1) **or** • using artificial insemination (see table 5.2). **[new 2013]**

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5.3 Frequency and timing of sexual intercourse or artificial insemination

Daily intercourse results in the highest probability of conception but is not the only factor influencing conception,[26] considering the viability of the egg and its short survival time. [Evidence level 3] Ejaculation eight times per week does not reduce the fertility of men though it tends to reduce sperm parameters,[27–30] The best sperm motility has been found in semen emission every three to four days on average.[27] [Evidence level 2b] Coitus every two to three days is likely to maximise the overall chance of natural conception, as spermatozoa survive in the female reproductive tract for up to 7 days after insemination.[17,30] [Evidence level 3]

It has been observed that most pregnancies can be attributed to sexual intercourse during a 6-day period starting 5 days before ovulation and including the day of ovulation,[31,32] with the highest estimated conception rates associated with intercourse 2 days before ovulation.[33] [Evidence level 3]

Six cohort studies that evaluated the use of basal body temperature or urinary luteinising hormone (LH) kits as indicators of ovulation to time intercourse did not report improvement in the chance of natural conception.[34–39] Timed intercourse has been suggested to be an emotionally stressful intervention in the initial evaluation of infertility.[40] However, for the minority of couples who find it difficult to have sexual intercourse every 2 to 3 days, the prediction of ovulation using LH kits can be useful.

In people who are trying to conceive using some form of artificial insemination, insemination should be timed to coincide with ovulation, for example by testing urinary LH levels using a standard kit and scheduling insemination on the day after a surge is detected (Cantineau et al., 2010).

Recommendation 15 (below) has been amended to reflect a revised guideline development group (GDG) interpretation of evidence and current clinical practice.

Recommendations

Number	Recommendation
15	People who are concerned about their fertility should be informed that vaginal sexual intercourse every 2 to 3 days optimises the chance of pregnancy. **[2004, amended 2013]**
16	People who are using artificial insemination to conceive should have their insemination timed around ovulation. **[new 2013]**

5.4 Alcohol

This section deals with the effect of alcohol intake on fertility in general. The impact of alcohol consumption on in vitro fertilisation (IVF) success rates, in contrast, is discussed in Chapter 13.

There is inconsistent evidence about the impact of alcohol intake on female fertility.[41–46] [Evidence level 2b] Excessive alcohol consumption is harmful to the fetus.[47] The Department of Health (DH) has recommended that women who are pregnant or trying to become pregnant should drink no more than one or two units of alcohol once or twice per week and should avoid episodes of intoxication.[48]

One cohort study showed that female wine drinkers (up to seven units per week) had slightly shorter waiting times to pregnancy than non-wine drinkers and drinkers of other alcoholic beverages, after adjusting for age, parity, smoking and body mass index (BMI).[49] [Evidence level 2b]

Excessive alcohol consumption can be detrimental to semen quality but the effect is reversible and there is no evidence of a causal association between moderate alcohol consumption and poor semen quality.[50–53] [Evidence level 2b] The current recommended guidelines on safe drinking limits for men allow three to four units per day.[54]

Recommendations

Number	Recommendation
17	Women who are trying to become pregnant should be informed that drinking no more than 1 or 2 units of alcohol once or twice per week and avoiding episodes of intoxication reduces the risk of harming a developing fetus. **[2004]**
18	Men should be informed that alcohol consumption within the Department of Health's recommendations of 3 to 4 units per day for men is unlikely to affect their semen quality. **[2004, amended 2013]**
19	Men should be informed that excessive alcohol intake is detrimental to semen quality. **[2004]**

5.5 Smoking

There is a significant association between smoking and reduced fertility among female smokers.[55,56] [evidence level 2b] There is an association in men between smoking and semen

parameters.[51,57–62] [Evidence level 2b] However, the relationship between male smoking habits and fertility is uncertain. Male and female exposure in utero is associated with reduced fertility later in life.[63] [Evidence level 2b]

It has been reported that passive smoking in women is associated with delayed conception.[64] [Evidence level 2b]

For women with fertility problems, basic information about the impact of smoking on fertility or a scripted three- to five-minute intervention with booklets specific to the woman's 'degree of motivation and commitment', together with exhaled carbon monoxide monitoring, were highly effective in stopping smoking but not in improving pregnancy rates.[65] [Evidence level 1b] We found no studies that investigated the effect of the use of nicotine replacement therapy on infertility.

There are significant associations between maternal cigarette smoking in pregnancy and increased risks of small-for-gestational-age infants,[66] stillbirth[67] and infant mortality.[68] [evidence level 2b] For further information please refer to the Antenatal Care Guideline.[1147]

Recommendations

Number	Recommendation
20	Women who smoke should be informed that this is likely to reduce their fertility. **[2004]**
21	Women who smoke should be offered referral to a smoking cessation programme to support their efforts in stopping smoking. **[2004]**
22	Women should be informed that passive smoking is likely to affect their chance of conceiving. **[2004]**
23	Men who smoke should be informed that there is an association between smoking and reduced semen quality (although the impact of this on male fertility is uncertain), and that stopping smoking will improve their general health. **[2004]**

5.6 Caffeinated beverages

This section deals with the effect of caffeine intake on fertility in general. The impact of caffeine consumption on IVF success rates is discussed in Chapter 13.

Caffeine is present in coffee, tea, colas and chocolate. The association between caffeine and female infertility is inconsistent.[45,69–80] [evidence level 2b] We did not find any studies reporting the effect of caffeine on pregnancy rates, nor studies which investigated the effect of decaffeinated beverages on fertility.

We found one study addressing the question of caffeine intake and male fertility. This study showed no evidence of an association between caffeine intake and poor semen parameters. However, the combination of coffee drinking with smoking diminished sperm motility and increased the proportion of dead sperm.[51] [evidence level 2b]

Recommendations

Number	Recommendation
24	People who are concerned about their fertility should be informed that there is no consistent evidence of an association between consumption of caffeinated beverages (tea, coffee and colas) and fertility problems*. **[2004]**

* See Recommendation 127 for a recommendation about caffeine intake and IVF treatment.

5.7 Body weight

Obesity

BMI is a measure of body fat calculated from an individual's weight and height (kg/m^2). The internationally accepted range for BMI is from less than 18.5 kg/m^2 (underweight) to 30 kg/m^2 or over (obese).[81] Women with BMI over 30 kg/m^2 take longer to conceive, compared with women with lower BMI, even after adjusting for other factors such as menstrual irregularity.[82–84] [evidence level 2b] For infertile anovulatory women with BMI of over 29 kg/m^2, there is evidence that a supervised weight loss programme or a group programme including exercise, dietary advice and support helps to reduce weight,[85,86] resume ovulation[85] and improve pregnancy rates.[86] [Evidence level 1b]

A BMI of 30 or over was reported to be an independent risk factor for spontaneous abortion in women who were oocyte recipients.[87] [Evidence level 3]

An increased risk of miscarriage has been reported in moderately obese women (BMI 25–27.9 kg/m^2) with polycystic ovary syndrome (PCOS; see Section 8.3) undergoing ovulation induction.[88] [Evidence level 2b]

An observational study reported an inverse relationship between BMI and the total number of normal-motile sperm cells. There was a significant reduced number of normal-motile sperm cells in men who were overweight (BMI 25–30) and obese (BMI greater than 30) when compared with men of normal weight (BMI 20–24).[89] [evidence level 3] A higher incidence of sperm DNA fragmentation has also been observed in men with a BMI of over 25.[90] [Evidence level 3]

Obesity may have a deleterious effect on erectile function in men with existing vascular risk factors such as heart disease and diabetes.[91] [Evidence level 2b]

More general guidance about about nutrition and exercise can be found in:

- NICE Public Health Guidance 2, Four commonly used methods to increase physical activity (2006)
- NICE Public Health Guidance 11, Maternal and Child Nutrition (2008).

Recommendations

Number	Recommendation
25	Women who have a body mass index (BMI) of 30 or over should be informed that they are likely to take longer to conceive. **[2004, amended 2013]**
26	Women who have a BMI of 30 or over and who are not ovulating should be informed that losing weight is likely to increase their chance of conception. **[2004, amended 2013]**
27	Women should be informed that participating in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone. **[2004]**
28	Men who have a BMI of 30 or over should be informed that they are likely to have reduced fertility. **[2004, amended 2013]**

Low body weight

Low body weight is recognised as an important cause of hypo-oestrogenic amenorrhoea. It is important that the subgroup of women who have anorexia nervosa are detected and managed appropriately. Many women with hypo-oestrogenic amenorrhoea associated with low body weight do

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not wish to conceive and the management priority for these women will lie outside the scope of this guideline.

In women, weight loss of over 15% of ideal body weight is associated with menstrual dysfunction and secondary amenorrhoea when over 30% of body fat is lost.[92] Restoration of body weight may help to resume ovulation and restore fertility.[93,94] [Evidence level 2b]

An increased risk of preterm delivery has been associated with women who are underweight, and ovulation induction in such women has been associated with a higher incidence of babies who were small for gestational age.[95] [Evidence level 2b]

More general guidance about about nutrition can be found in NICE Public Health Guidance 11, Maternal and Child Nutrition (2008).

Recommendations

Number	Recommendation
29	Women who have a BMI of less than 19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception. **[2004]**

5.8 Tight underwear

Increased scrotal temperature is closely associated with reduced semen quality in healthy populations.[96–98] [Evidence level 3] Important determinants of testicular temperature such as a sedentary work position and occupational heat exposure have been associated with abnormal semen quality (see Section 5.8).[98,99] [Evidence level 3] There is some evidence that, in a fertile population, wearing tight-fitting underwear can impair semen quality.[100] [Evidence level Ib] However, the effect of impaired semen quality on pregnancy rates has not been established. A cohort study of 97 men with subfertility showed that there was no difference in scrotal temperatures and semen parameters between a group wearing boxer shorts and a group wearing briefs.[101] [Evidence level 2b]

Recommendations

Number	Recommendation
30	Men should be informed that there is an association between elevated scrotal temperature and reduced semen quality, but that it is uncertain whether wearing loose-fitting underwear improves fertility. **[2004]**

5.9 Occupation

More than 104 000 chemical and physical agents have been identified in the workplace but the effects on reproduction of at least 95% of them have not been assessed, partly because of the fast rate of introduction of these agents into industry.[102] Tables 5.3 and 5.4 summarise the main occupational agents implicated in the reduction of human fertility.[103–109] [Evidence level 2b–3] The lists of agents presented in the tables is not exhaustive.

Evidence suggestive of a harmful effect on the human reproductive system has been recognised for specific agents, such as heat, X-rays, metals and pesticides, whereas for many other agents the association is only suspected and needs further evaluation.

Table 5.3 Occupational agents and their effects on male fertility

Occupational agents	Occupational groups	Effects on male fertility
Physical		
Shift work/long working hours	Shift workers	No association[110,111]
Heat (increase in scrotal temperature)	Welders, bakers, drivers	Abnormal sperm parameters[99]
X-ray	Radiotherapists	Azoospermia, reduced sperm count, may be reversible[112,113]
Non-iodising radiation: electromagnetic fields	Metal workers	Inconsistent association[114-116]
Vibrations	Engine drivers, diggers	Oligozoospermia, asthenozoospermia[117]
Chemical		
Dibromochloropropane (pesticide)	Agricultural workers	Oligozoospermia and azoospermia,reversible in most cases,[118–121] reduced fertilisation rate[122]
Ethylene dibromide (pesticide)		Abnormal sperm parameters[107]
Carbaryl (pesticide)		No association[123]
Polychlorinated biphenyls	Agricultural workers	Abnormal sperm parameters[124,125]
Lead, cadmium, manganese	Metal workers, smelters, battery factory workers	Reduced fertility, mainly affecting female partners,[126–131] No association[132]
Mercury	Dental amalgam	No association[133]
Acetone, carbon disulphide, glycol ethers (solvents)	Chemists, laboratory workers, painters	Abnormal sperm parameters,[135,136] reduced fecundability,[137] oligospermia[138]
Toluene, styrene (solvents)	Plastic and printing industry	No association[139,140]
Anaesthetic gases	Dentists, anaesthetists	No association[141,142]

Table 5.4 Occupational agents and their effects on female fertility

Occupational agents	Occupational groups	Effects on female fertility
Physical		
Shift work/intense physical work load/long working hours	Hospital workers	Reduced fecundability,[143,144] prolonged time to pregnancy,[110,111] no association[111]
Ionising radiation	Nuclear industry workers	Non-significant association[145]
Visual display units	Office workers	No association,[146] increased risk of infertility[147]
Chemical		
Pesticides	Agricultural workers	Inconsistent time to pregnancy[148]

Occupational agents	Occupational groups	Effects on female fertility
Lead	Smelters	No association at low levels,[149] prolonged time to pregnancy[150]
Mercury, cadmium	Nurses, pharmacists	Increased self-reported infertility[151]
Anti-neoplastics (chemotherapy drugs)		Small risk of prolonged time to pregnancy[152]
Antibiotics		
Nitrous oxide	Anaesthetists, theatre nurses, dental nurses	Reduced fecundability[143,153,154]
Chloroform, benzene		No association[141]
Mercury vapour	Lamp factory workers	No clear association,[155] reduced fecundability[156]
Solvents		Infertility[147]
Formaldehyde	Wood workers	Reduced fecundability[157]

Recommendations

Number	Recommendation
31	Some occupations involve exposure to hazards that can reduce male or female fertility and therefore a specific enquiry about occupation should be made to people who are concerned about their fertility and appropriate advice should be offered. **[2004]**

5.10 Prescribed, over-the-counter and recreational drug use

A number of prescribed, over-the-counter and recreational drugs may interfere with male or female fertility. However, the potential benefits and risks of certain medications need to be weighed and medical advice sought in order to determine the appropriate course for individual patients.

Prescribed drug use

There is evidence that nonsteroidal anti-inflammatory drugs inhibit ovulation.[158,159] [Evidence level 1b] Immunosuppressive and anti-inflammatory drugs for rheumatic diseases may affect conception.[160][evidence level 3] In a case–control study, women who had ever used thyroid replacement hormones, antidepressants, tranquilisers or asthma medication were reported to have elevated risks of anovulatory infertility.[161] [Evidence level 2b] Chemotherapy treatment with cytotoxic drugs can induce ovarian failure at different rates for various types of malignancies and treatment regimens.[162,163] [Evidence level 2b]

Medication such as cimetidine and sulphasalazine and long term-daily use of some antibiotics and androgen injections can affect semen quality and cause oligozoospermia.[164–166] The effect is generally reversible after three months following withdrawal of medication. Use of beta-blockers and psychotropic drugs may lead to impotence.[167] Chemotherapy treatment can induce azoospermia, which is permanent in most cases.[168] [Evidence level 3]

The effect of anti-psoriatic treatment for arthritis with methotrexate on male infertility is unclear.[169] [Evidence level 3]

Recreational drug use

The use of recreational drugs or drugs of abuse such as marijuana and cocaine can adversely affect ovulatory and tubal function.[170] The use of drugs such as anabolic steroids and cocaine can adversely affect semen quality.[171–173] [evidence level 2b–3] Overall, use of these recreational drugs diminishes the fertility potential of the couple. We did not find any studies that assessed the effect of recreational drug use on pregnancy rates.

Recommendations

Number	Recommendation
32	A number of prescription, over-the-counter and recreational drugs interfere with male and female fertility, and therefore a specific enquiry about these should be made to people who are concerned about their fertility and appropriate advice should be offered. **[2004]**

5.11 Complementary therapy

We found four RCTs that evaluated the effects of various substances on semen quality,[174,175] ovulation and pregnancy rates.[176,177] Three of the RCTs[174,176,177] were of poor design with unclear methods of randomisation and clinical heterogeneity. The fourth RCT[175] compared oral selenium supplementation with selenium plus vitamins or placebo in a group of subfertile men. This RCT reported an improvement in sperm motility and pregnancy rates in the selenium group compared with the placebo group (11% with selenium versus 0% with placebo).[175] [Evidence level 1b]

An increase in pregnancy rates was observed in a preliminary trial assessing the effect of intercessory prayer on patients undergoing IVF treatment. However, there is no biological mechanism to explain such an effect.[178]

Recommendations

Number	Recommendation
33	People who are concerned about their fertility should be informed that the effectiveness of complementary therapies for fertility problems has not been properly evaluated and that further research is needed before such interventions can be recommended. **[2004]**

5.12 Folic acid supplementation

A systematic review[119] of four RCTs (n = 6425 women) showed that periconceptional folate supplementation reduced the incidence of neural rube defects (anencephaly and spina bifida) in children (relative risk [RR] 0.28, 95% confidence interval [CI] 0.13 to 0.58). In all four RCTs, folic acid was taken before conception and up to 6–12 weeks of gestation. The dose assessed ranged from 0.36 to 4 mg. Multivitamins alone were not associated with prevention of neural tube defects and did not produce additional preventative effects when given in combination with folate.[179] An Expert Advisory Group to the Department of Health recommended a dose of 0.4 mg/day of folic acid for women who have not had a previous infant with a neural tube defect and a dose of 5.0 mg/day for women who have previously had an infant with a neural tube defect and those who are receiving anti-epileptic drugs. The NICE clinical guideline 63 Diabetes in Pregnancy (2010) also recommends the use of a higher dose of 5 mg/day in diabetic women planning a pregnancy. Supplementation should continue until 12 weeks into pregnancy.[180] The British National Formulary recommends that women taking anti-epileptic drugs wishing to become pregnant should be referred to an appropriate specialist

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to discuss the risk of teratogenecity.[181] The size of the effect for a given dose of folic acid was recently quantified and modelling has suggested that a reduced risk is associated with higher doses (that is 5 mg instead of 0.4 mg). The practical implication of an increased dose of folic acid has yet to be investigated.[182,183]

Recommendations

Number	Recommendation
34	Women intending to become pregnant should be informed that dietary supplementation with folic acid before conception and up to 12 weeks' gestation reduces the risk of having a baby with neural tube defects. The recommended dose is 0.4 mg per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication or who have diabetes (see Diabetes in pregnancy, NICE clinical guideline 63), a higher dose of 5 mg per day is recommended. **[2004, amended 2013]**

5.13 Defining infertility

The United Nations defines reproductive health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity in all matters relating to the reproductive system and to its functions and processes'.[190] [Evidence level 4] Infertility should, therefore, be considered to be a disease process worthy of investigation and treatment.

Infertility has been defined variably as failure to conceive after frequent unprotected sexual intercourse for one or two years.[1,3,191–213] Diagnosis of infertility based on a failure to conceive within 1 year has been argued to exaggerate the risk of infertility, since up to 50% of women who do not conceive in the first year are likely to do so in the second year.[118,119]

The prevalence of infertility in European countries is around 14%, affecting about one in seven couples.[1,3,193,196,197,201–205,208,210,212,214,215] Data from historical populations estimate the average prevalence of infertility to be 5.5%, 9.4% and 19.7%, respectively, at ages 25–29 years, 30–34 years and 35–39 years.[216]

The first consultation should include an assessment of the perceived fertility problem. For many couples, information about normal patterns of conception will provide reassurance that they are likely to have a good chance of conception. However, there should also be a specific enquiry about the medical, surgical, sexual, contraceptive and pregnancy history and a general physical examination to detect abnormalities, including measurement of height and weight to calculate BMI to identify couples who are likely to experience delays in conception.[217] Couples should be offered information about lifestyle such as smoking, alcohol intake, occupational factors and diet which may impact on their fertility.

The GDG considered it appropriate to use a pragmatic and practical approach to the definition of infertility, namely, defining the period of time people should be trying to conceive after which it would be reasonable to initiate formal assessment (see Chapter 6) and possible treatment.

For people having unprotected regular vaginal intercourse

Conception rates for women or couples having unprotected vaginal intercourse two or three times per week are shown in Figure 5.1. In summary, over 80% of couples where the women is age 39 years or less will conceive within 12 months. The figure is over 85% where the woman is less than 35 years.

Given these data, the GDG was of the opinion that where the woman is of reproductive age and having regular unprotected vaginal intercourse two to three times per week, failure to conceive within 12 months should be taken as an indication for further assessment and possible treatment. The GDG acknowledged that, in practice, there would be occasions where natural conception occurred before couples were waiting for their specialist appointment or during the period of investigation.

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If the woman is age 36 or over then such assessment should be considered after 6 months of unprotected regular intercourse since her chances of successful conception are lower and the window of opportunity for intervention is less. This age threshold was chosen as it was consistent with the age categories for IVF treatment agreed in The British Fertility Society and The Association of Clinical Embryologists standards (Cutting et al., 2008).

If, as a result of the investigation, a cause for the infertility is found, the GDG felt that the individual should be referred for appropriate treatment without further delay.

For men and women in same-sex relationships not having vaginal intercourse

The Scope of this guideline makes it clear that it is intended for people who have a possible pathological problem (physical or psychological) to explain their infertility.

For women in same-sex relationships, there should be some period of unsuccessful artificial insemination (AI) before they would be considered to be at risk of having an underlying problem and be eligible to be referred for assessment and possible treatment in the NHS. While the Scope did not allow the GDG members to make recommendations about this period of AI before referral for further assessment and possible treatment, they were of the majority view that ideally such AI should be undertaken in a clinical setting with an initial clinical assessment and appropriate investigations. However, they acknowledged that such pre-requisites and safeguards did not always apply.

Men in same-sex relationships wanting a baby can either adopt or use some form of surrogacy using the sperm of one partner, the latter being the usual way that male couples will be able to have a baby in which one of them will be a genetic parent. The Scope specified that surrogacy was not to be covered in this guideline. However, when a pregnancy does not occur through surrogacy after an appropriate period of time (equivalent to the 12 months with vaginal intercourse or 6 cycles of AI for other people) there is an increased risk of some underlying problem. In those circumstances, the man whose sperm is being used and the surrogate partner would be eligible to be referred for further clinical assessment and possible treatment.

In people using AI to conceive, as with people having vaginal intercourse, the success rates in women with normal fertility declines with age. Success rates also vary with the assisted reproduction method used. There are no data for the success of AI outside a clinical setting (sometimes called a 'do-it-yourself' approach where fresh donor semen is deposited in the upper vagina or even into the cervical os) and so the GDG was unable to comment on the efficacy of this approach. However, in a clinical setting, success rates are higher with fresh compared with frozen–thawed sperm and with intrauterine insemination (IUI) compared with intracervical insemination (ICI).

These data show that in the absence of any known cause of infertility, the cumulative chances of a pregnancy occurring after ICI or IUI in women who are 35 years or less are:

- after 12 cycles of treatment (approximately 85% cumulative success over 12 months for women having vaginal intercourse, see Figure 5.1):
    - over 60% for ICI using thawed semen (Schwartz et al., 1982)
    - over 70% for ICI using fresh semen (van Noord-Zaadstra et al., 1991)
    - over 80% for IUI using mainly thawed semen (HFEA data http://www.hfea.gov.uk/1270.html#1299)
- after 6 cycles (approximately 70% cumulative success over 6 months for women having vaginal intercourse, see Figure 5.1):
    - over 40% for ICI using thawed semen (Schwartz et al., 1982)
    - over 50% for ICI using fresh semen (van Noord-Zaadstra et al., 1991)
    - over 60% for IUI using mainly thawed semen (HFEA data http://www.hfea.gov.uk/1270.html#1299).

Given these data, the GDG discussed the options for the number of failed cycles of AI that should be undertaken before further assessment and possible treatment be initiated. The aim was to decide the number of failed AI cycles that would be equivalent to failure to conceive after 12 months of

unprotected vaginal intercourse. The GDG's discussions covered a number of ethical and practical issues relating to 'equivalence' including:

- the financial cost of AI and disadvantage of those attempting to conceive by that route
- the time to conception and disadvantage of those attempting to conceive by vaginal intercourse.

Women having vaginal intercourse do not have to pay to get pregnant, whereas those in same-sex relationships are at a disadvantage as they have to pay for a number of cycles of AI before they can be considered for assessment and possible treatment in the NHS. Therefore, the cost to the woman and her partner would be lower if 6 cycles of AI were recommended compared with 12 cycles of AI.

The GDG recommends that people having regular vaginal intercourse should be assessed and possibly treated if they have not conceived after 12 months (see Recommendation 29). The GDG decided that in a same-sex couple 'numerical equivalence' would be 12 cycles of AI, with the AI being undertaken once a month over 12 months, though the GDG acknowledged that using the criterion of 12 cycles of AI did not quite give equivalence in terms of cumulative success rate compared with vaginal intercourse. The GDG discussed using a lower number of cycles of AI in order to offset the financial impact and inconvenience of AI. However, the GDG stated that using a lower criteria could give same-sex couples a perceived advantage in terms of the time they had until further investigations were required.

Other factors that the GDG took into consideration in reaching a conclusion were:

- The acknowledged limited 'supply' of sperm donors in the UK.
- Recommending 6 cycles of AI would provide consistency with the recommended number of cycles of AI used in a therapeutic setting (see chapter 17).
- The cumulative success rates with AI are lower in cycles 7 to 12 compared with cycles 1 to 6.
- AI transfers are often not undertaken consecutively but spread over a longer period of time due to problems with scheduling of procedures. Therefore, undertaking 12 cycles of AI could take considerably longer than 12 months.

In the light of the AI data, the majority view of the GDG was that, for same-sex couples, failure to conceive after 6 cycles of AI within the 12 past months should be the indication for further assessment.

Again, if the woman is 36 years or over, then such assessment should be considered after fewer cycles of AI, since her chances of successful conception with AI are lower.

Other groups requiring special consideration

Three separate groups were considered under this heading:

- People where there is a known cause of infertility or a history of predisposing factors (such as amenorrhoea, oligomenorrhoea, pelvic inflammatory disease or undescended testes).
- People who are unable to, or would find it very difficult to, have vaginal intercourse (such as people with a clinically diagnosed disability or psychosexual problem) and would have to try to conceive using IUI with the male partner's fresh sperm. In these cases, the GDG was of the opinion that most of the points covered in the discussion in relation to women in same-sex couples trying to conceive with AI (above) applied in this setting. Specifically, the GDG felt that the same criteria (that is, 6 unsuccessful cycles of IUI with partner sperm) applied to people in this group for referral for formal investigation and possible treatment.
- People with conditions that require specific consideration in relation to methods of conception. This includes people who are about to be treated for cancer and wish to preserve their fertility (see Chapter 19), couples where the male is HIV positive or

Hepatitis C positive, and people where the woman wishing to conceive is Hepatitis B positive (see Chapter 6).

In these circumstances the GDG was of the opinion that all people in these groups should be referred for early assessment and appropriate treatment.

Because of the implications of these issues, it could be argued that it would be appropriate to offer an initial consultation to same-sex couples to discuss the options for attempting conception, further assessment and appropriate treatment.

Recommendations

Number	Recommendation
35	People who are concerned about delays in conception should be offered an initial assessment. A specific enquiry about lifestyle and sexual history should be taken to identify people who are less likely to conceive. **[2004]**
36	Offer an initial consultation to discuss the options for attempting conception to people who are unable to, or would find it very difficult to, have vaginal intercourse. **[new 2013]**
37	The environment in which investigation of fertility problems takes place should enable people to discuss sensitive issues such as sexual abuse. **[2004]**
38	Healthcare professionals should define infertility in practice as the period of time people have been trying to conceive without success after which formal investigation is justified and possible treatment implemented. **[new 2013]**
39	A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner. **[new 2013]**
40	A woman of reproductive age who is using artificial insemination to conceive (with either partner or donor sperm) should be offered further clinical assessment and investigation if she has not conceived after 6 cycles of treatment, in the absence of any known cause of infertility. Where this is using partner sperm, the referral for clinical assessment and investigation should include her partner. **[new 2013]**
41	Offer an earlier referral for specialist consultation to discuss the options for attempting conception, further assessment and appropriate treatment where: • the woman is aged 36 years or over • there is a known clinical cause of infertility or a history of predisposing factors for infertility. **[new 2013]**
42	Where treatment is planned that may result in infertility (such as treatment for cancer), early fertility specialist referral should be offered. **[2004, amended 2013]**.
43	People who are concerned about their fertility and who are known to have chronic viral infections such as hepatitis B, hepatitis C or HIV should be referred to centres that have appropriate expertise and facilities to provide safe risk-reduction investigation and treatment. **[2004]**

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6 Investigation of fertility problems and management strategies

6.1 Introduction

Infertility can be caused by a number of underlying conditions including ovulatory disorders, tubal damage, male factors and uterine or peritoneal problems. Before treatment is started, it is important that a clinical assessment, namely history taking and physical examination, is undertaken. In most cases, further diagnostic investigations are also undertaken in order to establish if a pathological condition is present. However, in 25% of cases no cause of fertility problems can be established, even after investigations, and the term 'unexplained infertility' is used. Once assessment and investigations have been undertaken, a management plan can then be established with the individual or couple in an attempt to improve their chances of conception. Testing can also be carried out for conditions that can affect the health of the mother and unborn child, such as rubella and HIV status.

This chapter reviews the evidence for the main investigations and the subsequent management pathways.

6.2 Investigation of suspected male factor infertility

Semen analysis

WHO criteria for assessing semen quality are based on populations of fertile men and are described as 'reference' values rather than 'normal' values (see Table 6.1) (World Health Organization, 2010). Definitions relating to semen quality are given in Table 6.2. However, these figures are only valid for the tests performed in accordance with the methodology described in the World Health Organization (WHO) document.

In the 2004 guideline, the guideline development group (GDG) reviewed the evidence in relation to the detection of male factor fertility problems. The review found that basic semen analysis using the WHO criteria was a sensitive test (sensitivity of 89.6%), but it has poor specificity (an abnormal test result does not always mean there is a true semen abnormality). The GDG concluded that analysis of repeat semen samples provided greater specificity in identifying semen abnormalities; a single-sample analysis will falsely identify about 10% of men as abnormal, but repeating the test reduces this to 2%.[286]

Table 6.1 WHO lower reference limits (5th centiles and their 95% confidence intervals) for semen characteristics (World Health Organization, 2010)

Criteria	Lower reference value
Sperm morphology (normal forms, %)	1.5 (1.4–1.7)
Total sperm number (106 per ejaculate)	39 (33–46)
Sperm concentration (106 per ml)	15 (12–16)
Total motility (PR + NP, %)	40 (38–42)

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Criteria	Lower reference value
Progressive motility (PR, %)	32 (31–34)
Vitality (live spermatozoa, %)	58 (55–63)
Sperm morphology (normal forms, %)	4 (3.0–4.0)
Other consensus threshold values	
pH	≥ 7.2
Peroxidase-positive leukocytes (106 per ml)	< 1.0
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (micromol/ejaculate)	≥ 2.4
Seminal fructose (micromol/ejaculate)	≥ 13
Seminal neutral glucosidase (milliunitsejaculate)	≥ 20

MAR mixed antiglobulin reaction, NP non-progressive motility (WHO, 1999 grade c), PR progressive motility (WHO, 1999 grades a + b)

Table 6.2 Definitions relating to semen quality (World Health Organization, 2010)

Term	Definition
Asthenozoospermia	Percentage of progressively motile (PR) spermatozoa below the lower reference limit
Asthenoteratozoospermia	Percentages of both progressively motile (PR) and morphologically normal spermatozoa below the lower reference limits
Azoospermia	No spermatozoa in the ejaculate (given as the limit of quantification for the assessment method employed)
Cryptozoospermia	Spermatozoa absent from fresh preparations but observed in a centrifuged pellet
Haemospermia (haematospermia)	Presence of erythrocytes in the ejaculate
Leukospermia (leukocytospermia, pyospermia	Presence of leukocytes in the ejaculate above the threshold value
Necrozoospermia	Low percentage of live, and high percentage of immotile, spermatozoa in the ejaculate
Normozoospermia	Total number (or concentration, depending on outcome reported)* of spermatozoa, and percentages of progressively motile (PR) and morphologically normal spermatozoa, equal to or above the lower reference limits
Oligoasthenozoospermia	Total number (or concentration, depending on outcome reported)* of spermatozoa, and percentage of progressively motile (PR) spermatozoa, below the lower reference limits
Oligoasthenoteratozoospermia	Total number (or concentration, depending on outcome reported)* of spermatozoa, and percentages of both progressively motile (PR) and morphologically normal spermatozoa, below the lower reference limits
Oligoteratozoospermia	Total number (or concentration, depending on outcome reported)* of spermatozoa, and percentage of morphologically normal spermatozoa, below the lower reference limits

Term	Definition
Oligozoospermia	Total number (or concentration, depending on outcome reported)* of spermatozoa below the lower reference limit
Teratozoospermia	Percentage of morphologically normal spermatozoa below the lower reference limit

* Preference should always be given to total number, as this parameter takes precedence over concentration.

Repeat semen measurements from the same individual will vary over time.[28,29] This has prompted the suggestion that two[285] or three semen samples[29] are needed in order to establish a reliable semen profile. However, as the WHO criteria provide a sensitive test (that is, the test is likely to identify most 'true' abnormalities), if the semen analysis is normal there is no need for a repeat analysis. To reduce false positives, it is suggested that a repeat semen analysis should be performed only if the result of the first analysis is abnormal.[288] Biologically, the optimal time for the second sample is at least three months after the initial sample because the cycle of spermatozoa formation takes about three months to complete.[289] [Evidence level 3] However, this delay may cause anxiety and the timing of the second sample should take into consideration the preferences of the man. If azoospermia or severe oligozoospermia is reported in the initial semen analysis, a repeat test should be undertaken within two to four weeks. If the repeat test is reported as normal the semen can be regarded as normal and no further test is needed. However, these men may need further assessment of semen quality if assisted reproduction is being considered.

Men who have two abnormal semen analyses may need further, more detailed, semen assessment. The tests should be interpreted within the clinical context and circumstances of the individual or couple. If azoospermia is confirmed, this should be explained sensitively to the patient, who should be referred for early specialist advice in order to minimise anxiety.

The WHO criteria reported in the original guideline includes assessment for the presence of autoimmune antisperm antibodies as a standard part of semen analysis.[287] [Evidence level 4] This analysis is performed using either an immunobead test or a mixed antiglobulin reaction test. However, opinions differ on the reliability of these tests and whether they should be used routinely in the initial investigation of fertility problems.[290–293] [Evidence level 3–4] Semen analysis should not include screening for antisperm antibodies because there is no effective treatment in terms of improving male fertility (see Section 7.2).

Sperm function tests vary in their ability to detect defects in the complex processes leading to fertilisation, and are of limited use from a practical point of view.[211,294] [Evidence level 4]

The reliability of the WHO reference values, especially that for sperm concentration, in predicting the chance of conception has been questioned.[295] [Evidence level 3]

Unless there is azoospermia, the predictive value of subnormal semen variables is limited. No functional test has yet been established that can unequivocally predict the fertilising capacity of spermatozoa. Sperm function tests such as computer-assisted semen analysis have not been found to be more predictive. Reliable sperm function tests are urgently required.[211,294] [Evidence level 4]

In the UK, low sperm count or quality is found to be the only cause of infertility in about 20% of couples, and is a contributory factor in a further 25% of couples.[1,2,296] It is estimated that in between 30% and 50% of men with poor semen quality no cause for this will be identified.[297,298] Impaired semen quality, azoospermia and inadequate coitus are contributing factors in nearly 50% of infertile couples.

Abnormal semen characteristics are usually idiopathic (idiopathic oligoasthenoteratozoospermia). Idiopathic semen abnormalities occur in about 26% of infertile men.[298] The spermatozoa are mostly dysfunctional and unable to fertilise but a proportion are often functionally normal. Sperm function may also be impaired by anti-sperm antibodies.

Azoospermia may be due to hypothalamic-pituitary failure, primary testicular failure (nonobstructive azoospermia) or obstruction of the genital tract (obstructive azoospermia).

Hypogonadotrophic hypogonadism, which is a condition caused by hypothalamic or pituitary dysfunction, accounts for less than 1% of male factor fertility problems.[296] It results in a deficiency of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which is associated with failure of spermatogenesis and testosterone secretion.

Primary testicular failure is the most common cause of male infertility due to oligozoospermia and is the cause of nonobstructive azoospermia. Testicular failure may be due to cryptorchidism, torsion, trauma, orchitis, chromosome disorders (Klinefelter's syndrome, Y-chromosome microdeletions), systemic disease, radiotherapy or chemotherapy; however, in the majority of cases (66%) the cause is unknown. The diagnosis is based on reduction in testicular size and elevation of serum FSH levels. There is no effective treatment to restore fertility in primary testicular failure. Men undergoing treatments that cause infertility should be offered the opportunity to cryopreserve semen (see Chapter 19).

Obstructive azoospermia is uncommon with a prevalence of less than 2%.[1] The diagnosis is based on normal testis size and normal serum FSH levels. This includes conditions such as congenital bilateral absence of vas deferens (CBAVD). CBAVD is commonly associated with cystic fibrosis mutations or renal tract abnormality (e.g. an absent kidney).

Anejaculation is defined as the total failure of seminal emission into the posterior urethra. Retrograde ejaculation is the substantial propulsion of seminal fluid from the posterior urethra into the bladder.[299] Anejaculation is a relatively uncommon occurrence in the general population,[300] and retrograde ejaculation accounts for about 0.3–2.0% of male fertility problems. Anejaculation and retrograde ejaculation may result from spinal cord injury, transurethral prostatectomy, retroperitoneal lymph node dissection, diabetes mellitus, transverse myelitis, multiple sclerosis or psychogenic (idiopathic) disorders. For example, it has been reported that only 7% of men retained ejaculation after transurethral resection of the prostate.[301] [Evidence level 2b] With the advent of ICSI, since only a small number of motile spermatozoa is required for a successful fertilisation,[302] both ejaculation disorders can be considered as treatable conditions. [Evidence level 3]

A varicocele is a collection of dilated veins in the spermatic cord and is a common physical anomaly. Varicoceles are found in 11.7% of men with normal semen and 25.4% of men with abnormal semen.[303] The mechanism by which varicoceles might impair fertility and spermatogenesis is not clear. Varicoceles may be associated with decreased ipsilateral testicular volume, elevated scrotal temperature and pain, as well as impaired semen quality.[303–305]

The information in Recommendation 44 has been updated to reflect changes in the WHO reference values for semen analysis since 2004.

Recommendations

Number	Recommendation
44	The results of semen analysis conducted as part of an initial assessment should be compared with the following World Health Organization reference values*: • semen volume: 1.5 ml or more • pH: 7.2 or more • sperm concentration: 15 million spermatozoa per ml or more • total sperm number: 39 million spermatozoa per ejaculate or more • total motility (percentage of progressive motility and non-progressive motility): 40% or more motile or 32% or more with progressive motility • vitality: 58% or more live spermatozoa • sperm morphology (percentage of normal forms): 4% or more. **[2004, amended 2013]**
45	Screening for antisperm antibodies should not be offered because there is no evidence of effective treatment to improve fertility. **[2004]**

* Please note the reference ranges are only valid for the semen analysis tests outlined by the World Health Organization

46	If the result of the first semen analysis is abnormal, a repeat confirmatory test should be offered. **[2004]**
47	Repeat confirmatory tests should ideally be undertaken 3 months after the initial analysis to allow time for the cycle of spermatozoa formation to be completed. However, if a gross spermatozoa deficiency (azoospermia or severe oligozoospermia) has been detected the repeat test should be undertaken as soon as possible. **[2004]**

Post-coital testing of cervical mucus

The value of postcoital testing of cervical mucus for the presence of motile sperm is controversial and is a subject of continuing debate.[406–411]

It has been reported that the postcoital test is an effective predictor of conception where defined female causes of infertility are absent and duration of infertility is less than three years.[412] [Evidence level 3] However, a systematic review of 11 observational studies (n = 3093 women) showed that the postcoital test has poor predictive power of fertility and lacks validity.[413] [Evidence level 3] One randomised contolled trial (RCT) (n = 444) compared cumulative pregnancy rates between couples offered a postcoital test versus couples who were not offered this test as part of their infertility investigation. No significant differences were shown in their respective cumulative pregnancy rates (49%, 95% CI 42% to 55% in the intervention group versus 48%, 95% CI 42% to 55% in the control group). The couples offered postcoital tests in this RCT also had more tests and treatments than those in the control group.[414] [Evidence level 1b]

It has been suggested that results of postcoital testing may have little influence on treatment strategy in the light of the widespread use of assisted reproduction treatments (for example, in vitro fertilisation (IVF) and intrauterine insemination (IUI)) for fertility problems associated with sperm-cervical mucus interaction. In addition, the lack of a reliable sperm function test may render post-coital testing unnecessary.[410] [Evidence level 4]

Recommendations

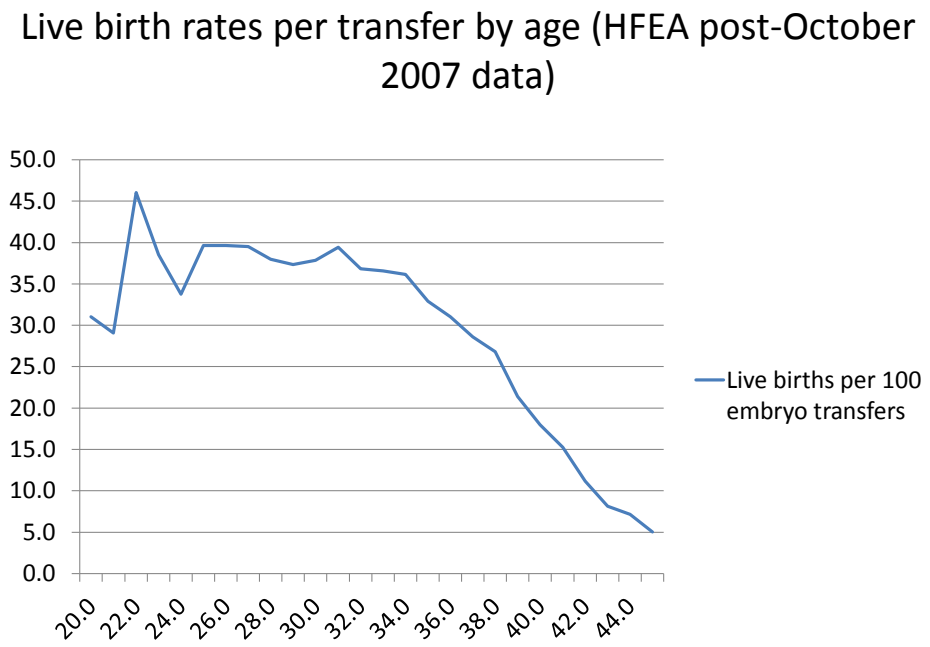
Number	Recommendation
48	The routine use of post-coital testing of cervical mucus in the investigation of fertility problems is not recommended because it has no predictive value on pregnancy rate. **[2004]**

6.3 Investigation of suspected ovulation disorders

Ovarian reserve testing

A woman's fertility is related to the number of oocytes remaining in her ovaries, referred to as 'ovarian reserve', which influences the chance of becoming pregnant. Ovarian reserve declines steadily from before birth until the menopause, thus age is the most easily available surrogate for ovarian reserve. Studies show how the number and quality of oocytes decline with a woman's age (Faddyet al., 1992; Faddy et al., 1996). In addition, there is clear evidence that overall fertility declines with age, which is in part related to a decline in ovarian reserve but also a lower rate of embryo implantation and an increased chance of pregnancy loss. These points are illustrated in Figure 5.1 and in the most recent Human Fertilisation and Embryology Authority (HFEA) data covering all (fresh and frozen) 52,996 embryo transfers using the woman's own eggs undertaken in the UK between 1 October 2007 and 30 June 2009 (93% of these were double embryo transfers) (see Figure 6.1, HFEA, personal communication). Both figures demonstrate a clear pattern of decline in IVF success rates from around age 35 years.

Figure 6.1 IVF success in terms of live births per 100 embryo transfers (vertical axis) according to age of woman (horizontal axis) based on 52,996 embryo transfers using the woman's own eggs undertaken in the UK between 1 October 2007 and 30 June 2009 (HFEA, personal communication; [note: small numbers of women below age 24 years in the HFEA database])



In addition to a woman's age, a number of tests exist which, directly or indirectly, estimate ovarian reserve. A number of new tests have become more widely available and studied since the 2004 guideline, including laboratory tests and ultrasound scan techniques. In particular, measurement of Anti-Mullerian Hormone (AMH) levels in the blood and transvaginal ultrasound measurement of the total antral follicle count (AFC). However, it remains unclear how useful any form of ovarian reserve testing is in predicting the chance of natural conception, the likelihood of pregnancy following fertility treatment and the outcome of the subsequent pregnancies. Clear guidance should help in a number areas, such as reducing the amount of unnecessary testing, providing criteria to determine access to IVF, and giving reliable information upon which to base treatment decisions.

The objective of the review was to determine the accuracy of measures of ovarian reserve in predicting outcomes in women undergoing treatment for infertility.

The review was undertaken in two parts. The first part was to assess all available tests for ovarian reserve against pre-specified accuracy criteria for specified outcomes (see Table 6.3 below). The criterion was a receiver operator characteristic area under the curve (ROC-AUC) of 0.8 or more, and three outcomes were specified by the GDG for the review: live birth, clinical pregnancy and response to ovarian stimulation (low/poor response defined as fewer than 4 oocytes retrieved or cancellation and high/excessive response defined as more than 15 oocytes or more than 20 oocytes retrieved or cancellation of cycle). Tests that met this criterion for any outcome were then included in the second part of the review where more detailed assessment was undertaken and likelihood ratios were calculated for the outcomes on which they were shown to be beneficial in part one of the review (see Tables 6.4 to 6.6).

Review question

How accurate are tests of ovarian reserve in predicting pregnancy and its outcomes for women undergoing treatment for infertility?

Evidence profiles

As described above, the review was undertaken in two parts:

- Part one: accuracy of tests of ovarian reserve using the receiver operator characteristic area under the curve (ROC-AUC) data (Evidence profile 6.3)
- Part two included:
    - GRADE findings for evaluation of ovarian reserve using likelihood ratios for the antral follicle count (AFC) test (Evidence profile 6.4)
    - GRADE findings for evaluation of accuracy of tests of ovarian reserve using likelihood ratios for the Anti-Mullerian Hormone (AMH) test (Evidence profile 6.5
    - GRADE findings for evaluation of accuracy of tests of ovarian reserve using likelihood ratios for the follicle-stimulating hormone (FSH) test (Evidence profile 6.6).

Description of included studies

Accuracy of tests of ovarian reserve: receiver operator characteristic area under the curve (ROC-AUC) data

Thirteen studies (Bancsi et al., 2002; Hendriks et al., 2004; Khairy et al., 2008; Lee et al., 2009; McIlveen et al., 2007; van Rooij et al., 2002; Younis et al., 2010; Aflatoonian et al., 2009, Al-Azemi et al., 2011; Andersen et al., 2011; Li et al., 2010, Lee et al., 2011; Ben-Haroush et al., 2011) met the inclusion criteria and provided ROC-AUC data. All of the studies were of women about to undergo gonadotrophin stimulation as part of IVF treatment, and eight of the nine studies used prospective cohort designs.

The mean age of participants ranged from 27.5 (standard deviation [SD] 3.6) to 37.3 (SD 3.9) years in the three studies that reported on age; while the duration of infertility was 55.2 (SD 44.4) months in the only study that reported on duration of infertility. Male factors were the cause of infertility for 38% to 49% of participants (two studies), while other causes and tubal factors were the cause of infertility in 15 % and 46% of participants respectively (one study). Measurements in all studies were taken in women who were not undergoing ovarian stimulation.

Table 6.3 Accuracy of tests of ovarian reserve: area under the curve data

No. of studies	Other considerations	Pooled area under the curve	Quality
Live full-term singleton birth			
Antral follicle count (AFC) on day 3 of cycle			
1 (N = 243) (Li et al., 2010)	None	0.622	Very low
Anti-mullerian hormone (AMH) on day 3 of cycle			
1 (N = 324) (Lee et al., 2009)	None	0.52	Low
1 (N = 243) (Li et al., 2010)	None	0.682	Very low
Age			
1 (N = 324) (Lee et al., 2009)	None	0.55	Low
Clomifene citrate challenge test (CCCT)			
No evidence reported			
Oestradiol (E2)			
No evidence reported			

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No. of studies	Other considerations	Pooled area under the curve	Quality
Follicle-stimulating hormone (FSH) on day 3 of cycle			
1 (N = 324) (Lee et al., 2009)	None	0.52	Low
1 (N = 243) (Li et al., 2010)	None	0.623	Very low
Inhibin B			
No evidence reported			
Ovarian volume (OV)			
No evidence reported			
Ovarian blood flow			
No evidence reported			
Low response following ovarian stimulation			
AFC on day 2–4 of cycle			
4 (N = 470)[a] (Bancsi et al., 2002; Hendriks et al., 2004; van Rooij et al., 2002; Younis et., al 2010)	None	0.83	Moderate
AMH on day 2–4 of cycle			
3 (N = 757)[a] (van Rooij et al., 2002; Al-Azemi, 2011; Andersen, 2011)	None	0.83[i]	Moderate
Age			
5 (N = 618)[a] (Bancsi et al., 2002; Hendriks et al., 2004; Khairy et al., 2008; van Rooij et al., 2002; Younis et al., 2010)	None	0.73[i]	Moderate
CCCT on day 3 of cycle			
1 (N = 63) (Hendriks et al., 2004)	None	0.85	Moderate
E2 on day 3 of cycle			
3 (N = 302)[a] (Bancsi et al., 2002; Hendriks et al., 2004; van Rooij et., al 2002)	None	0.52[i]	Moderate
FSH on day 2–4 of cycle			
4 (N = 470) (Bancsi et al 2002, Hendriks et al 2004, van Rooij et al 2002, Younis et al 2010)	None	0.81[i]	Moderate
Inhibin B on day 3 of cycle			
3 (N = 302)[a] (Bancsi et al., 2002; Hendriks et al., 2004; van Rooij et al., 2002)	None	0.76[i]	Moderate
OV on day 2–4 of cycle			
1 (N = 168) (Younis et al., 2010)	None	0.67	Moderate
Ovarian blood flow			
No evidence reported			

No. of studies	Other considerations	Pooled area under the curve	Quality
Age + FSH on day 2 – 4 of cycle [b]			
1 (N = 148) (Khairy et al., 2008)	None	0.75	Moderate
Age +AFC on day 3 of cycle [c]			
1 (N = 148) (Khairy et al., 2008)	None	0.80	Moderate
FSH on day 2–4 of cycle + AFC on day 3 of cycle[d]			
2 (N =183) (Bancsi et al., 2002; Hendricks et al., 2004)	None	0.90[i]	Moderate
Age + FSH on day 2–4 of cycle + AFC on day 3 of cycle[b]			
1 (N = 148) (Khairy et al., 2008)	None	0.81	Moderate
Age + FSH + Inhibin B + AMH			
1 (N = 352) (Al-Azemi et al., 2010)	None	0.819	Moderate
AMH + Smoking			
1 (N = 119)[e] (Ansersen et al , 2011)	None	0.85	Moderate
High response following ovarian stimulation			
AFC on day 3 of cycle			
1 (N = 119)[e] van Rooij 2002	NA	0.86	Moderate
AMH on day 3 of cycle			
3 (N = 544) [e](van Rooij et al., 2002; Aflatoonian et al., 2009; Andersen et al., 2011)	-	0.83[i]	Low
Age			
1 (N = 143) (Aflatoonian et al., 2009)	-	0.409	Low
E2 on day 3 of cycle			
1 (N = 143) (Aflatoonian et al., 2009)	-	0.474	Low
CCCT on day 3 of cycle			
No evidence reported			
FSH			
1 (N = 143) (Aflatoonian et al., 2009)	-	0.385	Low
Inhibin B on day 3 of cycle			
1 (N = 119)[e] (van Rooij et al., 2002)	None	0.76	Moderate
Ovarian blood flow			
No evidence reported			
AMH + AFC + FSH			
1 (N = 119)[e] (Ansersen et al , 2011)	None	0.80	Moderate

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No. of studies	Other considerations	Pooled area under the curve	Quality
Cancellation following ovarian stimulation			
AFC on day 2–4 of cycle			
1 (N = 84)[f] (McIlveen et al., 2007)	None	0.74	Moderate
AMH on day 2 of cycle			
2 (N = 200 (McIlveen et al., 2007; Lee, 2011)	-	0.77[i]	Low
Age			
No evidence reported			
CCCT			
No evidence reported			
E2 on day 2–4 of cycle			
No evidence reported			
FSH on day 2–4 of cycle			
1 (N = 84) (McIlveen et al., 2007)	None	0.64	Moderate
Inhibin B on day 2–4 of cycle			
1 (N = 84) (McIlveen et al., 2007)	None	0.78	Moderate
OV on day 2 of cycle			
1 (N = 84) (McIlveen et al., 2007)	None	0.78	Moderate
Ovarian blood flow			
No evidence reported			
Pregnancy			
AFC (cut-off at <15)			
1 (N = 115; Ben-Haroush, 2011)	None	0.613	Low
AMH on day 3–5 of cycle			
No evidence reported			
Age			
No evidence reported			
CCCT			
No evidence reported			
1 (N = 115; Ben-Haroush, 2011)	None	0.595	Low
FSH			
1 (N = 115; Ben-Haroush, 2011)	None	0.459	Low
Inhibin B			
No evidence reported			

No. of studies	Other considerations	Pooled area under the curve	Quality
OV			
1 (N = 115; Ben-Haroush, 2011)	None	0.513	Low
Ovarian blood flow (based on peak systolic velocity)			
1 (N = 115; Ben-Haroush, 2011)	None	0.393	Low

AFC antral follicle count, AMH Anti-Mullerian Hormone, CCCT: clomifene citrate challenge test, E2 oestradiol, FSH follicle-stimulating hormone, hCG human chorionic gonadotrophin, OV ovarian volume

[a] Low response defined as < 4 oocytes or cycle cancellation due to < 3 follicles or absent follicular growth

[b] High age + high FSH

[c] High age + low AFC

[d] High FSH + low AFC

[e] High response defined as > 15 oocytes or E2 > 3000 pg/ml

[f] Defined as < 4 follicles with a diameter of > 14 mm after 8 days of stimulation or when requirement for hCG not met after 4-5 days or no oocytes retrieved

GRADE findings for evaluation ovarian reserve: likelihood ratios for the antral follicle count (AFC) test, Anti-Mullerian Hormone (AMH) and follicle-stimulating hormone (FSH)

Results from part 1 showed that four tests (AFC, AMH, FSH and clomifene citrate challenge test [CCCT]) independently fulfilled the identified accuracy criteria (an ROC-AUC greater than or equal to 0.8) for one or more of the agreed outcomes. However, CCCT was excluded due to the low quality of the evidence and the fact it is not used in clinical practice in the UK. For each of the remaining tests likelihood ratios were calculated for a range of different thresholds. The likelihood ratios were calculated as they provide more detailed information on the characteristics of a test than ROC-AUC curves. Similarly, we did not calculate the likelihood ratios for combinations of tests as they did not demonstrate any better accuracy than these three tests in isolation.

The likelihood ratio data are presented in the GRADE evidence profiles for each of the three tests (Tables 6.4 to 6.6) followed by supporting evidence statements. The NICE accepted criteria are:

- A ‘definitely useful’ test is defined as one that has:
  - a positive likelihood ratio of greater than 10, and
  - a negative likelihood ratio of less than 0.1.
- A ‘moderately useful’ test is defined as one that has:
  - a positive likelihood ratio of 5–10, and
  - a negative likelihood ratio of 0.1–0.5.

Nine papers (Bancsi et al., 2004a; Bancsi et al., 2004b; Hendriks et al., 2004; Kwee et al., 2006; Kwee et al., 2007; La Marca et al., 2007; McIlveen et al., 2007; Aflatoonian et al., 2009, Al-Azemi, 2011) reporting on seven studies examined the accuracy of different threshold values for the high and low response outcomes (the only outcomes that reached the AUC threshold). All were prospective observational (cohort) studies. In addition, data from a meta-analysis on high responders to ovarian stimulation was included (Broer, 2011).

The mean age of participants ranged from 27.5 (SD ± 3.6) to 37.3 (SD ± 3.9) years in the 4 studies that reported on age while the duration of infertility ranged from 35 (SD ± 25) to 55.2 (SD ± 44.4) months in the two studies that reported on duration of infertility. Tubal factors were the cause of infertility in 12% to 20.6% of participants (four studies), male factors in 38.1% to 65% of participants (four studies) and other causes in 23% to 46.4% of participants (four studies).

Table 6.4 GRADE findings for evaluation ovarian reserve: likelihood ratios for the Antral Follicle Count (AFC) test

Number of studies	Number of patients /women	Measure of diagnostic accuracy						Quality
		Sensitivity	Specificity	PPV	NPV	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)	
Low response following ovarian stimulation								
≤ 2 oocytes								
1 (Bancsi et al., 2004a)	N = 120	-	-	-	-	14.0 (3.30, 59.4)	0.68 (0.54, 0.86)	Moderate
≤ 3 oocytes								
1 (Bancsi et al., 2004a)	N = 120	-	-	-	-	6.61 (2.84,15.39)	0.57 (0.41, 0.78)	Moderate
≤ 4 oocytes								
1 (Bancsi et al., 2004a)	N = 120	-	-	-	-	5.13 (2.71, 9.71)	0.44 (0.29, 0.67)	Moderate
≤ 5 oocytes								
1 (Bancsi et al., 2004a)	N = 120	-	-	-	-	4.04 (2.45, 6.68)	0.34 (00.20, 0.58)	Moderate
≤ 6 oocytes								
1 (Bancsi et al., 2004a)	N = 120	-	-	-	-	3.56 (2.32, 5.46)	0.25 (0.13, 0.49)	Moderate
≤ 8 oocytes								
1 (Bancsi et al., 2004a)	N = 120	-	-	-	-	2.75 (2.00, 3.78)	0.13 (0.04, 0.37)	Moderate
≤ 10 oocytes								
1 (Bancsi et al., 2004a)	N = 120	-	-	-	-	2.20 (1.70, 2.86)	0.10 (0.03, 0.38)	Moderate
High response following ovarian stimulation								
>9 oocytes								
1 (Ng et al., 2000)	N = 128	-	-	-	-	2.07	0.56	Low
>10 oocytes								
1 (Kwee et al., 2007)	N = 110	-	-	-	-	3.24 (2.30, 4.55)	0.08 (0.01, 0.56)	Moderate

Number of studies	Number of patients /women	Measure of diagnostic accuracy						Quality
		Sensitivity	Specificity	PPV	NPV	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)	
>12 oocytes								
1 (Kwee et al., 2007)	N = 110	-	-	-	-	4.31 (2.79, 6.69)	0.15 (0.04, 0.55)	Moderate
>14 oocytes								
1 (Kwee et al., 2007)	N = 110	-	-	-	-	7.66 (4.10, 14.32)	0.20 (0.07, 0.55)	Moderate
1 (Ng et al., 2000)	N = 128	-	-	-	-	3.33	0.85	Low
1 (Van RooiJ et al., 2002)	N = 114	-	-	-	-	2.49	0.13	Low
1 (Eldar-Geva et al., 2005)	N = 56	-	-	-	-	1.40	0.18	Low
>16 oocytes								
1 (Kwee et al 2007)	N = 110	-	-	-	-	10.94 (3.70, 32.32)	0.55 (0.35, 0.87)	Moderate
1 Aflatoonian et al 2009	N = 143	-	-	-	-	11.11	0.12	Low
>18 oocytes								
1 (Kwee et al.,2007)	N = 110	-	-	-	-	13.68(2.88, 64.84)	0.72 (0.53, 0.98)	Moderate

LR+ positive likelihood ration, LR- negative likelihood ration, NPV negative predictive valie, PPV positive predictive value

Table 6.5 GRADE findings for evaluation of accuracy of tests of ovarian reserve: likelihood ratios for the Anti-Mullerian Hormone (AMH) test

Number of studies	Number of patients /women	Measure of diagnostic accuracy						Quality
		Sensitivity	Specificity	PPV	NPV	LR+	LR-	
Low response following ovarian stimulation								
≤ 0.5 ng/ml								
1 (La Marca et al., 2007)	N = 48	-	-	-	-	4.58 (2.76, 7.64)	0.20 (0.06, 0.72)	Moderate

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Number of studies	Number of patients /women	Measure of diagnostic accuracy						Quality
		Sensitivity	Specificity	PPV	NPV	LR+	LR-	
≤ 0.75 ng/ml								
1 (La Marca et al., 2007)	N = 48	-	-	-	-	11.00 (4.76, 25.44)	0.27 (0.10, 0.72)	Moderate
≤ 1.25 ng/ml								
1 (McIlveen et al., 2007)	N = 84	-	-	-	-	2.33 (1.26, 4.31)	0.56 (0.38, 0.82)	Moderate
= 1.36 ng/ml								
1 (Al-Azemi et al., 2011)	N = 356	-	-	-	-	2.99	0.34	Low
≤ 2.97 ng/ml (based on poor responder being < 5 oocytes								
1 (Kunt et al., 2011)	N = 180	-	-	-	-	7.14	0.14	Low
High response following ovarian stimulation (as reported in Broer et al., 2011)								
= 1.59 ng/ml								
1 (Riggs et al.,2008)	N = 123	-	-	-	-	2.55	0.24	Very Low
= 1.66 ng/ml								
1 (Ebner et al., 2006)	N = 135	-	-	-	-	1.38	0.16	Low
= 1.99 ng/ml								
1 (Lee et al.,2008)	N = 262	-	-	-	-	2.37	0.16	Low
= 2.10 ng/ml								
1 (Nelson et al.,2007)	N = 314	-	-	-	-	4.19	0.15	Low
= 2.60 ng/ml								
1 (La Marca et al.,2007)	N = 48	-	-	-	-	1.95	0.25	Low
= 3.36 ng/ml								
1 (Lee et al.,2008)	N = 262	-	-	-	-	4.77	0.44	Low

Number of studies	Number of patients /women	Measure of diagnostic accuracy						Quality
		Sensitivity	Specificity	PPV	NPV	LR+	LR-	
= 3.50 ng/ml								
1 (Van RooiJ et al.,2002)	N = 114	-	-	-	-	8.00	0.63	Low
1 (Eldar-Geva et al.,2005)	N = 53	-	-	-	-	6.55	0.31	Low
1 (Nelson et al.,2007)	N = 314	-	-	-	-	14.25	0.45	Low
1 (Nardo et al.,2009)	N = 165	-	-	-	-	2.93	0.17	Low
= 4.52 ng/ml								
1 (Ebner et al.,2006)	N = 135	-	-	-	-	2.89	0.56	Low
= 4.83 ng/ml								
1 (Aflatoonian et al.,2009)	N = 159	-	-	-	-	4.23	0.09	Low
= 7.00 ng/ml								
1 (La Marca et al.,2007)	N = 48	-	-	-	-	3.35	0.52	Very low

LR+ positive likelihood ratio, LR- negative likelihood ratio, NPV negative predictive value, PPV positive predictive value

Table 6.6 GRADE findings for evaluation of accuracy of tests of ovarian reserve: likelihood ratios for the Follicle-Stimulating Hormone (FSH) test

Number of studies	Number of patients /women	Measure of diagnostic accuracy						Quality
		Sensitivity	Specificity	PPV	NPV	LR+	LR-	
Low response following ovarian stimulation								
=7.0 IU/L								
1 (Al-Azemi et al., 2011)	N = 356	-	-	-	-	2.17	0.46	Low

Number of studies	Number of patients /women	Measure of diagnostic accuracy						Quality
		Sensitivity	Specificity	PPV	NPV	LR+	LR-	
≥8.9 IU/L								
1 (Bancsi et al., 2004b)	N = 120	-	-	-	-	6.41 (3.16, 13.04)	0.43 (0.28, 0.65)	Moderate
≥ 10 IU/L								
1 (Hendriks et al., 2004)	N = 63	-	-	-	-	13.53 (3.26, 55.56)	0.43 (0.24, 0.76)	Moderate
≥11 IU/L								
1 (Bancsi et al., 2004b)	N = 120	-	-	-	-	6.22 (2.65, 14.60)	0.60 (0.44, 0.81)	Moderate
≥13.4 IU/L								
1 (Bancsi et al., 2004b)	N = 120	-	-	-	-	7.58 (2.65, 21.68)	0.67 (0.52, 0.86)	Moderate
≥ 15 IU/L								
1 (Hendriks et al., 2004)	N = 63	-	-	-	-	13.53 (1.70, 107.62)	0.72 (0.53, 0.98)	Moderate
High response following ovarian stimulation								
≤ 4 IU/L								
1 (Kwee et al., 2006)	N = 110	-	-	-	-	16.41 (1.81, 148.62)	0.83 (0.67, 1.04)	Moderate
≤ 5 IU/L								
1 (Kwee et al., 2006)	N = 110	-	-	-	-	4.56 (1.57, 13.27)	0.75 (0.55, 1.03)	Moderate
≤ 6 IU/L								
1 (Kwee et al., 2006)	N = 110	-	-	-	-	2.74 (1.65, 4.54)	0.46 (0.24, 0.89)	Moderate
≤ 7 IU/L								
1 (Kwee et al., 2006)	N = 110	-	-	-	-	2.13 (1.52, 2.98)	0.29 (0.10, 0.81)	Moderate

Number of studies	Number of patients /women	Measure of diagnostic accuracy						Quality
		Sensitivity	Specificity	PPV	NPV	LR+	LR-	
≤ 8 IU/L								
1 (Kwee et al., 2006)	N = 110	-	-	-	-	1.59 (1.29, 1.96)	0.14 (0.02, 0.98)	Moderate

IU international unit, LR+ positive likelihood ration, LR- negative likelihood ration, NPV negative predictive valie, PPV positive predictive value

Evidence statements

Phase 1 – All tests

Live singleton birth rate

None of the studies reported the number of live full-term singleton births, so the number of live births was used instead. The data in the GRADE profile has been downgraded for indirectness accordingly.

Low quality evidence from two studies was reviewed. The studies examined the use of AFC, AMH, age and FSH. None of the tests achieved the specified cut-off for accuracy on this outcome and therefore they were not considered to be useful in predicting live birth.

Pregnancy rate

Low quality evidence from one study reported that neither AFC, E2, FSH, ovarian volume nor ovarian blood flow could be considered a useful test for determining a woman's likelihood of subsequently becoming pregnant. No data was identified on the use of AMH, age, CCCT or Inhibin B.

Low response following ovarian stimulation

Moderate quality evidence from six studies (examining eight tests of ovarian reserve) was reviewed. The results showed that Antral Follicle Count (AFC), Anti-Mullerian Hormone (AMH), Clomifene Citrate Challenge (CCC) and Follicle-Stimulating Hormone (FSH) tests achieved the specified cut-off for accuracy for this outcome, but that age, E2, Inhibin B and ovarian volume did not.

The following combinations of tests met the specified cut-off for accuracy on this outcome: age + AFC (one study, moderate quality); FSH + AFC (two studies, moderate quality); age + FSH + AFC (one study, moderate quality); age + FSH + Inhibin B + AMH (one study, moderate quality); and AMH + smoking (one study, low quality).

High response following ovarian stimulation

Moderate to low quality evidence from three studies (examining three tests of ovarian reserve) was reviewed. AFC and AMH tests achieved the specified cut-off for accuracy on this outcome, but age, E2, FSH and Inhibin B did not. No evidence was found on CCCT or ovarian blood flow.

Cancellation ratesfollowing ovarian stimulation

Very low to moderate quality evidence from two studies examining AFC, AMH, FSH, Inhibin B and ovarian volume was reviewed. None of the tests achieved the specified cut-off for accuracy on this outcome. No data was found on the use of age, CCCT, E2 or ovarian blood flow.

Phase 2 – tests meeting ROC-AUC criteria

For the three tests currently used in the UK with suitable quality of evidence and that met the ROC-AUC criteria of 0.8 or more, the following outcomes were found.

Antral Follicle Count (AFC) test

Low response following ovarian stimulation

Moderate quality evidence from one study demonstrates that an AFC of 2 or less is definitely useful in predicting if a low response to ovarian stimulation will occur and that AFC of 4 or less is moderately useful in predicting if a low response will occur.

Moderate quality evidence from one study demonstrated that an AFC of more than 4 is moderately useful in predicting if a low response to ovarian stimulation will not occur and that an AFC of 10 or more is definitely useful in predicting a low response will occur.

High response following ovarian stimulation

Moderate to low quality evidence from two studies demonstrated that an AFC of more than 16 is definitely useful in predicting if a high response will occur following ovarian stimulation.

Moderate to low quality evidence from four studies demonstrated that an AFC of 14 or less is moderately useful for predicting if a high response will not occur.

Moderate quality evidence from one study demonstrated that an AFC of more than 10 and less than 12 is definitely useful in predicting if a high response will not occur.

Anti-Mullerian Hormone (AMH) test

Low response following ovarian stimulation

Moderate quality evidence from one study demonstrated that an AMH of 0.75 ng/ml or less is definitely useful in predicting if a low response following ovarian stimulation will occur and that a value greater than 0.75 ng/ml is moderately useful in excluding a low response.

High response following ovarian stimulation

Low quality evidence from three studies demonstrated that an AMH of 3.50 ng/ml or more is moderately or definitely useful in predicting if a high response following ovarian stimulation will occur.

Follicle-Stimulating Hormone (FSH) test

Low response following ovarian stimulation

Moderate quality evidence from two studies demonstrated that an FSH greater than 8.9 IU/L is moderately useful in predicting if a low response will occur following ovarian stimulation and that a result less than 8.9 IU/L is moderately useful at excluding a low response following ovarian stimulation.

Moderate quality evidence from one study demonstrated that an FSH of more than 10 IU/L is definitely useful in predicting if a low response will occur following ovarian stimulation and that a result less than 10 IU/L is moderately useful in excluding a low response. Moderate quality evidence from one study demonstrated that an FSH of 11 IU/L or more is moderately useful in predicting a low response following ovarian stimulation. Moderate quality evidence from one study demonstrated that an FSH of 13.4 IU/L or more is moderately useful in predicting a low response following ovarian stimulation.

Moderate quality evidence from one study demonstrated that an FSH of more than 15 IU/L is definitely useful in predicting if a low response will occur following ovarian stimulation.

High response following ovarian stimulation

Moderate quality evidence from one study demonstrated that an FSH of less than 4 IU/L is definitely useful in predicting if a high response will occur following ovarian stimulation.

Moderate quality evidence from one study demonstrated that an FSH of greater than 6 IU/L is moderately useful in excluding a high response following ovarian stimulation.

Health economics profile

No health economic papers were identified and no specific health economic analysis was undertaken.

Evidence to recommendations

Relative value placed on the outcomes considered

There were three outcomes selected as being important to consider:

- live full-term singleton birth
- clinical pregnancy rate

- response to ovarian stimulation, including low/poor response, high/excessive response or cancellation of cycle.

Live full-term singleton birth

As discussed in the Methodology chapter (Chapter 3), live full-term singleton birth was agreed by the GDG to be the most important outcome and the main goal of fertility treatment. However, none of the studies reported in this review reported this specific outcome and the data in the GRADE profile has been downgraded for indirectness accordingly. Thus, the number of live births was used instead, though very few studies reported this outcome.

Clinical pregnancy rate

This outcome was reported more commonly in the studies reviewed and it is a reasonable surrogate outcome for live birth rates. However, it is acknowledged that not all clinical pregnancies continue to live birth.

Response to ovarian stimulation (low/poor response, high/excessive response or cancellation of cycle)

This is an important outcome from the perspective of determining treatment strategies, including the decision to not commence IVF. Thus, for example, if there is an increased chance of a low response then either IVF could be not commenced or different treatment strategies, such as an increased dose of ovarian stimulation drugs, used. Conversely, if there is an increased chance of a high response then lower doses of drugs or other strategies could be used.

The GDG felt it was important to stress that this review examined the role of different investigations in women with infertility where IVF is being considered.

Consideration of clinical benefits and harms

The GDG agreed that the evidence presented was representative of their clinical experience and that recommendations could be made. Also, there is no internationally agreed assay for AMH and the GDG highlighted that this needed to be taken into account when using the figures quoted in the recommendation.

Correct identification of high and low responders has the benefit of allowing treatment to be customised and for patients to make informed treatment decisions. Failure to identify likely high and low responders before treatment could have implications for outcomes such as ovarian hyperstimulation syndrome (OHSS) in the case of high responders and unnecessary subsequent interventions for low responders.

AFC, AMH and FSH all reached the specified threshold for prediction of ovarian response to ovarian stimulation (set as ROC-AUC of 0.8 or more based on criteria outlined by Hosmer and Lemeshow).

The GDG considered the evidence was robust enough to define cut-offs for high and low response for AMH, AFC and FSH. The GDG set this cut-off where a test was at least moderately useful in predicting outcome. The reason for this was to ensure the safest management strategy was used. The evidence also showed that ovarian volume, ovarian blood flow, Inhibin B and E2 should not be used alone to determine ovarian response. It was noted that the identification of a low ovarian response was often used in clinical practice as a reason for not proceeding to IVF in individual cases. The GDG discussed the wider use of ovarian reserve testing as a criterion for accessing IVF.

The main area of discussion was the use of age. The available evidence showed that age had an AUC-ROC value of 0.55 for live birth, 0.59 for high response and 0.73 for low response, none of which meet the Hosmer and Lemeshow criteria. Yet age is the most commonly used initial predictor of ovarian reserve in practice (see Figures 5.1 and 6.1). The GDG members highlighted that, in their clinical experience, age was a useful initial test for determining ovarian response which was then complemented by other tests which allowed a more individualised estimate of ovarian reserve for each woman. However, they agreed that the accuracy of age as a test in the studies identified was not as good as AMH, AFC or FSH.

The GDG also stated that all those involved in the field of reproductive medicine were aware of the significant relationship between female age and the chance of live birth, whether by natural or assisted conception (see Figures 5.1 and 6.1). This is due to increasing age being associated with

both a reduction in ovarian reserve and an increased rate of oocyte, and therefore embryo, chromosomal abnormality (aneuploidy), which leads to lower implantation and higher miscarriage rates. The impact of advancing age on success of IVF is well documented in reports based on a number of large databases, including the HFEA database (see Figure 6.1).

However, female age in isolation did not meet the specified threshold for ROC-AUC in the available studies. The GDG felt that the well accepted strong relationship may not have been demonstrated in the included studies due to a combination of small sample sizes, restrictive (unreported pre-selection) age criteria, and the relatively few numbers of cycles studied in women aged over 40 years.

In the light of the identification of these *serious* limitations in the studies included in the review undertaken for this question and the well established relationship between maternal age as a predictor of pregnancy success, the GDG recommended that age should be used as an initial predictor of the likely success of pregnancy both for natural or assisted conception. Furthermore, women should be shown illustrations of the chance of conception according to age using Figures 5.1 and 6.1. They were of the opinion that AFC, AMH or FSH could then be used as a secondary test in an individual woman to more accurately reflect her chances of successful conception.

Consideration of health benefits and resource uses

The GDG noted that an AMH test is more expensive than an FSH test (with an FSH test costing £28–£50 and an AMH test £45–£100) but that the AMH test has significantly less inter- and intra-menstrual cycle variability compared with FSH testing. Also, AMH can be measured at any point of the menstrual cycle unlike FSH, which is only interpretable when measured during the first few days of the cycle ('baseline'). Furthermore, particularly during the earlier stages of decreased ovarian reserve, there are often wide fluctuations in FSH levels from cycle to cycle, but this fluctuation is not seen with AMH. However, there are issues with AMH including the lack of international assay standardisation. This may limit the application of data from studies performed using one assay in the past to assays currently used.

The AFC is measured using trans-vaginal ultrasound (TVS). It is standard practice within fertility clinics for patients to undergo baseline TVS assessment of the pelvis during work-up to exclude pathologies such as uterine fibroids or ovarian cysts. Many clinics will routinely perform an AFC as part of this work-up. If not, then performance of an AFC will add an estimated 2-5 minutes to the scan time: any additional cost is minimal as no extra equipment is needed, just additional time. If undertaking an AFC requires a separate or repeat TVS then the costs increase to £53 or £69, depending on whether the scan takes less or more than 20 minutes respectively. Studies generally perform the AFC during the early follicular phase: however, there are no good data to suggest that any AFC variation during the menstrual cycle affects test outcome. Inter-observer variability has been documented in studies, though this also does not appear to affect the predictive power of the test. Appropriate training and undertaking of the AFC in a standardised manner would be expected to minimise variability (Broekmans et al., 2010).

Quality of evidence

Evidence was of moderate to very low quality. There were a number of issues which influenced the quality including:

- The numbers of women in the studies are relatively small with wide confidence intervals, and this can lead to spurious results.
- The GDG attempted to overcome any inclusion/selection bias in the studies (by excluding studies where this had clearly occurred), but there was still the possibility that there was unreported bias in the patients included in some studies.
- There was heterogeneity in terms of the definitions of low or high response used by studies.
- There were differences in the underlying prevalence of conditions likely to cause high or low response, such as polycystic ovary syndrome (PCOS).

The GDG specifically suspected that there was selection bias operating in the form of age thresholds. This was of particular concern as the numbers of women at the extremes of age were limited, and the reported predictive accuracy of age was relatively poor. This was especially true of the women aged

over 40 years, who would be at an increased risk of low ovarian reserve. That group would be at increased risk of low ovarian reserve and theoretically likely to benefit most from testing and targeted treatment. In addition, most patients entering IVF treatment programmes (and therefore included in the studies described) have already had a degree of ovarian reserve testing (for example using FSH). Women with very high levels of FSH are unlikely to either be offered or to accept IVF treatment, which will bias the study results and interpretability. These problems are likely, in part, to explain the limitations of the tests in predicting pregnancy and live birth.

Other considerations

Outcome problem

An issue with using estimates of ovarian reserve to predict ovarian response, and potentially to restrict treatment, is that women with a poor response to IVF stimulation may still produce suitable embryos for transfer and achieve successful conception. Also, none of the tests were predictive of live birth, let alone live full-term singleton birth, which is the main outcome of interest.

Evidence problem

The GDG stated that all those involved in the field of reproductive medicine are aware of the significant relationship between female age and the chance of live birth, whether by natural or assisted conception. This is due to increasing age being associated with both reducing ovarian reserve and the increased risk of oocyte chromosomal abnormalities. The impact of advancing age on success of IVF is well documented in reports based on a number of large databases.

However, female age in isolation did not meet the specified threshold for ROC-AUC in the available studies. The well accepted strong relationship may not have been demonstrated in the included studies, due to a combination of small sample sizes, restrictive (unreported pre-selection) age criteria, as discussed above, and the relatively few numbers of cycles studied in women aged over 40 years.

Selection of tests

Threshold data were examined for AFC, AMH and FSH tests. Threshold data were not examined for the CCCT due to the poor quality of studies and because the test is not widely used in the UK.

Age in combination with AFC and/or FSH could be used to predict low response to IVF, though in the studies reviewed the addition of age appeared to reduce the predictive accuracy of the other tests. Similarly, AFC and FSH in combination could be used to predict low response to IVF. However, while these test combinations reached the ROC-AUC threshold, as AFC and FSH individually predict low and high response, and the combinations did not have any better predictive accuracy criteria, the GDG felt there was no merit in recommending them in combination.

The GDG did not wish to rank the three recommended tests (AFC, AMH and FSH) and felt the choice should be based on local provision, such as laboratory resources and availability of a skilled ultrasonographer.

There was no evidence to support the use of CCCT, Inhibin B or Oestradiol as individual tests to predict IVF outcome.

It is unknown if any of these tests are predictive of future fertility in women who are not considering IVF as this topic was not in the scope of this guideline and thus studies in those populations were not reviewed.

Use of tests

All the tests outlined in this section require specialist equipment and knowledge to be used. The GDG highlighted that variation in equipment and assays used meant that results could vary from those quoted in the recommendation, and that manufacturers' own cut-offs should be used. The GDG stated it was important that anyone involved in using these tests had suitable knowledge to correctly order and interpret the results.

Equalities

The people considered in this review were:

- people who have vaginal sexual intercourse
- specific patient subgroups listed in the guideline Scope who may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychological problem
    - people with conditions or disabilities that require specific consideration in relation to methods of conception
- people who are preparing for cancer treatment who may wish to preserve their fertility.

Apart from the very relevant issue of age, which was considered at length by the GDG (see above), there were no other specific issues that needed to be addressed with respect to any of these subgroups as the tests woud be the same for everyone.

Recommendations

Number	Recommendation
49	Use a woman's age as an initial predictor of her overall chance of success through natural conception (figure 5.1) or with in vitro fertilisation (IVF) (figure 6.1). **[new 2013]**
50	Use one of the following measures to predict the likely ovarian response to gonadotrophin stimulation in IVF: • total antral follicle count of less than or equal to 4 for a low response[*] and greater than 16 for a high response[†] • anti-Müllerian hormone of less than or equal to 5.4 pmol/l for a low response[‡] and greater than or equal to 25.0 pmol/l for a high response[§] • follicle-stimulating hormone greater than 8.9 IU/l for a low response and less than 4 IU/l for a high response[**]. **[new 2013]**
51	Do not use any of the following tests individually to predict any outcome of fertility treatment: • ovarian volume • ovarian blood flow • inhibin B • oestradiol (E2). **[new 2013]**

2013 Update

[*] Follicle of ≤5 mm measured by TVS on day 3 of cycle: low response was <4 oocytes.
[†] Follicles of 2–10 mm measured by TVS on day 3 of cycle: high response was ≥15 oocytes or ≥20 oocytes.
[‡] Beckman Coulter assay: poor response defined as <4 oocytes or cancellation.
[§] Beckman Coulter or DSL assays: defined high response as ≥15 oocytes to >21 oocytes.
[**] Long protocol of down-regulation: low response defined as <4 oocytes or cancellation; high response defined as >20 oocytes.

Number	Research recommendation
RR 3	Larger well-designed studies are needed to further define test thresholds for prediction of all outcomes, especially live birth
RR 4	What is the value of these tests in the prediction of spontaneous pregnancy in the general population?

Regularity of menstrual cycles

Regular menstrual cycles in the range 26 to 36 days are usually indicative of ovulation.[306] A review of patient-monitored basal body temperature charts showed that they were not sufficiently reliable for detection of ovulation (see Section 5.3).[34–39] Ovulation involves leutinisation of the mature follicle and release of the oocyte. Both are triggered by the LH surge. In practice, testing for release of the oocyte by observing follicle rupture is impractical so ovulation detection is based on the detection of circulating progesterone produced following lutinisation of the follicle. Urinary LH kits used by couples can suggest when ovulation is imminent. Ovulation can be confirmed retrospectively by measurement of serum progesterone in midluteal phase, approximately on day 21 of a 28-day cycle. For women with irregular cycles, this test may need to be performed later in the cycle (e.g. day 28 of a 35-day cycle) and repeated weekly until the next menstrual cycle starts, unless the bleeds are so infrequent that ovulation induction therapy will be needed in any case. Values range from 16 to 28 nmol/l as the lowest limit indicative of ovulation.[211,307–309] [Evidence level 2b]

Anovulation and oligo-ovulation are ovulatory disorders that are estimated to cause 21% of female infertility.[1] The WHO classifies ovulation disorders into three groups (see Table 6.3).[207]

Table 6.7 WHO Classification of ovulation disorders

Term	Definition
Group 1 Hypothalamic pituitary failure (hypothalamic amenorrhoea or hypogonadotrophic hypogonadism)	This group of disorders is characterised by low gonadotrophins, normal prolactin and low oestrogen, and it accounts for about 10% of ovulatory disorders. Failed ovarian follicular development results in hypo-oestrogenic amenorrhoea in this group of disorders. (see Chapter 8 further discussion of the management of these disorders)
Group 2 Hypothalamic pituitary dysfunction	This group, which is characterised by gonadotrophin disorder and normal oestrogen, accounts for about 85% of ovulatory disorders. This group of disorders results in anovulatory oligo/amenorrhea, predominately involving women with polycystic ovaries. Polycystic ovaries are present in about 80–90% of women with oligomenorrhoea and 30% of women with amenorrhoea.310 In women who have polycystic ovaries, where there are associated clinical symptoms (such as menstrual cycle disturbances, obesity and hyperandrogenism presenting as hirsutism, acne or androgen-dependent alopecia), this is referred to as PCOS. About 30% of the PCOS population is of normal weight.[311] Over many years, the diagnostic criteria for polycystic ovaries and PCOS have been evolving and different researchers have used differing definitions. An international consensus definition of PCOS, which includes a new definition of the polycystic ovary, provides the possibility that future research will be based on a consistent definition. The new definition for the diagnosis of a polycystic ovary (which is usually obtained from an ultrasound scan) requires the presence of at least 12 follicles measuring 2–9 mm in diameter and/or an ovarian volume in excess of 10 cm3.[312–314] [Evidence level 3–4] The new definition for the diagnosis of PCOS requires the presence at least two

Term	Definition
	of the following three criteria:[312,313] [Evidence level 3–4] • oligo- and/or anovulation • clinical and/or biochemical hyperandrogenism • polycystic ovaries, with the exclusion of other aetiologies. (See Chapter 8 for further discussion of the management of these disorders)
Group 3 Ovarian failure	This group, which is characterised by high gonadotrophins with hypogonadism and low oestrogen, accounts for about 4–5% of ovulatory disorders

Recommendations

Number	Recommendation
52	Women who are concerned about their fertility should be asked about the frequency and regularity of their menstrual cycles. Women with regular monthly menstrual cycles should be informed that they are likely to be ovulating. **[2004]**
53	Women who are undergoing investigations for infertility should be offered a blood test to measure serum progesterone in the mid-luteal phase of their cycle (day 21 of a 28-day cycle) to confirm ovulation even if they have regular menstrual cycles. **[2004, amended 2013]**
54	Women with prolonged irregular menstrual cycles should be offered a blood test to measure serum progesterone. Depending upon the timing of menstrual periods, this test may need to be conducted later in the cycle (for example day 28 of a 35-day cycle) and repeated weekly thereafter until the next menstrual cycle starts. **[2004]**
55	The use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and is not recommended. **[2004]**
56	Women with irregular menstrual cycles should be offered a blood test to measure serum gonadotrophins (follicle-stimulating hormone and luteinising hormone). **[2004]**

Prolactin measurement

Hyperprolactinaemia is an endocrine disorder caused by an increased secretion of prolactin from the pituitary gland, resulting in galactorrhoea, irregular menstruation and possible infertility. The incidence of raised prolactin in infertile but ovulatory women ranges from 3.8% to 11.5%.[315–317] [Evidence level 3] There is no significant association between prolactin, progesterone levels and cumulative conception rates in ovulatory women.[318,319] [Evidence level 3] Estimation of prolactin levels should be reserved for women with symptoms of an ovulatory disorder, galactorrhoea or a pituitary tumour.

It has recently been proposed that hyperprolactinaemia attributable to macroprolactin, rather than prolactin, may be associated with fertility problems.[320–322] [Evidence level 3] However, further research is needed to determine whether women with raised serum prolactin should have macroprolactin excluded

Recommendations

Number	Recommendation
57	Women who are concerned about their fertility should not be offered a blood test to measure prolactin. This test should only be offered to women who have an ovulatory disorder, galactorrhoea or a pituitary tumour. **[2004]**

Number	Research recommendation
RR 5	Further research is needed to determine whether women with raised serum prolactin should have macroprolactin excluded.

Thyroid function tests

Thyroid dysfunction can lead to menstrual and ovulatory disorder associated with infertility.[343,344] It has been common practice to screen women with infertility for thyroid dysfunction using thyroid function tests, whether or not symptoms of thyroid disease are present.

Asymptomatic hypothyroidism occurs in up to 7% of the general population.[345] Abnormal thyroid function test measurements have been reported in 1.3–5.1% of infertile women.[316,346–349] [Evidence level 3] It has been estimated that subclinical hypothyroidism occurs in 0.88–11.3% of women with ovulation disorders.[347,348] [Evidence level 3]

Recommendations

Number	Recommendation
58	Women with possible fertility problems are no more likely than the general population to have thyroid disease and the routine measurement of thyroid function should not be offered. Estimation of thyroid function should be confined to women with symptoms of thyroid disease. **[2004]**

Endometrial biopsy

Luteal-phase defect has been defined as either a defect of progesterone secretion by the corpus luteum or a defect in endometrial response to hormonal stimulation, resulting in an inadequate endometrium for blastocyst implantation and subsequent pregnancy.[350] The defect is estimated to affect 3–20% of the infertile population and 23–60% of women with recurrent miscarriage.[351] [Evidence level 3]

There is no consensus of opinion about the diagnosis or effective treatment of luteal-phase defect, and its role as a cause of infertility has been questioned.[352,353] The benefit of treatment for luteal-phase defect on pregnancy rates has not been established.[354,355] [Evidence level 1b–3]

Traditionally, luteal-phase defect is diagnosed by a timed endometrial biopsy based on a standard set of criteria,[356] repeated on at least two occasions. [Evidence level 2b] It has been suggested that diagnosis of luteal-phase defect based on histological dating of endometrial biopsy could be a chance event.[355]

Recommendations

Number	Recommendation
59	Women should not be offered an endometrial biopsy to evaluate the luteal phase as part of the investigation of fertility problems because there is no evidence that medical treatment of luteal phase defect improves pregnancy rates. **[2004]**

6.4 Investigation of suspected tubal and uterine abnormalities

Assessing tubal damage

It is estimated that tubal factors account for 14% of the causes of subfertility in women.1 Tubal blockage involves the proximal part (which is closest to the uterus), the mid part or the distal part (which is furthest from the uterus). Proximal (uterotubal) obstruction occurs in 10–25% of women with tubal disease.[370] The results of semen analysis and assessment of ovulation should be known before a test for tubal patency is performed.

Tubal disease includes tubal obstruction and pelvic adhesions due to infection, endometriosis and previous surgery. Endometriosis accounts for about 5% of female infertility.[1] It is defined as the presence of endometrial tissue occurring outside the uterine cavity which causes peritoneal lesions, adhesions and ovarian cysts and is associated with pelvic pain, dysmenorrhoea and infertility.

The diagnosis and severity of endometriosis are established by laparoscopy and biopsy using the revised American Fertility Society system,[371] which classifies the severity of endometriosis into four stages: stage I (minimal), stage II (mild), stage III (moderate); and stage IV (severe).This classification system is widely used and includes visual assessment, which is subject to inter- and intra-observer error. However, disease severity has not been shown to predict the chance of pregnancy.[372,373]

An ideal (or 'gold standard') test for tubal disease would correctly identify all women with tubal disease. It would be a sensitive test (i.e. all true positives would be identified by a positive test result and a negative test result would rule out disease in all those without disease) and it would also be specific (i.e. the test result would be positive only in women with the disease).

Hysterosalpingography compared with laparoscopy and dye

HSG and laparoscopy with dye are the two most widely used methods to test for tubal pathology. HSG and laparoscopy are both invasive procedures but HSG is less so. Among women whose tubes were found to be patent (unobstructed) using HSG, 18% were found to have tubal obstruction or peritubal adhesions using laparoscopy and a further 34% were found to have endometriosis and/or fibroids.[374] However, the detection and treatment of pathology missed by HSG did not increase live birth rates.[374] [Evidence level 2b]

The diagnostic accuracy of HSG has been compared with that of laparoscopy and dye in a systematic review of 20 studies that distinguished between tubal obstruction and peritubal adhesions.[375] However, only three studies involved judgement of laparoscopy without knowledge of HSG results. Meta-analysis based on these three studies gave pooled estimates of sensitivity and specificity for HSG as a test for tubal obstruction of 0.65 (95% CI 0.50 to 0.78) and 0.83 (95% CI 0.77 to 0.88), respectively.375 [Evidence level 2b] It is estimated that tubal damage accounts for 14% of fertility problems,1 which suggests that when HSG suggests the presence of tubal obstruction this will be confirmed by laparoscopy in only 38% of women. Thus, HSG is a not a reliable indicator of tubal occlusion. However, when HSG suggests that the tubes are patent, this will be confirmed at laparoscopy in 94% of women, and so HSG is a reliable indicator of tubal patency.

Results from another review[306] suggest that HSG could be used as a screening test for couples with no history of pelvic infection, and if abnormal, confirmatory laparoscopy would follow.[376] [Evidence level 2b] Considerable interobserver variability in interpretation of HSGs has been reported,

depending on the type of pathology being assessed.[377,378] Women with possible comorbidity such as pelvic and tubal diseases may need a laparoscopic assessment.

The choice of laparoscopy as a gold standard in the diagnosis of tubal pathology has been questioned in a cohort study that formed part of the Canadian Infertility Treatment Evaluation Study.[379] [Evidence level 3] This study compared the prognostic significance of HSG and laparoscopy using adjusted fecundity rate ratios, which express the probability of spontaneous pregnancy per unit time for women with a particular feature, relative to those without that feature. One-sided occlusion detected using HSG was found to decrease spontaneous pregnancy rates slightly compared with the absence of tubal occlusion at HSG (fecundity rate ratio 0.80) and two-sided occlusion at HSG decreased spontaneous pregnancy rates further (fecundity rate ratio 0.49).[379] [Evidence level 3] However, occlusion detected using laparoscopy was associated with even lower spontaneous pregnancy rates (fecundity rate ratio 0.51 for one-sided occlusion and 0.15 for two-sided occlusion).[379] [Evidence level 3] Thus, tubal pathology detected at laparoscopy has a stronger effect on future fertility than that detected at HSG.

A meta-analysis of 23 test evaluation studies found that the discriminative capacity of chlamydial antibody testing, using enzyme-linked immunosorbent assay (ELISA), immunofluorescence or microimmunofluorescence is comparable to that of HSG in the diagnosis of tubal pathology.[380] [Evidence level 2b] Elevated titres of chlamydial antibodies in women were significantly associated with tubal disease.[381] The titre of chlamydial antibodies has also been reported to be more accurate in predicting severe tubal pathology than unspecified tuboperitoneal abnormalities.[382] However, it has been reported that the negative predictive value for pelvic pathology from the use of clinical features in addition to the chlamydial antibody titre is not significantly higher than that from the chlamydial antibody titre alone at 53%; this may not justify the avoidance of a diagnostic and confirmatory laparoscopy.[383] [Evidence level 3]

A cohort study found that chlamydial antibody levels are quantitatively related to severity and extent of tubal pelvic damage. An elevated chlamydial antibody titre result is significantly associated with poor live birth rates, but not pregnancy rates.[384] [Evidence level 2b] However, the chance of conception with or without tubal surgery is related to the degree of damage found at laparoscopy, with the chlamydial antibody titre adding no further diagnostic value.[385] [Evidence level 2b]

Hysterosalpingo-contrast-sonography compared with laparoscopy and dye or hysterosalpingography

Evaluative studies of hysterosalpingo-contrast-sonogaphy (HyCoSy) showed good statistical comparability and concordance with HSG and laparoscopy combined with dye.[386] [Evidence level 1b] HyCoSy is well-tolerated and can be a suitable alternative outpatient procedure.[387] [Evidence level 1b] HyCoSy using contrast agent Infoson® appears to be more efficient than saline solution in detecting tubal obstruction.[388] [Evidence level 1b]

Fertiloscopy and falloposcopy

Fertiloscopy is a relatively new procedure, defined as the combination in one investigation of transvaginal hydropelviscopy, dye test, optional salpingoscopy and hysteroscopy performed under local anaesthesia or neuroleptanalgesia.[389] Diagnostic fertiloscopy has also been used to identify tubal pathology as an alternative to laparoscopy.[389] [Evidence level 3] However, the procedure is not without risk, and bowel[390] and rectal injuries[389] following fertiloscopy have been reported. [Evidence level 3] The diagnostic accuracy of fertiloscopy in comparison to HSG and laparoscopy needs further evaluation.

Falloposcopy is defined as transvaginal microendoscopy of the fallopian tubes and direct visualisation of the entire fallopian tube lumen.[391] It has been suggested that it may be a more discriminatory test of tubal pathology because women with normal fallopian tubes at falloposcopy achieve higher spontaneous pregnancy rates (27.6%) than those with mild or severe endotubal lesions (11.5% to 0%).[392] In another study, the management plan was changed in 90% of women following falloposcopy and 24% conceived naturally.[393] [Evidence level 3] However, further diagnostic evaluation studies are required, and technical problems with falloposcopy limit the use of the procedure in routine clinical practice.[394,395]

Tubal flushing

The potential therapeutic effect of diagnostic tubal patency testing has been debated for over 40 years. Tubal flushing might involve water- or oil-soluble media. Current practice usually involves water-soluble media when tubal flushing is performed at laparoscopy. A systematic review of eight RCTs showed a significant increase in pregnancy rates with tubal flushing using oil-soluble contrast media when compared with no treatment (OR 3.57, 95% CI 1.76 to 7.23). Tubal flushing with oil-soluble contrast media was associated with an increase in the odds of live birth (OR 1.49, 95% CI 1.05 to 2.11), but not pregnancy rates (OR 1.23, 95% CI 0.95 to 1.60) when compared with tubal flushing with water-soluble media.[396] [Evidence level 1a] There were no significant differences in miscarriage, ectopic pregnancy and infection rates between tubal flushing with oil or water, or between oil plus water media versus water media only.[396] [Evidence level 1a] There were no trials assessing tubal flushing with water-soluble media versus no treatment.

The potential consequences of extravasations of oil-soluble contrast media into the pelvic cavity and fallopian tubes may be associated with anaphylaxis and lipogranuloma.

Recommendations

Number	Recommendation
60	Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography (HSG) to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion, and it is less invasive and makes more efficient use of resources than laparoscopy. **[2004]**
61	Where appropriate expertise is available, screening for tubal occlusion using hysterosalpingo-contrast-ultrasonography should be considered because it is an effective alternative to hysterosalpingography for women who are not known to have comorbidities. **[2004]**
62	Women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pelvic pathology can be assessed at the same time. **[2004]**

Number	Research recommendation
RR 6	Further research is needed to ascertain the value of fertiloscopy and falloposcopy in the investigation of couples who experience problems with fertility.
RR 7	Further randomised controlled trials are needed to evaluate the potentially therapeutic effects of tubal flushing with water-soluble media.

Assessing uterine abnormalities

Uterine abnormalities such as adhesions, polyps, submucous leiomyomas and septae have been found in 10% to 15% of women seeking treatment for fertility problems.398 Compared with HSG, hysteroscopy is recognised as the ‘gold standard’ test for identifying uterine abnormalities as it allows direct visualisation of the uterine cavity.[399] [Evidence level 2b]

Opinions differ as to whether hysteroscopy should be considered as a routine investigation in addition to HSG and laparoscopy and dye in the infertile couple. A causal relationship between leiomyoma and infertility has not been established.[400] [Evidence level 2b] In women undergoing assisted reproduction, the presence of uterine leiomyoma is associated with a reduced chance of clinical pregnancy or

delivery.[401,402] [Evidence level 2b–3] However, the effectiveness of surgical treatment of uterine abnormalities to enhance pregnancy rates is not established.

Ultrasound of the pelvis

Compared with bimanual pelvic examination, transvaginal ultrasound enables pelvic anatomy to be identified with more accuracy and reliability. Ultrasound can be used in the evaluation of pelvic pathology, such as endometriosis, endometrioma, cysts, polyp, leiomyoma, adnexal and ovarian abnormality, where such abnormalities are present.[403–405] [Evidence level 2b–3]

The diagnostic criteria for polycystic ovaries and PCOS, in which ultrasonic parameters have an important role, have been evolving over many years, and have recently been clarified in an international consensus statement (see Section 8.3).

Recommendations

Number	Recommendation
63	Women should not be offered hysteroscopy on its own as part of the initial investigation unless clinically indicated because the effectiveness of surgical treatment of uterine abnormalities on improving pregnancy rates has not been established. **[2004]**

Number	Research recommendation
RR 8	The role of pelvic ultrasound in women who are not suspected to have pelvic pathology requires further evaluation.

6.5 Additional investigations for viral infection and cancer

Testing for viral status

A case series study showed that among patients seeking infertility treatment at an IVF clinic, 0.06% were seropositive for HIV, 0.5% were seropostive for the hepatitis B virus and 0.54% were seropositive for the hepatitis C virus.[819] A cross-sectional study with 409 patients (248 women and 161 men) attending an infertility clinic reported a prevalence of anti-hepatitis C virus positivity of 3.2 % among women and 3.7% among men.[820] Hepatitis C virus was detected in 5% of semen samples from men (N = 39) entering an IVF programme. Consideration needs to be given to the risk of hepatitis C virus transmission not only to the mother and child, but also through laboratory contamination of other non-infected couples' gametes and of technicians, and even through storage and manipulation of cryopreserved semen.[821] [Evidence level 3]

Screening for C. trachomatis infection before uterine instrumentation is discussed below.

In the 2004 guideline recommendations 64 and 65 appeared as a single recommendation. They have been split into two recommendations in the updated guideline to improve terminology and clarity.

Recommendations

Number	Recommendation
64	People undergoing IVF treatment should be offered testing for HIV, hepatitis B and hepatitis C (for donor insemination see recommendation 185). **[2004, amended 2013]**
65	People found to test positive for one or more of HIV, hepatitis B, or hepatitis C should be offered specialist advice and counselling and appropriate clinical management. **[2004, amended 2013]**

Viral transmission

An important area of work for fertility specialists has been assisting couples where one has a sexually transmissable viral infection, such as HIV, to become pregnant while minimising the risk of viral transfer using assisted reproduction treatments.

The approach chosen to minimise the risk of transmission varies depending on the virus. For hepatitis B (HBV), transmission rates are minimised by the use of pre-exposure vaccination. Hepatitis C (HCV) has a low transfer rate via sexual intercourse, but sperm washing is has been used to reduce this risk of transmission. For HIV the standard approach for female to male transmission is use of assisted reproductive techniques (ART), such as IUI or IVF. For male to female transmission the standard approach has been sperm washing. Sperm washing is used to reduce the viral load in prepared sperm to a very low or undetectable level. The washed sperm preparation can then be transferred to the women using IUI or used to fertilise eggs in IVF or ICSI. However, alternatives to sperm washing are now being proposed.

Advances in antiretroviral therapy for the management of HIV positive serodiscordant couples (where one partner has the virus) may offer an alternative which is equally effective, less invasive and more cost effective for a specific cohort of these patients.

This alternative will not suit all patients and is clearly of no clinical benefit in situations where any form of female infertility is diagnosed or suspected. However, alongside existing sperm washing procedures, the practice of timed intercourse in a suitable sub-population does increase the treatment options available to the virologist and clinician involved in the couple's care.

Because sperm washing as a possible treatment in the case of the male partner being HIV positive was not reviewed in the 2004 version of this guideline, it was included as a topic in the Scope for the guideline update. The circumstance where the female partner is HIV positive was not included as a topic in the Scope.

This review examines the evidence for each of these options.

Review question

What is the effectiveness and safety of sperm washing to reduce the risk of viral transmission?

The original purpose of this review was to investigate the effectiveness and safety of sperm washing. However, the review question was further broadened in the context of HIV. This resulted in three additional sub-questions:

- What is the risk of transmission by vaginal intercourse when HIV positive male partners are on treatment?
- What is the risk of transmission by vaginal intercourse when HIV positive male partners have a low viral load?
- What is the risk of transmission by vaginal intercourse when HIV negative women use pre-exposure anti-retroviral prophylaxis?

Description of included studies

Sperm washing

Twelve cohort studies were identified for this review question (Bujan et al., 2007a; Bujan et al., 2007b; Garrido et al., 2004; Kashima et al., 2009; Marina et al., 1998; Mencaglia et al., 2005; Nicopoullos et al., 2010; Sauer et al., 2009; Savasi et al., 2007; Schuffner et al., 2011 ; Semprini et al., 1992; Wu et al., 2011).

All 12 studies investigated sperm washing for men with HIV. Three studies (Nicopoullos et al., 2010; Sauer et al., 2007; Savasi et al., 2007) reported comorbidities of hepatitis B and hepatitis C in male partners. Another study (Garrido et al., 2004) included men who had hepatitis C without HIV, but seroconversions and pregnancy outcomes were not reported separately for the group with hepatitis C alone. There were no studies that reported on the use of washed sperm from men with hepatitis B alone.

Safety

Seven studies reported that post-wash testing for HIV took place (Garrido., et al., 2004; Kashima et al., 2009; Marina et al., 1998; Nicopoullos et al., 2010; Savasi et al., 2007; Semprini et al., 1992; Wu et al., 2011). One study also tested for hepatitis C after sperm washing (Garrido et al., 2004). (See Table 6.8.)

All 12 studies reported on HIV seroconversions in mothers and/or children after using washed sperm in association with different methods of assisted conception. (see Table 6.9). Three of these studies compared HIV seroconversions in mothers and/or children between the different methods of assisted conception. (See Table 6.10.)

Effectiveness

All but one of the studies (Mencaglia et al., 2005) reported on the efficacy of sperm washing in terms of pregnancy outcomes.

Three studies compared washed sperm from HIV positive males with non-washed sperm from control groups (Bujan et al., 2007a; Kashima et al., 2009; Wu et al., 2011). (See Table 6.11)

One study compared washed sperm from HIV positive males in different ART groups (Nicopoullos et al., 2010). (See Table 6.12)

Non-comparative effectiveness data was available from nine studies (Bujan., et al 2007b; Garrido., et al., 2004; Marina et al., 1998; Nicopoullos., et al., 2010; Sauer.,et al., 2007; Savasi.,et al., 2007; Semprini et al., 1992; Schuffner et al., 2011 ; Wu et al., 2011). (See Table 6.13)

Variation in HIV transmission rates with HAART and viral load

Two cohort studies (Castilla et al., 2005; Melo et al., 2008) reported data on seroconversion rates in partners of HIV-positive men who used HAART compared with those not using HAART (see Table 6.14). One randomised controlled trial (Cohen et al., 2011) compared seroconversion rates in HIV serodiscordant couples who received an ‘early therapy’ with those who received a ‘delayed therapy’. An additional cohort study (Quinn et al., 2000) reported data on plasma viral loads of HIV-positive men who were not taking HAART (‘HAART-naive’) and the incidence of seroconversion in their partners.

Pre-exposure prophylaxis to prevent HIV transmission

Two studies were identified (see Table 6.15). One randomised controlled trial (Peterson et al., 2007) compared seroconversion rates in women using pre-exposure prophylaxis with rates in those using placebo. One case series (Vernazza et al., 2011) reported seroconversion rates in couples where the HIV-positive male partner was ‘fully suppressed’ taking HIV therapy and the female negative partner was using pre-exposure prophylaxis.

Evidence profiles

The evidence profiles can be found within the following GRADE tables:

- The evidence on sperm washing is presented in the first six GRADE tables (see Tables 6.8 to 6.13).

- The evidence on HIV treatment and viral load is presented in one summary table (Table 6.14) There is further evidence on seroconversion within a population that is not receiving highly active antiretroviral therapy (HAART) presented in the evidence statement for this profile.
- The evidence on pre-exposure prophylaxis is presented in one summary table (Table 6.15).

Table 6.8 Post-wash testing for presence of virus: summary of included studies

Study	Post-wash testing performed	Positive post wash testing results			Kit failures
		HIV	HCV	HBV	
(Bujan et al., 2007a)	Not reported	-	-	-	-
(Bujan et al., 2007b)	Not reported	-	-	-	-
(Garrido et al., 2004)	Yes	8 (20%)	10 (18%)	-	Not reported
(Kashima et al., 2009)	Yes	Not reported	-	-	Not reported
(Marina et al., 1998)	Yes	6 (101 cycles, but total number of tests conducted not reported)	Not tested	-	Not reported
(Mencaglia et al., 2005)	Not reported	-	-	-	-
(Nicopoullos et al., 2010)	Yes	10 (439 cycles, but total number of tests conducted not reported)	Not tested	-	1 (439 cycles, but total number of tests conducted not reported)
(Sauer et al., 2009)	Not reported	-	-	-	-
(Savasi et al., 2007)	Yes	4% (2400 cycles, but total number of tests conducted not reported)	Not tested	-	2% (2400 cycles, but total number of tests conducted not reported)
(Schuffner et al., 2011)	Not reported	-	-	-	-
(Semprini et al., 1992)	Yes	Not reported	-	-	Not reported
(Wu et al., 2011)	Yes	Not reported	-	-	Not reported

HBV hepatitis B virus, HCV hepatitis C virus, HIV human immunodeficiency virus

Table 6.9 GRADE findings of non-comparative seroconversion data resulting from sperm washing used in association with different ART methods

Number of studies	Number of people		Effect		Quality
	Sero-con-version	Comparator	Relative (95% CI)	Absolute (95% CI)	
Seroconversion rate in mothers					
IUI with washed sperm from HIV positive males					
(Savasi et al., 2007)	0/2400 (0%)	-	-	-	Very low
(Marina et al., 1998)	0/101 (0%)	-	-	-	Very low
(Bujan et al., 2007b)	0/2840 (0%)	-	-	-	Very low
(Bujan et al., 2007a)	0/294 (0%)	-	-	-	Very low
(Schuffner et al., 2011)	0/10 (0%)	-	-	-	Very low
Total	0/5645 (0%)				Very low
ICSI with washed sperm from HIV positive males					
(Savasi et al., 2007)	0/283 (0%)	-	-	-	Very low
Mencaglia (2005)	0/78 (0%)	-	-	-	low
(Kashima et al., 2009)	0/23 (0%)	-	-	-	Very Low
(Sauer et al., 2009)	0/420 (0%)	-	-	-	Very low
(Bujan et al., 2007b)	0/394 (0%)	-	-	-	Very low
(Wu et al., 2011)	0/14 (0%)	-	-	-	Very low
Total	0/1212 (0%)				Very low
ICSI with washed sperm from HIV or HCV positive males					
(Garrido et al., 2004)	0/113 (0%)	-	-	-	Very low
IVF with washed sperm from HIV positive males					
(Bujanet al., 2007b)	0/107 (0%)	-	-	-	Very low
(Kashima et al., 2009)	0/13 (0%)	-	-	-	Very low
Total	0/120 (0%)				Very low

Number of studies	Number of people		Effect		Quality
	Sero-con-version	Comparator	Relative (95% CI)	Absolute (95% CI)	
Seroconversion rate in children					
IUI with washed sperm from HIV positive males					
(Savasi et al., 2007)	0/2400 (0%)	-	-	-	Very low
(Marina et al., 1998)	0/101 (0%)	-	-	-	Very low
(Semprini et al., 1992)	0/59 (0%)	-	-	-	Very low
(Nicopoullos et al., 2010)	0/439 (0%)	-	-	-	Very low
(Schuffner et al., 2011)	0/10 (0%)	-	-	-	Very low
Total	0/3009 (0%)				Very low
ICSI with washed sperm from HIV positive males					
(Savasi et al., 2007)	0/283 (0%)	-	-	-	Very low
(Mencaglia et al., 2005)	0/78 (0%)	-	-	-	Low
(Kashima et al., 2009)	0/23 (0%)	-	-	-	Very low
(Sauer et al., 2009)	0/420 (0%)	-	-	-	Very low
(Nicopoullos et al., 2010)	0/117 (0%)	-	-	-	Very low
(Wu et al., 2011)	0/14 (0%)	-	-	-	Very low
Total	0/935 (0%)				Very low
IVF with washed sperm from HIV positive males					
(Nicopoullos et al., 2010)	0/114 (0%)	-	-	-	Very low
(Kashima et al., 2009)	0/13 (0%)	-	-	-	Very low
Total	0/117 (0%)				Very low

ART assisted reproduction technology, CI confidence interval, HBV hepatitis B virus, HCV hepatitis C virus, HIV human immunodeficiency virus, ICSI intracytoplasmic sperm injection, IUI intrauterine insemination, IVF in vitro fertilisation

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Table 6.10 GRADE findings of seroconversion data comparing different methods of ART

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Seroconversion rate in mothers					
IUI with washed sperm from HIV positive males compared with ICSI with washed sperm from HIV-positive males					
1 (Savasi et al., 2007)	0/2400 (0%)	0/283 (0%)	Not calculable	-	Very low
1 (Bujan et al., 2007b)	0/2840 (0%)	0/394 (0%)	Not calculable	-	Very low
IUI with washed sperm from HIV positive males compared with IVF with washed sperm from HIV positive males					
1 (Bujan et al., 2007b)	0/2840 (0%)	0/107 (0%)	Not calculable	-	Very low
IVF with washed sperm from HIV positive males compared with ICSI with washed sperm from HIV positive males					
1 (Bujan et al., 2007b)	0/107 (0%)	0/394 (0%)	Not calculable	-	Very low
Seroconversion rate in children					
IUI with washed sperm from HIV positive males compared with ICSI with washed sperm from HIV positive males					
1 (Savasi et al., 2007)	0/2400 (0%)	0/283 (0%)	Not calculable	-	Very low
1(Nicopoullos et al., 2010)	0/439 (0%)	0/117 (0%)	Not calculable	-	Very low
IUI with washed sperm from HIV positive males compared with IVF with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	0/439 (0%)	0/114 (0%)	Not calculable	-	Very low
IVF with washed sperm from HIV positive males compared with ICSI with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	0/114 (0%)	0/117(0%)	Not calculable	-	Very low

ART assisted reproduction technology, CI confidence interval, HIV human immunodeficiency virus, ICSI intracytoplasmic sperm injection, IUI intrauterine insemination, IVF in vitro fertilisation

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Table 6.11 GRADE findings for comparing the use of washed sperm from HIV- and/or HCV- positive males with unwashed sperm in control couples

Number of studies	Number of people		Effect		Quality
	Sperm washed	No sperm wash	Relative (95% CI)	Absolute (95% CI)	
Live full term singleton birth					
IVF with washed sperm from HIV positive males compared to IVF in control couples with sperm from HIV negative males					
1 (Kashmina et al., 2009)	8/13 (62%)	91/465 (20%)	6.6 (2.1 to 20.6)	526 more per 1000 (from 161 more to 878 more)	Very low
ICSI with washed sperm from HIV positive males compared to ICSI in control couples with sperm from HIV negative males					
1 (Kashmina et al., 2009)	9/23 (39%)	47/209 (22%)	2.2 (0.9 to 5.4)	194 more per 1000 (from 19 fewer to 500 more)	Very low
IUI with washed sperm from HIV positive males compared to IUI in control couples with sperm from HIV negative males					
1 (Bujan et al., 2007a)	44/294 (15%)	37/320 (12%)	1.3 (0.8 to 2.2)	35 more per 1000 (from 17 fewer to 109 more)	Very low
Pre-term birth (< 37 weeks)					
No evidence reported					
Multiple births					
IVF with washed sperm from HIV positive males compared to IVF in control couples with sperm from HIV negative males					
1 (Kashmina et al., 2009)	3/13 (23%)	15/465 (4%)	9.0 (2.2 to 36.1)	32 fewer per 1000 (from 32 fewer to 37 more)	Very low
ICSI with washed sperm from HIV positive males compared to ICSI in control couples with sperm from HIV negative males					
1 (Kashmina et al., 2009)	2/23 (9%)	6/209 (3%)	3.2 (0.6 to 17.0)	58 more per 1000 (from 11 fewer to 306 more)	Very low
IUI with washed sperm from HIV positive males compared to IUI in control couples with sperm from HIV negative males					
1 (Bujan et al., 2007a)	7/294 (2%)	7/320 (2%)	1.1 (0.4 to 3.1)	3 more per 1000 (from 21 fewer to 65 more)	Very low

Number of studies	Number of people		Effect		Quality
	Sperm washed	No sperm wash	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy					
ICSI with washed fresh sperm from HIV positive males compared to frozen semen and TESE/MESA from HIV negative males					
	ICSI with washed sperm	ICSI with frozen sperm	ICSI with TESE / MESA sperm		
1 (Wu et al., 2011)	5/14 (35.7%)	30/68 (44.1%)	20/36 (55.6%)	NS	NS	Very low
Congenital abnormalities					
No evidence reported					
Adverse pregnancy outcome (including miscarriages, ectopic pregnancies, intrauterine deaths)					
IUI with washed sperm from HIV positive males compared to IUI in control couples with sperm from HIV negative males					
1 (Bujan et al., 2007a)	9/294 (3%)	10/320 (3%)	1.0 (0.4 to 2.4)	1 fewer per 1000 (from 19 fewer to 42 more)	Very low

ART assisted reproduction technology, CI confidence interval, HIV human immunodeficiency virus, ICSI intracytoplasmic sperm injection, IUI intrauterine insemination, IVF in vitro fertilisation, MESA microsurgical epididymal sperm aspiration, NS not significant, TESE testicular sperm extraction

Table 6.12 GRADE findings for comparing the use of washed sperm from HIV -positive men using different ARTs

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full term singleton birth					
IUI with washed sperm from HIV positive males compared with ICSI with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	31/439 (7%)	17/117 (15%)	0.4 (0.2 to 0.8)	76 fewer per 1000 (from 21 fewer to 107 fewer)	Very low
IUI with washed sperm from HIV positive males compared with IVF with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	31/439 (7%)	21/114 (18%)	0.3 (0.2 to 0.6)	116 fewer per 1000 (from 65 fewer to 146 fewer)	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
IVF with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	21/114 (18%)	17/117 (15%)	1.3 (0.7 to 2.7)	41 more per 1000 (from 45 fewer to 181 more)	Very low
Pre-term birth (< 37 weeks)					
No evidence reported					
Multiple births					
IUI with washed sperm from HIV positive males compared with IVF with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	2/439 (1%)	7/114 (6%)	0.0 (0.0 to 0.1)	61 fewer per 1000 (from 55 fewer to 61 fewer)	Very low
IUI with washed sperm from HIV positive males compared with ICSI with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	2/439 (1%)	5/117 (4%)	0.1 (0.0 to 0.5)	38 fewer per 1000 (from 21 fewer to 43 fewer)	Very low
IVF with washed sperm from HIV positive males compared with ICSI with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	7/114 (6%)	5/117 (4%)	1.5 (0.5 to 4.8)	20 more per 1000 (from 21 fewer to 134 more)	Very low
Congenital abnormalities					
No evidence reported					
Adverse pregnancy outcome (including miscarriages, ectopic pregnancies, intrauterine deaths)					
IUI with washed sperm from HIV positive males compared with IVF with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	20/439 (5%)	14/114 (12%)	0.3 (0.2 to 0.7)	78 fewer per 1000 (from 34 fewer to 101 fewer)	Very low
IUI with washed sperm from HIV positive males compared with IVF with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	20/439 (5%)	14/114 (12%)	0.3 (0.2 to 0.7)	78 fewer per 1000 (from 34 fewer to 101 fewer)	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
IUI with washed sperm from HIV positive males compared with ICSI with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	20/439 (5%)	7/117 (6%)	0.8 (0.3 to 1.8)	14 fewer per 1000 (from 41 fewer to 45 more)	Very low
IVF with washed sperm from HIV-positive males compared with ICSI with washed sperm from HIV positive males					
1 (Nicopoullos et al., 2010)	14/114 (12%)	7/117 (6%)	2.2 (0.9 to 5.7)	65 more per 1000 (from 8 fewer to 212 more)	Very low

CI confidence interval, HIV human immunodeficiency virus, ICSI intracytoplasmic sperm injection, IUI intrauterine insemination, IVF in vitro fertilisation

Table 6.13 GRADE findings of non-comparative effectiveness data of outcomes for sperm washing in different ART groups

Number of studies	Number of people		Effect		Quality
	Sperm washed	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full term singleton birth					
IUI with washed sperm from HIV positive males					
(Savasi et al., 2007)	325/2400 (14%)	-	-	-	Very low
(Marina et al., 1998)	20/101 (20%)	-	-	-	Very low
(Semprin et al., 1992)	5/59 (8%)	-	-	-	Very low
(Nicopoullos et al., 2010)	31/439 (7%)	-	-	-	Very low
ICSI with washed sperm from HIV positive males					
(Sauer et al., 2009)	68/420 (16%)	-	-	-	Very low
(Nicopoullos et al., 2010)	17/117 (15%)	-	-	-	Very low
ICSI with washed sperm from HIV or HCV positive males					
(Garrido, 2004)	23/113 (20%)	-	-	-	Very low
IVF with washed sperm from HIV positive males					
(Nicopoullos et al., 2010)	21/114 (18%)	-	-	-	Very low

Number of studies	Number of people		Effect		Quality
	Sperm washed	Comparator	Relative (95% CI)	Absolute (95% CI)	
IVF or IUI or ICSI with washed sperm from HIV positive males					
(Bujan et al., 2007b)	368/3341 (11%)	-	-	-	Very low
Pre-term birth (< 37 weeks)					
IUI with washed sperm from HIV positive males					
(Semprini, 1992)	1/59 (2%)	-	-	-	Very low
ICSI with washed sperm from HIV positive males					
(Sauer et al., 2009)	74/420 (18%)	-	-	-	Very low
Multiple births					
IUI with washed sperm from HIV positive males					
(Marina, 1998)	8/101 (8%)	-	-	-	Very low
(Semprin et al., 1992)	3/59 (5%)	-	-	-	Very low
(Nicopoullos et al., 2010)	2/439 (1%)	-	-	-	Very low
ICSI with washed sperm from HIV positive males					
(Sauer et al., 2009)	48/420 (11%)	-	-	-	Very low
(Nicopoullos et al., 2010)	5/117 (4%)	-	-	-	Very low
IVF with washed sperm from HIV positive males					
(Nicopoullos et al., 2010)	7/114 (6%)	-	-	-	Very low
IVF or IUI or ICSI with washed sperm from HIV positive males					
(Bujan et al., 2007b)	42/3341 (1%)	-	-	-	Very low
Clinical pregnancy					
IUI with washed sperm from HIV positive males					
(Schuffner et al., 2011)	4/10 (40%)	-	-	-	Very low
ICSI with fresh washed sperm from HIV positive males					
(Wu et al., 2011)	3/14 (21.4%)	-	-	-	Very low

Number of studies	Number of people		Effect		Quality
	Sperm washed	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancy					
ICSI with washed sperm from HIV positive males					
(Wu et al., 2011)	2/14 (14.3%)	-	-	-	Very low
Congenital abnormalities					
ICSI with washed sperm from HIV positive males					
(Sauer et al 2009)	1/420 (< 1%)	-	-	-	Very low
Adverse pregnancy outcomes (including spontaneous abortions, ectopic pregnancies, miscarriages, pre-clinical miscarriages, extra-uterine pregnancies and intrauterine deaths)					
IUI with washed sperm from HIV positive males					
(Savasi et al., 2007)	59/2400 (2%)	-	-	-	Very low
(Semprin et al., 1992)	5/59 (8%)	-	-	-	Very low
(Nicopoullos et al., 2010)	20/439 (5%)	-	-	-	Very low
ICSI with washed sperm from HIV positive males					
(Sauer et al 2009)	26/420 (6%)	-	-	-	Very low
(Nicopoullos et al., 2010)	7/117 (6%)	-	-	-	Very low
(Wu et al., 2011)	1/14 (7.1%)	-	-	-	Low
IVF with washed sperm from HIV positive males					
(Nicopoullos et al., 2010)	14/114 (12%)	-	-	-	Very low
IVF or IUI or ICSI with washed sperm from HIV positive males					
(Bujan et al., 2007b)	121/3341 (4%)	-	-	-	Very low

ART assisted reproduction technology, CI confidence interval, HIV human immunodeficiency virus, ICSI intracytoplasmic sperm injection, IUI intrauterine insemination, IVF in vitro fertilisation.

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Table 6.14 Seroconversion rates in couples discordant for HIV status on the basis of whether the seropositive partner took HAART

Study	Design	HAART	Non-HAART	Odds ratio (95% CI)	Other information
Castilla et al., 2005 (N = 179 couples)	Retrospective cohort study	0/66 (0%)	7/113 (6%)	0.11 (0.01 to 1.90)	Study reported the risk of seroconversion in couples where one was HIV positive and the other was HIV negative. Male data was not reported separately. Overall, 142 (79%) of the couples were male. Results reflect outcome during early HAART and late HAART period
Melo et al., 2008 (N = 26 couples)	Prospective cohort study	0/5 (0%)	4/21 (19%)	0.35 (0.02 to 7.65)	Study reported the risk of secoconversion in couples where the male was HIV positive and the female was HIV negative. Median viral load of male index cases = 18,031 copies/mL
Study	**Design**	**Early therapy**	**Delayed therapy**	**Hazard ratio (95% CI)**	**Other information**
Cohen et al., 2011 (N = 1763 couples)	RCT	1/886 (0.1%)	28/877 (3.2%)	0.04 (0.01 to 0.27)	Study reported the risk of seroconversion in couples were one was HIV positive and the other was HIV negative. Male-to-female transmission data was not reported separately.3% of the couples were same sex couples. A singlet ransmission in the early therapy group was diagnosed 3 months after the infected partner started treatment. Also, a man was the source of the transmission and it is not clear whether he was in a heterosexual or same sex relationship.

CI confidence interval, HAART highly active antiretroviral therapy, HIV human immunodeficiency virus, RCT randomised controlled trial

Table 6.15 Summary results of seroconversion after using pre-exposure prophylaxis

Study	Design	Prophylaxis	Placebo	Odds ratio (95% CI)	Other information
Peterson et al., 2007 (N = 936)	RCT	2/469 (0.4%)	6/467 (1.3%)	0.33 (0.07 to 1.64)	Women were considered to be 'at high risk' by virtue of having an average of three or more coital acts per week and four or more sexual partners per month. No information on the HIV status of the men they had sex with. Two study sites were closed hence reducing the power of the study (which in any case was a safety study and now powered to look at the effect on transmission)
Vernazza et al., 2011 (N = 46)	Case series	0/37 (0%)	-	-	The male index cases were under a fully suppressed HIV therapy (< 50 copies/ml of HIV-RNA) for at least 6 months. It is important to note that as this study is non-comparative, It is unclear what the seroconversion rates would be if the women were given placebo. 9/46 women took no PREP and also were not infected

CI confidence interval, HIV human immunodeficiency virus, PREP pre exposure prophylaxis, RCT randomised controlled trial

Evidence statements

Sperm washing

All of the data was low or very low in quality. Some studies undertook post-wash testing prior to insemination and some studies did not. This may have affected the number of seroconversions reported in the studies, as samples that tested positive for HIV or HCV were not used. If a positive post-wash result was found on fresh sperm, some couples chose not to proceed with the procedure. Others used frozen sperm that had a negative post-wash test result. Two studies reported results separately for fresh and frozen sperm. One study used only ICSI while the other study used IUI or ICSI. In the latter, results may have been confounded by the reproductive method used, as fresh sperm was used with IUI and frozen sperm was used with ICSI.

Safety data

Post-wash testing

When post-wash testing was reported, some samples were found to be still HIV and/or HCV positive (see Table 6.8). It is difficult to determine the incidence of positive results, as only two studies provided full data on post-wash testing. One study reported HIV positive results in 20% of samples and HCV positive results in 18% of samples, while another reported HIV positive results in only 4% of samples but kit failures in 2% of tests.

Seroconversions

'Low' and 'very low' quality evidence from 11 studies was reviewed (see Tables 6.9 and 6.10). No seroconversions in mothers or children were reported. This was true for both HIV and hepatitis C, and was unaffected by the choice of assisted reproduction treatment.

Effectiveness data

Comparison of the use of washed sperm from HIV- and/or HCV-positive men with sperm from control groups of HIV- and/or HCV-negative men

Very low quality evidence from two studies was reviewed (see Table 6.11). There was no significant difference in the number of live singleton births when comparing the washed sperm groups and control groups with the use of ICSI or IUI. There was no significant difference in the number of multiple births in the washed sperm groups compared with the control groups, regardless of the

method of ART. There was no significant difference in the number of adverse pregnancy outcomes between washed sperm and control groups with the use of IUI.

When comparing the use of IVF with washed sperm and IVF in a control group, there were significantly more live singleton births with the use of IVF in the washed sperm group. However, the prevalence of female fertility problems in the washed sperm and control groups was not reported or compared and these may have confounded the results.

No comparative studies reported on the difference in congenital abnormalities or pre-term births between washed sperm and control groups.

Comparison of the outcomes of the use of washed sperm from HIV-positive men using different ARTs

Very low quality evidence from one study comparing the use of washed sperm with different ARTs was reviewed (see Table 6.12). The IUI group showed significantly more live singleton births with significantly fewer multiple births than both the ICSI and IVF groups. The IUI group showed significantly fewer adverse pregnancy outcomes when compared with the IVF group, although this was not significantly different when the IUI group was compared with the ICSI group. There were no significant differences in the number of live singleton births, the number of multiple pregnancies or the number of adverse pregnancy outcomes between the ICSI and IVF groups.

No studies reported the number of pre-term births and congenital abnormalities by ART. Data comparing ARTs in couples where the man has hepatitis C without HIV was not reported in the studies.

Non-comparative data

Very low quality evidence from eight studies was reviewed (see Table 6.13). When using washed sperm from HIV-positive males in various ARTs, the live singleton birth rate ranged from 7 to 20%. The pre-term birth rate ranged from 2 to 18%. The multiple birth rates ranged from 1 to 11%. The rate of congenital abnormalities was reported as less than 1%. The rate of adverse pregnancy outcomes ranged from 2 to 12%. Rates for fresh cycle clinical pregnancy (35.7%), frozen cycle clinical pregnancy (21.4%) and multiple pregnancy (14.3%) were only reported by one study.

Variation in HIV transmission rates with viral load

Seroconversion

Low and very low quality evidence from three studies was reviewed (see Table 6.14). The two very low quality studies showed no transmissions in cases when HAART was used. One low quality RCT showed significantly lower transmissions in cases that received an early therapy compared with those that had a delayed therapy.

Viral load as indication of transmission of HIV (in populations not receiving HAART)

One study found no seroconversion in couples where the HIV-positive male partner had undetectable viral load (less than 400 HIV-RNA copies/ml). HIV-positive men with female partners who seroconverted were found to have significantly higher viral loads ($P = 0.01$). The main limitation of the study was that the sampling took place every 10 months, resulting in some imprecision as to the viral load at the time transmission took place.

Pre-exposure prophylaxis to prevent HIV transmission

For the second review, there was low and very low quality evidence (see Table 6.15). One low quality RCT found lower seroconversion rates in those using prophylaxis but this difference was not statistically significant. However, that was a study of the safety of the interventional drugs and not powered to look at differences in transmission. One very low quality case series found no seroconversion in those using prophylaxis: however, the seropositive males in that study also had 'fully suppressed' viral loads.

Health economics profile

No formal health economics investigation was undertaken.

Evidence to recommendations

Relative value placed on the outcomes considered

This review focused on transmission from a male to a female, and the GDG's primary safety outcome was viral transmission rates (to the woman and then subsequently to the child). The GDG also considered post-wash testing as a proxy for the likelihood of transmission if that sperm were to be used.

The GDG then considered the effect that treatment would have on fertility, and for this used the same outcomes used when assessing ART, namely:

- live full-term singleton birth
- pre-term birth
- multiple births
- congenital abnormalities
- adverse pregnancy outcome.

Consideration of clinical benefits and harms

The main risk of viral infection in the male partner in the context of fertility is the transmission of the virus to the woman during vaginal intercourse. This has potentially serious consequences for her and, in turn, the fetus/baby should she become pregnant. The standard approach to reduce this risk has been sperm washing, to reduce the viral load in semen, followed by IUI. The main disadvantage of this approach is that the fertility rates following sperm washing and IUI are lower than those achieved with natural conception.

Initially, the GDG considered sperm washing to be the only therapeutic option, but it became clear that other options were available and needed to be considered, and hence other strategies were reviewed in the context of a man with HIV infection.

The GDG considered evidence on transmission rates where the male partner was on HAART and his viral load (if measured) was undetectable. The studies found that where a male was on HAART, viral transfer was extremely rare and comparable with the results from sperm washing.

The GDG also considered the use of pre-exposure prophylaxis in collaboration with a reduced viral load to reduce the risk of seroconversion from male to female. The evidence presented did not show an added benefit of treating the women with pre-exposure prophylaxis when the male had undectable viral copy count and was compliant with HAART. The GDG did note that while the evidence for pre-exposure prophylaxis showed no additional benefit for a man with an undetectable viral load, the evidence base was limited. Furthermore, this is an area where the evidence base is new and more research is expected and needed. Currently, pre exposure prophylaxis (PREP) is occasionally offered in clinical practice, its cost is relatively low and the perceived extra security it provides is welcomed by some. The GDG concluded that the evidence was not sufficient to make a recommendation for or against the use of PrEP.

Efficacy of sperm washing

For both HIV and HCV, the evidence showed that although sperm washing did not appear to completely eliminate the virus in the semen on the basis of post-wash testing of prepared sperm, the procedure appears to be very effective in reducing viral transmission, in that no case of seroconversion of the woman or the baby has been documented and this applied to all ART methods (IUI, IVF and ICSI).

The evidence of the effect of sperm washing on pregnancy outcome was considered in two ways. The first approach was a comparison of the pregnancy outcomes in pregnancies conceived following all ART methods using washed sperm in couples with a viral positive male partner with those in pregnancies conceived with the same range of ART methods but without sperm washing. The main limitation of this approach is that the group having assisted conception following sperm washing were likely to be undergoing assisted conception to avoid HIV transmission and may not have had fertility problems. In comparison, the group who had ART without sperm washing were more likely to be receiving ART to overcome fertility problems. This possible confounder could have resulted in the

differences in outcomes seen. In particular, it might have contributed to the higher live full-term singleton birth rates seen with IVF in the sperm washing group. There appeared to be no other differences in pregnancy outcome between the two groups.

The second approach was to compare the pregnancy outcomes for sperm washing between different ART methods. Consistent with other studies, IUI cycles had fewer singleton live births than both IVF cycles with and without ICSI, but it also had fewer multiple births. The GDG thought that this may reflect the transfer of more than one embryo in IVF cycles with and without ICSI.

Unprotected vaginal intercourse.

Given the lower rate of live births with sperm washing, the GDG considered it important to examine whether the treatment of the HIV positive male with HAART in order to achieve a resultant low viral load may in itself have an impact on seroconversion in the woman and baby and possibly avoid the need for sperm washing. Though the evidence in this area was of limited quantity and quality, the GDG noted that there had been no reports of seroconversion in the woman when the HIV positive male partner was compliant with HAART or had a viral load of less than 400 copies/ml. Given that evidence, the GDG was of the view that where the male partner was compliant with HAART and the viral load was less than 50 copies/ml (currently the way in which most laboratories indicate that there is no detectable virus), couples could be advised to have unprotected vaginal intercourse at the time of ovulation. The GDG favoured the 50 copies/ml threshold rather than 400 copies/ml both to be consistent with recommendations in other fields of health care and be assured the recommendation would be as robust as the evidence would allow.

The GDG was clear that the recommendation for unprotected vaginal intercourse was specifically for conception, instructing the couple to limit unprotected vaginal intercourse to the time of ovulation within its recommendations. The context of this recommendation should not be extrapolated away from this remit. Furthermore, the GDG was aware that other infections in either partner may heighten the risk of seroconversion. The type of infection will determine to what extent the risk is increased (a sexually transmitted infection was considered the greatest added risk to seroconversion). Adding this caveat, the GDG felt, would be in concordance with ‘Swiss criteria’ and would add another layer of strength to the recommendation. The Swiss criteria state that if a person meets all of the following criteria then they are not sexually infectious:

- the person adheres to antiretroviral therapy, the effects of which must be evaluated regularly by the treating physician
- the viral load has been suppressed (less than 40 copies/ml – which means ‘undetectable virus’ and equivalent to laboratories reporting ‘less than 50 copies/ml’) for at least six months
- there are no other sexually transmitted infections.

The GDG made its recommendation to include the Swiss criteria clause that the viral load must be maintained below 50 copies/ml for 6 months. Like the Swiss criteria, its inclusion allows more confidence that the HAART has been effective in all parts of the body (specifically the seminal fluid). Furthermore, the maintenance of an undetectable viral load demonstrates a good adherence to HAART and removes the margin of error that could arise from a single miscalculated or mistaken laboratory result.

Those couples where these criteria were not met would be advised to have sperm washing. The GDG anticipated that there might be some couples who would still be anxious about transmission with unprotected vaginal intercourse and request sperm washing, not withstanding the HIV positive male partner being HAART compliant and having a viral load of less than 50 copies/ml. In such circumstances the GDG felt the request should be considered. The discussion should include the fact that fertility rates would be lower with sperm washing and IUI compared with unprotected vaginal intercourse at the time of ovulation.

The GDG debated the use of sperm washing in situations where HAART was being used and viral loads were undetectable. The GDG highlighted that sperm washing only reduced viral loads rather than eliminating it, so there would be little or no added benefit from this option.

HCV and HBV

The GDG acknowledged that male partners who are hepatitis C (HCV) positive have a low likelihood of transmitting the virus through sexual intercourse (approximately 2%) and it was believed there was insufficient evidence about the value of sperm washing to reduce that risk even further. However, the GDG members also noted that there was a not uncommon risk of co-infection with HIV and in that situation they felt the guidance for management of HIV, including sperm washing, should apply. In order to make conclusive recommendations more research is needed: the research recommendation therefore reflects the areas in which the GDG noted evidence is required. Because the evidence did not show that a comprehensive intervention could be used to remove or reduce risk of transmission of hepatitis C (within the context of fertility), it is particularly important that HCV positive men should receive specialist advice before continuing on the fertility pathway. Similarly, although the GDG was unable to recommend a specific intervention within the context of fertility treatment, it was noted that treatment should be sought to eradicate the virus before regular unprotected intercourse is undertaken.

The 2004 version of the guideline stated “partners of individuals with hepatitis B should be vaccinated before fertility treatments begin and sperm washing will not be necessary. The normal course of pregnancy is not affected by hepatitis B infection and vertical transmission to neonates can be minimised with hepatitis B vaccination within 24 hours of birth and at six months”. The GDG concurred with this stament and agreed with the conclusion made in 2004 that sperm washing is not relevant in this clinical setting, therefore no sperm washing recommendation was made.

Although no new evidence about HBV transmission was found for this update, the GDG felt that it was appropriate to make a recommendation in light of initiatives made in other NICE guidelines. The GDG recommended that, where one of the parents has hepatitis B, hepatitis B vaccinations and treatment for their baby and any unvaccinated siblings should be given according to the NICE public health guidance 21 Immunisation for children and young people (2009). Furthermore, the couple should not attempt to conceive until the vaccinated partner has been tested to ensure an adequate level of risk of transmission has been reached. Until this outcome has been met, a barrier method of contraception (that is, condoms) should be used for all forms of sexual contact to reduce the risk of transmission.

The GDG was aware of ongoing developments in the screening of Hepatitis B (HBV), in particular the HFEA consultation on the serological testing for HBsAg and anti-HBc. The GDG was content that the recommendations made within this chapter are complementary to new screening initiatives and would be adequately supportive to those tested positive for hepatitis B.

Consideration of health benefits and resource uses

The GDG discussed the financial considerations that should be made when offering sperm washing to men who are HIV positive. The cost of sperm washing should also include the subsequent intrauterine insemination or (depending on motility of the sperm) ICSI. The evidence showed that there had been no seroconversions following sperm washing, but did not conclude that it was an infallible procedure. The GDG was of the view that a reduction of the viral copy count to undetectable levels (the GDG defined this as 50 copies/ml) along with time unprotected vaginal intercourse (where there are no other infections) was as equally as effective at reducing the risk of seroconversion. The GDG concluded that this option was more cost effective than sperm washing, citing the high cost of sperm washing and the trade-off made with lower birth rates.

Quality of evidence

The quality of the evidence was generally low and very low for this topic.

Other considerations

The three viral infections in the male partner considered by the GDG were HIV, HBV and HCV. Most evidence was found for HIV. However, that evidence was of poor quality.

Plasma and seminal viral load

The GDG also considered the use of viral load within plasma and seminal fluid. The majority of evidence presented to the GDG seldom used both, with most reporting plasma viral loads. In the context of fertility treatment, seminal viral loads are more appropriate but the GDG acknowledged that plasma viral load would give an acceptable estimation of this value. Furthermore, in practice, seminal viral load testing is rarely offered and has a limited use. On this basis the GDG did not recommend its

routine use. In addition, if a man maintains a plasma viral load at undetectable levels for 6 months then it can be assumed that HAART has been effective in all parts of the body and therefore the levels of virus should not differ widely between the two samples.

Provision of care

The GDG was aware that the provision of specialist HIV management and fertility treatment are seldom found within the same centre. When offering fertility treatment or advice for men with positive viral status, a viral specialist and fertility specialist should work together and where one service is not available the couple should be referred.

Equalities

Throughout the guideline any potential inequalities created by recommendations were discussed by the GDG. Three main groups outlined in the scope were:

- people in same-sex relationships who have unexplained infertility after donor insemination
- people who are unable to, or would find it very difficult to, have vaginal intercourse (such as those with a clinically diagnosed physical disability or psychosexual problem)
- people with conditions that require specific consideration in relation to methods of conception (such as a couple where the male is HIV positive).

The GDG considered people at risk of viral transmission to have specific requirements that warrant earlier investigation should they wish to conceive. Those who fall within these populations should expect to receive assistance from healthcare professionals (both fertility and HIV specialists). The GDG was aware that there have been occurrences where inequality of treatment has been reported by patients with transmittable viruses within centres providing assisted reproduction. The recommendations within this and other chapters have been created with the view that all populations should have access to the treatment to which they are entitled and that by using the recommendations, service users and clinicians should be able to make informed choices.

Recommendations

Number	Recommendation
66	For couples where the man is HIV positive, any decision about fertility management should be the result of discussions between the couple, a fertility specialist and an HIV specialist. **[new 2013]**
67	Advise couples where the man is HIV positive that the risk of HIV transmission to the female partner is negligible through unprotected sexual intercourse when all of the following criteria are met: • the man is compliant with highly active antiretroviral therapy (HAART) • the man has had a plasma viral load of less than 50 copies/ml for more than 6 months • there are no other infections present • unprotected intercourse is limited to the time of ovulation. **[new 2013]**
68	Advise couples that if all the criteria in recommendation 67 are met, sperm washing may not further reduce the risk of infection and may reduce the likelihood of pregnancy. **[new 2013]**
69	For couples where the man is HIV positive and either he is not compliant with HAART or his plasma viral load is 50 copies/ml or greater, offer sperm washing. **[new 2013]**
70	Inform couples that sperm washing reduces, but does not eliminate, the risk of HIV transmission. **[new 2013]**

71	If couples who meet all the criteria in recommendation 67 still perceive an unacceptable risk of HIV transmission after discussion with their HIV specialist, consider sperm washing. **[new 2013]**
72	Inform couples that there is insufficient evidence to recommend that HIV negative women use pre-exposure prophylaxis, when all the criteria in recommendation 67 are met. **[new 2013]**
73	For partners of people with hepatitis B, offer vaccination before starting fertility treatment. **[new 2013]**
74	Do not offer sperm washing as part of fertility treatment for men with hepatitis B. **[new 2013]**
75	For couples where the man has hepatitis C, any decision about fertility management should be the result of discussions between the couple, a fertility specialist and a hepatitis specialist. **[new 2013]**
76	Advise couples who want to conceive and where the man has hepatitis C that the risk of transmission through unprotected sexual intercourse is thought to be low. **[new 2013]**
77	Men with hepatitis C should discuss treatment options to eradicate the hepatitis C with their appropriate specialist before conception is considered. **[new 2013]**

Number	Research recommendation
RR 9	What is the clinical and cost effectiveness of pre-exposure prophylaxis in HIV negative women in discordant couples?
RR 10	What is the relationship between seminal and plasma HIV viral load?
RR 11	What is the effectiveness of sperm washing in reducing the transmission of hepatitis C from men to their partner?
RR 12	Is seminal HIV viral load a better predictor of the risk of transmission than plasma HIV viral load?

Susceptibility to rubella

Rubella infection during pregnancy is associated with a significant teratogenic risk to the fetus, resulting in multiple congenital abnormalities.[184] [Evidence level 2b] The introduction of the rubella vaccine has resulted in a decrease of rubella infections and infants with congenital rubella syndrome. The reported proportion of infertile women who were rubella susceptible ranged from 2% to 12%.[185–188] [Evidence level 3] The rubella vaccine is a live attenuated virus; thus, when vaccination is given conception should be deferred for one month.

Recommendations

Number	Recommendation
78	Women who are concerned about their fertility should be offered testing for their rubella status so that those who are susceptible to rubella can be offered vaccination. Women who are susceptible to rubella should be offered vaccination and advised not to become pregnant for at least 1 month following vaccination. **[2004, amended 2013]**

Cervical cancer screening

The reported proportion of infertile women with abnormal cervical smears ranges from 5% to 13%.[186,188] [Evidence level 3] As part of the national screening programme, women between the age of 20 years and 64 years are offered cervical screening every three years or five years. Around 60% of health authorities invite women every three years and 15% have a mixed policy, inviting women every three to five years, depending upon their age.[189] Abnormal cervical cytology that is overlooked may lead to increased delay in fertility treatment[186] because treatment of cervical intraepithelial neoplasia is more complicated during pregnancy.

Recommendations

Number	Recommendation
79	To avoid delay in fertility treatment a specific enquiry about the timing and result of the most recent cervical smear test should be made to women who are concerned about their fertility. Cervical screening should be offered in accordance with the national cervical screening programme guidance. **[2004]**

Screening for *Chlamydia trachomatis*

Chlamydia trachomatis is present in 11% of the sexually active population aged 19 years or less.[357] It is a major cause of pelvic inflammatory disease, leading to chronic abdominal pain, ectopic pregnancy and tubal factor infertility.[358,359] Asymptomatic chlamydial infection may go unrecognised and untreated. Although the prevalence of *C. trachomatis* among subfertile women in the UK is only 1.9%,[360] uterine instrumentation carried out routinely as part of the infertility investigation may reactivate or introduce upper tract dissemination of endocervical chlamydial infection, resulting in iatrogenic pelvic inflammatory disease. [Evidence level 2b]

Clinical pelvic infection following hysterosalpingography (HSG) has been reported in up to 4% of cases and in 10% of patients with tubal disease.[361] [Evidence level 3] Prophylactic antibiotics are effective in reducing this and should be considered.[360,362] [Evidence level 3] Both doxycycline and azithromycin are effective prophylaxis and treatment for chlamydia.[363] [Evidence level 1b]

There is evidence that screening for and treating cervical chlamydial infection can reduce the incidence of pelvic inflammatory disease in women at increased risk of chlamydia.[364] [Evidence level 1b] The Chief Medical Officer's Expert Advisory Group on Chlamydia has called for action to reduce the prevalence and morbidity of chlamydial infection. It recommends that consideration be given to screening couples attending fertility clinics and women undergoing procedures requiring instrumentation of the uterus.[365] [Evidence level 4] Women who are found to have chlamydial infection should be treated for the infection before proceeding.

DNA techniques such as polymerase chain reaction and ligase chain reaction for analysis of cervical and urine specimens are highly sensitive and specific for diagnosing chlamydial infection.[366–368] [Evidence level 2b]

Chlamydial infection has been implicated in male infertility[369] and it may cause epididymitis and obstruction. If chlamydial infection is detected in the female partner, male partners should be notified and treated to limit re-infection and the potential need for retreatment.

The Chief Medical Officer's Expert Advisory Group on Chlamydia advises referral to genitourinary medicine clinics so that sexual partners can be traced and treated if either partner is found to have chlamydial infection.[365] [Evidence level 4]

Recommendations

Number	Recommendation
80	Before undergoing uterine instrumentation women should be offered screening for *Chlamydia trachomatis* using an appropriately sensitive technique. **[2004]**
81	If the result of a test for *Chlamydia trachomatis* is positive, women and their sexual partners should be referred for appropriate management with treatment and contact tracing. **[2004]**
82	Prophylactic antibiotics should be considered before uterine instrumentation if screening has not been carried out. **[2004]**

6.6 Strategies for management of fertility problems

The investigation of people with fertility problems will lead to a number of possible diagnostic categories. Each diagnostic category tends to have its own management strategy but these strategies are based on a core of techniques that apply across many conditions. This applies particularly to the techniques involved in assisted reproduction. The importance of psychological support and counselling applies at every stage of the management strategy and process (see Section 4.3). Diagnostic categories and their corresponding management strategies are described below, and where the individual techniques are described in subsequent chapters.

Male factor fertility problems

Techniques for managing ejaculatory failure (anejaculation and retrograde ejaculation) are discussed in Section 7.4.

Semen quality can be marginally improved by lifestyle or medical measures (see Chapters 5 and 7) but natural pregnancy is rare because the spermatozoa remain predominantly dysfunctional.

Endocrine therapy for hypothalamic–pituitary failure and reconstructive surgery in selected cases of obstructive azoospermia may restore fertility by returning functional spermatozoa to the semen and natural pregnancy is feasible (see Chapter 7). In nonobstructive azoospermia there are foci of spermatogenesis in about 50% of cases but there is little potential for restoring fertility. However, in some cases lifestyle measures (see Chapter 5) may return sperm to the ejaculate and thereby avoid the need for surgical sperm recovery. Cases of irreversible obstructive azoospermia and nonobstructive azoospermia are managed by surgical sperm recovery from the epididymis or testis (see Section 15.6) followed by ICSI (see Chapter 16) because of the immaturity of the recovered sperm.

Leucocytospermia has been associated with adverse effects on semen parameters and function.[415,416] Antibiotics have been considered in the treatment of leucocytospermia (see Chapter 7).

Surgical treatment for varicocele is discussed in Section 7.3.

A specific male factor should be identified and corrected where possible to try to initiate natural pregnancy. The diagnosis of 'mild' male factor infertility is an example of a situation where natural conception remains a possibility and is equivalent to unexplained infertility (see Chapters 7 and 12). Where this is not feasible, the man's sperm is normally used for assisted reproduction, to avoid the need to consider sperm donation. However, an improvement in semen quality may reduce the complexity, costs and potential risks of future assisted reproduction for both partners and any resulting children.

Assisted reproduction treatments are indicated by the quantity and quality of spermatozoa that can be isolated by semen preparation techniques. While IVF (see Chapter 15) is feasible in mild–moderate oligozoospermia, ICSI (see Chapter 16) is usually required to achieve fertilisation, especially in moderate–severe oligozoospermia, asthenozoospermia or teratozoospermia. As there are no reliable sperm function tests, different sperm quality criteria are used by different clinics when considering

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allocating couples to treatments. There is no evidence or even consensus-based recommendations for good practice to support any particular sperm quality criteria for ICSI or other forms of assisted reproduction.

If only non-viable spermatozoa are isolated from the semen, surgical sperm recovery from the testis may be required to obtain viable sperm for IVF and/or ICSI (see Section 15.6). Alternatively, assisted reproduction uses sperm isolated from the semen or urine following physical methods involving vibration or electrostimulation to induce ejaculation (see Chapter 7).

Donor insemination (see Chapter 17) is an alternative treatment option for male factor subfertility, and is the only option for the one in 200 of infertile men (and their partners) who have no sperm because of anorchia or complete germ-cell aplasia.

Ovulation disorders

World Health Organization Group I ovulation disorders

The management options for women with this diagnosis include increasing body weight and moderating exercise in women with a low BMI and menstrual abnormality, and/or the use of pulsatile gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity.

The management of women with these disorders is discussed in detail in Chapter 8.

World Health Organization Group II ovulation disorders

The management options for women with this diagnosis include losing weight in overweight women and/or the use of clomifene or metformin as first-line treatment. Ovarian ultrasound should be undertaken with the first month of clomifene use to lower the chances of a multiple pregnancy. Women who are resistant to clomifene citrate can be offered laparoscopic ovarian drilling, combined treatment (clomifene citrate and metformin) if a combined treatment was not used as first line treatment, or gonadotrophins.

The management of women with these disorders is discussed in detail in Chapter 8.

World Health Organization Group III ovulation disorders

Ovarian failure and its management by oocyte donation is discussed in Chapter 18.

Hyperprolactinaemia

Where a diagnosis of hyperprolactinaemia is made, the management must include investigation to exclude the presence of a pituitary adenoma or extrapituitary tumours, which would require specific management before proceeding with fertility treatment. Dopamine agonists are widely used in the treatment of hyperprolactinaemia.[417] There are several newer dopamine agonists but the effects of these on reproductive outcomes has not been evaluated fully, and their safety in women intending to become pregnant has not been established (see Chapter 8).

Tubal disease

The management of tubal disease traditionally involved surgery but IVF has become the predominant approach in recent years. The surgical approaches to management of tubal disease are discussed in Chapter 9. The management of tubal disease by IVF does not generally differ from the use of IVF for other indications (see Chapter 15).

Endometriosis

In the management of fertility problems associated with endometriosis, it is widely accepted that minimal and mild endometriosis may be considered equivalent to unexplained infertility and managed accordingly (see below). Medical management, in the absence of pelvic pain, is no longer thought to be an appropriate strategy (see Chapter 10). Surgical management by the ablation of endometriotic lesions and the removal of endometriomas is an established approach (see Chapter 10) but many women with endometriosis of all severities choose to have IVF treatment (see Chapter 15).

Uterine abnormalities

Uterine abnormalities such as adhesions, polyps, submucous leiomyomas and septae may be associated with infertility but their role in causing infertility is not clear. Surgical approaches to management of uterine abnormalities are discussed in Chapter 9.

Unexplained fertility problems

Unexplained infertility is a diagnosis made by exclusion in couples who have not conceived and in whom standard investigations have not detected any abnormality. It accounts for about 40% of female infertility[418] and 8–28% of infertility in couples.[1,3] The management of unexplained infertility is discussed in Chapter 11.

7 Medical and surgical management of male factor fertility problems

7.1 Introduction

Approximately 1% of men are permanently sterile, with about 20% of men having sperm quality below the threshold thought compatible with normal fertility (conception within 1 year). In infertile couples undergoing in vitro fertilisation (IVF), male factor infertility is solely implicated in 20% of cases and is contributory in up to 50%.

In the majority of cases the aetiology of male factor infertility is unknown, but probably relates to an inherent poor sperm production capacity of the testes that is likely to have a genetic origin. Other causes include specific endocrine problems, or structural or anatomical defects of the male urogenital tract.

The term 'mild' male factor infertility is used extensively in practice and in the literature. However, there is no formally recognised definition of what this means. Therefore, where the term 'mild' male factor infertility is applied in this guideline, it is defined as meaning: two or more semen analyses that have one or more variables which fall below the 5th centile as defined by the World Health Organization (WHO, 2010), and where the effect on the chance of pregnancy occurring naturally through vaginal intercourse within a period of 24 months would then be similar to people with unexplained infertility or mild endometriosis.

The options for management are:

- Medical (see Section 7.2), including treatment with gonadotrophins, androgens, anti-oestrogens, kinin-enhancing drugs, bromocriptine, alpha-blockers, mast-cell blockers, corticosteroids, antibiotics and antioxidants
- Surgical (see Section 7.3): in cases of obstructive azoospermia, surgical options are either the use of sperm recovered by invasive procedures for IVF or intra cytoplasmic sperm injection (ICSI), or surgical correction. Sperm retrieval using invasive procedures for IVF/ICSI is used in cases of ejaculatory failure.
- Assisted reproductive treatments: IVF (see Chapter 15) and ICSI (see Chapter 16) are the preferred approaches with increasing degrees of sperm defects.

This chapter reviews the evidence for the clinical effectiveness of the first two of these groups of interventions.

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7.2 Medical management

Gonadotrophin therapy for hypogonadotrophic hypogonadism

We found no randomised control trials (RCTs) that evaluated gonadotrophin treatment for hypogonadotrophic hypogonadism. Two case series suggest that treatment with human chorionic gonadotrophin (hCG) and human menopausal gonadotrophin (hMG) increases sperm counts within the normal range in men with hypogonadotrophic hypogonadism of postpubertal onset,[427,428] except in men who also have cryptorchidism.[429] [Evidence level 3]

In one case series, it was suggested that gonadotrophin (hCG and hMG) treatment may improve fertility (92%) in men with hypogonadotrophic hypogonadism.[430] [Evidence level 3] Self-administration of follicle stimulating hormone (FSH) and hCG was reported to be well-tolerated and effective in stimulating spermatogenesis in hypogonadotrophic hypogonadism men, with 80% achieving a positive sperm count.[431] [Evidence level 2b]

Pulsatile gonadotropin-releasing hormone (GnRH) may be as effective as hCG and hMG in enhancing sperm production in men with hypogonadotrophic hypogonadism.[432–434] [Evidence level 2b]

Gonadotrophin therapy for idiopathic male factor fertility problems

Two RCTs showed no significant difference in pregnancy rates between gonadotrophin treatment when compared with placebo (n = 65, 5.8% with recombinant FSH versus 0% with placebo)[435] or no treatment (n = 136, 44.8% with FSH versus 37.2% with no treatment) in couples with idiopathic male infertility.[436] [Evidence level 1b]

Anti-oestrogens (clomifene and tamoxifen)

A systematic review of ten RCTs examined the effect of anti-oestrogens in pregnancy rates.[438] It did not detect a beneficial effect of anti-oestrogens in pregnancy rates (odds ratio [OR] 1.54, 95% confidence interval [CI] 0.99 to 2.40) when compared with placebo or no treatment for men with oligo- and/or asthenozoospermia. [Evidence level 1a]

Androgens

A 1996 systematic review of nine RCTs showed no benefit of androgens in improving pregnancy rate (OR 1.10, 95% CI 0.75 to 1.61) when compared with placebo or no treatment.[439] [Evidence level 1a]

Kinin-enhancing drugs

A systematic review of 12 RCTs did not provide conclusive evidence that kinin-enhancing drugs improve pregnancy rates (OR 1.65, 95% CI 0.98 to 2.77) when compared with placebo.[440] Nonsignificant results were also reported in an additional RCT (9.6% versus 14%).[441] [Evidence level 1a]

Bromocriptine

A 1996 systematic review of four RCTs found no benefit of bromocriptine on either sperm parameters or pregnancy rates (OR 0.70, 95% CI 0.15 to 3.24) when compared with placebo or no treatment in men with idiopathic semen abnormalities.[442] [Evidence level 1a] We did not identify any new trials since this review was published.

Antioxidants

Two placebo-controlled RCTs found that vitamin E has a beneficial effect on semen parameters in infertile men,[443,444] but improvement in pregnancy rates was only shown in one trial (n = 87, 21% versus 0%).[444] Another RCT showed no significant improvement in semen parameters with vitamins C and E versus placebo and there was no pregnancy in either group.[445] [Evidence level 1b] Selenium is also an antioxidant, and selenium supplementation has been reported to improve sperm motility and pregnancy rate in subfertile men (see Section 5.11).[175,]

Glutathione was found to have a significant positive effect on sperm motility and morphology in one RCT but pregnancy rate was not reported.[446] [Evidence level 1b]

Alpha blockers

One RCT (n = 31) showed that alpha blocker (bunazosin) significantly improved semen density and count, but not pregnancy rates, when compared with placebo (25% versus 6.7%).[447] [Evidence level 1b]

Mast-cell blockers

One RCT (n = 46) found that treatment with mast-cell blocker (tranilast) significantly improved semen parameters and pregnancy rate at one year (28.6% versus 0%) when compared with placebo in men with severe oligozoospermia.[448] [Evidence level 1b]

Corticosteroid treatment of antisperm antibodies

Immunological male infertility refers to the presence of antisperm antibodies in the seminal fluid or bound to spermatozoa. It accounts for about 3% of male factor infertility.[296]

Five RCTs compared corticosteroid treatment with placebo or no treatment in men with antisperm antibodies. No significant difference in pregnancy rates was found in three trials.[449–451] One RCT (n = 60) showed a significant increase in pregnancy rate with prednisolone versus placebo (27% versus 7%).[452] Another RCT (n = 77) showed a significant increase in pregnancy rate with low-dose prednisolone versus no treatment (18% versus 3%).[453] All these trials have small sample sizes. [Evidence level 1b] A significant incidence and severity of side effects (including dyspepsia, facial flushing, weight gain and rare complications such as aseptic necrosis of the hip) were reported.[449,454–456] [Evidence level 3]

Antibiotic treatment of leucocytospermia

An RCT in men with leucocytospermia assigned patients to antibiotic treatment, antibiotics with frequent ejaculation, frequent ejaculation at one month or no treatment. The effect of these interventions on pregnancy rates is not clear; however, treatment groups showed resolution of leucocytospermia (40% versus 68% versus 32% versus 4%).[457] The resolution was sustained at two and three months only in those who took antibiotics and frequently ejaculated.[457] [Evidence level 1b]

Two other RCTs showed that treatment with antibiotics did not improve semen parameters in patients with leucocytospermia,[459] nor resolution of leucocytospermia.[460] [Evidence level 1b] Pregnancy outcomes were not assessed in these trials.

In an RCT (n = 23) patients with male accessory gland infection (epididymo-prostao-vesiculitis), antibiotic treatment compared with placebo was shown to have no significant effect on pregnancy rates or sperm parameters (10% with antibiotics versus 8% with placebo).[461] Another RCT (n = 122) showed significant improvement with antibiotics in sperm parameters at three months and pregnancy rates (28.2% with antibiotics versus 5.4% with no treatment).[462] [Evidence level 1b] Treatment with antibiotics did not affect pregnancy rates in couples with mycoplasma-related infertility.[463] [Evidence level 1b]

One RCT (n = 120) found that treatment with antibiotics and kallikrein improved sperm motility and pregnancy rates (32% with kallikrein plus antibiotics versus 17% with antibiotics alone; RR 1.84, 96% CI 0.95 to 3.56) in infertile men with genital tract infections.[464] [Evidence level 1b]

Recommendations

Number	Recommendation
83	Men with hypogonadotrophic hypogonadism should be offered gonadotrophin drugs because these are effective in improving fertility. **[2004]**
84	Men with idiopathic semen abnormalities should not be offered antio-estrogens, gonadotrophins, androgens, bromocriptine or kinin-enhancing drugs because they have not been shown to be effective. **[2004]**
85	Men should be informed that the significance of antisperm antibodies is unclear and the effectiveness of systemic corticosteroids is uncertain. **[2004]**
86	Men with leucocytes in their semen should not be offered antibiotic treatment unless there is an identified infection because there is no evidence that this improves pregnancy rates. **[2004]**

Number	Research recommendation
RR 13	Alpha blockers and mast-cell blockers* need further evaluation before they can be considered in the treatment of men with semen abnormalities.
RR 14	Research into the optimum dose and duration of alpha blockers to improve semen parameters in infertile men is needed.

7.3 Surgical management

Surgical treatment of obstructive azoospermia

A case-series study of 370 men with obstructive azoospermia showed that epididymovasostomy with postinfective caudal block gave a patency rate of 52% and pregnancy rate of 38%, respectively. Postinfective vasal blocks were better corrected by total anatomical reconstruction (patency of 73% and pregnancy rate of 27%) than by transvasovasostomy (patency 9% and no pregnancy).[465] [Evidence level 3] Another case series of 44 men found that 58% achieved patency and 23% of couples achieved a pregnancy following surgery for ejaculatory duct obstruction.[466] [Evidence level 3] Another study showed that transurethral resection of ejaculatory ducts improved semen quality and gave an overall pregnancy rate of 20% in 46 couples where the male partner had ejaculatory obstruction.[467] [Evidence level 3] Recovery and cryopreservation of spermatozoa for use in assisted reproduction should be considered during surgical reconstruction to avoid a second surgical procedure at a later date (see Section 15.6). Sperm should be evident within 6 to 12 months of successful surgery and so it may be reasonable to discuss assisted reproduction with men whose partners have not conceived 12 to 18 months after surgery. Alternatively, men with congenital bilateral absence of vas deferens (CBAVD) may be offered surgical retrieval of spermatozoa for use in assisted reproduction (see Section 15.6).

Surgical treatment of varicoceles

A systematic review of seven RCTs compared pregnancy rates of varicocele repair in men with normal semen (two RCTs), subclinical varicoceles (three RCTs) and clinical varicoceles with abnormal semen (two RCTs).[468] [Evidence level 1a] The review found that varicocele repair did not improve pregnancy rates in couples with male fertility problems or unexplained fertility problems (61 pregnancies among 281 treated couples versus 50 pregnancies among 259 controls; relative risk (RR) 1.01, 95% CI 0.73 to 1.40 using a fixed effects model; RR 1.04, 95% CI 0.62 to 1.75 using a random effects model). Subgroup analysis showed that varicocele treatment was not effective in RCTs restricted to male subfertility with clinical varicoceles or in those that included men with subclincial varicoceles or normal semen analysis.[469] [Evidence level 1a] The trials reviewed were of varying sizes with no clear description of allocation concealment; there was clinical heterogeneity in the subjects selected. Mean age of the male partners and duration of subfertility differed between the RCTs[470,471] which considered clinical varicoceles with abnormal semen and both of these studies had high drop-out rates. Meta-analysis of these two RCTs showed no improvement in pregnancy rate with varicocele repair (pooled RR 2.33; 95% CI 0.47 to 11.6 using a random effects model; RR 1.47; 95% CI 0.87 to 2.50 using a fixed effects model), although a significantly higher pregnancy rate was reported in one of the RCTs (RR 6.0, 95% CI 1.55 to 23.2).[470] This was a report from one of 12 centres involved in a WHO-sponsored multicentre RCT that started in 1984. The systematic review excluded three further publications relating to the multicentre trial[472–474] because they were only reported in abstract or summary form. The exclusion could have made a difference to the conclusions of the systematic review. Of the three additional publications, two showed a significant two-fold relative improvement in pregnancy rates following varicocele repair in men with abnormal semen.[472,474] However, the definitive WHO trial remains unpublished and the results are, therefore, not available to secondary researchers. Until such time as a full report of the WHO multicentre trial is

* Since 2004 a Cochrane review (Showell et al., 2011) has shown a benefit in pregnancy rates with use of antioxidants; therefore 'antioxidants' has been removed from this research recommendation in the 2013 update.

published, the effectiveness of varicocele repair in men with abnormal semen will remain uncertain. Further primary research to clarify this issue seems unlikely, given the advances in alternative treatments such as ICSI. However, research comparing the effectiveness of varicocele treatment and in vitro fertilisation, taking into consideration patient preference and cost effectiveness would be useful.[475,476] [Evidence level 4]

Recommendations

Number	Recommendation
87	Where appropriate expertise is available, men with obstructive azoospermia should be offered surgical correction of epididymal blockage because it is likely to restore patency of the duct and improve fertility. Surgical correction should be considered as an alternative to surgical sperm recovery and IVF. **[2004]**
88	Men should not be offered surgery for varicoceles as a form of fertility treatment because it does not improve pregnancy rates. **[2004]**

Number	Research recommendation
RR 15	Randomised controlled trials are needed to compare the effectiveness of surgery for varicocele and in vitro fertilisation treatment in men with abnormal semen quality.

7.4 Management of ejaculatory failure

We identified a systemic review that assessed treatment options for anejaculation and retrograde ejaculation in men with ejaculatory disorders or in men undergoing fertility treatment.[299] [Evidence level 1b–3] This review included 88 studies assessing treatment of anejaculation (n = 2346 patients) and 132 studies assessing treatment of retrograde ejaculation (n = 342 patients). The designs of these studies ranged from RCT (n = 1) to observational or small case studies.

Medical treatment of anejaculation has included the use of alpha-agonistic drugs such as imipramine, pseudoephedrine or parasympathomimetic and neostigmine. The systematic review found that treatment with alpha-agonistics had significantly lower success rates than treatment with parasympathetic drugs in the reversal of anejaculation (19% with alpha-agonists versus 51% with parasympathomimetics). Considerable adverse effects such as headache, nausea and vomiting were reported. Medical treatment of anejaculation is not generally recommended as treatment of first choice.

Medical treatment of retrograde ejaculation aims to increase sympathetic tone of the bladder or decrease parasympathetic activity using alpha-agonistic or anticholinergic and antihistamine drugs such as imipramine, milodrin, chlorpheniramine or brompheniramine. The systematic review found no significant differences between the different medical treatments in the reversal of retrograde ejaculation and spontaneous or assisted reproduction pregnancies (ranged from 56% to 79%), irrespective of the underlying diagnosis. Adverse effects such as dizziness, restlessness, dry mouth and nausea were reported. If medical treatment of retrograde ejaculation fails, the use of penile electrovibration stimulation and sperm recovery from the urine can be considered.

Penile electrovibration stimulation initiates reflex spinal cord activity, causing ejaculation. The systematic review reported pregnancy rates of between 42% and 89% following intrauterine insemination (IUI), in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI) and gamete intrafallopian transfer (GIFT) in partners of men who underwent electrovibration stimulation for reversal of anejaculation.

Transrectal electroejaculation stimulates the nerves responsible for ejaculation. The systematic review reported pregnancy rates of between 16% and 80% following IUI, IVF, ICSI and GIFT in partners of men who underwent electroejaculation for reversal of anejaculation.

Urine is known to have a deleterious effect on sperm quality and alkalisation of urine pH (a buffer) may be necessary for the retrieval of the retrograde ejaculate from the bladder. The systematic review reported pregnancy rates of between 50% and 100% following IUI, IVF, ICSI and GIFT in partners of patients who underwent sperm retrieval from the urine for reversal of retrograde ejaculation.

Due to the heterogeneous nature of the studies included in the review, such as in the different equipment and techniques used, dosage, outcomes measurement and study design, it remains questionable which modality offers the best chances for men with ejaculatory failure. RCTs comparing different treatment options are urgently needed.

Although sperm quality in men with anejaculation or retrograde ejaculation is often impaired, spermatozoa obtained with electrovibratory stimulation were reported to have better quality and a higher patient preference when compared with electroejaculation.[477] [Evidence 1b] However, the quality of semen obtained by electroejaculation was not reported to be significantly different from sperm obtained naturally after successful electroejaculation in a group of men with ejaculatory disorder.[478] [Evidence level 3] If only spermatozoa of poor quality can be retrieved, IVF/ICSI should be considered as first choice of treatment, whereas ICSI is a viable alternative for anejaculatory men in whom IUI or IVF failed.[479,480] [Evidence level 3] The combination of ICSI and electroelaculation may improve the fertility chances of patients with psychogenic anejaculation resistant to conventional treatment modalities.[481] [Evidence level 3]

Fertilisation and pregnancy rates in ICSI of cryopreserved sperm from transrectal electroejaculation are comparable to those of freshly obtained sperm in patients with psychogenic anejaculation.[482] [Evidence level 3]

If no viable spermatozoa can be retrieved with these treatment modalities, surgical sperm retrieval together with IVF and ICSI provides a good alternative option (see Section 15.6). A case study presented a successful outcome of an IVF cycle complicated by failure to produce a sperm sample on the morning of oocyte retrieval, by the use of testicular aspiration of sperm for ICSI.[483] [Evidence level 3]

Anxiolytic drugs and/or sildenafil may also be helpful in cases of ejaculation failure associated with erectile dysfunction caused by psychogenic disorders.[484] [Evidence level 1a]

The relative merits of electroejaculation and surgical sperm retrieval remain uncertain.

Recommendations

Number	Recommendation
89	Treatment of ejaculatory failure can restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction procedures. However, further evaluation of different treatment options is needed. **[2004]**

8 Ovulation disorders

8.1 Introduction

Ovulation disorders, presenting as menstrual disturbance, are the cause of infertility in around 25% of couples who have difficulty conceiving. The World Health Organization (WHO) categorises ovulation disorders into three groups:

- Group I ovulation disorders are caused by hypothalamic pituitary failure. This category includes conditions such as hypothalamic amenorrhea and hypogonadotrophic hypogonadism. Typically, women present with amenorrhoea (primary or secondary) which is characterised by low gonadotrophins and oestrogen deficiency. Approximately 10% of women with ovulation disorders have a group I ovulation disorder.
- Group II ovulation disorders are defined as dysfunctions of the hypothalamic-pituitary-ovarian axis. This category includes conditions such as polycystic ovary syndrome and hyperprolactinaemic amenorrhoea. Around 85% of women with ovulation disorders have a group II ovulation disorder.
- Group III ovulation disorders are caused by ovarian failure. Around 5% of women with ovulation disorders have a group III ovulation disorder.

This chapter focuses on the management of women with WHO group I or group II ovulation disorders. These two groups of disorders can be managed with drug treatments, lifestyle modifications and/or surgical interventions. Women with a group III ovulation disorder ('ovarian failure') can only conceive through oocyte donation and then IVF treatment (see Chapters 18 and 15, respectively).

8.2 WHO Group I ovulation disorders

Introduction

WHO Group I ovulation disorders, also known as hypogonadotrophic hypogonadism, are caused by hypothalamic pituitary failure. Women with these conditions typically present with amenorrhoea (primary or secondary), often called hypothalamic amenorrhoea, which is characterised by low gonadotrophins levels and oestrogen deficiency.

Hypogonadotrophic hypogonadism has usually an unknown cause. However, it may be congenital, for example when it is associated with anosmia it is known as Kallmann's syndrome. Hypothalamic amenorrhoea commonly develops as a result of low body weight or excessive exercise. Hypopituitarism is uncommon and, as with all causes of infertility, must be appropriately investigated before ovulation induction is considered.

Treatment of WHO Group I ovulation disorders depends on the diagnosis. Treatment options include:

- lifestyle interventions (normalising weight and exercise)
- pulsatile gonadotrophin-releasing hormone (GnRH) ('GnRH pump')
- gonadotrophins (human menopausal gonadotrophin [hMG]).

Review question

What is the effectiveness and safety of ovulation induction strategies in women with WHO Group I ovulation disorders?

2013 Update

Description of included studies

In the 2004 version of this guideline two studies were identified examining the value of pulsatile GnRH in women with WHO Group I ovulation disorders. One was a case series study which reported the use of pulsatile GnRH in women with WHO Group I ovulation disorders and a study comparing hMG with pulsatile GnRH. Evidence from these two studies is reported below.

No prospective comparative studies were found in the 2004 or 2013 reviews that reported on the use of gonadotrophins, GnRH analogues or lifestyle interventions for women with WHO Group I ovulation disorders.

Evidence profile

Five reviews were undertaken to answer this review question. These were a comparison of:

- drugs compared with no treatment or placebo for women with WHO Group I ovulation disorders
- different types of drugs for women with WHO Group I ovulation disorders
- lifestyle interventions compared with no treatment or placebo for women with WHO Group I ovulation disorders
- different lifestyle interventions for women with WHO Group I ovulation disorders
- lifestyle interventions versus drugs.

2013 Update

Pulsatile gonadotrophin-releasing hormone

In case series studies, pulsatile GnRH induces ovulation, achieving cumulative pregnancy rates of up to 82% in women with hypogonadotrophic hypogonadism and 95% in women with weight-related amenorrhoea after 12 cycles. The corresponding figures for live birth rates were 65% and 85%, respectively.[571–573] [Evidence level 3]

A study comparing hMG with pulsatile GnRH reported no difference in multiple gestation rates (14.8% versus 8.3%) but a lower rate of triplets in the pulsatile GnRH group.[575] [Evidence level 2b]

Evidence to recommendations

Relative value placed on the outcomes considered

Clinical pregnancies and live full-term singleton births were selected as the primary outcomes since they allow clinicians to inform women of their chances of conception and consequent live birth. However, both studies only reported live birth rates and not live full-term singleton live births. Secondary outcomes relating to adverse effects of the treatments were also searched for in the evidence as they provide women with information of the potential risks of treatment.

Trade-off between clinical benefits and harms

The evidence that was identified on pulsatile GnRH was of very low quality. The guideline development group (GDG) highlighted that the population in the case series data was not the same as the population considered in this question, but as this was the only data identified that considered GnRH it was included. The case series data suggested that pulsatile GnRH improves pregnancy and live birth rates and reduces the risk of triplets. There was no evidence identified for any of the other ovulation induction strategies covered by the clinical question. Consequently, the GDG did not make recommendations on interventions other than pulsatile GnRH. The evidence from case series concurred with the GDG members' clinical opinions.

2013 Update

Quality of evidence

The quality of the evidence was very low. Nevertheless, the benefits of pulsatile GnRH identified in the case series data concurred with the clinical experience of the GDG members. Therefore, the GDG considered that the 2004 recommendation on pulsatile GnRH reflected standard practice and that, in the absence of any new evidence, it should remain unchanged in the guideline.

Other considerations

The GDG empasised that appropriate expertise is needed when using pulsatile GnRH.

The GDG's clinical opinion was that a low body mass index (BMI), irregular menstruation or amenorrhea and/or a high level of exercise are associated with anovulation. To establish evidence for this would require studies that included women with these risk factors and were of sufficient power to undertake subgroup analyses. The GDG acknowledged that such studies were unlikely to be undertaken. In the absence of evidence, the GDG considered that advice to women with a low BMI to increase their weight and to moderate high levels of exercise was very unlikely to be harmful and could be beneficial. Therefore it should be considered as part of the initial advice offered to women seeking treatment for ovulation disorders (see Chapter 5). This might include information from a dietician, warnings of the potential risks in pregnancy and, if appropriate, the offer of access to exercise advice and psychosocial support.

Equalities

The people considered in this review were

- People in same sex relationships who cannot have heterosexual intercourse.
- Specific patient subgroups listed in the guideline Scope who may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, or who have been advised not to, have heterosexual intercourse
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
- People who are preparing for cancer treatment who may wish to preserve their fertility.

There were no specific issues that needed to be addressed with respect to any of these subgroups for this review.

Recommendations

Number	Recommendation
90	Advise women with WHO Group I anovulatory infertility that they can improve their chance of regular ovulation, conception and an uncomplicated pregnancy by: • increasing their body weight if they have a BMI of less than 19 **and/or** • moderating their exercise levels if they undertake high levels of exercise. **[new 2013]**
91	Offer women with WHO Group I ovulation disorders pulsatile administration of gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity to induce ovulation. **[2013]**

8.3 WHO Group II ovulation disorders

Introduction

Polycystic ovary syndrome (PCOS) is a heterogenous group of disorders affecting 5–10% of women of reproductive age and is the most commonly encountered type of WHO Group II ovulation disorder. Common clinical features of PCOS include oligo- or amenorrhoea, anovulatory infertility, obesity and hyperandrogenism. Insulin resistance plays an important role in the pathogenesis of the disorder. Ultrasound examination of the ovaries reveals characteristic appearances, with multiple (12 or more) small antral follicles present. In 2003, the Rotterdam consensus meeting (sponsored by European Society of Human Reproductive and Embryology [ESHRE/American Society for Reproductive

Medicine [ASRM]) agreed a definition for PCOS, namely the presence of at least two of the following three criteria with the exclusion of other causes of menstrual cycle disturbance or androgen excess:

- oligo-ovulation and/or anovulation,
- hyperandrogenism (clinical and/or biochemical)
- polycystic ovaries on ultrasound scan;.

Options for treatment include:

- weight loss
- medical treatment
- second-line treatments including laparoscopic ovarian diathermy (LOD) and injectable gonadotrophin ovulation induction
- assisted conception (usually in vitro fertilisation [IVF]).

Obesity is associated with increased insulin resistance and an exacerbation of PCOS. Weight loss is therefore often the first line treatment for obese PCOS patients.

Medical treatment of anovulatory infertility due to PCOS is often initially undertaken with the oral anti-oestrogen clomifene citrate and/or the oral insulin sensitising agent metformin hydrochloride (though metformin is unlicensed for this indication). Clomifene is associated with a multiple pregnancy rate of around 10% and so ultrasound follicular monitoring, particularly in the first cycle of treatment, is indicated. The requirement for access to scan monitoring may limit the ability for prescribing in primary care. Conventionally, clomifene is taken as a single daily dose for 5 days from early in the menstrual cycle. If ovulation is not achieved at the lowest dose (usually 50 mg) then in subsequent cycles the dose is escalated. If no ovulation occurs at doses of 100–150 mg daily then the term 'clomifene resistance' is used. Metformin is taken every day in divided doses and since the aim is to restore 'normal' mono-ovulation then arguably no scan monitoring is required. The most common side-effect is gastro-intestinal upset.

Potential advantages of laparoscopy include the ability to assess the pelvis for additional treatable causes of infertility, such as endometriosis and/or adhesions, and to assess tubal patency. An electrical current (diathermy) is applied to a number of points on each ovary. If successful, then mono-ovulation occurs which can continue for months and/or years without the need for ultrasound scan monitoring. Risks of LOD include those associated with surgery and general anaesthesia, and a low risk of causing ovarian damage and/or peri-ovarian adhesions.

Gonadotrophin ovulation induction involves sub-cutaneous injections once daily for around 10–20 days per cycle. Frequent ultrasound scan monitoring is required and risks include multiple pregnancy and, uncommonly, ovarian hyperstimulation syndrome (OHSS).

Assisted conception is the third-line treatment option for WHO Group II ovulation disorders. The most important risks of IVF are OHSS (particularly for women with PCOS) and multiple pregnancy (see Chapter 15).

Hyperprolactinaemic amenorrhoea is another, though much less common, WHO Group II ovulation disorder. Clinically, in addition to amenorrhoea and infertility, women with the condition have galactorrhoea. The most common source of the excess prolactin production is a pituitary microadenoma. Treatment is with dopamine agonists.

The evidence for the clinical effectiveness and safety of these interventions for WHO Group II ovulation disorders is reviewed in this section.

Growth hormone as an adjunct to ovulation induction therapy

For women with clomifene citrate-resistant PCOS, co-treatment with recombinant human growth hormone plus gonadotrophin-releasing hormone agonist (GnRHa), or growth hormone plus hMG, has no significant effect on the amount and duration of hMG used, ovulation (respectively: 93% versus 93%; 88% versus 100%) and pregnancy rates (respectively: 26% versus 20%; 25% versus 13%) when compared with GnRHa and hMG alone.[569] [Evidence level 1b] It has been suggested that co-

treatment with growth hormone may improve ovarian responses to exogenous gonadotrophins, thus reducing the overall gonadotrophin requirement.[570]

Pulsatile gonadotrophin-releasing hormone

A systematic review of three RCTs, one non-RCT and 18 uncontrolled case series studies found insufficient evidence for or against a beneficial effect of pulsatile GnRH in women with clomifene citrate-resistant PCOS when compared with other ovulatory agents (hMG, follicle-stimulating hormone [FSH], with and without pretreatment with GnRHa).[574] [Evidence level 1a]

Review question

What is the effectiveness and safety of ovulation induction strategies in women with WHO Group II ovulation disorders?

Description of included studies

In total, 29 papers reporting on 29 separate randomised controlled trials (RCTs) were included in this review (Abdel et al., 1990; Abu Hashim et al., 2010; Atay et al., 2006; Badawy et al., 2008; Badawy et al., 2009; Bayar et al., 2006; Bayram et al., 2004; Begum et al., 2009; Cheng et al., 2010; Dasari et al., 2009; Dehbashi et al., 2009; Elsedeek et al., 2011; Farquhar et al., 2002; George et al., 2003; Hwu et al., 2005; Johnson et al., 2010; Kamel et al., 2004; Karimzadeh et al., 2010; Legro et al., 2007; Lopez et al., 2004; Malkawi & Qublan, 2002; Moll et al., 2006; Palomba et al., 2005; Qublan et al., 2007; Sahin et al., 2004; Sohrabvand et al., 2006; Vandermolen et al., 2001; Zain et al., 2009; Zakherah et al., 2010).

Evidence profile

The evidence is presented separately for women receiving first line treatment for WHO Group II ovulation disorders and for those who are known to be clomifene resistant. Treatments were compared in three main groups:

- drugs currently used as standard treatment compared with non-standard drugs
- surgical interventions compared with drugs
- lifestyle modifications (such as changes to diet and level of exercise) compared with drugs and/or surgery.

The evidence is presented in the following profiles:

- Ovarian stimulation as first-line treatment in women with WHO Group II ovulation disorders:
    - clomifene citrate or tamoxifen compared with other drugs (see Table 8.2)
    - surgery compared with drugs (see Table 8.3)
    - lifestyle modification compared with drugs and/or surgery (see Table 8.4).
- Ovarian stimulation treatment in women with WHO Group II ovulation disorders who are known to be clomifene citrate resistant:
    - metformin plus clomifene compared with other drugs (see Table 8.5)
    - surgery compared with drugs (see Table 8.6)
    - lifestyle compared with drugs and/or surgery (see Table 8.7).

Definitions

The studies used various definitions of PCOS and also of clomifene citrate resistance, particularly in studies conducted prior to 2003 when the Rotterdam consensus criteria regarding PCOS were published. These are outlined in Table 8.1.

Table 8.1 The definition of PCOS and clomifene citrate resistance variation across studies

Study	Definition of PCOS	Definition of clomofene citrate resistance
Atay et al., 2006	A history of oligo- or amenorrhoea and ovaries with at least 10 subcapsular cysts 2–10 mm in diameter and hyperechogenic stroma	Not applicable – First-line treatment studies
Badawy et al., 2009	Revised 2003 consensus diagnostic criteria for PCOS (European Society of Human Reproductive and Embryology [ESHRE/American Society for Reproductive Medicine [ASRM], 2004)	
Bayar et al., 2006	2003 Rotterdam criteria	
Dasari et al., 2009	Rotterdam revised criteria	
Dehbashi et al., 2009	2003 ESHRE/ASRM Rotterdam consensus	
Elsedeek et al., 2011	Rotterdam criteria, with anovulation as one of the two required criteria	
Johnson et al., 2010	Anovulatory or oligo-ovulatory women with PCOS defined by the Rotterdam consensus criteria	
Karimzadeh et al., 2010	According to 2003 Rotterdam criteria, as including at least two of the following three criteria: chronic anovulation; clinical or biochemical signs of hyperandrogenism; and polycystic ovary morphology shown on ultrasound scan	
Legro et al., 2007	Oligomenorrhea (with a history of no more than eight spontaneous menses per year) and hyperandrogenemia (with elevated testosterone level documented within the previous year in an outpatient setting on the basis of local laboratory results, with a predetermined cutoff level set by the principal investigator at each study site)	
Lopez et al., 2004	2003 ESHRE/ASRM Rotterdam consensus	
Moll et al., 2006	Revised Rotterdam 2003 consensus	
Palomba et al., 2005	National Institutes of Health criteria	
Qublan et al., 2007	Rotterdam ESHRE/ASRM workshop group	
Sahin et al., 2004	Three or more of the following criteria: Polycystic ovaries on pelvic ultrasound examination, oligo/amenorrhoea, hirsutism, hyperandrogenaemia (total testosterone > 80 ng/dl and/or free testosterone > 3.18 pg/ml) and elevated serum LH:FSH levels ratio	
Zain et al., 2009	Rotterdam 2003 criteria	
Abdel et al., 1990	Not clearly defined. Inclusion criteria: • Infertile women with oligomenorrhoea or amenorrhoea attributable to polycystic ovarian disease and had failed to respond to CC therapy in incremental doses • No other factor contributing to their infertility as verified by HSG, diagnostic laparoscopy and repeated semen analysis	Failed previously to respond to CC therapy in incremental doses up to 150 mg daily for 5 days for 3 cycles

Study	Definition of PCOS	Definition of clomofene citrate resistance
	• Normal prolactin levels • Euthyroid • Normal serum DHEAS	
Abu Hashim et al., 2010	Rotterdam 2003 criteria	Previously treated with 150 mg of CC daily for 5 days per cycle, for 3 cycles with persistent anovulation
Badawy et al., 2008	Revised 2003 consensus on diagnostic criteria and long-term health risks related to PCOS (Rotterdam ESHRE/ASRM, 2004)	Failure of ovulation after administration of 150 mg of CC for 5 days
Bayram et al., 2004	Not explicity stated. Inclusion criteria: • - Chronic anovulation (WHO group II) and PCO diagnosed by TVUS • - CC-resistant PCOS	Persistent anovulation after taking 150 mg of CC daily for 5 days
Begum et al., 2009	2003 Rotterdam criteria	Patients with PCOS who failed to ovulate by taking 100 mg of CC/day for 5 days in 2 consecutive cycles
Cheng et al., 2010	Rotterdam revised criteria	Failure to ovulate with a CC dose of 150 mg/day for 5 days from day 3 of the period for 3 months consecutively
Farquhar et al., 2002	Not explicitly defined. Inclusion criteria were: • age 20 to 38 years • clomifene citrate resistance • infertility > 12 months duration • polycystic ovaries on ultrasound scan • BMI < 33 kg/m^2 for women of European descent and < 35 kg/m^2 for women of Pacific Island or NZ Maori descent • normal semen analysis (WHO criteria)	No ovulation after 1 or more cycles of 150 mg of CC from day 2 to day 6 each month
George et al., 2003	Based on clinical features of oligomenorrhoea and hyperandrogenism, along with either biochemical abnormalities of a raised LH/FSH ratio or LH or ultrasound features of polycystic ovary	Failure to ovulate to dose schedule of 200 mg/day for 5 days
Hwu et al., 2005	Chronic oligomenorhea • clinical symptoms of hyperandrogenism or biochemical hyperandrogenemia • polycystic ovaries seen on ultrasound (12 or more follicles 2–9 mm in diameter in each ovary)	Failure to follicular development after CC treatment up to 150 mg daily for 5 days for 2 cycles
Kamel et al., 2004	Based on finding bilateral enlarged ovaries with finding at least 10 small follicles (2–8 mm), in one plane, in each ovary encircling the ovarian cortex, together with an expanded, brightly echogenic stromal compartment	CC (starting from 100mg daily from day 3–7 of the cycle for 2 cycles and if anovulation persisted in the third cycle, 250 mg daily from day 3–7) with ovulation monitoring by serial TVUS

Study	Definition of PCOS	Definition of clomofene citrate resistance
Malkawi & Qublan, 2002	Presence of polycystic ovaries on vaginal ultrasound examination combined with 3 or more of the following criteria: oligomenorrhea (< 6 menstrual periods in the preceding year), hirsutism (when Ferriman-Gallwey score > 7), hyperandrogenemia (elevated free testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), and elevated concentrations of LH/FSH ratio > 2	Failure to ovulate or to conceive after CC treatment up to daily dose of 150 mg from cycle day 5–9 for at least 3 consecutive cycles
Sohrabvand et al., 2006	2003 Rotterdam criteria of PCOS	Patients who had failed to become pregnant after 3 courses of 150 mg of clomifene citrate
Vandermolen et al., 2001	Not explicitly defined. Inclusion criteria: • age 18–35 years • desire to become pregnant • anovulation/CC-resistant PCOS • hyperandrogenism (androstenedione, free T or total T or clinical evidence of hirsutism) • normal levels of TSH, PRL and 17-hydroxyprogesterone • normal renal function • normal results on liver function tests • tubal patency on HSG • partner with normal semen analysis (WHO 1999 criteria)	Anovulatory response to a 5-day course of CC, 150 mg/day
Zakherah et al., 2010	2003 ESHRE/ASRM Rotterdam consensus	Lack of ovulation after 6 consecutive induction cycles with 50 mg of CC. then with 150 mg daily for 5 days

ASRM American Society for Reproductive Medicine, CC clomofene citrate, DHEAS dehydroepiandrosterone sulphate, ESHRE European Society of Human Reproductive and Embryology, FSH follicle-stimulating hormone, LH luteinizing hormone, HSG hysterosalpingography, PCOS polycystic ovary syndrome, PRL prolactin, TSH thyroid-stimulating hormone, TVUS transvaginal ultrasound.

First-line ovarian stimulation treatment for women with polycystic ovary syndrome (PCOS)

Clomifene citrate or tamoxifen compared with other drugs

Fourteen of the 29 papers reported on trials of clomifene citrate or tamoxifen compared with other drugs as first-line ovarian stimulation treatment in women with PCOS (Atay et al., 2006; Badawy et al., 2009; Bayar et al., 2006; Dasari et al., 2009; Dehbashi et al., 2009; Elsedeek et al., 2011; Johnson et al., 2010; Karimzadeh et al., 2010; Legro et al., 2007; Lopez et al., 2004; Moll et al., 2006; Palomba et al., 2005; Sahin et al., 2004; and Zain et al., 2009).

Surgery compared with drugs

No papers reported on trials of surgery compared with drugs for first-line ovarian stimulation treatment in women with PCOS.

Lifestyle modification compared with drugs or surgery

One paper reported on a trial comparing a low calorie diet with exercise compared with clomifene citrate as a first-line ovarian stimulation treatment in women with PCOS (Karimzadeh et al., 2010). Only women with a BMI of 25–29.9 were included in the study. Another paper reported on a trial

comparing a low calorie diet to metformin (Qublan et al., 2007). Only women with a BMI of over 30 were included in the study.

Ovarian stimulation treatment in women who are clomifene citrate resistant

Metformin plus clomifene compared with other drugs

Nine papers reported on trials that compared metformin in combination with clomifene citrate with other drugs as ovarian stimulation treatment for women with PCOS who were resistant to clomifene citrate (Abu Hashimet al., 2010; Begumet al., 2009; Badawyet al., 2008; Chenget al., 2010; Georgeet al., 2003; Hwuet al., 2005; Malkawi & Qublan, 2002; Sohrabvandet al., 2006; Vandermolenet al., 2001).

Surgery compared with drugs

Six papers reported on trials that compared drugs with surgery as treatments to stimulate the ovaries in women with PCOS who were clomifene citrate resistant (Abdelet al., 1990; AbuHashim et al., 2010; Bayram et al., 2004; Farquhar et al., 2002; Kamel et al., 2004; Zakherah et al., 2010).

Lifestyle compared with drugs or surgery

No papers were found that reported trials of lifestyle modifications compared with drugs or surgery or other lifestyle modifications in women with PCOS who are clomifene citrate resistant.

Table 8.2 GRADE findings for comparison of clomifene citrate or tamoxifen with other drugs (first-line treatment for PCOS)

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Metformin vs. clomifene citrate					
4 (Johnson et al., 2010; Legro et al., 2007; Palomba et al., 2005; and Zain et al., 2009)	54/331 (16%) women	75/334 (22%) women	RR 0.8 (0.3 to 2.3) [i]	45 fewer per 1000 (from 164 fewer to 301 more)	Very low
Metformin + clomifene citrate vs. clomifene citrate					
5 (Johnson et al., 2010; Legro et al., 2007; Moll et al., 2006; Sahin et al., 2004; and Zain et al., 2009)	103/404 (25%) women	99/228 (43%) women	RR 1.1 (0.8 to 1.3)	45 fewer per 1000 (from 164 fewer to 301 more)	Very low
Metformin vs. Metformin + clomifene citrate					
3 (Johnson et al., 2010; Legro et al., 2007; and Zain et al., 2009)	28/281(10%) women	79/282 (28%) women	RR 0.4 (0.2 to 0.8) [i]	168 fewer per 1000 (from 62 fewer to 221 fewer)	Very low
Letrozole vs. clomifene citrate					
1 (Dehbashi et al., 2009)	10/50 (20%) women	6/50 (12%) women	RR 1.7 (0.7 to 4.2)	80 more per 1000 (from 41 fewer to 389 more)	Low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. clomifene citrate					
1 (Lopez et al., 2004)	11/38 (29%) women	6/38 (16%) women	RR 1.8 (0.8 to 4.5)	131 more per 1000 (from 39 fewer to 545 more)	Very low
Clinical pregnancy					
Metformin vs. clomifene citrate					
5 (Karimzadeh et al., 2010; Zain et al., 2009; Johnson et al., 2010; Palomba et al., 2005; Legro et al., 2007)	79/421 (19%) women	97/424 (23%) women	RR 0.9 (0.4 to 1.8) [i]	27 fewer per 1000 (from 130 fewer to 185 more)	Very low
Metformin + clomifene citrate vs. clomifene citrate					
7(Karimzadeh et al., 2010; Sahin et al., 2004; Dasari et al., 2009; Legro et al., 2007; Zain et al., 2009; Johnson et al., 2010; Moll et al., 2006)	158/508(31%) women	138/522 (26%) women	RR 1.2 (1.0 to 1.4)	45 more per 1000 (from 1 more to 108 more)	Very low
Metformin vs. metformin + clomifene citrate					
4 (Karimzadeh et al., 2010; Legro et al., 2007; Zain et al., 2009; Johnson et al., 2010)	48/371 (13%) women	105/370 (28%) women	RR 0.5 (0.3 to 1.0) [i]	133 fewer per 1000 (from 204 fewer to 1 fewer)	Very low
Letrozole vs. clomifene citrate					
3 (Atay et al., 2006; Dehbashi et al., 2009; Elsedeek, 2011)	44/160 (28%) women	28/162 (17%) women	RR 1.6 (1.0 to 2.4)	99 more per 1000 (from 7 more to 237 more)	Low
rFSH vs. clomifene citrate					
1(Lopez et al., 2004)	16/38 (42%) women	9/38 (24%) women	RR 1.8 (1.0 to 3.5)	185 more per 1000 (from 24 fewer to 597 more)	Low

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcomes					
Metformin vs. clomifene citrate (death of woman)					
1 (Legro et al., 2007)	1/208 (1%) women	0/209 (0%) women	RR 3.0 (0.1 to 73.6)	Not estimable	Very low
Metformin vs. clomifene citrate (miscarriage)					
4 (Zain et al., 2009; Johnson et al., 2010; Palomba et al., 2005 Legro et al. 2007)	17/331 (5%) women	20/334 (6%) women	RR 0.9 (0.3 to 2.4) [i]	9 fewer per 1000 (from 42 fewer to 84 more)	Very low
	17/73 (23%) pregnancies	20/108 (43%) pregnancies	RR 1.4 (0.4 to 5.0) [i]	65 more per 1000 (from 117 fewer to 735 more)	
Metformin vs. clomifene citrate (ectopic pregnancy)					
2 (Johnson et al., 2010; Legro et al., 2007)	0/243 (0%) women	2/245 (1%) women	RR 0.2 (0.0 to 4.2)	7 fewer per 1000 (from 8 fewer to 26 more)	Very low
	0/32 (0%) pregnancies	2/76 (3%) pregnancies	RR 0.7 (0.0 to 13.2)	9 fewer per 1000 (from 26 fewer to 322 more)	
Metformin vs. clomifene citrate (gestational hypertension)					
2 (Johnson et al., 2010; Palomba et al., 2005)	1/85 (1%) women	0/86 (0%) women	RR 3.0 (0.1 to 71.9)	Not estimable	Very low
	1/45 (2%) pregnancies	0/40 (0%) pregnancies	RR 2.5 (0.1 to 59.6)	Not estimable	
Metformin vs. clomifene citrate (gestational diabetes)					
2 (Johnson et al. 2010; Legro et al., 2007)	2/244 (1%) women	9/245 (4%) women	RR 0.2 (0.1 to 1.0)	29 fewer per 1000 (from 35 fewer to 1 more)	Very low
	2/32 (6%) pregnancies	9/64 (14%) pregnancies	RR 0.6 (0.2 to 2.6)	53 fewer per 1000 (from 120 fewer to 224 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. clomifene citrate (preterm labour or premature rupture of membranes)					
2 (Johnson et al., 2010; Legro et al., 2007)	1/244 (<1%) women	2/245 (1%) women	RR 0.6 (0.1 to 4.5)	3 fewer per 1000 (from 8 fewer to 28 more)	Very low
	1/32 (3%) pregnancies	2/64 (3%) pregnancies	RR 1.0 (0.2 to 5.9)	1 fewer per 1000 (from 26 fewer to 153 more)	
Metformin vs. clomifene citrate (intrauterine fetal death)					
1 (Palomba et al., 2005)	1/50 (2%) women	1/50 (2%) women	RR 1.0 (0.1 to 15.6)	0 fewer per 1000 (from 19 fewer to 291 more)	Moderate
	1/31 (3%) pregnancies	1/26 (4%) pregnancies	RR 0.8 (0.1 to 12.8)	6 fewer per 1000 (from 36 fewer to 452 more)	
Metformin vs. clomifene citrate (placenta previa)					
1 (Legro et al., 2007)	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
	0/18 (0%) pregnancies	1/50 (2%) pregnancies	RR 0.9 (0.0 to 21.0)	2 fewer per 1000 (from 19 fewer to 401 more)	
Metformin vs. clomifene citrate (postpartum haemorrhage)					
1 (Legro et al., 2007)	0/208 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.2)	8 fewer per 1000 (from 9 fewer to 30 more)	Very low
	0/18 (0%) pregnancies	2/50 (4%) pregnancies	RR 0.5 (0.0 to 10.7)	18 fewer per 1000 (from 39 fewer to 387 more)	
Metformin vs. clomifene citrate (placental abruption)					
1 (Legro et al., 2007)	0/208 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.2)	2 fewer per 1000 (from 19 fewer to 401 more)	Very low
	0/18 (0%) pregnancies	2/50 (4%) pregnancies	RR 0.5 (0.0 to 10.7)	3 fewer per 1000 (from 5 fewer to 34 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. clomifene citrate (pregnancy loss in second or third trimester)					
1 (Legro et al., 2007)	0/208 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.2)	8 fewer per 1000 (from 9 fewer to 30 more)	Very low
	0/18 (0%) pregnancies	2/62 (3%) pregnancies	RR 0.7 (0.0 to 13.2)	11 fewer per 1000 (from 31 fewer to 394 more)	
Metformin vs. clomifene citrate (cervical incompetence or preterm labour)					
1 (Legro et al., 2007)	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
	0/18 (0%) pregnancies	1/50 (2%) pregnancies	RR 0.9 (0.0 to 21.0)	2 fewer per 1000 (from 19 fewer to 401 more)	
Metformin vs. clomifene citrate (severe preeclampsia)					
1 (Legro et al., 2007)	0/208 (0%) women	0/209 (0%) women	Not estimable		Low
	0/18 (0%) pregnancies	0/50 (0%) pregnancies	Not estimable		
Metformin vs. clomifene citrate (HELLP syndrome)					
1 (Legro et al., 2007)	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
	0/18 (0%) pregnancies	1/50 (2%) pregnancies	RR 0.9 (0.0 to 21.0)	2 fewer per 1000 (from 19 fewer to 401 more)	
Metformin + clomifene citrate vs. clomifene citrate (death of woman)					
1 (Legro et al., 2007)	0/209 (0%) women	0/209 (0%) women	Not estimable		Low
Metformin + clomifene citrate vs. clomifene citrate (preterm birth)					
2 (Sahin et al., 2004; Moll et al., 2006)	5/122 (4%) women	3/124 (2%) women	RR 1.6 (0.4 to 5.9)	14 more per 1000 (from 14 fewer to 118 more)	Very low
	5/49 (10%) pregnancies	3/55 (5%) pregnancies	RR 1.7 (0.5 to 6.0)	35 more per 1000 (from 30 fewer to 274 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (miscarriage)					
5 (Sahin et al., 2004; Legro et al., 2007; Zain et al., 2009; Johnson et al., 2010; Moll et al., 2006)	38/404 (9%) women	26/408 (6%) women	RR 1.5 (0.9 to 2.3)	29 more per 1000 (from 6 fewer to 83 more)	Very low
	38/156 (24%) pregnancies	26/137 (19%) pregnancies	RR 1.3 (0.9 to 2.0)	57 more per 1000 (from 28 fewer to 190 more)	
Metformin + clomifene citrate vs. clomifene citrate (pregnancy loss in second or third trimester)					
1 (Legro et al., 2007)	4/209 (2%) women	2/209 (1%) women	RR 2.0 (0.4 to 10.8)	10 more per 1000 (from 6 fewer to 94 more)	Very low
	4/80 (5%) pregnancies	2/62 (3%) pregnancies	RR 1.6 (0.3 to 8.2)	18 more per 1000 (from 23 fewer to 232 more)	
Metformin + clomifene citrate vs. clomifene citrate (gestational diabetes)					
3 (Legro et al., 2007; Johnson et al., 2010; Moll et al., 2006)	7/355 (2%) women	11/359 (3%) women	RR 0.7 (0.3 to 1.6)	10 fewer per 1000 (from 22 fewer to 19 more)	Very low
	7/128 (5%) pregnancies	11/116 (9%) pregnancies	RR 0.5 (0.2 to 1.3)	45 fewer per 1000 (from 74 fewer to 27 more)	
Metformin + clomifene citrate vs. clomifene citrate (gestational hypertension)					
2 (Legroet al., 2007; Moll et al., 2006)	5/146 (3%) women	2/150 (1%) women	RR 2.3 (0.5 to 9.9)	17 more per 1000 (from 6 fewer to 119 more)	Very low
	5/63 (8%) pregnancies	2/66 (3%) pregnancies	RR 2.3 (0.5 to 10.1)	41 more per 1000 (from 14 fewer to 275 more)	
Metformin + clomifene citrate vs. clomifene citrate (pre-eclampsia)					
2 (Legroet al., 2007; Moll et al., 2006)	8/320 (3%) women	8/253 (3%) women	RR 0.7 (0.1 to 3.4) [i]	10 fewer per 1000 (from 28 fewer to 74 more)	Very low
	8/109 (7%) pregnancies	8/102 (8%) pregnancies	RR 0.8 (0.3 to 2.1)	13 fewer per 1000 (from 53 fewer to 89 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (severe preeclampsia)					
1 (Legro et al., 2007)	2/209 (1%) women	0/209 (0%) women	RR 5.0 (0.2 to 103.5)	Not estimable	Very low
	2/65 (3%) pregnancies	0/50 (0%) pregnancies	RR 3.9 (0.2 to 78.7)	Not estimable	
Metformin + clomifene citrate vs. clomifene citrate (HELLP syndrome)					
1 (Legro et al., 2007)	1/209 (<1%) women	1/209 (<1%) women	RR 1.0 (0.1 to 15.9)	0 fewer per 1000 (from 4 fewer to 71 more)	Very low
	1/65 (2%) pregnancies	1/50 (2%) pregnancies	RR 0.8 (0.1 to 12.0)	5 fewer per 1000 (from 19 fewer to 220 more)	
Metformin + clomifene citrate vs. clomifene citrate (preterm labour or premature rupture of membranes)					
2 (Legro et al. 2007; Johnson et al., 2010)	4/244 (2%) women	2/245 (1%) women	RR 2.0 (0.4 to 10.9)	8 more per 1000 (from 5 fewer to 81 more)	Very low
	4/84 (5%) pregnancies	2/64 (3%) pregnancies	RR 0.8 (0.1 to 6.0)	16 more per 1000 (from 22 fewer to 218 more)	
Metformin + clomifene citrate vs. clomifene citrate (preterm labour or cervical incompetence)					
1 (Legro et al., 2007)	1/209 (<1%) women	1/209 (<1%) women	RR 1.0 (0.1 to 15.9)	0 fewer per 1000 (from 4 fewer to 71 more)	Very low
	1/65 (2%) pregnancies	1/50 (2%) pregnancies	RR 3.2 (0.2 to 50.0)	5 fewer per 1000 (from 19 fewer to 220 more)	
Metformin + clomifene citrate vs. clomifene citrate (ectopic pregnancy)					
2 (Legro et al., 2007; Johnson et al., 2010)	3/244 (1%) women	2/245 (1%) women	RR 1.4 (0.3 to 7.1)	3 more per 1000 (from 6 fewer to 49 more)	Very low
	3/99 (3%) pregnancies	2/76 (3%) pregnancies	RR 2.5 (0.5 to 13.3)	2 more per 1000 (from 21 fewer to 113 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin + clomifene citrate vs. clomifene citrate (placental abruption)					
1 (Legro et al., 2007)	2/209 (1%) women	2/209 (1%) women	RR 1.0 (0.1 to 7.0)	0 fewer per 1000 (from 8 fewer to 58 more)	Very low
	2/65 (3%) pregnancies	2/50 (4%) pregnancies	RR 3.2 (0.5 to 22.3)	9 fewer per 1000 (from 36 fewer to 171 more)	
Metformin + clomifene citrate vs. clomifene citrate (placenta previa)					
1 (Legro et al., 2007)	1/209 (<1%) women	1/209 (<1%) women	RR 1.0 (0.1 to 15.9)	0 fewer per 1000 (from 4 fewer to 71 more)	Very low
	1/65 (2%) pregnancies	1/50 (2%) pregnancies	RR 3.2 (0.2 to 50.0)	5 fewer per 1000 (from 19 fewer to 220 more)	
Metformin + clomifene citrate vs. clomifene citrate (postpartum haemorrhage)					
1 (Legro et al., 2007)	0/209 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.1)	8 fewer per 1000 (from 9 fewer to 30 more)	Very low
	0/65 (0%) pregnancies	2/50 (4%) pregnancies	RR 0.6 (0.0 to 13.2)	34 fewer per 1000 (from 40 fewer to 86 more)	
Metformin vs. metformin+ clomifene citrate (death of woman)					
1 (Legro et al., 2007)	1/208 (1%) women	0/209 (0%) women	RR 3.0 (0.1 to 73.6)	Not estimable	Very low
Metformin vs. metformin + clomifene citrate (miscarriage)					
2 (Legroet al., 2007; Johnson et al., 2010)	15/281 (5%) women	23/282 (8%) women	RR 0.7 (0.4 to 1.2)	28 fewer per 1000 (from 52 fewer to 19 more)	Very low
	15/47 (32%) pregnancies	23/102 (23%) pregnancies	RR 1.6 (0.9 to 2.8)	142 more per 1000 (from 14 fewer to 413 more)	

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. metformin+ clomifene citrate (ectopic pregnancy)					
2 (Legroet al., 2007; Johnson et al., 2010)	0/243 (0%) women	3/244 (1%) women	RR 0.3 (0.0 to 2.2)	9 fewer per 1000 (from 12 fewer to 15 more)	Very low
	0/32 (0%) pregnancies	3/99 (3%) pregnancies	RR 0.6 (0.1 to 5.2)	12 fewer per 1000 (from 28 fewer to 128 more)	
Metformin vs. metformin+ clomifene citrate (pregnancy loss in second or third trimester)					
1 (Legro et al., 2007)	0/208 (0%) women	4/209 (2%) women	RR 0.1 (0.0 to 2.1)	17 fewer per 1000 (from 19 fewer to 20 more)	Very low
	0/18 (0%) pregnancies	4/80 (5%) pregnancies	RR 0.5 (0.0 to 8.4)	26 fewer per 1000 (from 49 fewer to 372 more)	
Metformin vs. metformin+ clomifene citrate (cervical incompetence or preterm labour)					
1 (Legro et al., 2007)	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
	0/18 (0%) pregnancies	1/65 (2%) pregnancies	RR 1.2 (0.1 to 27.3)	2 more per 1000 (from 15 fewer to 404 more)	
Metformin vs. metformin+ clomifene citrate (gestational hypertension)					
1 (Johnsonet al., 2010)	0/35 (0%) pregnancies	1/35 (3%) women	RR 0.3 (0.0 to 7.9)	19 fewer per 1000 (from 28 fewer to 197 more)	Very low
	0/14 (0%) pregnancies	1/19 (5%) pregnancies	RR 0.4 (0.0 to 10.2)	29 fewer per 1000 (from 52 fewer to 482 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. Metformin + clomifene citrate (mild preeclampsia)					
1 (Legro et al., 2007)	1/208 (<1%) women	7/209 (3%) women	RR 0.1 (0.0 to 1.2)	29 fewer per 1000 (from 33 fewer to 5 more)	Very low
	1/18 (6%) pregnancies	7/65 (11%) pregnancies	RR 0.5 (0.1 to 3.9)	52 fewer per 1000 (from 100 fewer to 314 more)	
Metformin vs. Metformin + clomifene citrate (severe preeclampsia)					
1 (Legro et al., 2007)	0/208 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.2)	8 fewer per 1000 (from 9 fewer to 30 more)	Very low
	0/18 (0%) pregnancies	2/65 (3%) pregnancies	RR 0.7 (0.0 to 13.9)	10 fewer per 1000 (from 30 fewer to 396 more)	
Metformin vs. Metformin + clomifene citrate (HELLP syndrome)					
1 (Legro et al., 2007)	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
	0/18 (0%) pregnancies	1/65 (2%) pregnancies	RR 1.2 (0.1 to 27.3)	2 more per 1000 (from 15 fewer to 404 more)	
Metformin vs. Metformin + clomifene citrate (gestational diabetes)					
2 (Legro et al., 2007; Johnson et al., 2010)	2/244 (1%) women	6/244 (2%) women	RR 0.4 (0.1 to 1.6)	15 fewer per 1000 (from 22 fewer to 15 more)	Very low
	2/32 (6%) pregnancies	6/84 (7%) pregnancies	RR 1.1 (0.3 to 4.2)	5 more per 1000 (from 51 fewer to 226 more)	

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Metformin vs. Metformin + clomifene citrate (preterm labour or premature rupture of membranes)					
2 (Legro et al., 2007; Johnson et al., 2010)	1/244 (<1%) women	4/244 (2%) women	RR 0.3 (0.1 to 2.1)	11 fewer per 1000 (from 16 fewer to 18 more)	Very low
	1/32 (3%) pregnancies	4/84 (5%) pregnancies	RR 0.8 (0.1 to 4.8)	8 fewer per 1000 (from 41 fewer to 180 more)	
Metformin vs. Metformin + clomifene citrate (placental abruption)					
1 (Legro et al., 2007)	0/208 (0%) women	2/209 (1%) women	RR 0.2 (0.0 to 4.2)	8 fewer per 1000 (from 9 fewer to 30 more)	Very low
	0/18 (0%) pregnancies	2/65 (3%) pregnancies	RR 0.7 (0.0 to 13.9)	10 fewer per 1000 (from 30 fewer to 396 more)	
Metformin vs. Metformin + clomifene citrate (placenta previa)					
1 (Legro et al., 2007)	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	3 fewer per 1000 (from 5 fewer to 34 more)	Very low
	0/18 (0%) pregnancies	1/65 (2%) pregnancies	RR 1.2 (0.1 to 27.3)	2 more per 1000 (from 15 fewer to 404 more)	
Metformin vs. Metformin + clomifene citrate (postpartum haemorrhage)					
1 (Legro et al., 2007)	0/209 (0%) women	0/208 (0%) women	Not estimable		Low
	0/65 (0%) pregnancies	0/18 (0%) pregnancies	Not estimable		
Letrozole vs. clomifene citrate (miscarriage)					
3 (Bayar et al., 2006; Badawyet al., 2009; Dehbashiet al., 2009	8/306 (3%) women	5/310 (2%) women	RR 1.6 (0.5 to 4.5)	9 more per 1000 (from 7 fewer to 57 more)	Very low
1(Dehbashiet al., 2009)	3/13 (23%) pregnancies	1/7 (14%) pregnancies	RR 1.6 (0.2 to 12.8)	89 more per 1000 (from 114 fewer to 1683 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. clomifene citrate (miscarriage)					
1 (Lopez et al., 2004)	5/38 (13%) women	3/38 (9%) women	RR 1.7 (0.4 to 6.5)	53 more per 1000 (from 45 fewer to 433 more)	Very low
	5/16 (31%) pregnancies	3/9 (33%) pregnancies	RR 0.9 (0.3 to 3.0)	20 fewer per 1000 (from 237 fewer to 680 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Metformin vs. clomifene citrate					
5 (Johnson et al., 2010; Karimzadeh et al., 2010; Legro et al., 2007; Palomba et al., 2005; Zain et al., 2009)	1/421 (<1%) women	6/424 (1%) women	RR 0.3 (0.1 to 1.4)	10 fewer per 1000 (from 13 fewer to 5 more)	Very low
	1/79 (1%) pregnancies	6/97 (6%) pregnancies	RR 0.4 (0.1 to 1.9)	38 fewer per 1000 (from 57 fewer to 53 more)	
Metformin + clomifene citrate vs. clomifene citrate					
5 (Johnson et al., 2010;Karimzadeh et al., 2010; Legro et al., 2007; Moll et al., 2006; Zain et al., 2009)	5/481 (1%) women	9/488 (2%) women	RR 0.6 (0.2 to 1.7)	8 fewer per 1000 (from 15 fewer to 12 more)	Very low
	5/149 (3%) pregnancies	9/133 (7%) pregnancies	RR 0.5 (0.2 to 1.4)	35 fewer per 1000 (from 56 fewer to 28 more)	
Metformin vs. metformin + clomifene citrate					
4 (Johnson et al., 2010; Karimzadeh et al., 2010; Legro et al., 2007; Zain et al., 2009)	1/371 (0%) women	4/370 (1%) women	RR 0.7 (0.1 to 3.5)	6 fewer per 1000 (from 10 fewer to 11 more)	Very low
	1/48 (2%) pregnancies	4/105 (4%) pregnancies	RR 0.4 (0.1 to 2.0)	11 fewer per 1000 (from 33 fewer to 97 more)	

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Letrozole vs. clomifene citrate					
4 (Johnson et al., 2010; Karimzadeh et al., 2010; Legro et al., 2007; Zain et al., 2009)	1/359 (<1%) women	5/365 (1%) women	RR 0.3 (0.1 to 1.7)	9 fewer per 1000 (from 13 fewer to 9 more)	Very low
	1/57 (2%) pregnancies	5/53 (9%) pregnancies	RR 0.3 (0.1 to 1.3)	71 fewer per 1000 (from 90 fewer to 25 more)	
Letrozole vs. clomifene citrate					
4 (Atay et al.l 2006; Badawy et al., 2009; Bayar et al., 2006; Dehbashi et al., 2009)	1/359 (<1%) women	5/365 (1%) women	RR 0.3 (0.1 to 1.7)	9 fewer per 1000 (from 13 fewer to 9 more)	Very low
	1/57 (2%) pregnancies	5/53 (9%) pregnancies	RR 0.3 (0.1 to 1.3)	71 fewer per 1000 (from 90 fewer to 25 more)	
rFSH vs. clomifene citrate					
1 (Lopez et al., 1994)	3/38 (8%) women	1/38 (3%) women	RR 3.0 (0.3 to 27.6)	53 more per 1000 (from 18 fewer to 699 more)	Very low
	3/16 (19%) pregnancies	1/9 (11%) pregnancies	RR 1.7 (0.2 to 13.9)	77 more per 1000 (from 89 fewer to 1437 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence was reported					
Ovarian hyperstimulation syndrome (OHSS)					
Letrozole + hCG vs. clomifene citrate + hCG					
1 (Badawy et al., 2009)	0/218 (0%) women	0/220 (0%) women	Not estimable		Low
	Number of clinical pregnancies not reported				
rFSH + hCG vs. clomifene citrate + hCG					
1 (Lopez et al., 2004)	2/38 (5%) women	0/38 (0%) women	RR 5.0 (0.3 to 100.8)	Not estimable	Very low
	2/16 (13%) pregnancies	0/9 (0%) pregnancies	RR 2.9 (0.2 to 55.3)	Not estimable	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Congenital abnormalities					
Metformin vs. clomifene citrate					
2 (Legro et al., 1997; Johnson et al., 2010)	0/243 (0%) women	0/245 (0%) women	RR 0.3 (0.0 to 8.1)	3 fewer per 1000 (from 4 fewer to 29 more)	Very low
	0/32 (0%) pregnancies	1/64 (2%) pregnancies	RR 0.3 (0.0 to 7.6)	10 fewer per 1000 (from 15 fewer to 102 more)	
Metformin + clomifene citrate vs. clomifene citrate					
3 (Legro et al., 1997; Johnson et al., 2010; Moll et al., 2006)	4/355 (1%) women	2/356 (1%) women	RR 1.7 (0.4 to 7.1)	4 more per 1000 (from 3 fewer to 34 more)	Very low
	4/128 (3%) pregnancies	2/116 (2%) pregnancies	RR 1.5 (0.4 to 6.0)	8 more per 1000 (from 11 fewer to 86 more)	
Metformin vs. Metformin + clomifene citrate					
2 (Legro et al., 1997; Johnson et al., 2010)	0/243 (0%) women	2/244 (1%) women	RR 0.2 (0.0 to 4.2)	7 fewer per 1000 (from 8 fewer to 26 more)	Very low
	0/32 (0%) pregnancies	2/84 (2%) pregnancies	RR 0.7 (0.0 to 13.9)	7 fewer per 1000 (from 23 fewer to 306 more)	
Letrozole vs. clomifene citrate					
1 (Dehbashi et al., 2009)	0/50 (0%) women	1/50 (2%) women	RR 0.3 (0.0 to 8.0)	Not estimable	Very low
	0/13 (0%) pregnancies	1/7 (14%) pregnancies	RR 0.2 (0.0 to 4.2)	Not estimable	
Patient satisfaction					
No evidence was reported					
Health related quality of life					
No evidence was reported					

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Anxiety and/or depression					
Metformin vs. clomifene citrate (postpartum depression requiring intervention)					
1 (Legro et al., 2007)	0/208 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.2)	Not estimable	Very low
	0/18 (0%) pregnancies	1/50 (2%) pregnancies	RR 0.9 (0.0 to 21.0)	Not estimable	
Metformin + clomifene citrate vs. clomifene citrate (postpartum depression requiring intervention)					
1 (Legro et al., 2007)	0/209 (0%) women	1/209 (<1%) women	RR 0.3 (0.0 to 8.1)	Not estimable	Very low
	0/65 (0%) pregnancies	1/50 (2%) pregnancies	RR 0.3 (0.0 to 6.2)	Not estimable	
Metformin vs. metformin + clomifene citrate (postpartum depression requiring intervention)					
1 (Legro et al., 2007)	0/208 (0%) women	0/209 (0%) women	Not estimable		Low
	0/18 (0%) pregnancies	0/65 (0%) pregnancies	Not estimable		

CI confidence interval, hCG human chorionic gonadotrophin, HELLP heamolysis, elevated liver enzymes and low platelets, OHSS ovarian hyperstimulation syndrome, PCOS polycystic ovary syndrome, rFSH recombinant follicle-stimulating hormone, RR relative risk

Table 8.3 GRADE findings for surgery compared with drugs (first-line treatment for PCOS)

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
No evidence reported					
Clinical pregnancy					
No evidence reported					
Adverse pregnancy outcome					
No evidence reported					
Multiple pregnancies (the number of pregnancies with more than one fetus)					
No evidence reported					
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
No evidence reported					
Congenital abnormalities					
No evidence reported					

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, OHSS ovarian hyperstimulation syndrome, PCOS polycystic ovary syndrome, RR relative risk

Table 8.4 GRADE findings for comparison of lifestyle modification compared with drugs or surgery (first-line treatment for PCOS)

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
No evidence reported					
Clinical pregnancy					
Low calorie diet + exercise vs. clomifene citrate					
1(Karimzadeh et al., 2010)	15/75 (20%) women	11/90 (12%) women	RR 1.6 (0.8 to 3.4)	78 more per 1000 (from 24 fewer to 287 more)	Very low
Low calorie diet + exercise vs. metformin					
2 (Karimzadeh et al., 2010; Qublan, 2007)	23/99 (23%) women	19/112 (17%) women	RR 1.3 (0.8 to 2.3)	56 more per 1000 (from 39 fewer to 217 more)	Very low
Low calorie diet + exercise vs. clomifene citrate + metformin					
1(Karimzadeh et al., 2010)	15/75 (20%) women	13/88 (14%) women	RR 1.4 (0.7 to 2.7)	55 more per 1000 (from 43 fewer to 248 more)	Very low
Adverse pregnancy outcome					
1 (Qublan, (2007)	1/24 (4%) women	1/22 (5%) women	RR 0.9 (0.1 to 13.8)	4 fewer per 1000 (from 43 fewer to 581 more)	Low
	1/8 (13%) pregnancies	1/6 (17%) pregnancies	RR 0.8 (0.1 to 9.7)	42 fewer per 1000 (from 157 fewer to 1000 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Low calorie diet + exercise vs. clomifene citrate					
1 (Karimzadeh et al., 2010)	0/75 (0%) women	2/90 (2%) women	RR 0.2 (0.0 to 4.9)	17 fewer per 1000 (from 22 fewer to 87 more)	Low
	0/15 (0%) pregnancies	2/11 (18%) pregnancies	RR 0.2 (0.0 to 2.8)	155 fewer per 1000 (from 180 fewer to 335 more)	
Low calorie diet + exercise vs. metformin					
2 (Karimzadeh et al., 2010; Qublan, 2007)	1/99 (1%) women	1/112 (1%) women	RR 0.9 (0.1 to 13.8)	1 fewer per 1000 (from 8 fewer to 114 more)	Very low
	1/23 (4%) pregnancies	1/19 (5%) pregnancies	RR 0.8 (0.1 to 9.7)	13 fewer per 1000 (from 49 fewer to 459 more)	
Low calorie diet + exercise vs. clomifene citrate + metformin					
1 (Karimzadeh et al., 2010)	0/75 (0%) women	0/88 (0%) women	Not estimable		Low
	0/15 (0%) pregnancies	0/13 (0%) pregnancies	Not estimable		
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
No evidence reported					
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, OHSS ovarian hyperstimulation syndrome, PCOS polycystic ovary syndrome, RR relative risk

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Table 8.5 GRADE findings for comparison of other drugs with clomifene plus metformin (clomifene resistant PCOS)

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Clomifene citrate vs. metformin + clomifene citrate					
2 (Vandermolen et al., 2001; Hwu et al., 2005)	1/55 (2%) women	8/52 (15%) women	RR 0.2 (0.0 to 0.9)	129 fewer per 1000 (from 22 fewer to 149 fewer)	Very low
hMG vs. metformin + clomifene citrate					
1 (George et al., 2003)	6/30 (20%) women	2/30 (7%) women	RR 3.0 (0.7 to 13.7)	133 more per 1000 (from 23 fewer to 846 more)	Very low
Letrozole + metformin vs. metformin + clomifene citrate					
1 (Sohrabvand et al., 2006)	11/30 (37%) women	3/30 (10%) women	RR 3.7 (1.1 to 11.8)	267 more per 1000 (from 14 more to 1084 more)	Very low
Clinical pregnancy					
Clomifene citrate vs. metformin + clomifene citrate					
4 (Hwu et al., 2005; Malkawi & Qublan, 2002; Cheng et al., 2010; Vandermolen et al., 2001)	9/97(9%) women	34/98(35%) women	RR 0.3 (0.2 to 0.5)	246 more per 1000 (from 160 fewer to 295 fewer)	Low
hMG vs. metformin + clomifene citrate					
1 (George et al., 2003)	7/30 (23%) women	5/30 (17%) women	RR 1.4 (0.5 to 3.9)	67 more per 1000 (from 83 fewer to 487 more)	Very low
Letrozole vs. clomifene citrate					
1 (Begumet al., 2009)	13/32 (63%) women	6/32 (19%) women	RR 2.2 (0.9 to 5.0)	200 more per 1000 (from 22 fewer to 762 more)	Very low
Letrozole + metformin vs. metformin + clomifene citrate					
1 (Sohrabvand et al., 2006)	11/30 (37%) women	5/30 (17%) women	RR 2.2 (0.9 to 5.6)	219 more per 1000 (from 11 fewer to 748 more)	Very low

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
uFSH vs. metformin + clomifene citrate					
1 (Abu Hashim et al., 2010)	32/78 (41%) women	18/75 (24%) women	RR 1.7 (1.1 to 2.8)	170 more per 1000 (from 12 more to 425 more)	Moderate
Adverse pregnancy outcome					
Clomifene citrate vs. metformin + clomifene citrate(miscarriage)					
2 (Vandermolen et al., 2001; Hwu et al.2005	0/55 (0%) women	4/52 (8%) women	RR 0.2 (0.0 to 1.5)	63 fewer per 1000 (from 75 fewer to 37 more)	Very low
	0/1 (0%) pregnancies	4/12 (33%) pregnancies	RR 0.7 (0.1 to 9.4)	100 fewer per 1000 (from 317 fewer to 2803 more)	
Metformin + clomifene citrate vs. hMG (miscarriage)					
1 (George et al., 2003)	1/30 (3%) women	1/30 (3%) women	RR 1.0 (0.1 to 15.3)	0 fewer per 1000 (from 31 fewer to 475 more)	Very low
	1/7 (14%) pregnancies	1/5 (20%) pregnancies	RR 0.7 (0.1 to 8.9)	58 fewer per 1000 (from 188 fewer to 1580 more)	
Metformin + clomifene citrate vs. hMG (intrauterine death at 28 weeks)					
1 (George et al., 2003)	1/30 (3%) women	0/30 (0%) women	RR 3.0 (0.1 to 70.8)	Not estimable	Very low
	1/5 (20%) pregnancies	0/7 (0%) pregnancies	RR 4.0 (0.2 to 82.0)	Not estimable	
Metformin + clomifene citrate vs. hMG (ectopic pregnancy)					
1 (George et al., 2003)	1/30 (3%) women	0/30 (0%) women	RR 3.0 (0.1 to 70.8)	Not estimable	Very low
	1/5 (20%) pregnancies	0/7 (0%) pregnancies	RR 4.0 (0.2 to 82.0)	Not estimable	
Letrozole vs. clomifene citrate (miscarriage)					
1 (Begum et al., 2009)	2/32 (6%) women	0/32 (0%) women	RR 5.0 (0.3 to 100)	Not estimable	Very low
	2/13 (15%) pregnancies	0/6 (0%) pregnancies	RR 2.5 (0.1 to 45.3)	Not estimable	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
hMG vs. clomifene citrate (miscarriage)					
1 (Badawy et al., 2008)	4/158 (3%) women	5/160 (3%) women	RR 0.8 (0.2 to 3.0)	6 fewer per 1000 (from 24 fewer to 61 more)	Very low
	Number of clinical pregnancies not reported				
Letrozole + metformin vs. metformin + clomifene citrate (miscarriage)					
1 (Sohrabvand et al., 2006)	0/30 (0%) women	2/30 (7%) women	RR 0.2 (0.0 to 4.0)	53 fewer per 1000 (from 66 fewer to 200 more)	Very low
	0/11 (0%) pregnancies	2/5 (40%) pregnancies	RR 0.1 (0.0 to 1.8)	360 fewer per 1000 (from 396 fewer to 308 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Clomifene citrate vs. metformin + clomifene citrate					
1 (Vandermolen et al., 2001)	0/15 (0%) women	0/12 (0%) women	Not estimable		Low
	0/1 (0%) pregnancies	0/6 (0%) pregnancies	Not estimable		
Letrozole vs. clomifene citrate					
1 (Begum et al., 2009)	0/32 (0%) women	0/32 (0%) women	Not estimable		Low
	0/13 (0%) pregnancies	0/6 (0%) pregnancies	Not estimable		
hMG vs. clomifene citrate					
1 (Badawy et al., 2008)	4/158 (3%) women	1/160 (1%) women	RR 4.1 (0.5 to 35.8)	19 more per 1000 (from 3 fewer to 218 more)	Very low
	4/20 (20%) pregnancies	1/28 (4%) pregnancies	RR 5.6 (0.7 to 46.4)	164 more per 1000 (from 11 fewer to 1622 more)	
Letrozole vs. metformin + clomifene citrate					
1 (Abu Hashim et al., 2010)	0/123 (0%) women	3/127 (2%) women	RR 0.2 (0.0 to 2.8)	20 fewer per 1000 (from 23 fewer to 43 more)	Very low
	Number of clinical pregnancies not reported				

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
uFSH vs. metformin + clomifene citrate					
1 (Abu Hashim et al., 2010)	6/78 (8%) women	2/75 (3%) women	RR 2.9 (0.6 to 13.9)	50 more per 1000 (from 11 fewer to 343 more)	Low
	6/32 (19%) pregnancies	2/18 (11%) pregnancies	RR 2.9 (0.6 to 13.9)	209 more per 1000 (from 44 fewer to 1000 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
Clomifene citrate vs. metformin + clomifene citrate					
1(Malkawi & Qublan, 2002)	2/12 (17%) women	0/16 (0%) women	RR 6.5 (0.3 to 124.8)	Not estimable	Very low
hMG vs. clomifene citrate					
1(Badawy et al., 2008)	2/158 (1%) women	0/160 (0%) women	RR 5.1 (0.2 to 105)	Not estimable	Very low
Letrozole vs. metformin + clomifene citrate					
1 (Abu Hashim et al., 2010)	0/123 (0%) women	0/127 (0%) women	Not estimable		Low
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, hMG human menopausal gonadotrophin, OHSS ovarian hyperstimulation syndrome, PCOS polycystic ovary syndrome, RR relative risk, uFSH urinary follicle-stimulating hormone

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Table 8.6 GRADE findings for comparison of surgery with drugs (clomifene resistant PCOS)

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Surgery vs. clomifene citrate + tamoxifen					
1(Zakherah et al., 2010)	33/75 (44%) women	37/75 (49%) women	RR 0.9 (0.6 to 1.3)	54 fewer per 1000 (from 183 fewer to 128 more)	Low
Surgery vs. hMG					
1(Abdel et al., 1990)	11/29 (37%) women	7/30 (23%) women	RR 1.6 (0.7 to 3.6)	147 more per 1000 (from 63 fewer to 609 more)	Very low
Surgery vs. FSH or rFSH					
2 (Abdel et al., 1990; Bayram et al., 2004)	39/112 (35%) women	51/114 (45%) women	RR 1.0 (0.4 to 2.9) [e]	0 fewer per 1000 (from 291 fewer to 832 more)	Very low
Surgery vs. HMG or rFSH					
1 (Farquhar et al., 2002)	4/29 (14%) women	4/21 (19%) women	RR 0.7 (0.2 to 2.6)	53 fewer per 1000 (from 152 fewer to 299 more)	Very low
Clinical pregnancy					
Surgery vs. clomifene citrate + tamoxifen					
1 (Zakherah et al., 2010)	38/75 (51%) women	40/75 (53%) women	RR 1.0 (0.7 to 1.3)	27 fewer per 1000 (from 160 fewer to 155 more)	Moderate
Surgery vs. metformin + clomifene citrate					
1 (Abu Hashim et al., 2010)	95/144 (66%) women	89/138 (65%) women	RR 1.0 (0.9 to 1.2)	13 more per 1000 (from 90 fewer to 135 more)	High
Surgery vs. rFSH					
1 (Bayram et al., 2004)	31/83 (37%) women	64/85 (75%) women	RR 0.5 (0.4 to 0.7)	376 fewer per 1000 (from 248 fewer to 474 fewer)	Moderate
Surgery vs. hMG or rFSH					
1(Farquhar et al., 2002)	8/29 (28%) women	7/21 (33%) women	RR 0.8 (0.4 to 1.9)	57 fewer per 1000 (from 213 fewer to 310 more)	Low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Surgery + clomifene citrate vs. FSH					
1(Kamel et al., 2004)	2/30 (7%) women	4/25 (16%) women	RR 0.4 (0.1 to 2.1)	93 fewer per 1000 (from 147 fewer to 174 more)	Very low
Adverse pregnancy outcome					
Surgery vs. clomifene citrate + tamoxifen (miscarriage)					
1 (Zakherah et al., 2010)	5/75 (7%) women	3/75 (4%) women	RR 1.7 (0.4 to 6.7)	27 more per 1000 (from 24 fewer to 229 more)	Moderate
	5/38 (13%) pregnancies	3/40 (8%) pregnancies	RR 1.8 (0.5 to 6.9)	56 more per 1000 (from 41 fewer to 438 more)	
Surgery vs. hMG or rFSH (miscarriage)					
1 (Farquhar et al., 2002)	3/29 (12%) women	3/21 (14%) women	RR 0.7 (0.2 to 3.2)	40 fewer per 1000 (from 120 fewer to 320 more)	Very low
	3/8 (38%) pregnancies	3/7 (43%) pregnancies	RR 0.9 (0.3 to 3.0)	51 fewer per 1000 (from 321 fewer to 866 more)	
Surgery vs. rFSH (miscarriage)					
1 (Bayram et al., 2004)	3/83 (4%) women	7/85 (8%) women	RR 0.4 (0.1 to 1.6)	46 fewer per 1000 (from 72 fewer to 53 more)	Moderate
	3/31 (10%) pregnancies	7/64 (11%) pregnancies	RR 0.9 (0.3 to 3.2)	13 fewer per 1000 (from 82 fewer to 240 more)	
Surgery vs. rFSH (premature birth)					
1 (Bayram et al., 2004)	0/83 (0%) women	6/85 (7%) women	RR 0.1 (0.0 to 1.3)	65 fewer per 1000 (from 71 fewer to 24 more)	Moderate
	0/31 (0%) pregnancies	6/64 (9%) pregnancies	RR 0.2 (0.0 to 2.7)	79 fewer per 1000 (from 93 fewer to 158 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Surgery vs. metformin + clomifene citrate (miscarriage)					
1 (Abu Hashim et al., 2010)	9/144 (6%) women	8/138 (6%) women	RR 1.1 (0.4 to 2.7)	5 more per 1000 (from 33 fewer to 99 more)	Moderate
	9/95 (10%)pregnancies	8/89 (9%)pregnancies	RR 1.1 (0.4 to 2.6)	4 more per 1000 (from 51 fewer to 145 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Surgery vs. hMG					
1 (Abdel et al., 1990)	0/29 (0%) women	3/30 (10%) women	RR 0.2 (0.0 to 2.7)	85 fewer per 1000 (from 99 fewer to 174 more)	Very low
	Number of clinical pregnancies not reported				
Surgery vs. FSH or rFSH					
	0/112 (0%) women	11/114 (10%) women	RR 0.1 (0.0 to 0.6)	89 fewer per 1000 (from 35 fewer to 96 fewer)	
	0/31 (0%) pregnancies	9/64 (14%) pregnancies	RR 0.1 (0.0 to 1.8)	125 fewer per 1000 (from 139 fewer to 110 more)	
Surgery vs. hMG or rFSH					
1 (Farquhar et al., 2002)	0/29 (0%) women	0/21 (0%) women	Not estimable		Moderate
	0/8 (0%) pregnancies	0/7 (0%) pregnancies	Not estimable		
Surgery vs. metformin + clomifene citrate					
1 (Abu Hashim et al., 2010)	0/144 (0%) women	4/138 (3%) women	RR 0.1 (0.0 to 2.0)	26 fewer per 1000 (from 29 fewer to 28 more)	Moderate
	0/95 (0%) pregnancies	4/89 (5%) pregnancies	RR 0.1 (0.0 to 1.9)	40 fewer per 1000 (from 44 fewer to 41 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence was reported					

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Ovarian hyperstimulation syndrome (OHSS)					
Surgery vs. hMG or rFSH					
1 (Farquhar et al., 2002)	0/29 (0%) women	0/21 (0%) women	Not calculable		Moderate
	0/8 (0%) pregnancies	0/7 (0%) pregnancies	Not calculable		
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, FSH follicle-stimulating hormone, hMG human menopausal gonadotrophin, OHSS ovarian hyperstimulation syndrome, PCOS polycystic ovary syndrome, rFSH recombinant follicle-stimulating hormone, RR relative risk

Table 8.7 GRADE findings for comparison of lifestyle with drugs or surgery (clomifene resistant PCOS)

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
No evidence reported					
Clinical pregnancy					
No evidence reported					
Adverse pregnancy outcome					
No evidence reported					
Multiple pregnancies (the number of pregnancies with more than one fetus)					
No evidence reported					
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
No evidence reported					
Congenital abnormalities					
No evidence reported					

Patient satisfaction
No evidence reported
Health related quality of life
No evidence reported
Anxiety and/or depression
No evidence reported

CI confidence interval, OHSS ovarian hyperstimulation syndrome, PCOS polycystic ovary syndrome

Evidence statements

First line ovarian stimulation treatment for women with PCOS

Clomifene citrate or tamoxifen compared with other drugs

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births when comparing metformin, metformin plus clomifene citrate, letrozole or FSH to clomifene citrate alone.

There were significantly more live births with metformin plus clomifene citrate than metformin alone.

Clinical pregnancy

There was no significant difference in the number of clinical pregnancies with metformin compared with clomifene citrate alone.

There were significantly more clinical pregnancies with metformin plus clomifene citrate compared with clomifene citrate alone or metformin alone. There were significantly more clinical pregnancies with letrozole compared with clomifene citrate, and when using recombinant follicle-stimulating hormone (rFSH) compared with clomifene citrate.

Adverse pregnancy outcomes

There were no significant differences between metformin and clomifene citrate in the number of miscarriages, ectopic pregnancies, cases of gestational hypertension, cases of gestational diabetes, women with preterm labour or premature rupture of membranes, intrauterine fetal deaths, cases of placenta previa, cases of postpartum haemorrhage, placental abruptions, second or third trimester pregnancy losses, cervical incompetence or preterm labour, cases of severe pre-eclampsia, cases of HELLP syndrome (a severe form of pre-eclampsia comprising haemolysis, elevated liver enzymes and low platelets), or number of maternal deaths.

There were no significant differences between metformin plus clomifene citrate compared with clomifene citrate alone in the number of maternal deaths, preterm births, miscarriages, second or third trimester pregnancy losses, ectopic pregnancies or cases of: gestational diabetes, gestational hypertension, pre-eclampsia, severe pre-eclampsia, HELLP syndrome, preterm labour or premature rupture of membranes, preterm labour or cervical incompetence, placental abruption, placenta previa, or postpartum haemorrhage.

There were no significant differences between metformin compared with metformin plus clomifene citrate in the number of maternal deaths, miscarriages, ectopic pregnancies, second or third trimester pregnancy loss, or cases of: cervical incompetence of preterm labour, gestational hypertension, mild pre-eclampsia, severe pre-eclampsia, HELLP syndrome, gestational diabetes, pre-term labour or premature rupture of membranes, placental abruption, placenta previa or postpartum haemorrhage.

There were no significant differences in the number of miscarriages per woman or per pregnancy when comparing letrozole to clomifene citrate, or when comparing rFSH to clomifene citrate.

Multiple pregnancies

There were no significant differences in the number of multiple pregnancies when comparing metformin, metformin plus clomifene citrate, letrozole or rFSH to clomifene citrate alone. There was no significant difference in the number of multiple pregnancies when comparing metformin to metformin plus clomifene citrate.

Multiple births

No evidence was reported regarding multiple births.

OHSS

There were no significant differences in the number of cases of OHSS when comparing letrozole plus hCG to clomifene citrate plus hCG, or when comparing rFSH plus hCG to clomifene citrate plus hCG.

Congenital abnormalities

There were no significant differences in the number of congenital abnormalities when comparing metformin, metformin plus clomifene citrate, or letrozole to clomifene citrate alone. There was no significant difference in the number of congenital abnormalities when comparing metformin plus clomifene to metformin alone.

Patient satisfaction

No evidence was reported regarding patient satisfaction.

Health related quality of life

No evidence was reported regarding health related quality of life.

Anxiety and/or depression

There were no significant differences in the number of women with anxiety and/or depression when comparing metformin or metformin plus clomifene citrate with clomifene citrate alone. There was also no significant difference when comparing metformin plus clomifene citrate to metformin alone.

Surgery compared with drugs

Live full-term singleton birth

No evidence was reported regarding live births.

Clinical pregnancy

No evidence was reported regarding clinical pregnancy.

Adverse pregnancy outcomes

No evidence was reported regarding adverse pregnancy outcomes.

Multiple pregnancies

No evidence was reported regarding multiple pregnancies.

Multiple births

No evidence was reported regarding births from multiple pregnancies.

OHSS

No evidence was reported regarding cases of OHSS.

Congenital abnormalities

No evidence was reported regarding congenital abnormalities.

Patient satisfaction

No evidence was reported regarding patient satisfaction.

Health related quality of life

No evidence was reported regarding health related quality of life.

Anxiety and/or depression

No evidence was reported regarding the number of women with anxiety and/or depression.

Lifestyle modification compared with drugs or surgery

Live full-term singleton birth

No evidence was reported regarding live births.

Clinical pregnancy

There were no significant differences in the number of clinical pregnancies when comparing lifestyle modification (low calorie diet plus exercise) with clomifene citrate alone, metformin alone, or clomifene citrate plus metformin.

Adverse pregnancy outcomes

No evidence was reported regarding adverse pregnancy outcomes.

Multiple pregnancies

There were no significant differences in the number of multiple pregnancies when comparing lifestyle modification (low calorie diet plus exercise) with clomifene citrate alone, metformin alone, or clomifene citrate plus metformin.

Multiple births

No evidence was reported regarding births from multiple pregnancies.

OHSS

No evidence was reported regarding cases of OHSS.

Congenital abnormalities

No evidence was reported regarding congenital abnormalities.

Patient satisfaction

No evidence was reported regarding patient satisfaction.

Health related quality of life

No evidence was reported regarding health related quality of life.

Anxiety and/or depression

No evidence was reported regarding the number of women with anxiety and/or depression.

Ovarian stimulation treatment in women who have clomifene citrate resistance

Metformin plusclomifene compared with other drugs

Live full-term singleton birth

There were significantly more live full-term singleton births after metformin plus clomifene citrate compared with clomifene citrate alone. There were significantly more live full-term singleton births after letrozole plus metformin compared with metformin plus clomifene citrate. There was no significant difference when comparing hMG to metformin plus clomifene citrate.

Clinical pregnancy

There were significantly more clinical pregnancies after metformin plus clomifene citrate compared with clomifene citrate alone, and after uFSH compared with metformin plus clomifene citrate. There were no significant differences when comparing hMG to metformin plus clomifene citrate, letrozole to clomifene citrate, or letrozole plus metformin to metformin plus clomifene citrate.

Adverse pregnancy outcomes

There was no significant difference in the number of miscarriages per woman or per pregnancy when comparing clomifene citrate to metformin plus clomifene citrate.

There were no significant differences in the number of miscarriages, intrauterine deaths at 28 weeks, or the number of ectopic pregnancies per woman or per pregnancy when comparing hMG to metformin plus clomifene citrate.

There was no significant difference in the number of miscarriages when comparing letrozole or hMG to clomifene citrate.

There were no significant differences in the number of miscarriages when comparing metformin plus clomifene citrate to letrozole plus metformin or to uFSH.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing metformin plus clomifene citrate, letrozole, or hMG to clomifene citrate alone. There was no significant difference

in the number of multiple pregnancies when comparing uFSH or letrozole to metformin plus clomifene citrate.

Multiple births

No evidence was reported regarding births from multiple pregnancies.

OHSS

There were no significant differences in the number of cases of OHSS when comparing metformin plus clomifene citrate, or hMG to clomifene citrate alone. There was no significant difference in the number of cases of OHSS when comparing metformin plus clomifene citrate to letrozole.

Congenital abnormalities

No evidence was reported regarding congenital abnormalities.

Patient satisfaction

No evidence was reported regarding patient satisfaction.

Health related quality of life

No evidence was reported regarding health related quality of life.

Anxiety and/or depression

No evidence was reported regarding the number of women with anxiety and/or depression.

Surgery compared with drugs

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births when comparing surgery to clomifene plus tamoxifen, hMG, FSH or rFSH.

Clinical pregnancy

There were no significant differences in the number of clinical pregnancies when comparing surgery to clomifene plus tamoxifen, metformin plus clomifene citrate, hMG, FSH or rFSH. There was also no significant difference in the number of clinical pregnancies when comparing surgery plus clomifene citrate to FSH.

Adverse pregnancy outcomes

There were no significant differences in the number of miscarriages when comparing surgery to clomifene citrate plus tamoxifen, metformin plus clomifene citrate, hMG or rFSH.

There was no significant difference per woman or per pregnancy in the number of preterm births when comparing surgery with rFSH.

Multiple pregnancies

There were significantly more multiple pregnancies per woman with FSH or rFSH compared with surgery. However, the difference was not significant per pregnancy.

There was no significant difference in the number of multiple pregnancies when comparing surgery to hMG, rFSH or metformin plus clomifene citrate.

Multiple births

No evidence was reported regarding the number of babies born from multiple pregnancies.

OHSS

There was no significant difference in the number of cases of OHSS after surgery compared with after hMG or rFSH.

Congenital abnormalities

There was no evidence reported regarding the number of congenital abnormalities.

Patient satisfaction

There was no evidence reported regarding patient satisfaction.

Health related quality of life

There was no evidence reported regarding health related quality of life.

Anxiety and/or depression

There was no evidence reported regarding the number of women with anxiety and/or depression.

Lifestyle compared with drugs or surgery

Live full-term singleton birth

No evidence was reported regarding the number of live full-term singleton birth

Clinical pregnancy

No evidence reported regarding the number of clinical pregnancies

Adverse pregnancy outcome

No evidence was reported regarding adverse pregnancy outcomes.

Multiple pregnancies

No evidence was reported regarding the number of multiple pregnancies.

Multiple births

No evidence was reported regarding the number of multiple pregnancies resulting in birth

OHSS

No evidence was reported regarding the number of cases of OHSS

Congenital abnormalities

No evidence was reported regarding the number of congenital abnormalities

Patient satisfaction

No evidence was reported regarding patient satisfaction

Health related quality of life

No evidence was reported regarding health related quality of life

Anxiety and/or depression

No evidence was reported regarding the number of women with anxiety and/or depression.

Body mass index (BMI)

Eight included studies set inclusion/exclusion criteria based on BMI (Bayar et al., 2006; Elsedeek et al., 2011; Farquahar et al., 2002; George et al., 2003; Johnson et al., 2010; Karimzadeh et al., 2010; Palomba et al., 2005; Qublan et al., 2007). For three of these studies of BMI restricted populations, the treatment regimens were unique to these studies and not found in the unrestricted studies reported above (Farquaharet al., 2002; Georgeet al., 2003; Karimzadehet al., 2010). Thus it was not possible to analyse the effect of BMI. For the five remaining studies of BMI restricted populations, while they used treatment regimens that were reported in the unrestricted populations above, the studies were of insufficient size to allow a confident comparison to be made.

Although a subgroup analysis by BMI was not undertaken, the GDG noted that the studies that only included women with a BMI of 32 or less (Johnson et al., 2010 [BMI 32 or less], Karimzadeh et al., 2010 [BMI 25 to 29.9], Palomba et al., 2005 [BMI 30 or less]) showed a trend towards the effectiveness of metformin over clomifene citrate for live birth and clinical pregnancy rates (although this was not significant). Of the two studies that did not restrict the entry of women according to their BMI, one found a significant advantage of clomifene over metformin for live birth but not clinical pregnancy (Zain et al, 2009) while the other found a significant advantage of clomifene over metformin for clinical pregnancy but not live birth (Legro et al., 2007), and both of the non-significant effects showed a trend towards favouring clomifene.

Health economics profile

A formal health economic profile was not undertaken for this review.

Evidence to recommendations

Relative value placed on the outcomes considered

Live full-term singleton birth is the most important outcome which allows clinicians to inform couples of their chances of having a baby. However, all of the studies in this review reported only live birth rates, which may have included pre-term births and/or births from multiple pregnancies, and were therefore downgraded for 'indirectness' as a consequence. Clinical pregnancy is the second most important measure as it reflects a woman's ability to conceive. The other outcomes in this review relate to side-effects of the treatments and are important when informing women of potential risks of treatment.

Consideration of clinical benefits and harms

First-line treatment

The review found that metformin plus clomifene resulted in significantly more live full-term singleton births and clinical pregnancies than metformin alone, and that it was significantly more effective than clomifene citrate alone in terms of live full-term singleton births. The additional benefit of the drugs in combination was more marked in comparison with metformin than clomifene. The evidence showed that the standard UK first-line treatment (clomifene citrate) did not result in significantly more live births than the alternatives of metformin, letrozole or FSH. The GDG noted that there was not a large difference in the absolute number of clinical pregnancies or live births when comparing metformin, clomifene citrate and a combination of metformin and clomifene citrate. However, the GDG was aware from studies of women with lower BMI that metformin may be more effective than clomifene citrate alone in these women, while clomifene citrate may be more effective than metformin alone in other women. There was no significant difference in the number of adverse pregnancy outcomes or cases of OHSS for the different drugs. However, the GDG acknowledged that adverse effects, such as nausea, are more prevalent with metformin compared with clomifene citrate.

There are limited data comparing the number of cases of OHSS and the number of multiple pregnancies with letrozole alone to clomifene citrate alone. The GDG noted that there are concerns surrounding the safety of letrozole, and do not consider these to be outweighed by the limited evidence. The GDG also notes that letrozole is not used in standard practice in the UK.

No studies were found that compared surgery to drugs as first-line treatment.

Studies on lifestyle modification found no significant difference in the number of clinical pregnancies following a low calorie diet with exercise than clomifene citrate alone, metformin alone or clomifene citrate with metformin. However, the GDG noted that one of the two studies that reported evidence on lifestyle modification only included women with a BMI of 25 to 29.9, which may not be applicable to women with WHO Group II ovulatory infertility with higher BMIs. Also, the effect of diet and exercise on live birth rates was not reported. The GDG acknowledged the complexities of using diet and exercise advice to improve ovulation disorders, including patient compliance and the amount of time that may be required to reduce weight to a level that has a significant effect on ovulation. The GDG emphasised that losing weight should be considered as part of the fertility treatment for women with WHO Group II ovulatory infertility and, furthermore, that a woman's BMI should not be considered a barrier to treatment.

Overall, the GDG's considered view was that, as a first-line treatment for women with WHO Group II ovulatory disorders, clomifene citrate and metformin offer similar chances of live birth. It is biologically plausible that the addition of clomifene to metformin may increase the chances of live birth compared with the use of either drug alone but the evidence was not strong enough to make a recommendation that metformin should be used with clomifene to increase the chances of a singleton live birth.

Second-line treatment

Women with PCOS who are resistant to clomifene citrate

There were significantly more live full-term singleton births and clinical pregnancies after double treatment with metformin plus clomifene citrate compared with clomifene citrate alone. There was no significant difference in live births when comparing hMG with metformin plus clomifene citrate. There were significantly more clinical pregnancies after uFSH compared with metformin plus clomifene citrate, and no significant difference in the number of clinical pregnancies when comparing hMG to metformin plus clomifene citrate. These findings imply that gonadotrophins may be as effective in

women with PCOS who are resistant to clomifene citrate as a combination of metformin plus clomifene citrate.

The GDG's view was that gonadotrophins are used in second-line treatment when there is clomifene citrate resistance, and metformin in combination with clomifene citrate is less common practice for second-line treatment.

Surgery and drugs were equally effective in terms of live full-term singleton births or clinical pregnancies.

No evidence was reported comparing lifestyle modification (such as diet and exercise) to drugs and/or surgery in clomifene citrate resistant women.

Data reporting adverse pregnancy outcomes and OHSS was either not reported or found no significant difference between interventions.

Consideration of health benefits and resource use

No studies were identified that considered the relative cost effectiveness of interventions for women requiring ovarian stimulation. Lifestyle interventions, such as dietary advice and exercise, are likely to have lower cost to the NHS than medical or surgical intervention, but low-cost interventions are not necessarily the most cost effective. The time taken to provide counselling and advice to alter lifestyles takes time to provide by a healthcare professional. If it is not effective, it takes resources away from more cost-effective treatments.

The cost of metformin is relatively low compared with clomifene and results in fewer multiple pregnancies (which also increase the cost of birth). The cost of combination therapy is higher with limited evidence of improved effectiveness. However, the GDG noted that the cost of medical management includes resources other than the cost of the drugs themselves. Clomifene requires more scanning and monitoring than metformin due to the increased risk of multiple pregnancies (as acknowledged in the 2004 guidance), and this increases the cost of clomifene. On the other hand, general practitioners are unable to prescribe clomifene citrate, whereas they are able to prescribe metformin, so there is the additional cost of at least one outpatient visit for clomifene.

The GDG considered that, overall, there is a higher cost associated with treatment with clomifene. Nevertheless, clomifene is an established drug and is part of standard clinical practice. The GDG concluded that the evidence was not strong enough to change the existing recommendation that clomifene should be one of the drugs offered.

Quality of evidence

The quality of the evidence was mainly very low due to limitations of the studies, particularly the lack of reporting on blinding and power analysis, and wide confidence intervals. Clomifene citrate resistance is defined in this guideline as ovulation that is not induced after treatment of up to 3 cycles with dose escalation but the definition of clomifene citrate resistance and PCOS varied from study to study. Moreover, the included studies only reported on a PCOS population. Therefore, the conclusions may not be generalisable to all types of WHO Group II ovulation disorders.

Limited reporting on patient characteristics and outcomes in the studies included in the review meant that it was not possible to undertake all relevant analyses. For example, a sub-group analysis on BMI was not undertaken. No studies reported patient satisfaction and a limited number reported relevant adverse outcomes.

Other considerations

Gonadotrophin-releasing hormone analogues in ovulation induction therapy

The 2004 version of the guideline included a review comparing the use of gonadotrophins alone to the use of gonadotrophins in conjunction with gonadotrophin-releasing hormone (GnRH) agonists to achieve pituitary down-regulation and facilitate cycle control in ovarian stimulation. As the 2004 guideline recommends the use of clomifene citrate or tamoxifen for women with WHO Group II ovulation disorders, a review was undertaken for the 2013 update of the guideline to compare clomifene citrate and/or tamoxifen with other drugs, including gonadotrophins with or without GnRH agonists. The 2004 review comparing the use of gonadotrophins with and without GnRH agonists is therefore no longer relevant to the consideration of the evidence for ovulation induction therapy in women with WHO Group II disorders, and has been removed from the guideline text.

Lifestyle advice

The evidence base for weight loss was very limited. Also, the effect of diet and exercise on live birth rates was not evaluated. However, it did show that that weight loss was as effective as clomifene at achieving ovulation. The GDG acknowledged the complexities of using diet and exercise advice to improve ovulation disorders, including patient compliance and the amount of time required to reduce weight to a level that has a significant effect on ovulation. However, based on clinical experience, the considered view of the GDG was that overweight women should be counselled to lose weight because of the positive impact on conception rates and pregnancy outcomes and the negative impact of high BMI on pregnancy outcomes. The advice might include specific advice from a dietician, warnings of the potential risks in pregnancy and, if appropriate, the offer of access to exercise advice and psychosocial support.

Medical management

Metformin is currently not licensed for use in the treatment of PCOS (its license is for use in diabetes). The GDG took into account that metformin needs to be taken multiple times a day whereas clomifene citrate is taken 5 days per month, and that this could be a consideration when discussing the best treatment for each individual. In addition, clomifene citrate requires appropriate monitoring which, along with the duration of treatment, should be taken into consideration when discussing the most appropriate treatment for each woman. The GDG noted that clomifene citrate is licensed for use for up to 6 months at a time. The GDG believed 6 months use of clomifene citrate is an adequate amount of time to determine whether a woman will respond or is resistant to it, and so recommended that clomifene citrate should not be continued after this time.

The GDG took into account that gonadotrophins are often used in second-line treatment when the woman is resistant to clomifene citrate, and that metformin in combination with clomifene citrate is less common practice in England and Wales.

Surgical intervention

The GDG also considered laparoscopic ovarian drilling as a second-line treatment following clomifene resistance. A significant benefit is the elimination of the increased risk of multiple pregnancies and thus laparoscopic ovarian drilling could be an option that would be preferable for some women. Although no evidence was identified to support its use, the view of the GDG was that it should remain a treatment option depending on the individual woman's clinical circumstances and preferences.

Equalities

The people considered in this review were:

- People in same sex relationships who cannot have heterosexual intercourse.
- Specific patient subgroups listed in the guideline Scope who may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, or who have been advised not to, have heterosexual intercourse
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
- People who are preparing for cancer treatment who may wish to preserve their fertility.

There were no specific issues that needed to be addressed with respect to any of these subgroups for this review.

Recommendations

Number	Recommendation
	In women with WHO Group II ovulation disorders receiving first-line treatment for ovarian stimulation:
92	Advise women with WHO Group II anovulatory infertility who have a BMI of 30 or over to lose weight (see recommendation 26). Inform them that this alone may restore ovulation, improve their response to ovulation induction agents, and have a positive impact on pregnancy outcomes. **[new 2013]**
93	Offer women with WHO Group II anovulatory infertility one of the following treatments, taking into account potential adverse effects, ease and mode of use, the woman's BMI, and monitoring needed: • clomifene citrate **or** • metformin* **or** • a combination of the above. **[new 2013]**
94	For women who are taking clomifene citrate, offer ultrasound monitoring during at least the first cycle of treatment to ensure that they are taking a dose that minimises the risk of multiple pregnancy. **[2013]**
95	For women who are taking clomifene citrate, do not continue treatment for longer than 6 months. **[2013]**
96	Women prescribed metformin* should be informed of the side effects associated with its use (such as nausea, vomiting and other gastrointestinal disturbances). **[2004]**
	In women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate:
97	For women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate, consider one of the following second-line treatments, depending on clinical circumstances and the woman's preference: • laparoscopic ovarian drilling **or** • combined treatment with clomifene citrate and metformin* if not already offered as first-line treatment **or** • gonadotrophins. **[new 2013]**
98	Women with polycystic ovary syndrome who are being treated with gonadotrophins should not be offered treatment with gonadotrophin-releasing hormone agonist concomitantly because it does not improve pregnancy rates, and it is associated with an increased risk of ovarian hyperstimulation. **[2004]**
99	The use of adjuvant growth hormone treatment with gonadotrophin-releasing hormone agonist and/or human menopausal gonadotrophin during ovulation induction in women with polycystic ovary syndrome who do not respond to clomifene citrate is not recommended because it does not improve pregnancy rates. **[2004]**
100	The effectiveness of pulsatile gonadotrophin-releasing hormone in women with clomifene citrate-resistant polycystic ovary syndrome is uncertain and is therefore not recommended outside a research context. **[2004]**

2013 Update

* At the time of publication (February 2013), metformin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Number	Research recommendation
RR 16	What is the cost effectiveness and safety of using clomifene citrate or metformin or a combination of the two to induce ovulation in women with WHO Group II ovulation disorders?

8.4 Hyperprolactinaemic amenorrhoea – dopamine agonists

Introduction

Two RCTs (n = 306) comparing cabergoline to bromocriptine in women with hyperprolactinaemic amenorrhoea reported that cabergoline was more effective in restoring ovulation and increased pregnancy rates (72% and 72% with cabergoline versus 52% and 48% with bromocriptine, respectively).[576,577] [Evidence level 1b] However, the manufacturer advises discontinuation of cabergoline at least one month before pregnancy.[181] [Evidence level 4]

A systematic review of three RCTs found no improvement in pregnancy rates (OR 1.12, 95% CI 0.48 to 2.57) following treatment with bromocriptine versus placebo in couples with unexplained infertility.[578] [Evidence level 1a]

Recommendations

Number	Recommendation
101	Women with ovulatory disorders due to hyperprolactinaemia should be offered treatment with dopamine agonists such as bromocriptine. Consideration should be given to safety for use in pregnancy and minimising cost when prescribing. **[2004]**

8.5 Monitoring ovulation induction during gonadotrophin therapy

Ovarian monitoring provides information on ovarian response to ovulation induction agents by ascertaining the number and size of the developing follicles.

Ultrasonography is regarded as a safe, accurate and efficient method of monitoring follicular development in response to ovulation induction,[579–581] in helping to reduce multiple pregnancy rates, especially in women with PCOS[571] when compared with oestrogen monitoring. [Evidence level 2b] Oestrogen monitoring provides no additional information compared with ovarian ultrasound.[579] [Evidence level 2b] Ultrasonography was found to have good predictive value in the occurrence of OHSS which was associated with larger number of immature follicles at time of hCG administration.[582] [Evidence level 3] An observational study reported that follicular sonography performed during ovarian stimulation predicted 88% of cycle decisions.[583] [Evidence level 3]

Ovarian hyperstimulation syndrome

The aim of ovulation induction therapy is to stimulate the ovaries to produce more than one egg. This carries the risk of overstimulation and OHSS. OHSS is a potentially fatal condition when many follicles are stimulated, leading to ascites, pleural and pericardial effusion, haemoconcentration and coagulopathy.[584]

The exact incidence of severe OHSS when fertility drug therapy is used has not yet been determined. Available data suggest an incidence of 3% of cycles when hMG is used,[585] and in 0.2% to 1.0% of all assisted reproduction cycles.[586–588] Results generated by the European Society for Human

Reproduction and Embryology (ESHRE) on assisted reproductive technology in Europe in 1999 reported an incidence of OHSS of 0.9% (range 0.3 % to 2.7%; 1083 cases of OHSS after 114,628 cycles).[589] [Evidence level 3]

Clinics that provide ovarian stimulation should have protocols in place for the prevention, diagnosis and management of OHSS (see Section 15.5).

Multiple pregnancy

Prevention of iatrogenic multifetal gestation involves judicious use of ovulation induction drugs and monitoring with ultrasound to chart follicular development. It is best carried out in a specialist clinic.

There is a strong correlation between the initial number of embryos, the final number and the risks of pregnancy loss and prematurity.[590,591] [Evidence level 3] Multiple gestations are high-risk pregnancies associated with higher obstetric complications, perinatal, neonatal and infant mortality,[592] as well as significant financial[593,594] and psychological[595] consequences. [Evidence level 3] However, assisted reproduction multiple pregnancies do not appear to be at any more risk of poor obstetric and neonatal outcomes than those conceived spontaneously.[596,597] [Evidence level 3] Recent surveys have suggested that multiple pregnancies may not be viewed as an adverse outcome by women with fertility problems.[598–602] [Evidence level 3–4]

The exact numbers of multiple pregnancies arising from ovarian stimulation, with or without IUI, are unknown, as there are no national registers that record the outcome of controlled ovarian stimulation,[603] as there are with IVF and ICSI, such as the register monitored by the HFEA. Multiple pregnancy occurs in 2–13% of women with all causes of infertility taking clomifene citrate.[604] This compares with a spontaneous multiple pregnancy rate of about 1–2% of women in the North American and European populations.[605,606] Women with clomifene citrate-resistant PCOS treated with conventional regimens of gonadotrophins have a 36% multiple pregnancy rate.[607] [Evidence level 3] A one-year survey of triplets and higher-order pregnancies in the UK found that 31% of the triplet pregnancies were spontaneous, 34% were from various methods of ovulation stimulation and 35% were from IVF/GIFT. Triplet pregnancies accounted for 56% of all pregnancies attributable to clomifene citrate.[608] [Evidence level 3]

The issue of multiple pregnancies arising from IVF is discussed in Chapter 15.

Multifetal pregnancy reduction refers to the termination of one or more normal fetuses in a multifetal pregnancy in order to improve the survival rates for the remaining fetuses and to decrease maternal morbidity.[590] [Evidence level 4] For any initial number of embryos, reduction to twins has the highest survival rate.[591] [Evidence level 3] Reduction to singletons rather than twins is associated with a higher gestational age at delivery but a lower survival rate.[590] [Evidence level 3]

Recommendations

Number	Recommendation
102	Women who are offered ovulation induction with gonadotrophins should be informed about the risk of multiple pregnancy and ovarian hyperstimulation before starting treatment. **[2004]**
103	Ovarian ultrasound monitoring to measure follicular size and number should be an integral part of gonadotrophin therapy to reduce the risk of multiple pregnancy and ovarian hyperstimulation. **[2004]**

9 Tubal and uterine surgery

9.1 Introduction

Tubal disease, especially proximal tubal occlusion, is a common cause of tubal infertility. However, it has been found that it is probably overdiagnosed, as intrauterine pregnancies do occur spontaneously in women with proximal tubal blockage diagnosed by hysterosalpingography (HSG) and/or laparoscopy and dye.[626] If tubal surgery is effective it may enable couples to conceive naturally without further intervention.[627]

Uterine fibroids, adhesions and congenital abnormalities, such as bicornuate or septate uterus, have all been reported to be causes of infertility.

This chapter reviews the evidence for effective interventions for these conditions.

9.2 Tubal microsurgery and laparoscopic tubal surgery

Microsurgical tubocornual anastomosis has been regarded as the standard treatment for proximal tubal blockage. However, we did not find any randomised controlled trials (RCTs) or controlled observational studies comparing microsurgery with no treatment or with in vitro fertilisation (IVF). A case series study reported that 27%, 47% and 53% of women with proximal tubal blockage who had microsurgical tubocornual anastomosis achieved a live birth within one, two and 3.5 years of surgery, respectively.[628] [Evidence level 3] A review of nine other case series studies reported that about 50% of women with proximal tubal blockage who had microsurgical tubocornual anastomosis achieved a term pregnancy but it did not specify the time period upon which this figure was based.[629] [Evidence level 3]

A cohort study with a follow-up period of three years reported higher pregnancy rates in women who underwent tubal surgery compared with those who did not (29% with surgery versus 12% without surgery; $P < 0.05$).[630] [Evidence level 2b] The surgery was more effective in women with milder pelvic disease (stage I, 67% with surgery versus 24% without surgery, $P < 0.05$; stage II, 41% with surgery versus 10% without surgery, $P < 0.05$; stage III, 12% with surgery versus 3% without surgery, not significant; and stage IV, 0% with surgery, pelvic disease so severe that surgery not offered). Several case series reported that pregnancy rates after tubal surgery were comparable with those resulting from IVF in women with filmy adhesions, mild distal occlusion or proximal tubal blockage.[631–635] [Evidence level 2b–3]

Case series following up women after surgery for distal tubal occlusion reported live birth rates of 20–30%.[631,636,637] [Evidence level 3] The success of tubal microsurgery assessed in case series was reported to range from 5% term pregnancy rate at 36 months[284] to 25% cumulative pregnancy rates at 12 months and 40% at 50 months.[637] [Evidence level 3] This included a heterogeneous group of women with proximal or distal tubal disease. The severity of tubal damage was linked closely to outcome, with better results in those with filmy adhesions and limited damage, compared with those with more extensive pathology. Success rates with tubal surgery are also thought to depend upon the severity of the tubal damage as well as the age of the woman, duration of infertility and other associated infertility factors.[637] [Evidence level 3] It has also been suggested that specialised training, experience and availability of equipment have a major effect on the outcome of tubal surgery.[2,284,637] [Evidence level 4]

A narrative review of ten case series (n = 1128) reported a cumulative ectopic pregnancy rate per pregnancy of 23% in women who underwent salpingoneostomy for distal tubal occlusion.[636] [Evidence level 3] Another narrative review of five case series studies (n = 118) reported a cumulative ectopic pregnancy rate per pregnancy of 8% in women who underwent tubocornual anastomosis for proximal tubal occlusion.[629] [Evidence level 3]

A number of trials have evaluated different surgical techniques for tubal surgery. One systematic review of eight RCTs and 14 observational studies evaluating various surgical techniques for treating tubal infertility found no difference in pregnancy rates between the different techniques used such as CO2 laser adhesiolysis versus diathermy adhesiolysis (53% with laser versus 52% with diathermy; odds ratio [OR] 1.04; 95% confidence interval [CI] 0.65 to 1.67), with laser salpingostomy versus diathermy salpingostomy (35% with laser versus 27% with diathermy; OR 1.30; 95% CI 0.77 to 2.19) or the use of an operating microscope versus magnifying lenses (loupes) (72% with microscope versus 78% with loupes; OR 0.75; 95% CI 0.26 to 2.15).[638] [Evidence level 1a] Women with proximal and distal tubal disease and reversal of sterilisation were included in this review. [Evidence level 1a] The review of the 14 observational studies did not detect a difference between laparoscopic adhesiolysis and microsurgical adhesiolysis in improving outcome. [Evidence level 2b]

A systematic review of five RCTs (n = 588) found no improvement in pregnancy rates with the use of postoperative hydrotubation (OR 1.12; 95% CI 0.57 to 2.21) or hydrotubation with steroids (OR 1.10; 95% CI 0.74 to 1.64) or hydrotubation with antibiotics (OR 0.67; 95% CI 0.30 to 1.47) or second-ook laparoscopy with adhesiolysis (OR 0.96; 95% CI 0.44 to 2.07). The comparison groups received no treatment but the trials were small and of poor quality.[639] [Evidence level 1a]

The appropriate therapeutic approach to tubal infertility will depend upon careful patient selection according to the individual's clinical circumstances and involving the couple in the decision-making process.[640–643]

Retrospective case series suggest that most pregnancies occur between 12 and 14 months after tubal surgery, although conception have occurred sooner in those with minimal disease.[627,631,637,644–646] [Evidence level 3] It may be reasonable to discuss IVF with women who have not conceived 12 to 18 months after tubal surgery.

Recommendations

Number	Recommendation
104	For women with mild tubal disease, tubal surgery may be more effective than no treatment. In centres where appropriate expertise is available it may be considered as a treatment option. **[2004]**

Number	Research recommendation
RR 17	Further research is needed to evaluate the clinical and cost effectiveness of tubal surgery compared with no treatment and other treatment options, particularly in vitro fertilisation. This research should include consideration of any adverse consequences of treatment, such as ectopic pregnancy.

9.3 Tubal catheterisation or cannulation

Tubal catheterisation/cannulation can be performed using either a radiographic approach (selective salpingography combined with tubal cannulation) or a hysteroscopic approach (hysteroscopic tubal cannulation).

Selective salpingography can provide information about proximal and distal tubal obstruction. An RCT (n = 273) reported that selective salpingography was a better diagnostic test for proximal tubal obstruction than laparoscopy and dye.[647] [Evidence level 1b] Selective salpingography combined with tubal cannulation can be adopted as a 'see and treat' approach for proximal tubal obstruction in appropriately selected patients.

We found no RCTs that compared the effects of selective salpingography plus tubal catheterisation or hysteroscopic cannulation with no treatment on pregnancy rates in women with proximal tubal obstruction.

A systematic review of observational studies included ten cohort and 11 other observational studies of selective salpingography and tubal catheterisation (n = 482 women), and four observational studies of hysteroscopic tubal cannulation for proximal tubal blockage (n = 133 women). Hysteroscopic tubal cannulation was associated with a higher pregnancy rate than selective salpingography plus tubal catheterisation (49% with hysteroscopy versus 21% with salpingography).[648] [Evidence level 2b–3] As no untreated group was included in any of the studies reviewed, the likelihood of spontaneous pregnancy without treatment cannot be determined. Intrauterine pregnancy in women with proximal tubal blockage diagnosed by both HSG and laparoscopy/dye does occur without surgical treatment.[626] [Evidence level 3]

Tubal perforation (a complication associated with tubal cannulation) has been reported to occur in 2–5% of women undergoing tubal cannulation,[649,650] although the clinical significance of this was not reported. Ectopic pregnancy occurred in 3–9% of women undergoing selective salpingography plus tubal catheterisation.[648] [Evidence level 2b–3]

Recommendations

Number	Recommendation
105	For women with proximal tubal obstruction, selective salpingography plus tubal catheterisation, or hysteroscopic tubal cannulation, may be treatment options because these treatments improve the chance of pregnancy. **[2004]**

9.4 Surgery for hydrosalpinges before in vitro fertilisation treatment

Hydrosalpinx is dilation of the fallopian tube in the presence of distal tubal obstruction, which may result from a number of causes.[730] In women undergoing IVF, the presence of hydrosalpinx is associated with early pregnancy loss and poor implantation and pregnancy rates,[730,731] probably due to alteration in endometrial receptivity.[732,733] [Evidence level 2b]

A systematic review of three RCTs showed that tubal surgery such as laparoscopic salpingectomy significantly increased live birth rate (OR 2.13; 95% CI 1.24 to 3.65) and pregnancy rate (OR 1.75; 95% CI 1.07 to 2.86) in women with hydrosalpinges before IVF when compared with no treatment.[734] [Evidence level 1a] There were no significant differences in the odds of ectopic pregnancy (OR 0.42; 95% CI 0.08 to 2.14), miscarriage (OR 0.49; 95% CI 0.16 to 1.52), treatment complication (OR 5.80; 95% CI 0.35 to 96.79) or implantation (OR 1.34; 95% CI 0.87 to 2.05).[734]

Recommendations

Number	Recommendation
106	Women with hydrosalpinges should be offered salpingectomy, preferably by laparoscopy, before IVF treatment because this improves the chance of a live birth. **[2004]**

Number	Research recommendation
RR 18	For women who have hydrosalpinges, the effectiveness of draining of hydrosalpinges or performing salpingostomy on improving live birth rate during in vitro fertilisation needs further evaluation.

9.5 Uterine surgery

Uterine myoma (leiomyoma)

We did not find any RCTs comparing myomectomy versus expectant management for women with leiomyomas. The incidence of myoma in women with infertility without any obvious cause of infertility is estimated to be 1.0–2.4%.[651,652]

A systematic review of 11 cohort studies suggests that women with submucous myoma have lower pregnancy rates compared with women with other causes for their infertility (relative risk [RR] 0.30, 95% CI 0.13 to 0.70). Myomectomy was not associated with an increase in live birth rate (RR 0.98, 95% CI 0.45 to 2.41) but was associated with a higher pregnancy rate (RR 1.72, 95% CI 1.13 to 2.58).[653] [Evidence level 2b] Another cohort study found that women with intramural uterine fibroids had a reduced chance of pregnancy when compared with women with no fibroids following assisted reproduction (OR 0.46, 95% CI 0.24 to 0.88), having adjusting for number of embryos replaced and for age of over 40 years.[401] [Evidence level 2b]

A case–control study found a lower pregnancy rate in women with myoma when compared with women without myoma (11% versus 25%). The pregnancy rate in women following myomectomy was higher than that in women with untreated myoma (42% versus 25%).[654] [Evidence level 3]

An RCT (n = 109) that compared different surgical methods for undertaking myomectomy (abdominal myomectomy versus laparoscopic myomectomy) found no differences in pregnancy rates (55.9% with abdominal myomectomy versus 53.6% with laparoscopic myomectomy) or miscarriage rates (12% versus 20%) in women with large myomas. There was significantly higher incidence of postoperative fever and a drop in haemoglobin and hospital stay in the group following abdominal myomectomy.[655] [Evidence level 1b]

Septate uterus

Uterine septum is a congenital anomaly of the female reproductive tract. The incidence is not increased among women with infertility compared with other women (2–3%).[656,657] It is more common in women who have had recurrent pregnancy loss or preterm birth.[658–660] Hysteroscopic metroplasty has not been shown to increase pregnancy rates in women with infertility who have a septate uterus.[661–664] [Evidence level 2b–3]

Intrauterine adhesions

Intrauterine adhesions are rare but they may result from previous uterine evacuation or surgery. They are associated with oligo/amenorrhoea. A case series (n = 40) suggests that hysteroscopic adhesiolysis restored normal menstrual pattern in 81% of women of the 16 infertile women in the series, 63% (n = 10) conceived and 37% (n = 6) delivered a viable infant.[665] [Evidence level 3]

Recommendations

Number	Recommendation
107	Women with amenorrhoea who are found to have intrauterine adhesions should be offered hysteroscopic adhesiolysis because this is likely to restore menstruation and improve the chance of pregnancy. **[2004]**

Number	Research recommendation
RR 19	Randomised controlled trials are needed to evaluate any benefits of surgical treatment of leiomyoma on improving the chance of live birth.
RR 20	Further research is needed to evaluate any benefit on live birth rates of surgical resection of uterine septum in women with fertility problems.

10 Medical and surgical management of endometriosis

10.1 Introduction

Endometriosis is an oestrogen-dependent disorder characterised by and defined as the presence of endometrial tissue outside the uterine cavity. This extra-uterine endometrium produces a chronic inflammatory tissue response. Mainly found in women of reproductive age, it is recognised as an important cause of infertility, with a prevalence of 0.5–5% in fertile and 25–40% in infertile women (Ozkan et al., 2008)

The clinical features associated with endometriosis can vary from the classic symptoms (severe dysmenorrhoea, deep dyspareunia, chronic pelvic pain, ovulation pain, cyclical or perimenstrual symptoms and abnormal bleeding or pain as well as infertility) and signs (pelvic tenderness, a fixed, retroverted uterus, tender uterosacral ligaments or enlarged ovaries) to a woman having no symptoms apart from infertility and no abnormality on physical examination. The definitive diagnosis is made by visual identification of deposits of endometriosis in the pelvis at laparoscopy.

There are four options for the management of infertility associated with endometriosis:

- medical management (ovarian suppression)
- surgical ablation
- intra-uterine insemination (IUI) (see Chapter 12)
- in vitro fertilisation (IVF) (see Chapter 15)

The effectiveness of these interventions is assessed in this guideline. This chapter reviews the evidence for the clinical effectiveness of the first two interventions.

10.2 Medical management (ovarian suppression) of endometriosis

A systematic review and meta-analysis of 16 randomised controlled trials (RCTs) compared the effectiveness of ovulation suppression agents with no treatment (six RCTs) or danazol (ten RCTs). Treatment with ovulation suppression agents (medroxyprogesterone, gestrinone, combined oral contraceptives and gonadotrophin-releasing hormone agonist [GnRHa]) did not improve clinical pregnancy rates in women with endometriosis-associated infertility compared with no treatment (pooled odds ration [OR] 0.74; 95% confidence interval [CI] 0.48 to 1.15) or danazol (pooled OR 1.3; 95% CI 0.97 to 1.76).[666] [Evidence level 1a] Similar results were reported in a subsequent RCT comparing medroxyprogesterone acetate to placebo.[667] [Evidence level 1b] Two reviews in 1993 and 1994 which included RCTs and cohort studies also concluded that ovulation suppression was ineffective in the treatment of endometriosis-associated infertility.[668,669] [Evidence level 1b–2b]

Commonly used ovulation suppression agents have been known to cause significant adverse effects such as weight gain, hot flushes and bone loss.[666]

A systematic review of two small RCTs assessing the effect of danazol in the treatment of unexplained infertility found no significant difference in pregnancy rates (OR 2.57, 95% CI 0.53 to 12.46) when compared with placebo.[670] [Evidence level 1a]

Recommendations

Number	Recommendation
108	Medical treatment of minimal and mild endometriosis diagnosed as the cause of infertility in women does not enhance fertility and should not be offered. **[2004, amended 2013]**

10.3 Surgical ablation

Minimal and mild endometriosis

A systematic review and meta-analysis of two RCTs (n = 444) showed that laparoscopic ablation or resection of minimal and mild endometriosis plus laparoscopic adhesiolysis increased ongoing pregnancy and live birth rates compared with diagnostic laparoscopy (pooled OR 1.64; 95% CI 1.05 to 2.57).671 [Evidence level 1a] There was no difference in miscarriage rates between the two treatment groups (pooled OR 1.33; 95% CI 0.60 to 2.94). Surgical complications were reported in one of the trials but these were minor and did not require laparotomy or transfusion.[672] However, it was not clear from either trial whether the study subjects were blinded as to the treatments they received or whether intention-to-treat analysis was performed.

In women who had mild endometriosis as their only infertility factor, the pregnancy rate was higher after laser laparoscopy and laparotomy compared with medical treatment (81% with laser laparoscopy versus 84% with laparotomy versus 54% with medical treatment).[673] [Evidence level 2b] The benefits of surgery should be balanced against the risks of general anaesthesia and surgical complications[674] such as postoperative adhesions.

Endometrioma/ovarian cysts

One RCT found that laparoscopic cystectomy increased cumulative pregnancy rates at 24 months when compared with drainage and coagulation in the treatment of large ovarian endometrioma (66.7% versus 23.5%; OR 2.83, 95% CI 1.01 to 7.50).[675] [Evidence level 1b]

Moderate and severe endometriosis

Cohort studies of women with moderate and severe endometriosis operative treatment with laparoscopy or laparotomy suggest that pregnancy rates may be the same or increased in those treated by laparoscopy (54–66% with operative laparoscopy versus 36–45% with laparotomy).[676–679] [Evidence level 2b]

Postoperative medical treatment

Two RCTs compared postoperative GnRH with expectant management and found no significant difference in pregnancy rates between the two regimens (11.6% with goserelin versus 18.4% with expectant management and 33% with leuprolide depot versus 40% with expectant management, respectively).[680,681] [Evidence level 1b] Similar outcomes were shown between postoperative danazol (55% with danazol versus 50% with expectant management)[682] and between postoperative nafarelin and placebo (19% with nafarelin spray versus 18% with placebo),[683] in women with moderate to severe endometriosis. [Evidence level 1b]

Recommendations

Number	Recommendation
109	Women with minimal or mild endometriosis who undergo laparoscopy should be offered surgical ablation or resection of endometriosis plus laparoscopic adhesiolysis because this improves the chance of pregnancy. **[2004]**
110	Women with ovarian endometriomas should be offered laparoscopic cystectomy because this improves the chance of pregnancy. **[2004]**
111	Women with moderate or severe endometriosis should be offered surgical treatment because it improves the chance of pregnancy. **[2004]**
112	Post-operative medical treatment does not improve pregnancy rates in women with moderate to severe endometriosis and is not recommended. **[2004]**

11 Unexplained infertility

11.1 Introduction

Infertility is described as 'unexplained' when standard investigations, including semen analysis, tubal patency tests and assessment of ovulation (see Chapter 6), fail to identify any abnormalities or a specific diagnosis. It is therefore a diagnosis of exclusion. The literature on unexplained infertility is based on studies of heterosexual couples having vaginal intercourse.

Unexplained infertility affects about 15% of the couples seeking medical advice, although in some studies as many as 37% of people are categorized as being infertile for unexplained reasons (Aboulghar et al., 2003; Isaksson & Tiitinen, 2004). The reported incidence varies according to the age and selection criteria in the different studies (Aboulghar et al., 2003; Isaksson & Tiitinen, 2004). As unexplained infertility is a diagnosis of exclusion, it is dependent on the investigations undertaken before the diagnosis is applied (Aboulghar et al., 2003; Isaksson & Tiitinen, 2004). Many of these couples will conceive and go on to have a live birth without treatment. The spontaneous pregnancy rate in couples with unexplained infertility has been reported as 2% to 4% per menstrual cycle (Polyzos et al., 2008; Guzick et al., 1998).

Overall, about 15% of couples diagnosed with unexplained infertility will conceive without treatment within 1 year and 35% within 2 years (Isaksson & Tiitinen, 1998). However, the cumulative pregnancy rate over 3 years without treatment has been reported to be up to 80% in some groups (Guzick et al., 1998; Hull et al., 1985). Age of the woman is the most important predictor of successful conception without treatment with the rates falling at a greater rate after age 30 years (Isaksson & Tiitinen, 1998; Hunault et al., 2004) (see Figure 11.1). Some have suggested that unexplained infertility for more than 3 years is a poor prognostic feature for future chance of pregnancy, while others have not found this (Crosignani et al., 1993; Sundstrom et al., 1997; saksson & Tiitinen, 1998). As a result, couples with unexplained infertility are often given advice on lifestyle and successful conception, and told to return in a few months if they have still not become pregnant (this is known as 'expectant management'), but no active treatment is recommended

However, expectant management is often not attractive to couples (or their clinicians), both because they have been hoping for a pregnancy for some time and also because there is a preference for active treatment. As a result, a number of therapeutic approaches have been used to actively treat unexplained infertility. They are:

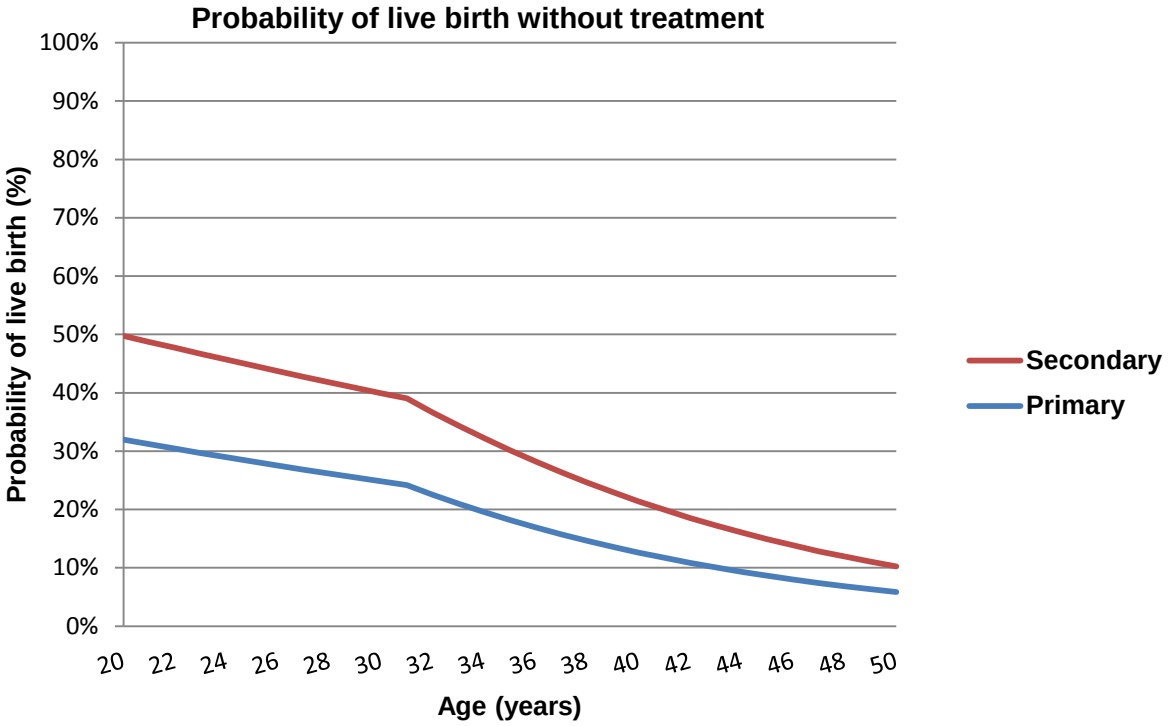
- ovarian stimulation
- intrauterine insemination (IUI) (see Chapter 12)
- in vitro fertilisation (IVF) (see Chapter 15)

This chapter reviews the evidence for the clinical effectiveness of ovarian stimulation for unexplained infertility.

2013 Update

Figure 11.1 Probability of a spontaneous live birth without treatment in a woman with either primary (no previous pregnancies) or secondary (previous pregnancies) infertility of 2 years duration, who is having regular intercourse and where she has normal ovulation, patent fallopian tubes and a partner with normal sperm motility (40%) (Hunault et al., 2004)

This chapter reviews the evidence for the clinical effectiveness of ovarian stimulation for unexplained infertility



11.2 Ovarian stimulation for unexplained infertility

Introduction

One of the commonly used first-line treatments for unexplained infertility is oral clomifene citrate as it is believed to correct subtle ovulatory dysfunction. However, concerns about the risk of clomifene-induced multiple pregnancies and reports of a possible link with ovarian cancer underline the need to weigh the risks, costs and benefits of this drug. More recently, aromatase inhibitors have been used to stimulate the ovaries in women with unexplained infertility, but there have been some concerns about potential teratogenic effects of these drugs.

Review question

What is the effectiveness and safety of ovarian stimulation agents in women with unexplained infertility?

Description of included studies

Comparison of ovarian stimulating agents versus no ovarian stimulating agents (Table 11.1)

One randomised controlled trial (RCT) was identified that was relevant for this review (Bhattacharya et al., 2008). The study randomised women to receive clomifene citrate, expectant management or unstimulated IUI. The expectant management protocol in the study consisted of no active management for six months (that is, no clinic visits or interventions) with general advice given regarding the need for regular intercourse. No specific measures were recommended to the couples.

Blinding was not possible in this study. The study included 580 couples, representing an estimated 2826 cycles.

Comparison of different types of ovarian stimulating agents (Table 11.2)

One RCT was identified that was relevant for this review (Badawy et al., 2009). The study randomised women to receive letrozole, anazstrozole or clomifene citrate, each with human chorionic gonadotrophin (hCG), and included a non-randomised age-matched group of women as controls (though data on this group is not used in this analysis). Blinding was not performed. The study included 996 couples, representing 1398 cycles.

No RCTs were identified that investigated the effectiveness of clomifene citrate compared with gonadotrophins or with placebo. No randomised controlled studies using a protocol that included gonadotrophin releasing hormone analogues were identified.

A 2010 Cochrane review was not included in this review (Hughes et al., 2010). The Cochrane review included seven studies, six of which did not meet the inclusion criteria for the current review. In two studies women received IUI. One of the studies was a crossover trial with data that could not be separated for each arm and two studies included couples without unexplained infertility (more than 10% in one study and 79% in another). In another study, all women received clomifene citrate before randomisation. The remaining study was included this review (Bhattacharya et al., 2008).

Evidence profile

Two evidence profiles are presented. They are a comparison of:

- ovarian stimulation agents with no ovarian stimulation agents
- different types of ovarian stimulation agents.

Table 11.1 GRADE findings for comparison of ovarian stimulation agents with no ovarian stimulation agents

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton births					
Clomifene citrate without hCG vs advice only					
1 (Bhattacharya et al., 2008)	26/192 women (14%)	32/193 women (17%)	RR 0.8 (0.5 to 1.3)	30 fewer per 1000 (from 81 fewer to 53 more)	Low
Clinical pregnancies					
Clomifene citrate without hCG vs advice only					
1 (Bhattacharya et al., 2008)	29/192 women (15%)	33/193 women (17%)	RR 0.9 (0.6 to 1.4)	21 fewer per 1000 (from 75 fewer to 68 more)	Low
Ovarian hyperstimulation					
No evidence reported					

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Clomifene citrate without hCG vs advice only					
1 (Bhattacharya et al., 2008)	2/192 women (1%)	2/192 women (1%)	RR 1 (0.1 to 7.0)	0 fewer per 1000 (from 9 fewer to 63 more)	Very low
	2/29 pregnancies (7%)	2/33 pregnancies (6%)	RR 1.1 (0.2 to 7.6)	8 more per 1000 (from 50 fewer to 398 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Adverse pregnancy outcomes					
Clomifene citrate without hCG vs advice only (Miscarriage)					
1(Bhattacharya et al., 2008)	10/129 women (8%)	14/193 women (7%)	RR 1.1 (0.5 to 2.3)	5 more per 1000 (from 37 fewer to 96 more)	Very low
	10/29 pregnancies (35%)	14/33 pregnancies (42%)	RR 0.8 (0.4 to 1.5)	81 fewer per 1000 (from 242 fewer to 229 more)	
Clomifene citrate without hCG vs advice only (Ectopic pregnancy)					
1(Bhattacharya et al., 2008)	0/192 women (0%)	1/193 women (1%)	RR 0.5 (0.0 to 12.1)	3 fewer per 1000 (from 5 fewer to 58 more)	Very low
	0/29 pregnancies (0%)	1/33 pregnancies (3%)	RR 0.4 (0.0 to 8.9)	19 fewer per 1000 (from 30 fewer to 240 more)	
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
Clomifene citrate without hCG vs advice only (Process of treatment acceptable)					
1(Bhattacharya et al., 2008)	159/192 women (83%)	123/193 women (64%)	RR 1.3(1.2 to 1.5)	191 more per 1000 (from 96 more to 300 more)	Moderate
Clomifene citrate without hCG vs advice only (Outcome of treatment acceptable)					
1(Bhattacharya et al., 2008)	100/192 women (52%)	82/193 women (43%)	RR 1.2 (1.0 to 1.5)	98 more per 1000 (from 4 fewer to 221 more)	Low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Anxiety or depression					
Clomifene citrate without hCG vs advice only (Anxiety)					
1(Bhattacharya et al., 2008)	34/192 women (18%)	31/193 women (16%)	RR 1.1 (0.7 to 1.7)	16 more per 1000 (from 47 fewer to 116 more)	Low
Clomifene citrate without hCG vs advice only (Depression)					
1(Bhattacharya et al., 2008)	4/192 women (2%)	4/193 women (2%)	RR 1.0 (0.3 to 4.0)	0 more per 1000 (from 15 fewer to 61 more)	Low

CI confidence interval, hCG human chorionic gonadotrophin, RR relative risk

Table 11.2 GRADE findings for comparison of different ovarian stimulation agents

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton births					
Letrozole + hCG vs. Clomifene citrate + hCG					
1 (Badawy et al., 2009)	26/269 (10%) women	63/420 (15%) women	RR 0.6 (0.4 to 1.0)	54 fewer per 1000 (from 1 fewer to 87 fewer)	Very low
Anastrozole + hCG vs. Clomifene citrate + hCG					
1 (Badawy et al., 2009)	10/107 (9%) women	63/420 (15%) women	RR 0.6 (0.3 to 1.2)	57 fewer per 1000 (from 101 fewer to 25 more)	Very low
Clinical pregnancies					
Letrozole + hCG vs. Clomifene citrate + hCG					
1 (Badawy et al., 2009)	36/269 (13%) women	77/420 (18%) women	RR 0.7 (0.5 to 1.1)	49 fewer per 1000 (from 90 fewer to 9 more)	Low
Anastrozole + hCG vs. Clomifene citrate + hCG					
1 (Badawy et al., 2009)	15/107 (14%) women	77/420 (18%) women	RR 0.8 (0.5 to 1.3)	44 fewer per 1000 (from 99 fewer to 49 more)	Low
Ovarian hyperstimulation					
Letrozole + hCG vs. Clomifene citrate + hCG					
1 (Badawy et al., 2009)	0/269 (0%) women	0/420 (0%) women	Not calculable	Not calculable	Moderate

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Anastrozole + hCG vs. Clomifene citrate + hCG					
1 (Badawy et al., 2009)	0/107 (0%) women	0/420 (0%) women	Not calculable	Not calculable	Moderate
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Letrozole + hCG vs. Clomifene citrate + hCG					
1 (Badawy et al., 2009)	3/269 (1%) women	7/420 (2%) women	RR 0.7 (0.2 to 2.6)	6 fewer per 1000 (from 14 fewer to 26 more)	Low
	3/36 (8%) pregnancies	7/77 (9%) pregnancies	RR 0.9 (0.3 to 3.3)	7 fewer per 1000 (from 68 fewer to 213 more)	
Anastrozole + hCG vs. Clomifene citrate + hCG					
1 (Badawy et al., 2009)	1/107 (1%) women	7/420 (2%) women	RR 0.6 (0.1 to 4.5)	7 fewer per 1000 (from 16 fewer to 59 more)	Low
	1/15 (7%) pregnancies	7/77 (9%) pregnancies	RR 0.7 (0.1 to 5.5)	25 fewer per 1000 (from 82 fewer to 412 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Adverse pregnancy outcomes					
Letrozole + hCG vs. Clomifene citrate + hCG (miscarriage)					
1 (Badawy et al., 2009)	6/269 (2%) women	11/420 (3%) women	RR 0.9 (0.3 to 2.3)	4 fewer per 1000 (from 18 fewer to 34 more)	Low
	6/36 (17%) pregnancies	11/77 (14%) pregnancies	RR 1.2 (0.5 to 2.9)	24 more per 1000 (from 76 fewer to 273 more)	
Letrozole + hCG vs. Clomifene citrate + hCG (ectopic)					
1 (Badawy et al., 2009)	0/269 (0%) women	1/420 (<1%) women	RR 0.5 (0.0 to 12.7)	1 fewer per 1000 (from 2 fewer to 28 more)	Low
	0/36 (0%) pregnancies	1/77 (1%) pregnancies	RR 0.7 (0.0 to 16.8)	4 fewer per 1000 (from 13 fewer to 206 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Anastrozole + hCG vs. Clomifene citrate + hCG (miscarriage)					
1 (Badawy et al., 2009)	3/107 (3%) women	11/420 (3%) women	RR 1.1 (0.3 to 3.8)	2 more per 1000 (from 18 fewer to 73 more)	Low
	3/15 (20%) pregnancies	11/77 (14%) pregnancies	RR 1.4 (0.4 to 4.4)	57 more per 1000 (from 80 fewer to 489 more)	
Anastrozole + hCG vs. Clomifene citrate + hCG (ectopic)					
1 (Badawy et al., 2009)	0/107 (0%) women	1/420 (<1%) women	RR 1.3 (0.1 to 31.7)	1 more per 1000 (from 2 fewer to 73 more)	Low
	0/15 (0%) pregnancies	1/77 (1%) pregnancies	RR 1.6 (0.1 to 38.1)	8 more per 1000 (from 12 fewer to 482 more)	
Congenital abnormalities					
Letrozole + hCG vs. Clomifene citrate + hCG					
1 (Badawy et al., 2009)	2/30 (7%) births	1/65 (2%) births	RR 4.3 (0.4 to 46.0)	51 more per 1000 (from 9 fewer to 692 more)	Low
	2/36 (6%) pregnancies	1/77 (1%) pregnancies	RR 4.3 (0.4 to 45.7)	43 more per 1000 (from 8 fewer to 580 more)	
Anastrozole + hCG vs. Clomifene citrate + hCG					
1 (Badawy et al., 2009)	0/11 (0%) births	1/65 (2%) births	RR 1.8 (0.1 to 42.4)	13 more per 1000 (from 14 fewer to 637 more)	Moderate
	0/15 (0%) pregnancies	1/77 (1%) pregnancies	RR 1.6 (0.1 to 38.1)	8 more per 1000 (from 12 fewer to 482 more)	
Patient satisfaction					
No evidence reported					
Anxiety or depression					
No evidence reported					

CI confidence interval, hCG human chorionic gonadotrophin, RR relative risk

Evidence statements

Comparison of ovarian stimulation agents vs. no ovarian stimulation agents (Table 11.1)

Live full-term singleton births

There was no significant difference in the number of live births per woman with the use of clomifene citrate compared with expectant management (advice only).

Clinical pregnancies

There was no significant difference in the number of clinical pregnancies with the use of clomifene citrate compared with advice only.

Ovarian hyperstimulation syndrome

No evidence was reported.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies per woman or per pregnancy when comparing the use of clomifene citrate with advice.

Multiple births

No evidence was reported regarding the number of births from multiple pregnancies when comparing ovarian stimulating agents to non-drug treatment.

Adverse pregnancy outcomes

There was no significant difference in the number of miscarriages or the number of ectopic pregnancies when comparing clomifene citrate to advice.

Congenital abnormalities

No evidence was reported regarding the number of congenital abnormalities when comparing ovarian stimulating agents to non-drug treatment.

Patient satisfaction

Significantly more women receiving clomifene found the process of their treatment acceptable compared with the women who received general pregnancy advice alone. There was no significant difference in the number of women in the two groups who found the outcome of their treatment acceptable.

Anxiety or depression

There was no significant difference in the number of women with anxiety or depression with the use of clomifene citrate without hCG compared with general pregnancy advice alone.

Comparison of different types of ovarian stimulation agents (Table 11.2)

Live full-term singleton births

There were significantly more live births following use of clomifene citrate compared with letrozole.

Similarly, there were more live births following use of clomifene citrate compared with anastrozole though the difference was not statistically significant.

Clinical pregnancies

There was no significant difference in the number of clinical pregnancies per woman following the use of clomifene citrate compared with letrozole or compared with anastrozole.

Ovarian hyperstimulation syndrome

There was no significant difference in the number of cases of ovarian hyperstimulation syndrome (OHSS) following the use of clomifene citrate compared with letrozole or compared with anastrozole.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies per woman or per pregnancy following the use of clomifene citrate compared with letrozole or compared with anastrozole.

Multiple births

No evidence was reported that compared the number of births resulting from multiple pregnancies after letrozole compared with clomifene citrate, or after anastrozole compared with clomifene citrate.

Adverse pregnancy outcomes

There was no significant difference in the number of miscarriages or ectopic pregnancies per woman or per pregnancy following the use of clomifene citrate compared with letrozole or compared with anastrozole.

Congenital abnormalities

There were no statistically significant differences in the number of congenital abnormalities per woman or per pregnancy when using clomifene citrate compared with letrozole or compared with anastrozole.

Patient satisfaction

No evidence was reported that compared patient satisfaction after clomifene citrate with patient satisfaction after letrozole or anastrozole.

Anxiety or depression

No evidence was reported that compared the number of women with anxiety or depression after clomifene citrate with the number of women with anxiety or depression after letrozole or anastrozole.

Health economics profile

As ovarian stimulation is not effective in women with unexplained infertility it will not be cost effective and thus no further health economic input is required.

Evidence to recommendations

Relative value placed on the outcomes considered

The guideline development group (GDG) considered rates of clinical pregnancies and live full-time singleton births to be important outcomes which allow clinicians to inform couples of their chances of conception and having a baby. The other important outcomes considered in this review were the adverse effects of the treatments. These also must be included in discussion with couples so that they are fully informed of both risks and benefits of treatment.

Consideration of clinical benefits and harms

The evidence for ovarian stimulation agents did not demonstrate any significant difference in the number of clinical pregnancies or live births associated with the use of clomifene citrate compared with expectant management or general pregnancy advice. There were significantly more live births to women who were offered clomifene citrate compared with letrozole, although this was of borderline significance. There was no significant difference in clinical pregnancy rates. The GDG inferred from this that aromatase inhibitors are also no more effective than general pregnancy advice.

The number of ectopic pregnancies and miscarriages did not differ significantly between clomifene citrate and general advice, or between clomifene citrate and letrozole or anastrozole. There was also no reported difference in congenital abnormalities or rates of anxiety or depression.

The evidence demonstrated that treatment with clomifene citrate was more acceptable to women than advice alone. However, the GDG view was that this may have reflected a societal preference for action when faced with unexplained infertility.

The evidence for letrozole or anastrozole reported significantly fewer clinical pregnancies or live births than clomifene citrate alone. There were also no differences in multiple pregnancy or adverse outcomes. The GDG acknowledged that there are ongoing trials investigating the safety of letrozole. The GDG believed, therefore, that the use of aromatase inhibitors could not be recommended in women with unexplained infertility.

After considering all the available evidence, the GDG's view was that ovarian stimulation with clomifene citrate, letrozole or anastrozole in women with unexplained infertility should not be offered in the NHS in light of the current evidence.

Consideration of health benefits and resource uses

An intervention that is not shown to be effective is not cost effective. An economic evaluation is not required in this case. The use of clomifene citrate and other ovarian stimulation agents costs more to deliver than general pregnancy advice offered on one occasion ('expectant management') and there is no evidence that it is more effective in women with unexplained infertility.

Quality of evidence

Despite being reported in RCTs, the data ranged from moderate to very low in quality. Limitations of the studies included a lack of power analysis, mixed populations and ambiguous outcome definitions.

Other considerations

Limitations of the evidence

The GDG was concerned about the limitations in the evidence, specifically with data on congenital abnormalities. There were only a small number of births in each study, which means the comparison was underpowered. The GDG consensus was that the background incidence of congenital abnormalities is 2%.

No studies using random allocation and double blinding reported on clomifene citrate compared with no treatment or compared with a placebo. This may have affected the satisfaction data. The GDG view was that women may report more satisfaction receiving a placebo than general pregnancy advice.

The GDG was unable to make evidence-based recommendations on what specific advice should be given to women as no studies were identified that evaluate this intervention. However, in the absence of evidence, the GDG made recommendations on the advice that should be offered to infertile couples, and in particular what should comprise 'expectant management', in Chapter 6 and Chapter 12.

Expectant management

The GDG discussed what constituted expectant management for groups of women with the diagnosis of unexplained infertility. The GDG concluded that expectant management should consist of supportively offering an individual or couple information and advice about the regularity and timing of intercourse and any lifestyle changes which might improve their chances of conceiving. It does not involve active clinical or therapeutic interventions.

For people having unprotected regular vaginal intercourse conception rates are shown in Figure 5.1. In summary, over 80% of couples where the women is aged 39 years or younger will conceive within 12 months. The figure is over 85% where the woman is less than 35 years old. If the couple continue to have unprotected regular intercourse for another 12 months, making 24 months in total, cumulative pregnancy success rates rise by about a further 15%.

The GDG did note that even after 2 years without a live birth, couples with unexplained infertility still had a chance of natural conception, but the additional cumulative success rates in the third year would be small. In addition, conception rates decline with the age of the woman. The GDG felt that this information should be explained early on to women with the diagnosis of unexplained infertility (see Figure 5.1). Thus, the GDG's view was that after 2 years of unexplained infertility IVF should be considered. Furthermore, of the 2 years, up to a maximum of 1 year should be included before investigation referal.

The cost effectiveness of IVF under specific circumstances is considered elsewhere (see Chapters 14 and 15) but the GDG consensus view was that women with a diagnosis of unexplained fertility should be told at the start of expectant management that they will be considered for IVF (but it will not necessarily be offered) after a total of 2 years without conception. This provides women diagnosed with unexplained infertility a clear idea of the period of time they should continue with regular unprotected vaginal intercourse before IVF will be considered. The GDG view was that this would represent a positive approach and lessen the anxiety and depression identified in the expectant management group in the trial reported here.

Other groups requiring special consideration

Three separate groups who use either donor or partner insemination to conceive were considered under this heading:

- people who are unable to, or would find it very difficult to have vaginal intercourse (such as people with with a clinically diagnosed physical disability or psychosexual problem)
- people who are in same-sex relationships
- people with conditions that require specific consideration in relation to methods of conception (such as couples where the male is HIV positive).

The term 'unexplained infertility' is not normally used in these groups. Nevertheless, the GDG was of the view that in such cases where there was normal ovulation, patent fallopian tubes and normal semenalysis, a failure to conceive after 6 cycles of insemination should be followed by an intervention that would equate to that offered to those people who have been recommended expectant management rather than proceeding directly to IVF. These issues are discussed in more detail in Chapter 12.

Recommendations

Number	Recommendation
113	Do not offer oral ovarian stimulation agents (such as clomifene citrate, anastrozole or letrozole) to women with unexplained infertility. **[new 2013]**
114	Inform women with unexplained infertility that clomifene citrate as a stand-alone treatment does not increase the chances of a pregnancy or a live birth. **[new 2013]**
115	Advise women with unexplained infertility who are having regular unprotected sexual intercourse to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**
116	Offer IVF treatment (see recommendations 129–130) to women with unexplained infertility who have not conceived after 2 years (this can include up to 1 year before their fertility investigations) of regular unprotected sexual intercourse. **[new 2013]**

Number	Research recommendation
RR 21	What is the optimum period of expectant management for women of different age groups before invasive treatment such as IVF is considered? **Why this is important** Where there is no known cause for infertility, expectant management increases the cumulative chances of successful conception.However, the chances of a live birth both by natural conception and by using assisted reproductive technology decline with advancing age because ofa woman's decreasing ovarian reserve.The guideline currently recommends a shorter period of expectant management for women who are 36 years or older. This is a very crude cut-off. If there were better evidence it might be possible to customise the period of expectant management based on a woman's age, including longer periods of expectant management for younger women.

2013 Update

12 Intrauterine insemination

12.1 Introduction

Intrauterine insemination (IUI) is a form of treatment where sperm are inserted into the uterine cavity around the time of ovulation. IUI can be carried out in a natural cycle, without the use of drugs, or the ovaries may be stimulated with oral anti-oestrogens or gonadotrophins.

Where oral anti-oestrogens are used to stimulate a cycle, a woman will take a course of tablets for 5 days. When gonadotrophins are used to stimulate a cycle, the woman usually receives a course of daily fertility injections for 7 to 10 days. However, the exact duration of stimulation will depend on which day of the cycle it is started. In both circumstances the treatment should be monitored by ultrasound scan to assess the ovarian response. When one to three follicles are seen to have developed to a suitable size, usually with one dominate follicle, then an injection of human chorionic gonadotrophin (hCG) is given which triggers ovulation. Insemination of prepared sperm will be undertaken 24 to 36 hours later. However, in order to reduce the risk of multiple pregnancies, insemination may not be undertaken if more than three follicles have developed or two or more mature follicles are seen.

IUI has been used in people with:

- unexplained infertility
- mild endometriosis
- 'mild' male factor infertility
- disability (physical or psychological) preventing vaginal sexual intercourse
- conditions that require specific consideration in relation to methods of conception (such as after sperm washing in a couple where the male is HIV positive)
- as part of donor insemination (see Chapter 17).

This chapter reviews the evidence for the clinical effectiveness of IUI in the first three of these settings.

12.2 Review question

What is the effectiveness of intrauterine insemination (IUI) in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?

Evidence profile

As the use of clomifene citrate alone for the treatment of unexplained infertility has not been recommended (see Chapter 11), studies including this as a comparator to IUI (with or without stimulation) have not been included in this review as it would not form part of the treatment pathway. Also, studies using a crossover design were excluded as these may be inappropriate in infertility research (Khan et al., 1996).

Three comparisons were included in this review.

- IUI without ovarian stimulation compared with expectant management (Table 12.1)
- IUI with ovarian stimulation compared with expectant management (Table 12.2)
- IUI with ovarian stimulation compared with IUI without ovarian stimulation (Table 12.3).

Description of included studies

The studies are presented in three GRADE profiles addressing the three comparisons listed above.

IUI without ovarian stimulation versus expectant management

Only one study was identified. It randomised couples with unexplained infertility, 'mild' male infertilty or endometriosis to receive either IUI without ovarian stimulation or expectant management (Bhattacharya et al., 2008). It is summarised in Table 12.1. The expectant management group consisted of 6 months of no clinic visits or medical interventions. Couples were given general advice regarding regular intercourse, but nothing else. No specific measures of assessing or timing ovulation were recommended to the couples. Blinding was not possible in the study.

The mean age of women in the study was 32 years. The mean duration of infertility was 2 years (range 1 to 3 years). Sub-group data on unexplained infertility only is also presented.

IUI with ovarian stimulation versus expectant management

Two randomised controlled trials (RCTs) were identified that were relevant to this review (Steures et al., 2006 and Tummons et al., 2007). They are summarised in Table 12.2.

The first study randomised women with unexplained inferitlity to receive either IUI combined with ovarian stimulation using gonadotrophins (follicle-stimulating hormone [FSH] or hMG) or expectant management. (Steures et al., 2006). The study included women who, based on a predictive algorithm, had a 30% to 40% likelihood of becoming pregnant without any intervention. Couples in the expectant management group in the study were followed up until an ongoing pregnancy occurred or for 6 months, whichever occured first. However, it is not clear if patients received advice regarding timing of intercourse. Blinding was not undertaken. Rates of ovarian hyperstimulation syndrome (OHSS) were not reported.

The mean age of women was 33 years. The mean duration of infertility was 2.0 years (standard deviation [SD] 0.5) in the IUI group and 1.9 years (SD 0.50) for the expectant management group (Steures et al., 2006).

The second RCT (Tummons et al., 1997) compared the outcomes of IUI with stimulation versus no treatment in women with endometriosis. In total, 117 couples were randomised into the study. This was the only included study where OHSS was reported, but found no cases.

The mean ages of women in the two groups were 31.2 and 30.6 years respectively, and the mean durations of infertility were 43 and 42 months respectively (Tummons et al., 1997).

IUI with ovarian stimulation versus IUI without ovarian stimulation

Two RCTs presented in three papers were identified that were relevant to this review (Guzick et al., 1999; Goverde et al., 2000; Goverde et al., 2005). They are summarised in Table 13.3. Both studies randomised women to receive either IUI combined with gonadotrophin (FSH) or natural cycle IUI. In Guzick et al.,1999, each couple received up to 4 treatment cycles unless pregnancy occurred. Couples in the Goverde et al. RCT (2000 and 2005) were offered up to 6 treatment cycles. Blinding was not reported in either of the studies. Neither study reported on OHSS.

Both RCTs combined unexplained infertility, 'mild' male factor and mild endometriosis. The mean age of women was 32 years (SD ± 4 years) in both studies. The mean duration of infertility was 3.5 years (SD ± 2.5) in Guzick (1999) and 4 years (SD ± 1.7 years) in Goverde (2000 and 2005).

In addition, data on sub-group analysis is reproduced for unexplained infertility and male factor infertility based on these two RCTs and one additional RCT (Cohlen et al., 1998) that was presented in two Cochrane reviews (Veltman-Verhulst et al., 2006; Bensdorp et al., 2007). Rates of OHSS were not reported. No separate data were found about mild endometriosis.

Table 12.1 GRADE findings for comparison of IUI without ovarian stimulation versus expectant management (unexplained infertility)

Number of studies	Number of patients/women		Effect		Quality
	IUI without ovarian stimulation	Expectant Management*	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
1 (Bhattacharya et al., 2008)	43/191 (22.5%)	32/193 (16.6%)	RR 1.36 (0.9 to 2.05)	60 more per 1000 (from 17 fewer to 174 more)	Very low
	38/165 (23%) Unexplained infertility only	26/167 (15.6%)	RR 1.48 (0.94 to 2.32)	75 more per 1000 (from 9 fewer to 206 more)	
Clinical pregnancy					
1 (Bhattacharya et al., 2008)	43/191 (22.5%)	33/193 (17.1%)	RR 1.32 (0.88 to 1.98)	55 more per 1000 (from 21 fewer to 168 more)	Low
Multiple pregnancies					
1 (Bhattacharya et al., 2008)	1/43 (2.3%) per pregnancy	2/33 (6.1%) per pregnancy	RR 0.38 (0.04 to 4.05)	38 fewer per 1000 (from 58 fewer to 185 more)	Low
	1/191 (0.52%) per woman	2/193 (1%) per woman	RR 0.51 (0.05 to 5.53)	5 fewer per 1000 (from 10 fewer to 47 more)	
Multiple births					
No evidence reported					
Miscarriage					
1 (Bhattacharya et al., 2008)	9/55 (16.4%) per pregnancy	14/46 (30.4%) per pregnancy	RR 0.54 (0.26 to 1.13)	140 fewer per 1000 (from 225 fewer to 40 more)	Low
	9/191 (4.7%) per woman	14/193 (7.3%) per woman	RR 0.65 (0.29 to 1.46)	25 fewer per 1000 (from 52 fewer to 33 more)	
Ectopic pregnancy					
1 (Bhattacharya et al., 2008)	2/55 (3.6%) per pregnancy	1/46 (2.2%) per pregnancy	RR 1.67 (0.16 to 17.86)	15 more per 1000 (from 18 fewer to 367 more)	Low
	2/191 (1%) per woman	1/193 (0.52%) per woman	RR 2.02 (0.18 to 22.1)	5 more per 1000 (from 4 fewer to 109 more)	

Number of studies	Number of patients/women		Effect		Quality
	IUI without ovarian stimulation	Expectant Management*	Relative (95% CI)	Absolute (95% CI)	
Pre-term birth					
1 (Bhattacharya et al., 2008)	6/43 (14%) per live birth	5/31 (16.1%) per live birth	RR 0.87 (0.29 to 2.58)	21 fewer per 1000 (from 115 fewer to 255 more)	Low
	6/191 (3.1%) per woman	5/193 (2.6%) per woman	RR 1.21 (0.38 to 3.91)	5 more per 1000 (from 16 fewer to 75 more)	
Treatment related hospital admissions					
1 (Bhattacharya et al., 2008)	0/163 (0%)	2/160 (1.3%)	RR 0.2 (0.01 to 4.06)	10 fewer per 1000 (from 12 fewer to 38 more)	Low
Vaginal bleeding					
1 (Bhattacharya et al., 2008)	12/164 (7.3%)	5/159 (3.1%)	RR 2.33 (0.84 to 6.45)	42 more per 1000 (from 5 fewer to 171 more)	Low
Nausea					
1 (Bhattacharya et al., 2008)	3/164 (1.8%)	4/159 (2.5%)	RR 0.73 (0.17 to 3.2)	7 fewer per 1000 (from 21 fewer to 55 more)	Low
Vomiting					
1 (Bhattacharya et al., 2008)	0/164 (0%)	0/158 (0%)	Not calculable	Not calculable	Low
Headache					
1 (Bhattacharya et al., 2008)	4/191 (2.1%)	6/193 (3.1%)	RR 0.67 (0.19 to 2.35)	10 fewer per 1000 (from 25 fewer to 42 more)	Low
Hot flushes					
1 (Bhattacharya et al., 2008)	0/164 (0%)	4/159 (2.5%)	RR 0.11 (0.01 to 1.99)	22 fewer per 1000 (from 25 fewer to 25 more)	Low
Bloating					
1 (Bhattacharya et al., 2008)	6/164 (3.7%)	0/158 (0%)	RR 12.53 (0.71 to 220.54)	Not calculable	Low

Number of studies	Number of patients/women		Effect		Quality
	IUI without ovarian stimulation	Expectant Management*	Relative (95% CI)	Absolute (95% CI)	
Process of treatment acceptable					
1 (Bhattacharya et al., 2008)	155/162 (95.7%)	123/153 (80.4%)	RR 1.19 (1.09 to 1.3)	153 more per 1000 (from 72 more to 241 more)	Low
Outcome of treatment acceptable					
1 (Bhattacharya et al., 2008)	117/159 (73.6%)	82/148 (55.4%)	RR 1.33 (1.12 to 1.58)	183 more per 1000 (from 66 more to 321 more)	Low
Anxiety					
1 (Bhattacharya et al., 2008)	22/173 (12.7%)	31/171 (18.1%)	RR 0.7 (0.42 to 1.16)	54 fewer per 1000 (from 105 fewer to 29 more)	Low
Depression					
1 (Bhattacharya et al., 2008)	2/172 (1.2%)	4/170 (2.4%)	RR 0.49 (0.09 to 2.66)	12 fewer per 1000 (from 21 fewer to 39 more)	Low

CI confidence interval, IUI intrauterine insemination, RR relative risk

* Expectant management = 6 months during which no clinic or medical interventions were scheduled. Couples were given general advice about the need for regular intercourse, but nothing else.

Table 12.2 GRADE findings for comparison of IUI with ovarian stimulation versus expectant management

Number of studies	Number of patients/women		Effect		Quality
	IUI with ovarian stimulation	Expectant management	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth (Unexplained infertility)					
1(Steures et al., 2006)	24/124 (19.4%)	29/122 (23.8%)	RR 0.81 (0.5 to 1.32)	45 fewer per 1000 (from 119 fewer to 76 more)	Very low
Live full-term singleton birth (Endometriosis)					
1(Tummons et al., 1997)	11/53 (20.8%)	4/50 (8%)	RR 2.59 (0.88 to 7.62)	127 more per 1000 (from 10 fewer to 530 more)	Low
Live multiple birth (Unexplained infertility)					
1(Steures et al., 2006)	2/124 (1.6%)	1/122 (0.82%)	RR 1.97 (0.18 to 21.42)	8 more per 1000 (from 7 fewer to 167 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	IUI with ovarian stimulation	Expectant management	Relative (95% CI)	Absolute (95% CI)	
Live multiple birth (Endometriosis)					
1(Tummons et al., 1997)	4/53 (7.5%)	0/50 (0%)	RR 8.5 (0.47 to 153.95)	-	Low
Ongoing singleton pregnancy (Unexplained infertility)					
1(Steures et al., 2006)	27/127 (21.3%)	33/126 (26.2%)	RR 0.81 (0.52 to 1.27)	50 fewer per 1000 (from 126 fewer to 71 more)	Very low
Multiple pregnancies (Unexplained infertility)					
1(Steures et al., 2006)	2/127 (1.6%)	1/126 (0.79%)	RR 1.98 (0.18 to 21.61)	8 more per 1000 (from 7 fewer to 164 more)	Very low
Clinical pregnancy (Unexplained infertility)					
1(Steures et al., 2006)	42/127 (33.1%)	40/126 (31.7%)	RR 1.04 (0.73 to 1.49)	13 more per 1000 (from 86 fewer to 156 more)	Very low
Miscarriage per clinical pregnancy (Unexplained infertility)					
1(Steures et al., 2006)	13/42 (31%) per pregnancy	6/40 (15%) per pregnancy	RR 2.06 (0.87 to 4.9)	159 more per 1000 (from 20 fewer to 585 more)	Very low
	13/127 (10.2%) per woman	6/126 (4.8%) per woman	RR 2.15 (0.84 to 5.48)	55 more per 1000 (from 8 fewer to 213 more)	
OHSS (Endometriosis)					
1(Tummons et al., 1997)	0/53 (0%)	0/50 (0%)	-	-	Low

CI confidence interval, IUI intrauterine insemination, OHSS ovarian hyperstimulation syndrome, RR relative risk

Table 12.3 GRADE findings for comparisonof IUI with ovarian stimulation versus IUI without ovarian stimulation for all types of infertility (unless otherwise stated)

Number of studies	Number of patients/women		Effect		Quality
	IUI with ovarian stimulation	IUI without stimulation	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
2 (Goverde et al., 2005; Guzick et al., 1999)	72/315 (22.9%)	53/318 (16.7%)	RR 1.37 (1 to 1.88)	62 more per 1000 (from 0 more to 147 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	IUI with ovarian stimulation	IUI without stimulation	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth (Unexplained infertility based on sub-group from main studies)					
1 (Veltman-Verhulst et al., 2006)	47/172 (27.3%)	24/159 (15.1%)	RR 1.83 (1.18 to 2.84)	125 more per 1000 (from 27 more to 278 more)	Very low
Live full-term singleton birth (Male factor infertility based on sub-group from main studies)					
1 (Bensdorp et al., 2007)	9/25 (36%)	11/28 (39.3%)	RR 0.92 (0.46 to 1.83)	31 fewer per 1000 (from 212 fewer to 326 more)	Very low
Pregnancy rates					
2 (Goverde et al., 2005; Guzick et al., 1999)	110/317 (34.7%)	70/317 (22.1%)	RR 1.57 (1.22 to 2.03)	126 more per 1000 (from 49 more to 227 more)	Very low
Pregnancy rates (Unexplained infertility based on sub-group from main studies)					
2 (Veltman-Verhulst et al., 2006)	47/172 (27.3%)	24/159 (15.1%)	RR 1.83 (1.18 to 2.84)	125 more per 1000 (from 27 more to 278 more)	Very low
Pregnancyrates (Male factor infertility based on sub-group from main studies)					
1 (Bensdorp et al., 2007)	49/180 (27.2%)	42/199 (21.1%)	RR 1.3 (0.91 to 1.85)	63 more per 1000 (from 19 fewer to 179 more)	Very low
Multiple births (the number of babies born from a multiple pregnancy)					
2 (Goverde et al., 2005; Guzick et al., 1999)	33/154 (21.4%) per pregnancy	2/93 (2.2%) per pregnancy	RR 10.51 (2.53 to 43.7)	205 more per 1000 (from 33 more to 918 more)	Very low
	33/550 (6%) per woman	2/553 (0.36%) per woman	RR 16.62 (4.01 to 68.85)	56 more per 1000 (from 11 more to 245 more)	
With stimulation vs. IUI natural cycle					
1 (Goverde et al., 2005)	9/33 (27.3%) per pregnancy	1/28 (3.6%) per pregnancy	RR 7.64 (1.03 to 56.63)	237 more per 1000 (from 1 more to 1000 more)	Very low
	9/85 (10.6%) per woman	1/86 (1.2%) per woman	RR 9.11 (1.18 to 70.32)	94 more per 1000 (from 2 more to 806 more)	

Number of studies	Number of patients/women		Effect		Quality
	IUI with ovarian stimulation	IUI without stimulation	Relative (95% CI)	Absolute (95% CI)	
Superovulation vs. no superovulation (IUI or ICSI)					
1 (Guzick et al., 1999)	24/121 (19.8%) per pregnancy	1/65 (1.5%) per pregnancy	RR 12.89 (1.78 to 93.15)	183 more per 1000 (from 12 more to 1000 more)	Very low
	24/465 (5.2%) per woman	1/467 (0.21%) per woman	RR 24.1 (3.27 to 177.43)	49 more per 1000 (from 5 more to 378 more)	
Pre-term birth per live birth					
1(Guzick et al., 1999)	9/50 (18%) per livebirth	2/30 (6.7%) per livebirth	RR 2.7 (0.62 to 11.67)	113 more per 1000 (from 25 fewer to 711 more)	Low
	9/231 (3.9%) per woman	2/234 (0.85%) per woman	RR 4.56 (1 to 20.87)	30 more per 1000 (from 0 more to 170 more)	
Stillbirth per pregnancy					
1 (Guzick et al., 1999)	0/76 (0%)	1/40 (2.5%)	RR 0.18 (0.01 to 4.26)	21 fewer per 1000 (from 25 fewer to 82 more)	Low
Miscarriage per pregnancy					
1 (Guzick et al., 1999)	22/77 (28.6%) per pregnancy	6/42 (14.3%) per pregnancy	RR 2 (0.88 to 4.54)	143 more per 1000 (from 17 fewer to 506 more)	Low
	22/230 (9.6%) per woman	6/232 (2.6%) per woman	RR 3.7 (1.53 to 8.95)	70 more per 1000 (from 14 more to 206 more)	
Miscarriage per woman (Male factor infertility sub-group from main studies)					
1 (Cohlen et al., 1999)	3/36 (8.3%)	3/38 (7.9%)	RR 1.06 (0.23 to 4.89)	5 more per 1000 (from 61 fewer to 307 more)	Very low
Ectopic pregnancy per pregnancy					
1 (Guzick et al., 1999)	4/77 (5.2%) per pregnancy	2/42 (4.8%) per pregnancy	RR 1.09 (0.21 to 5.71)	4 more per 1000 (from 38 fewer to 224 more)	Low
	4/230 (1.7%) per woman	2/232 (0.86%) per woman	RR 2.02 (0.37 to 10.91)	9 more per 1000 (from 5 fewer to 85 more)	

Number of studies	Number of patients/women		Effect		Quality
	IUI with ovarian stimulation	IUI without stimulation	Relative (95% CI)	Absolute (95% CI)	
Ectopic pregnancy per woman (Unexplained infertility sub-group from main studies)					
1 (Guzick et al., 1999)	3/111 (2.7%)	0/100 (0%)	RR 6.31 (0.33 to 120.72)	-	Very low

CI confidence interval, ICSI intracytoplasmic sperm injection, IUI intrauterine insemination, OHSS ovarian hyperstimulation syndrome, RR relative risk

Evidence statements

IUI without ovarian stimulation versus expectant management

The evidence quality was low; this was due to the study not being designed to detect differences in certain outcomes, such as multiple pregnancy rates.

Live full-term singleton birth rates

Low quality evidence from one study showed there were no significant differences in the number of live births with the use of IUI without ovarian stimulation when compared with expectant management.

Pregnancy rates

Low quality evidence from one study showed there were no significant differences in the number of clinical pregnancies with the use of IUI without ovarian stimulation when compared with expectant management.

Multiple births

No evidence was reported on multiple births.

Multiple pregnancies

Low quality evidence from one study showed there were no significant differences in the number of multiple pregnancies with the use of IUI without ovarian stimulation when compared with expectant management.

Adverse events

Low quality evidence from one study showed no significant differences in the incidences of miscarriage or ectopic pregnancies in women receiving IUI without ovarian stimulation compared with expectant management. Similarly, the difference in the incidence of preterm births was not statistically significant. Regarding adverse patient outcomes, there were no significant differences in the incidence of treatment related hospital admissions, nausea, vomiting, headache, hot flushes or bloating, vaginal bleeding or abdominal pain between women receiving intrauterine insemination compared with expectant management. Significantly more women receiving IUI without stimulation found both the process and the outcome of their treatment acceptable compared with expectant management. There was no significant difference in the number of women with anxiety or depression with the use of IUI without ovarian stimulation compared with expectant management.

Sub-group analyses for couples with unexplained infertility or with endometriosis showed no difference in live birth rates between IUI alone or expectant management.

IUI with ovarian stimulation versus expectant management

The evidence quality was very low due to limitations in the study design and wide confidence intervals.

Live full-term singleton birth rates

Very low quality evidence from one study showed no significant difference in the number of live singleton births in women with unexplained infertility with the use of stimulated IUI when compared with expectant management.

Low quality evidence from one study showed significantly more live singleton births in women with endometriosis with the use of stimulated IUI when compared with expectant management.

Multiple births

Very low quality evidence from one study showed there was no significant difference in the number of multiple births reported after the use of IUI with ovarian stimulation compared with expectant management.

Low quality evidence from one study showed significantly more live multiple births in women with endometriosis with the use of stimulated IUI when compared with expectant management.

Pregnancy rates

Very low quality evidence from one study from a population with unexplained infertility showed no significant differences in the number of clinical pregnancies or ongoing pregnancies with the use of stimulated IUI when compared with expectant management.

Multiple pregnancies

Very low quality evidence from one study showed no significant difference in multiple pregnancies in women with unexplained infertility with the use of stimulated IUI when compared with expectant management.

Adverse events

Low quality evidence from one study showed there was no significant difference in the number of miscarriages reported after the use of IUI with ovarian stimulation compared with either expectant management.

Low quality evidence from one study showed there was no difference in reported rates of OHSS in women with endometriosis.

IUI with ovarian stimulation versus IUI without ovarian stimulation

The evidence quality ranged from low to very low depending on outcome.

Live full-term singleton birth rates

Low quality evidence from two studies showed that there was a statistically significant difference in the number of live births (including preterm) with the use of IUI combined with gonadotrophin (FSH) compared with IUI alone.

Subgroup analysis showed this difference in birth rates was found in cases of unexplained infertility but not male factor infertility.

Pregnancy rates

Very low quality evidence from two studies showed that there were statistically significant differences in the number of clinical pregnancies with the use of IUI combined with gonadotrophin (FSH) compared with IUI alone.

Subgroup analysis showed this difference in clinical pregnancies was found in cases of unexplained infertility but not male factor infertility.

Multiple births

Very low quality evidence from two studies showed there were significantly more multiple pregnancies reported after the use of IUI combined with gonadotrophin (FSH) when compared with IUI alone.

Multiple pregnancies

No evidence was reported on multiple pregnancies.

Adverse events

Low and very low quality evidence from two studies showed there were significantly more miscarriages, stillbirths, preterm births or ectopic pregnancies per woman receiving IUI with ovarian stimulation than per woman receiving IUI without ovarian stimulation, and no difference in ectopic pregnancies or stillbirths.

Health economics profile

An initial literature search identified 101 papers. The abstracts were reviewed and four full text articles were ordered. In addition, one further article (Wordsworth et al., 2011) was identified as relevant to a review of the health economic literature on IUI.

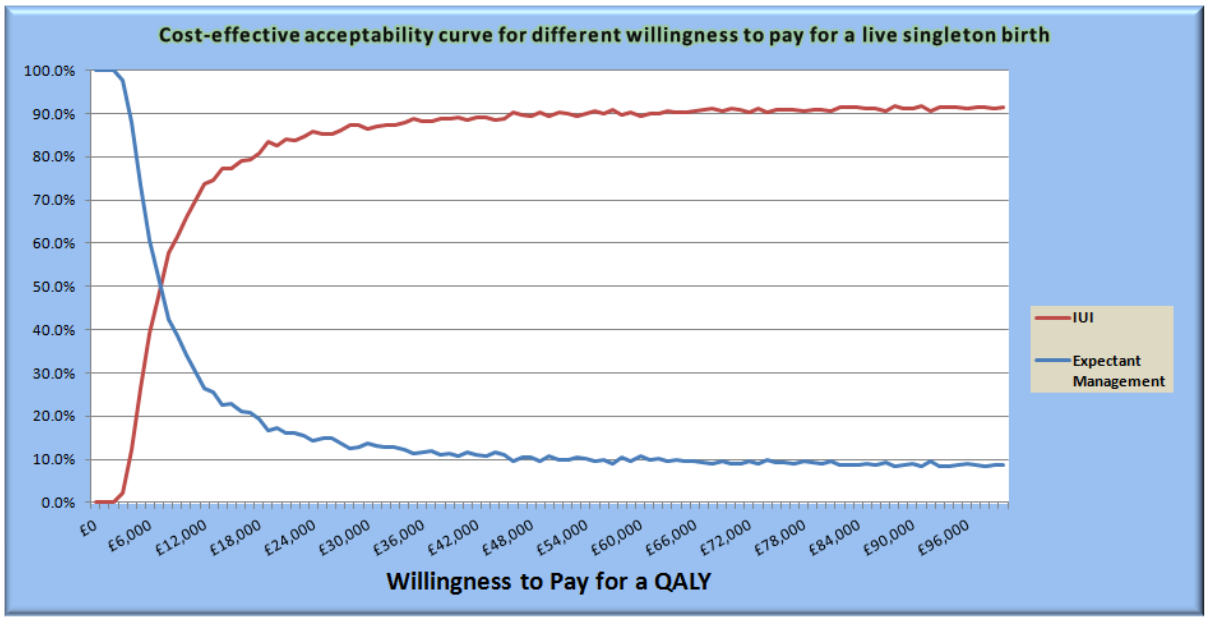
An economic evaluation (Wordsworth et al., 2011), based on the data from one randomised RCT comparing expectant management with IUI as first-line treatments for unexplained infertility and reviewed above (Bhattacharya et al., 2008), concluded that IUI was a more expensive treatment than expectant management yet did not offer higher live birth rates and therefore was unlikely to represent a cost-effective use of NHS resources. However, this conclusion seems to be a consequence of taking the often used, but arbitrary, 5% cut-off for statistical significance to determine which treatments are clinically effective. The point estimate of the live birth rate with IUI was five percentage points (22% compared with 17%, which is equivalent to a 29% absolute difference) higher than the live birth rate with expectant management. A probabilistic sensitivity analysis, which takes into account sampling error and therefore the likelihood that the difference is due to chance, estimates that at a 'willingness to pay' of £10,000 for a live birth, there is a 70% chance that IUI is cost effective.

A simple model undertaken for this guideline used the same SUIT (Scottish Unexplained Infertility Trial) trial data on treatment effect (Bhattacharya et al., 2008) to compare IUI with expectant management as a first-line treatment for women with unexplained infertility. It was assumed that treatment cost £255 (based on the NHS reference cost for IUI without stimulation) and the paper reported a mean number of cycles of 3.39, and this has been used to estimate the treatment cost per woman of offering up to 6 cyles (£255 x 3.39 = £864). Probabilistic sensitivity analysis was undertaken to estimate a cost effectiveness acceptability curve (CEAC), the probability that IUI would be cost effective at different willingness to pay (WTP) for a quality adjusted life year (QALY).

A recently published study estimated a utility decrement of 0.07 for a woman for being infertile (Scotland et al., 2011). Health state utilities are used to quantify health related quality of life and are ranked on a scale of 0–1, with 0 being equivalent to death and 1 being a state of perfect health. Health state utilities measured over time can be used to generate QALYs by multiplying the duration in a particular health state by the utility associated with that state. We used such an approach here to estimate the QALY gain for successful treatment assuming that the 0.07 disutility decrement from being infertile would be lifelong and constant. We assumed that the woman would give birth at age 29 years and have a remaining life expectancy of 54 years. Then, using the standard NICE discount rate of 3.5%, we derived a total QALY gain of 1.78 from a live birth.

The CEAC for this analysis is shown in Figure 12.1. This suggests this strategy would be cost effective at a WTP threshold of £30,000 per QALY.

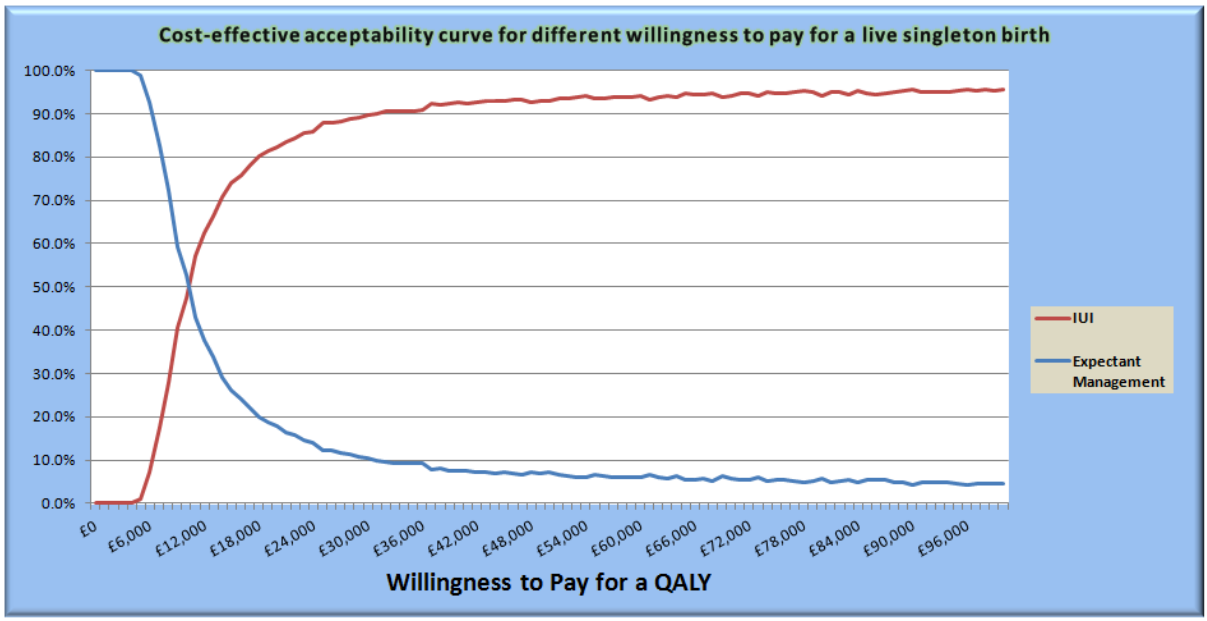
Figure 12.1 Cost effectiveness acceptability curve for 6 cycles of IUI and expectant management as first-line treatment for women with unexplained infertility based on data from Bhattacharya et al., 2008.



The SUIT data did not provide individual per cycle success rates, but an observational study (n = 3714) undertaken in the Netherlands did provide this data for up to 9 cycles of IUI (Custer et al., 2008). The study only included live pregnancy rates and so a deflator of 0.91 was used estimate the live birth rate. This was based HFEA data which for IUI without stimulation had a pregnancy rate of 12.6% per cycle and a live birth rate of 11.5% per cycle (11.5 ÷ 12.6 = 0.91).

Using the reference cost of £255, the average cost of a 6 cycle strategy would be £995 (assuming each cycle is paid for individually and a proportion of women become pregnant with each cycle). This suggests this strategy a WTP of £30,000 (see Figure 12.2).

Figure 12.2 Cost effectiveness acceptability curve for 6 cycles of IUI and expectant management as first-line treatment for women with unexplained infertility based on data from Custers et al., 2008.



Evidence to recommendations

Relative value placed on the outcomes considered

Live full-term singleton birth

The guideline development group (GDG) defined its primary outcome as live full-term singleton births, as this allow clinicians to inform couples of their chances of safely having a healthy baby. When this was not available then live birth had to be used as a proxy, but the quality of the evidence was downgraded.

Clinical pregnancy

Clinical pregnancy rates are more commonly recorded than live birth rates and are therefore used as a proxy for live full-term singleton birth where live birth rates are not reported.

Multiple birth

This is the main risk to a mother and her baby. Multiple birth is linked to increased rates of preterm birth, low birth weight and neonatal mortality in the baby, and preeclampsia in the mother.

Multiple pregnancies

Multiple pregnancies lead to multiple births.

Adverse outcomes

A number of adverse outcomes were outlined by the GDG. OHSS is a potentially life-threatening condition and one of the main reasons that treatment is stopped or cancelled. Other adverse events were miscarriage, stillbirth and ectopic pregnancies.

Consideration of clinical benefits and harms

The GDG members agreed that the evidence was accurate and matched their clinical experience.

Low quality evidence from two trials showed no difference between IUI (with or without stimulation) and expectant management in terms of both live birth rates and multiple births. However, the GDG did note that the study of IUI with stimulation compared with expectant management involved women who were selected as having a 30–40% chance of pregnancy without intervention which may have affected the results. Low quality evidence from trials showed significantly higher live birth rates with IUI with stimulation compared with IUI without stimulation, but also there were associated higher multiple pregnancy rates. The GDG members highlighted that in vitro fertilisation (IVF) was an alternative to IUI with stimulation, and, although evidence on this comparison was not reviewed, it was their experience that several cycles of IUI with stimulation were required to match live birth rates achieved by a single IVF cycle, but with higher multiple birth rates as there was less control over the number of embryos produced. Therefore, the GDG concluded that IUI with stimulation should not be recommended in any situation.

The GDG also commented on the fact that while the amount of data in cases of unexplained infertility was reasonable, there were small numbers of cases with endometriosis or 'mild' male factor infertility. The GDG felt that if there were much larger studies in all three groups and there were significant effects the conclusions may be different.

The GDG considered that IUI had previously been used as an alternative to expectant management in the belief that doing something was better than doing nothing, but felt that the evidence showed this position could no longer be supported. Therefore, it was the opinion of the GDG that IUI without stimulation was no better than expectant management, and it was unclear if IUI with stimulation was better than expectant management in all groups of women, but it was clear that it significantly increased the risk of multiple pregnancies. Based on this assessment the GDG recommends that IUI (with or without stimulation) should not be routinely offered.

However, it was accepted that for certain groups where vaginal sex is inappropriate or not possible that IUI without stimulation with sperm from a male partner or donor would be the first-line approach.

Consideration of health benefits and resource uses

The GDG highlighted that while health economic analysis showed that IUI could be cost effective, there were no apparent health benefits and indeed there were potentially increased risks associated with IUI (with or without stimulation) when compared with an alternative strategy of expectant management. Therefore, the GDG considered that considerable resources could be saved and used elsewhere if IUI was not offered.

Quality of evidence

The quality of evidence ranged from low to very low, and was downgraded due to studies not being adequately powered with insufficient sample numbers to detect differences between groups for certain outcomes, because it was not possible to blind allocation of treatment, and because they did not report on live full-term singleton births.

The GDG noted that most of the data on IUI with stimulation was from studies over 10 years old and from countries where higher doses of ovarian stimulation drugs are used than would be acceptable in current UK practice.

Other considerations

Expectant management

The GDG discussed what constituted expectant management for two groups of women with unexplained infertility, mild endometriosis or 'mild' male factor infertility. The GDG concluded that expectant management should consisit of supportively offering an individual or couple information and advice about the regularity and timing of intercourse and any lifestyle changes which might improve their chances of conceiving. It does not involve active clinical or therapeutic interventions.

For people having unprotected regular vaginal intercourse

Natural conception rates are shown in Figure 5.1. In summary, over 80% of couples where the women is age 39 years or less will conceive within 12 months. The figure is over 85% where the woman is less

than 35 years. If the couple continue to have unprotected regular intercourse for another 12 months, making 24 months in total, cumulative pregnancy success rates rise by about a further 15%.

The GDG did note that even after 2 years without a live birth, couples with unexplained infertility, mild endometriosis or 'mild' male factor infertility still had a chance of natural conception. However, the additional cumulative success rates in the third year would be very small. Furthermore, they declined with the age of the woman. The GDG felt that this information should be explained early on to women with the diagnosis of unexplained infertility (see Figure 5.1). Thus, the GDG's view was that after 2 years of unexplained infertility (including the 1 year before testing and diagnosis), IVF should be considered. The cost effectiveness of IVF under specific circumstances is considered elsewhere (see Chapter 14) but the GDG consensus view was that women with a diagnosis of unexplained fertility should be told at the start of their 12 months of expectant management, that they will be considered for IVF (but it will not necessarily be offered) after a total of 2 years without conception. This provides women with unexplained infertility a clear idea of the period of time they should continue with regular unprotected vaginal intercourse before IVF will be considered. The GDG view was that this would represent a positive approach and lessen the anxiety and depression identified in the expectant management group in the trial reported here.

For people in same-sex relationships where conception was being attempted by donor insemination

When, after assessment and investigation, the diagnosis of unexplained infertility, mild endometriosis or 'mild' male factor infertility has been made, the GDG felt that further attempts at conception should be made using IUI and donor sperm for a period of time. The GDG highlighted the cumulative success rates with intra cervical insemination (ICI) and IUI. Specifically, as reported in Chapter 5, they noted that, while after 6 cycles of donor insemination (DI) the cumulative chances of successful conception from ICI or IUI in women who are 35 years or less were:

- over 40% for ICI using thawed semen (Schwartz et al., 1982)
- over 50% for ICI using fresh semen (van Noord-Zaadstra et al., 1991)
- over 60% for IUI using mainly thawed semen (HFEA data http://www.hfea.gov.uk/1270.html#1299)

After a further 6 months (12 months in total) these figures rose to:

- over 60% for ICI using thawed semen (Schwartz et al., 1982)
- over 70% for ICI using fresh semen (van Noord-Zaadstra et al., 1991)
- over 80% for IUI using mainly thawed semen (HFEA data).

These additional cycles of IUI with donor sperm would be the same as expectant management in couples with unexplained infertility, mild endometrisis or 'mild' male factor infertility having vaginal intercourse. The GDG discussed options for the number of cycles of IUI that should constitute an acceptable period of expectant management. The same issues were raised in this discussion as were covered in the discussion on determining when to refer people for assessment and possible treatment of their infertility (see Chapter 5). The GDG felt that the practical barriers (availability of sperm, cost and time) to undertaking IUI with donor sperm meant, in reality, that same-sex couples with infertility, where there is a chance of a live birth without IVF, could not be expected to have 12 cycles of IUI in order to achieve numerical equivalence with people having vaginal intercourse with the same diagnosis having 12 months of expectant management.

In conclusion, if, as a result of infertility assessment, the diagnosis is made of unexplained infertility, mild endometriosis or 'mild' male factor infertility, the GDG was of the opinion that women in same-sex relationships should be advised to have a further 6 cycles of IUI with donor sperm (making a total of 12 cycles of DI in total) and that would be equivalent to expectant management for that group.

Other groups requiring special consideration

Three separate groups were considered under this heading

- People who are unable to, or would find it very difficult to, have vaginal intercourse (such as people with with a clinically diagnosed physical disability or psychosexual problem).

- People with conditions that require specific consideration in relation to methods of conception (such as couples where the male is HIV positive).
- People who could be offered IUI as an alternative to IVF where they may have an objection to having IVF (for example, social, cultural or religious objections).

In these circumstances the GDG was of the opinion that following early assessment of any of the three scenarios listed above, then, if necessary, IUI using partner or donor sperm without ovarian stimulation would be appropriate treatment for up to 12 cycles.

Recommendations

Number	Recommendation
117	Consider unstimulated intrauterine insemination as a treatment option in the following groups as an alternative to vaginal sexual intercourse: • people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem who are using partner or donor sperm • people with conditions that require specific consideration in relation to methods of conception (for example, after sperm washing where the man is HIV positive) • people in same-sex relationships. **[new 2013]**.
118	For people in recommendation 117 who have not conceived after 6 cycles of donor or partner insemination, despite evidence of normal ovulation, tubal patency and semenalysis, offer a further 6 cycles of unstimulated intrauterine insemination before IVF is considered. **[new 2013]**
119	For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse: • do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF) • advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**.

Number	Research recommendation
RR 22	What is the effectiveness of IUI (with and without stimulation) compared to expectant management for couples with endometriosis?
RR 23	What is the effectiveness of IUI (with and without stimulation) compared to expectant management for couples with "mild male factor infertility?
RR 24	Research is needed to define semen quality criteria for assisted reproduction to be effective in the management of male infertility.
RR 25	Research is needed to determine the relative effectiveness of oral (anti-oestrogen) and injectable (gonadotrophin) drugs in stimulated intrauterine insemination in couples with unexplained fertility problems.

2013 Update

13 Prediction of IVF success

13.1 Introduction

The success of any treatment is influenced by the characteristics and lifestyle of the individual who is having that treatment. This chapter outlines an update of the 2004 review of which factors are likely to influence the success of an in vitro fertilisation (IVF) treatment. In addition, data is available on a number of factors not included in the 2004 guideline and these have been added, including duration of infertility and cause of infertility.

The results of this review have been used in the development of the IVF health economics model outlined in Chapter 14.

13.2 Prediction of IVF success

Review questions

What are the factors which predict the success of IVF?

Overview

The primary focus of this review was to update the 2004 review of factors that predict live birth in IVF as part of the development of the health economics model.

The search strategy identified a total of 492 studies. Given the number of relevant studies available, the review was restricted to those using meta-analysis or large population datasets. Full copies of 38 papers were obtained. Of these, four studies were included in the review of factors that predict the outcome of IVF (Leushuis et al., 2009; van Loendersloot et al., 2010; Nelson & Lawlor, 2011; Roberts et al, 2010a). Two of these were systematic reviews (Leushuis et al., 2009; van Loendersloot et al., 2010) and two were recent models (Nelson & Lawlor, 2011; Roberts et al, 2010a) not included in the reviews.

The factors identified in the reviews and models as being predictive of live birth or pregnancy are summarised in Table 13.2. As with the 2004 review the results show that female age, number of embryos available, whether embryos are fresh or thawed, previous treatment success, previous pregnancy history and lifestyle factors and body mass index (BMI) are predictive. In addition, factors such as duration of infertility and type of infertility have been shown to be predictive of live birth or pregnancy.

Table 13.1 GRADE findings for prediction of IVF success

Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
1 (Leushuis et al., 2009)	Data presented in Table 13.2				High
1 (van Loendersloot et al., 2010)	Data presented in Table 13.2				Moderate
1 (Nelson & Lawlor, 2011)	Data presented in Table 13.3				Low
1 (Roberts et al, 2010a)	Data presented in Table 13.4				Low

Table 13.2 Summary of factors found to be predictive of pregnancy or live birth in IVF (models included in the systematic review have not been individually reviewed)

Study	Treatment	Female age	Duration of infertility	Cause of infertility	BMI	Previous pregnancy or live birth (IVF or not; ongoing or not	Method of treat-ment	Type of infertility (primary or sec-ondary)	Sperm assess-ment	Ovarian response (FSH etc)	Number of embryos transferred	Embryo quality	Number of embryos or oocytes available	Others – including lifestyle
Likelihood of pregnancy or live birth		Decreases with age after 35	Decreases with duration	Decreases with known cause	Increases between 19 and 30	Decreases with previous IVF failures Increases with previous live births	Amount of stimulation used; IVF or ICSI	Decreases with primary infertility	Decreases with poor sperm assess-ment	Decreases as ovarian reserve decreases	Increases with number of embryos (but risk of multiples)	Decreases with quality	Decreases with number of oocytes	Various outcomes
Templeton et al., 1996	No treatment	✓	✓	✓		✓								
Roberts et al., 2010	Agonist orantagonist	✓	✓	✓		✓	✓				✓		✓	✓
Ebbesen et al., 2009	Agonist	✓			✓		✓			✓			✓	✓
Sabatini et al., 2008	Agonist	✓								✓				
Wang et al., 2008	IVF	✓												
Ottosen et a.l, 2007	Agonist orantagonist	✓	✓	✓	✓		✓			✓		✓	✓	
Ferlitsch et al., 2004	Agonist orantagonist			✓	✓		✓			✓				

Study	Treatment	Female age	Duration of infertility	Cause of infertility	BMI	Previous pregnancy or live birth (IVF or not; ongoing or not	Method of treat-ment	Type of infertility (primary or sec-ondary)	Sperm assess-ment	Ovarian response (FSH etc)	Number of embryos transferred	Embryo quality	Number of embryos or oocytes available	Others – including lifestyle
Hauzman et al., 2004	Agonist	✓								✓	✓		✓	
Hunault et al., 2002	Agonist	✓	✓	✓				✓	✓	✓		✓	✓	
Sharma et al., 2002	Agonist	✓									✓		✓	
Maugey-Laulom et al., 2002	Agonist	✓		✓								✓		
Hart et al., 2001	Agonist	✓		✓			✓			✓		✓		
Bancsi et al., 2000	Agonist	✓	✓	✓				✓		✓				
Strandell et al., 2000	Agonist	✓		✓		✓	✓				✓	✓	✓	
Syrop et al., 1999	Agonist	✓								✓		✓		✓
Stolwijk et al., 1997	Agonist	✓												
Jerrzejczak et al., 2008	No treatment								✓					
Hunault et al., 2002	No treatment	✓	✓					✓	✓					✓
Snick et al., 1997	No treatment		✓	✓						✓				

2013 Update

Study	Treatment	Female age	Duration of infertility	Cause of infertility	BMI	Previous pregnancy or live birth (IVF or not; ongoing or not	Method of treat-ment	Type of infertility (primary or sec-ondary)	Sperm assess-ment	Ovarian response (FSH etc)	Number of embryos transferred	Embryo quality	Number of embryos or oocytes available	Others – including lifestyle
Collins et al., 1996	No treatment	✓	✓	✓				✓						
Bahamondes et al.,1994	No treatment	✓	✓					✓	✓					✓
Wichman et al., 1994	No treatment	✓	✓						✓			✓		
Elmers et al., 1994	No treatment	✓	✓					✓	✓	✓				✓
Bostofte et al., 1993	No treatment		✓	✓						✓				
Bostofte et al., 1987	No treatment								✓					✓
van Weert et al., 2008	IVF	✓		✓		✓		✓	✓					
Lintsen et al., 2007	IVF		✓	✓				✓						
Verberg et al., 2007	IVF				✓		✓					✓	✓	
Carrera et al., 2007	IVF	✓								✓				
Ottoson et al., 2007	IVF	✓			✓					✓		✓		
Ferkitsch., 2004	IVF				✓					✓				

2013 Update

Study	Treatment	Female age	Duration of infertility	Cause of infertility	BMI	Previous pregnancy or live birth (IVF or not; ongoing or not	Method of treat-ment	Type of infertility (primary or sec-ondary)	Sperm assess-ment	Ovarian response (FSH etc)	Number of embryos transferred	Embryo quality	Number of embryos or oocytes available	Others – including lifestyle
Hunault et al., 2002	IVF	✓										✓	✓	
Bancsi et al., 2000	IVF	✓		✓						✓		✓		
Stolwijk et al., 2000	IVF	✓						✓						
Minaretzis et al., 1998	IVF	✓										✓		
Commenges-Duces et al., 1998	IVF	✓				✓	✓							
Stolwijk et al., 1996	IVF	✓				✓								
Bouckaert et al., 1994	IVF	✓										✓	✓	
Haan et al., 1991	IVF	✓	✓	✓										✓
Hughes et al., 1989	IVF	✓				✓								
Nayudu et al., 1989	IVF						✓			✓				
Nelson et al., 2009	IVF	✓	✓	✓		✓	✓							✓
La Marca et al., 2011	IVF	✓								✓				

BMI body mass index, FSH follicle-stimulating hormone, ICSI intracytoplasmic sperm injection, IVF in vitro fertilisation

Table 13.2 shows the factors that have been found to predict pregnancy or live birth, both with and without treatment. The results for individual factors are described in more detail below. The updated figures are based on two meta-analyses (Leushuis et al., 2009; van Loendersloot et al., 2010) and two multivariate models (Nelson & Lawlor, 2011; Roberts et al, 2010a). The models are both based on retrospective Human Fertilisation and Embryology Authority (HFEA) data. The first model included 144,018 IVF cycles undertaken between January 2003 and December 2007 (Nelson and Lawlor, 2011). The second was based on 199,930 cycles undertaken between January 2000 and December 2005 (Roberts et al, 2010). The results are summarised in Ttables 13.3 and 13.4 respectively.

Female age

The 2004 guideline outlined both an upper and a lower age limit for IVF treatment. However, the lower age limit was based on a lack of robust data rather than evidence showing ineffectiveness. Since 2004 further data has become available on how age influences the outcome of IVF. The results of a meta-analysis of three studies shows that an increase in female age leads to a decrease in pregnancy rates (odds ratio [OR] 0.95, 95% confidence interval [CI] 0.94 to 0.96) (van Loendersloot et al, 2010), and two models using HFEA data show the same pattern (see Tables 13.3 and 13.4) (Nelson and Lawlor, 2011; Roberts et al., 2010). Finally, two figures presented earlier in the guideline (see Figures 5.1 and 6.1) confirm the association between age and likely success of IVF. These data do not suggest any lower age limit for IVF treatment

Number of embryos transferred and fresh or thawed embryos

It is now well established that the number of embryos transferred during IVF, whether the transfer is undertaken using fresh or thawed embryos and the stage of embryo transfer (cleavage or blastocyst) all affect live birth rates following IVF. These issues and the resultant recommendations are discussed in more detail in Chapter 15.

Ovarian reserve

Ovarian reserve, measured with tests such as follicle-stimulating hormone (FSH), is presented and discussed in Chapter 6. The conclusion of that chapter was that although ovarian reserve testing does predict the response to IVF (in the form of a ‘low’ or ‘high’ response), it does not predict treatment-independent pregnancy or live births, but can be used to predict response to ovarian stimulation.

Duration of infertility

A factor not highlighted in the 2004 guideline was duration of infertility. A meta-analysis of two studies (n = 1,077) showed that an increase in the duration of infertility was associated with a reduction in pregnancy rates in association with IVF treatment (OR 0.99, 95% CI 0.98 to 1.00) (van Loendersloot et al, 2010). Results from the two models show the same pattern, even when results are adjusted for female age (see Tables 13.3 and 13.4) (Nelson and Lawlor, 2011; Roberts et al., 2010).

Number of oocytes retrieved and number of embryos available

The number of oocytes retrieved and number of embryos available for IVF have been shown to predict pregnancy and live birth. A meta-analysis of four studies showed that an increasing number of oocytes retrieved was associated with increasing pregnancy rates (OR 1.04, 95% CI 1.02 to 1.07) (van Loendersloot et al, 2010). Results of univariate analysis based on HFEA data shows live birth rates increase with the number of embryos available (see Table 13.4) (Roberts et al., 2010).

Cause of infertility

The 2004 guideline assessed the management of all the major causes of infertility, but did not examine the impact of these causes on the outcome of IVF. Results from two models based on HFEA data show how live birth rates vary depending on the cause of infertility (see Tables 13.3 and 13.4) (Nelson and Lawlor, 2011; Roberts et al., 2010).

Recommendations

Number	Recommendation
120	Inform women that the chance of a live birth following IVF treatment falls with rising female age (see figure 6.1). **[2013]**

2013 Update

Number of previous treatment cycles

Data from two models examining the effect of previous IVF treatment are shown in Tables 13.3 and 13.4. Table 13.4 shows that there is a reduced likelihood of a live birth following IVF for women who have had previous IVF cycles (OR 0.73, 95% CI 0.68 to 0.77) for the 4th cycle compared to 1 cycle) (Roberts et al, 2010). Table 13.3 shows the results of a multivariate analysis, reporting that the chance of a live birth decreases as the number of unsuccessful cycles increases and begins to fall rapidly after 4 previous unsuccessful cycles (OR 0.55, 95% CI 0.45 to 0.69, 4th unsuccessful cycle compared to no unsuccessful cycles) (Nelson and Lawlor, 2011). 'However, this low value was not found with 5 or more unsuccessful cycles (OR 0.68, 95% CI 0.55 to 0.83). Furthermore, the data in Table 13.4 does not show a precipitate fall with 4 or more previous IVF cycles. Thus, overall, both sets of data suggest an inverse relationship between IVF success and the number of prior unsuccessful attempts.

Recommendations

Number	Recommendation
121	Inform people that the overall chance of a live birth following IVF treatment falls as the number of unsuccessful cycles increases. **[new 2013]**

Previous pregnancy history

Analysis of the HFEA database showed that having a previous pregnancy and live birth were both associated with increased treatment success.[723] [Evidence level 3] However, rates of secondary infertility are higher in the general population than in IVF clinic referrals.[798] Another study based on the FIVNAT register showed that women with primary infertility were significantly younger than women with secondary infertility; they also had significantly more oocytes and fewer embryos, and significantly decreased fertilisation and pregnancy rates.[799] [Evidence level 3] A further study that examined the relationship between the first cycle of IVF and subsequent cycles found that a previous pregnancy significantly improved a couple's probability of conception in a later IVF cycle.[763] [Evidence level 3]

The positive impact of a previous pregnancy and/or live birth on the outcome of IVF is supported by the most recent published detailed analysis of the HFEA data (see Tables 13.3 and 13.4) (Nelson and Lawlor, 2011; Roberts et al., 2010).

Recommendations

Number	Recommendation
122	People should be informed that IVF treatment is more effective in women who have previously been pregnant and/or had a live birth. **[2004, amended 2013]**

Table 13.3 Associations of potential predictors of live birth following IVF (Nelson and Lawlor, 2011)

Characteristic	Categories	Univariable odds ratio of live birth (95% CI)	Multivariable odds ratio of live birth (95% CI)	*P* -value
Maternal age (years)	18–34	1 (Reference)	1 (Reference)	< 0.001
	35–37	0.77 (0.75–0.79)	0.78 (0.76–0.81)	
	38–39	0.53 (0.51–0.55)	0.53 (0.51–0.56)	
	40–42	0.29 (0.28–0.30)	0.29 (0.28–0.31)	
	43–44	0.10 (0.09–0.12)	0.10 (0.09–0.12)	
	45–50	0.15 (0.12–0.19)	0.12 (0.09–0.15)	
Duration of infertility (years)	< 1	1.48 (1.34–1.65)	1.51 (1.35–1.68)	< 0.001
	1–3	1.10 (1.07–1.13)	1.11 (1.08–1.15)	
	4–6	1 (Reference)	1 (Reference)	
	7–9	0.91 (0.87–0.94)	0.94 (0.91–0.98)	
	9–12	0.81 (0.76–0.85)	0.87 (0.82–0.92)	
	> 12	0.71 (0.67–0.75)	0.89 (0.84–0.95)	
Cause of infertility	Unexplained	1 (Reference)	1 (Reference)	< 0.001
	Tubal only	0.94 (0.90–0.97)	0.87 (0.83–0.90)	
	Anovulatory only	0.93 (0.88–0.98)	0.95 (0.90–1.00)	
	Endometriosis only	1.05 (0.98–1.13)	0.96 (0.89–1.03)	
	Cervical only	0.41 (0.20–0.85)	0.39 (0.19–0.82)	
	Male only	1.16 (1.13–1.20)	0.91 (0.87–0.95)	
	Combination known causes	1.01 (0.96–1.06)	0.88 (0.83–0.92)	
Number of previous unsuccessful IVF	0	1 (Reference)	1 (Reference)	< 0.001
	1	0.74 (0.70–0.79)	0.72 (0.65–0.81)	
	2	0.69 (0.64–0.76)	0.70 (0.62–0.80)	
	3	0.74 (0.66–0.84)	0.77 (0.66–0.91)	
	4	0.51 (0.42–0.62)	0.55 (0.45–0.69)	
	≥ 5	0.57 (0.48–0.69)	0.68 (0.55–0.83)	
Mutually exclusive categories of previous IVF and obstetric history	No previous IVF, 0 pregnancy	1 (Reference)	1 (Reference)	< 0.001
	No previous IVF, at least 1 pregnancy, 0 live births	0.88 (0.86–0.91)	1.03 (0.99–1.06)	
	No previous IVF, at least 1 pregnancy, at least 1 live birth	0.92 (0.88–0.96)	1.19 (1.14–1.24)	

Characteristic	Categories	Univariable odds ratio of live birth (95% CI)	Multivariable odds ratio of live birth (95% CI)	*P* -value
	Previous IVF, 0 pregnancy	0.72 (0.68–0.76)	1.14 (1.01–1.28)	
	Previous IVF, at least 1 pregnancy, 0 live birth	0.68 (0.64–0.73)	1.02 (0.93–1.11)	
	Previous IVF, at least 1 pregnancy, at least 1 live birth	1.10 (1.03–1.17)	1.58 (1.46–1.71)	
Hormonal preparation	Antioestrogen	1 (Reference)	1 (Reference)	< 0.001
	Gonadatrophin	1.43 (1.24–1.63)	1.33 (1.15–1.53)	
	Hormone replacement	1.61 (1.38–1.89)	1.55 (1.31–1.82)	
Cycle number	1	1 (Reference)	1 (Reference)	< 0.001
	2	0.80 (0.78–0.83)	0.85 (0.82–0.87)	
	≥3	0.76 (0.74–0.79)	0.88 (0.85–0.91)	
Source of egg	Donor	1	1	< 0.001
	Patient	0.87 (0.74–1.02)	0.38 (0.32–0.45)	
Treatment type	IVF	1	1	< 0.001
	ICSI plus IVF	1.28 (1.25–1.31)	1.27 (1.23–1.31)	

CI confidence interval, ICSI intracytoplasmic sperm injection, IVF in vitro fertilisation,

Table 13.4 Associations of potential predictors of live birth following IVF (Roberts et al., 2010)

Factor	Unadjusted OR	95% CI
Age (years) (35 is reference)		
26	1.11	1.02 to 1.20
27–29	1.16	1.10 to 1.23
30	1.21	1.14 to 1.28
31	1.14	1.07 to 1.21
32	1.18	1.11 to 1.24
33	1.12	1.06 to 1.20
34	1.06	1.00 to 1.13
36	0.89	0.84 to 0.94
37	0.77	0.73 to 0.82
38	0.74	0.69 to 0.78
39	0.59	0.54 to 0.64
40–42	0.37	0.34 to 0.40
43	0.11	0.09 to 0.13

Factor	Unadjusted OR	95% CI
Number of embryos created (six embryos is the reference)		
1	0.50	0.43 to 0.57
2	0.54	0.51 to 0.58
3	0.70	0.66 to 0.74
4	0.81	0.76 to 0.86
5	0.90	0.85 to 0.96
7	1.01	0.95 to 1.07
8	1.12	1.05 to 1.18
9	1.09	1.03 to 1.16
10	1.18	1.10 to 1.28
11–12	1.19	1.12 to 1.26
13–16	1.22	1.15 to 1.30
17	1.18	1.10 to 1.28
Cycle (1st cycle is the reference)		
2nd	0.81	0.78 to 0.84
3rd	0.78	0.76 to 0.82
4th	0.73	0.68 to 0.77
5th	0.77	0.70 to 0.85
6th	0.66	0.60 to 0.72
Previous history (no pregnancy is the reference)		
Previous pregnancy	1.02	0.98 to 1.06
Previous live birth	1.38	1.32 to 1.43
Two or more previous live births	1.29	1.19 to 1.39
Duration of infertility (years) (4 years is the reference)		
0–1	1.19	1.12 to 1.26
2	1.09	1.03 to 1.16
3	1.05	1.00 to 1.08
5	0.95	0.90 to 1.01
6	0.92	0.87 to 0.98
7	0.89	0.84 to 0.95
8	0.88	0.81 to 0.95
9	0.89	0.80 to 0.98
10–11	0.87	0.81 to 0.95
≥12	0.82	0.78 to 0.88

Factor	Unadjusted OR	95% CI
Cause of infertility		
Tubal diagnosis	0.81	0.78 to 0.84
Diagnosis of PCOS	01.04	1.00 to 1.08
Endometriosis	1.00	0.94 to 1.06
Idiopathic diagnosis	1.05	0.99 to 1.11
Male factor diagnosis	1.10	1.05 to 1.14

CI confidence interval, IVF in vitro fertilisation, OR odds ratio

BMI

It has been reported that a weight loss programme may improve ovulation and pregnancy outcomes in obese infertile women for all forms of fertility treatment, including ovulation induction, intrauterine insemination (IUI) and IVF treatment (see Chapters 8,12 and 15).[497,498] [Evidence level 2b]

Obesity (BMI 25.8 to 30.8 kg/m^2) has been shown to be a risk factor for spontaneous abortion in women after IVF or intracytoplasmic sperm injection (ICSI).[807] [Evidence level 2b] Obesity is also associated with lower pregnancy rates after IVF when compared with women with a BMI of 25 kg/m^2 or under.[808] [Evidence level 2b]

Extremes of BMI (over 25–28 kg/m^2 or under 20 kg/m2) have been associated with negative effects on IVF parameters leading to decreased chances of pregnancy.[809,810] [Evidence level 2b]

Recommendations

Number	Recommendation
123	Women should be informed that female BMI should ideally be in the range 19–30 before commencing assisted reproduction, and that a female BMI outside this range is likely to reduce the success of assisted reproduction procedures. **[2004]**

Number	Research recommendation
RR 26	Further randomised controlled trials are needed to evaluate the effectiveness of assisted reproduction procedures in relation to female body mass index.

Lifestyle factors

Maternal and paternal alcohol consumption in excess of 12 g (one unit) daily up to 1 year before assisted reproduction has been associated with a significant decrease in the success rates of IVF.[800] [Evidence level 3]

Maternal and paternal smoking before assisted reproduction has been associated with significant decreases in the success rates of IVF.[801–804] Smoking by males is also associated with a decrease in the success rates of IVF and ICSI (OR 2.95, 95% CI 1.32 to 6.59).[805] [Evidence level 3]

While evidence shows that caffeine consumption does not affect natural fertility rates (see Section 5.6), a separate issue is whether the same is true for people undergoing IVF treatment, where subfertility has been established. In an observational study, caffeine consumption (over 2–50 mg/day compared with 0–2 mg/day; 100 mg caffeine in one cup of coffee) during a lifetime (that is, usual intake) and during the week of initial visit for infertility were strong risk factors for not achieving a live birth in women undergoing IVF, after adjusting for smoking, alcohol, age, race, education, parity, types of infertility, types of procedure, number of assisted reproduction attempts and number of

embryos transferred.[806] [Evidence level 3] This study also reported an association between maternal coffee consumption and decreased infant gestational age.[806] [Evidence level 3]

Recommendations

Number	Recommendation
124	People should be informed that the consumption of more than 1 unit of alcohol per day reduces the effectiveness of assisted reproduction procedures, including IVF. **[2004, amended 2013]**
125	People should be informed that maternal and paternal smoking can adversely affect the success rates of assisted reproduction procedures, including IVF treatment. **[2004, amended 2013]**
126	People should be informed that maternal caffeine consumption has adverse effects on the success rates of assisted reproduction procedures, including IVF treatment. **[2004, amended 2013]**

14 Access criteria for IVF

14.1 Introduction

Overview

The 2004 Fertility guideline recommended access to NHS funded in vitro fertilisation (IVF) for women aged 23 to 39 years. It considered the cost effectiveness of IVF but used age only as a criterion for access to IVF on the NHS. Data were presented on the cost per live birth using IVF by age and cycle, with live birth rates estimated using 1995–99 Human Fertilisation and Embryology Authority (HFEA) data. Using a threshold where the average success per IVF transfer was greater than 10%, the guideline recommended 3 cycles of IVF be offered to women aged 23 to 39 years.

For the 2013 guideline, the cost effectiveness analysis of IVF was redesigned to incorporate changes in IVF technology and health economic modelling techniques. The following differences in approach were adopted in the updated health economic evaluation:

- The inclusion of an expectant management comparator: this acknowledged that although for a few women IVF is the only way they can become pregnant, for the majority there remains the possibility of a spontaneous conception.
- An estimation of cumulative live birth over a woman's 'reproductive life' to reflect that expectant management is not time limited and that spontaneous conception can also occur after IVF treatment failure.
- The use of multi-factorial models incorporating many of the predictors reported in Chapter 13 to predict the chances of success of IVF and expectant management rather than by using age as the sole predictor.
- The inclusion of a comparison of the effects of double embryo transfer (DET) and elective single embryo transfer (eSET) and fresh and frozen embryo transfers with their different costs and success rates to reflect current IVF practices.
- The use of quality adjusted life years (QALYs) to measure benefits reflecting NICE's preferred approach to cost effectiveness.
- The adoption of a cost effectiveness threshold of £30,000 per QALY.

14.2 Review of existing cost effectiveness models

A review of existing literature was undertaken to inform model inputs. The literature search identified 15 health economic (HE) studies examining the cost effectiveness of IVF (De Sutter et al., 2002; Gerris et al., 2004; Fiddelers et al., 2006; Fiddelers et al., 2009; Goldfarb et al., 1996; Karande et al., 1999; Lukassen et al., 2005; Meldrum et al., 1998; Mol et al., 2000; Neumann et al., 1994; Peskin et al., 1996; Polinder et al., 2008; Scotland et al., 2011; Thurin et al., 2006; Kjellberg et al., 2006; Wolner-Hanssen et al., 1998). The main methodological approaches of these reports are summarised in Table 14.1.

While some of the health economic models were developed using data from randomised controlled trials (RCTs), the majority were not and used either unit/centre data or published literature from a variety of sources. The majority of studies examined the value of a single cycle of IVF in isolation rather than a sequential IVF strategy. Only the studies published in the last decade explored the

issues of fresh versus frozen/thawed embryos and single versus double embryo transfer strategies. A minority of studies looked at the impact of a woman's age and then usually as a categorical variable rather than continuous variable. Only one report examined the impact of the cause (Neumann et al., 1994),only one report examined duration of infertility on cost-effectiveness (Neumann et al., 1994) and only one study evaluated the cost effectiveness of IVF with respect to the expected conception rate without treatment. None of the studies accounted for the obstetric history and prior IVF outcome in their modelling. Finally, although all the studies included multiple pregnancies as part of the cost modelling, only about half of them included the additional costs of ovarian hyperstimulation syndrome (OHSS) and the cost savings of cancelled cycles.

In summary, none of the cost effectiveness analyses of IVF addressed all the core criteria the guideline development group (GDG) considered desirable. Hence, a new economic model was developed for this guideline.

Table 14.1 Health economic studies of the cost effectiveness of IVF

Study	Design	Was a Fresh/Thaw strategy included in the model?	Were single and double embryo transfer in the model?	Was ICSI in the model?	Was IVF success contrasted with expectant management?	Was the woman's age in the model? (Years)	Was the duration of infertility in the model?	Was the cause of infertility in the model?	Was the pregnancy history in the model?	Was the IVF history in the model?	Were twin costs in the model?	Was OHSS cost in the model?	Was a cycle cancellation discounted?
De Sutter et al., 2002	Modelling	Yes but single cycle	Yes	No	No	No	No	No	No	No	Yes	No	No
Gerris et al., 2004	2 centre databases	Yes but single cycle	Yes	No	No	< 38	No	No	No	No	Yes	No	No
Fiddelers et al., 2006	RCT eSET vs DET	Yes but single cycle	Yes	No	No	No	No	No	No	No	Yes	No	No
Fiddelers et al., 2009	Modelling 7 strategies	Yes 3 cycles strategy	Yes	No	No	≤38	No	No	No	No	Yes	No	No
Goldfarb et al., 1996	One unit database	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes
Karande et al., 1999	RCT of IVF vs normal	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes
Lukassen et al., 2005	RCT 2 eSET vs 1 DET	No	Yes	Yes	No	≤ 38	No	No	No	No	Yes	Yes	No
Meldrum et al., 1998	One unit database	Successive cycles	No	No	No	<40,40-42,>42	No	No	No	No	Yes	No	No
Mol et al., 2000	Modelling with EM	No	No	No	Yes	Yes	Yes	No	No	No	No	No	No
Neumann et al., 1994	6 units databases	No	No	No	No	No	No	Yes	No	No	No	Yes	Yes
Peskin et al., 1996	1 unit; small no	No	No	No	No	No	No	No	No	No	No	No	No

2013 Update

Study	Design	Was a Fresh/Thaw strategy included in the model?	Were single and double embryo transfer in the model?	Was ICSI in the model?	Was IVF success contrasted with expectant management?	Was the woman's age in the model? (Years)	Was the duration of infertility in the model?	Was the cause of infertility in the model?	Was the pregnancy history in the model?	Was the IVF history in the model?	Were twin costs in the model?	Was OHSS cost in the model?	Was a cycle cancellation discounted?
Polinder et al., 2008	RCT mild vs stand	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes
Scotland et al., 2011	RCT	Yes	Yes	No	No	Yes 30/36/ 39	No	No	No	No	Yes	Yes	Yes
ThurinKjellberg et al., 2006	RCT eSET vs DET	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	No
Wolner-Hanssen et al., 1998	Modelling	No	No	No	No	No	No	No	No	No	Yes	No	No

DET double embryo transfer, EM expectant management, eSET elective single embryo transfer, ICSI intracytoplasmic sperm injection, IVF in vitro fertilisation, OHSS ovarian hyperstimulation syndrome, RCT randomised controlled trial

14.3 Development of health economic model

Model structure

The HE model was developed in Microsoft Excel® to compare the cost effectiveness of 1 to 3 cycles of IVF. The model was restricted to a maximum of 3 cycles, reflecting what the GDG considered to be a reasonable maximum for the NHS to offer and consistent with practice in most other western European countries (Andersen et al., 2007). The model compared the cost effectiveness of both eSET and DET relative to expectant management. It did not explicitly compare the incremental cost effectiveness of DET relative to eSET.

The model included the following treatment strategies:

- expectant management (EM) for the remainder of the woman's reproductive life without IVF (no IVF)
- 1 cycle of IVF, followed by EM for the remainder of the woman's reproductive life if 1 full cycle of IVF was unsuccessful (IVF1)
- up to 2 cycles of IVF, followed by EM for the remainder of the woman's reproductive life if the 2 cycles of IVF were unsuccessful (IVF2)
- up to 3 cycles of IVF, followed by EM for the remainder of the woman's reproductive life if the 3 cycles of IVF were unsuccessful (IVF3).

The population considered for the HE model comprised women/couples who were eligible for IVF following the appropriate investigation and assessment recommended in this guideline.

Treatment effectiveness was measured in QALYs derived from the cumulative live births achieved by women over their remaining reproductive life but also taking into account ovarian hyperstimulation syndrome (OHSS), an important adverse effect of IVF treatment. This allowed the calculation of an incremental cost per QALY.

Central to the HE analysis were two prediction models of live birth with expectant management and IVF. These were considered the best available evidence for use in the HE analysis. These models and their adaptation for this HE analysis are described below.

Data sources for live birth rates used in the model

To populate the HE model it was necessary to estimate the probability of live birth over time for different treatment strategies. As with any analysis using secondary data sources, adjustments had to be made to accommodate the available data within the HE model.

Live birth rates with IVF compared with expectant management

A number of prospective comparative studies provide data on treatment independent ('spontaneously conceived') birth rates in subfertile couples who were trying IVF (Stewart et al., 2011; Brandes et al., 2009; Eijkemans et al., 2008; Herbert et al., 2012; Smith et al., 2011; Malizia et al., 2009; de La Rochebrochard et al., 2009; Lintsen et al., 2007).

Two of these studies came from Australia. The first study used routine datasets to identify 8275 women undergoing IVF. The study found that the highest cumulative rate of birth with IVF was in women aged 20 to 29 years, with rates of 58%; with a further 21% having treatment-independent deliveries. Rates declined with age: in women aged between 40 to 44 years the rates were ranged from 22% and 11%, respectively (Stewart et al., 2011). The second study was a community cohort that identified 1376 women reporting fertility problems. The study found that of this group, 53% of those who used assisted conception gave birth compared with 43.8% of women who did not use assisted conception (Herbert et al., 2012).

Three Dutch studies based on people involved in a national cohort of people accessing fertility treatment between 2002 and 2006 were identified. The first study of 1391 couples from a single fertility clinic found that 45.6% of pregnancies reported in this group were treatment-independent ('spontaneously conceived') (Brandes et al., 2009). The second study, based on 5962 couples, assessed outcomes in people while they were waiting for IVF treatment and found that the cumulative

probability of spontaneous ongoing pregnancy was 9% at 12 months (Eijkemans et al., 2008). The third study of 4928 couples starting IVF/intracytoplasmic sperm injection (ICSI) treatment found the 'optimistic' chance of an ongoing pregnancy for couples after 4 cycles was 63% if it was assumed that women who dropped out of the study had the same chance of pregnancy as those who remained in the study, whereas the 'realistic' chance after the fourth cycle was 42% if it was assumed women who dropped out had no chance of a live birth (Lintsen et al., 2007).

Two studies from the USA were identified. The first study was based on 6164 patients undergoing a total of 14,248 cycles between 2000 and 2005. The study found that the 'optimistic' cumulative live-birth rate after 6 cycles was 72% (95% confidence interval [CI] 70 to 74), and this compared to the 'realistic' chance of 51% (95% CI 49 to 52) (Malizia et al., 2009), The second study was of 408 couples attending community fertility clinics: this found that, compared to no treatment, IVF was associated with significant benefit for couples undergoing one (hazard ratio [HR] 2.8, 95% CI 1.5 to 5.2) or 2 cycles (HR 2.2, 95% CI 1.2 to 4.1). However, there was a non-statistically significant difference for couples undergoing 3 or more cycles (HR 1.3, 95% CI 0.7 to 2.4) (Smith et al., 2011).

A French study of 724 patients attending two fertility clinics calculated that the 'optimistic' chance of live birth after IVF was 81% and that the 'realistic' rate was 53% (de La Rochebrochard et al., 2009).

None of these studies were able to provide outcomes for detailed combinations of clinical variables or allow them to be calculated.

Using prediction models to estimate live birth probabilities for IVF and expectant management

In addition to prospective studies, the review found a number of models for predicting live birth after EM or IVF. These allowed estimates of live birth rates to be calculated given different clinical scenarios and offered a practical solution to populating the health economic model.

A systematic review was identified that assessed the validity of models predicting live birth rates for spontaneous pregnancy, intrauterine insemination (IUI) or IVF (Leushuis et al. 2009). The review assessed each model using the following criteria:

- Model derivation:
    - Identification of prediction variables based on prior knowledge and calculation of the regression coefficient/predictor weight.
- Model validation:
    - Internal – ability to predict outcomes in the group of patients in which it was developed.
    - External – ability to predict outcomes in other populations using discrimination and calibration methods.
- Impact:
    - The model improved decision making leading to improved patient outcomes.

A total of 36 papers were included in the review; however, some of those were discussion papers. Therefore, 29 published detailed prediction models were formally appraised:

- nine predicted spontaneous ('treatment-independent', EM) pregnancy rates
- three predicted pregnancies resulting from IUI
- 17 predicted pregnancies resulting from IVF.

Only eight models fulfilled the external validation phase criteria (model derivation and validation, above) of which just one (Hunault et al. 2004) also complied with the requirements of impact analysis (see above). All models for spontaneous ('treatment independent') pregnancies had poor discrimination* but Hunault et al. (2004) had good calibration. The only externally validated model for pregnancy after IUI (Steures et al., 2004) had poor discrimination (area under the curve [AUC] 0.59)

* Poor calibration (AUC: 0.5 to 0.7); reasonable calibration (AUC: 0.7 to 0.8), good discrimination (AUC: >0.8)

but good calibration; being able to distinguish between a group with poor chances of pregnancy (0–5%) and a group with better chances (8–11%). Of the three externally validated IVF prediction models, Templeton (1996) had poor discrimination but good calibration. The Stolwijk (1996) model had poor discrimination and also had poor calibration due to poor performance with respect to the identification of women with a very low probability of pregnancy. For the Hunault (2002) IVF model the AUC was 0.63, but calibration was poor with a statistically significant difference between the observed predicted pregnancies.

The authors of the review concluded that three models could be considered to have good performance: Templeton 1996 for IVF, Hunault 2004 for spontaneous pregnancy, and Stueres 2004 for IUI. No unified model was identified for predicting outcomes for expectant management and IVF in combination.

As a result of this review it was decided that the Hunault model (2004) would provide the best estimates of live birth rates with expectant management for the health economic analysis. Furthermore, its inclusion of cause and duration of sub-fertility meant that it could be used to estimate cumulative live birth rates over time. Since the systematic review was published, another prediction model for IVF (Nelson and Lawlor, 2011) has been published and was evaluated for use in the health economic model. The Nelson and Lawlor model (IVFPredict.com © 2010, hereafter referred to as IVFPredict) has been shown to have better performance than the Templeton model in terms of calibration, is based on more recent UK data and practice, and allows for analysis of different clinical scenarios. Therefore, it was decided to use IVFPredict in the health economic model to estimate live birth probabilities with IVF.

The GDG highlighted that these models may provide biased results, especially as they were developed in patient populations selected for IVF treatment. It was also recognised that there are inherent limitations in using two separate models developed using different methodologies and in different populations.

Hunault model

The Hunault model was developed based on primary data from 2459 sub-fertile couples from three different studies (Eimers et al., 1994, Collins et al., 1995; Snick et al., 1997). This model allows the prediction of spontaneous conception leading to live birth within 1 year based on:

- duration of subfertility
- women's age
- primary (never conceived) or secondary infertility (difficulty conceiving having previously conceived)
- percentage of motile sperm, and
- whether the couple was referred by a general practitioner or by a gynaecologist (referral status).

The Hunault model had good calibration and performed well when externally validated in a different population (van der Steeg et al., 2007), but less well in others (Gabbanini et al., 2010).

The formula used in this model to predict a spontaneous conception leading to live birth is given by:

$$P = (1 - 0.181^{\exp(\mathbf{PI})})$$

Where:

P is the predicted probability of spontaneous conception leading to live birth within 1 year

PI is the Prognostic Index, given by:

PI = -0.03 x AGE1 -0.08 x AGE2 - 0.19 x duration of sub-fertility - 0.58 x primary subfertility + 0.008 x percentage of motile sperm - 0.25 x tertiary-care couple*

* Primary subfertility and tertiary care are dichotomous outcomes, therefore would have a value of either 1 or 0 according to whether they meet the condition or not

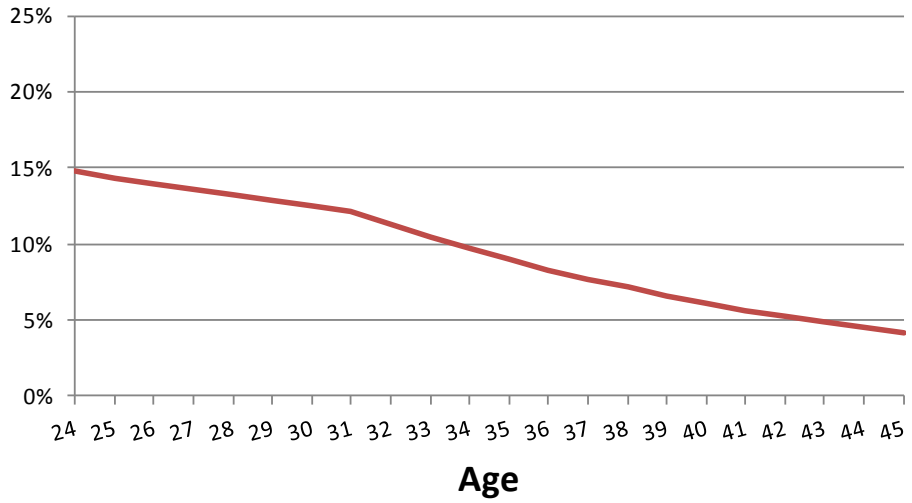
Where:

AGE1 is the woman's age if she is is 31 years or younger, or 31 if the woman's age is more than 31 years.

AGE2 is the difference between woman's age and 31 years if the woman's age is more than 31 years and zero if the woman is 31 years or younger.

Figure 14.1 shows an example of the outputs of the Hunault model used in this analysis to estimate the probability of live birth with expectant management over 12 months.

Figure 14.1: An example of the live birth estimates with expectant management derived from the Hunault model for a woman with primary sub-fertility, a duration of sub-fertility of 6 years and 40% motile sperm.



A cumulative approach was achieved by incrementing the age and duration of sub-fertility by 1 in the above equation until age reaches 45 years.

The Hunault model was also used to estimate the expectant management probability of live birth for women between IVF cycles and in the remaining months of an IVF treatment year following completion of all IVF cycles. To do this it is assumed that there is a constant monthly probability of live birth, consistent with the probability estimated by the Hunault model over 12 months:

Probability birth = 1 - (1 - [1 - 0.181 ^ exp{PI}]) ^ (months / 12)

However, the Hunault predictions are not based on datasets that included patients with failed IVF. It would be expected that such patients, by virtue of their treatment failure, would have a systematically lower probability of success with expected management than that predicted by Hunault. Therefore, we assumed a proportion of the IVF failures would have a zero probability of live birth from EM and applied the Hunault prediction to the remainder. To estimate a proportion that would have a zero chance of expectant management success we used the proportion who failed to have a live birth on a strategy of EM over their reproductive life. It was assumed that the remainder would have the probability of live birth predicted by the Hunault model. As an example, for those on EM for their entire reproductive lives there will be a proportion who do not achieve a birth by age 45 (in this example we will use 40%). In those who have failed IVF the model assumes that this proportion (40%) have no chance of an EM birth. The remaining 60% of IVF failures have the same probability as their EM counterparts. Thus the actual live birth rate from expectant management following IVF failure would be a weighted average of these two groups; that is, those with a zero chance and those with a probability estimated using the Hunault model.

It should be noted that the Hunault model was not used to generate expectant management probabilities where it is assumed there is no chance of spontaneous conception leading to live birth in such scenarios, for example in women with severe tubal disease or severe endometriosis.

There are some potential limitations with using this model:

- It is based on cohorts where the average age of women is younger than the population covered by this HE model. Based on their clinical experience, the GDG members thought that the estimates of live birth from the Hunault model were higher than would be expected, particularly in older age groups.
- It included women who were attending clinics for sub-fertility, but the degree of subfertility may not have been as severe as a population referred for IVF (as used in IVFPredict), which could lead to a higher estimate of live birth arising from natural conception than would occur in a population who might be considered for IVF on the NHS.
- It has not been validated as a cumulative predictor of live birth.

The potential impact of these limitations was assessed in the health economic model using sensitivity analysis (see below).

Nelson and Lawlor IVFpredict.com model

The IVFPredict model was based on data of 144,018 fresh IVF cycles undertaken in the UK between 2003 and 2007 held on the HFEA database. A multivariable logistic regression model used to assess associations between pre-defined characteristics and live birth formed the basis of the prediction model. Live birth can be predicted using woman's age, duration of subfertility, cause of subfertility, pregnancy history, own/donor eggs, IVF attempts, medication and whether ICSI is used.

The predictive ability of the new model and the validated Templeton model was undertaken using AUROC and calibration, with the latter assessed by ranking patients in deciles according to the Templeton model prediction of their probability of live birth. The respective AUROC curve was 0.618 (95% CI 0.615 to 0.622) for the Templeton model and 0.634 (95% CI 0.620 to 0.637) for the new model. Calibration of the Templeton model was poor, with it systematically under-estimating the probability of live birth across all deciles.

The formula used in IVFPredict is as follows:

$P = \exp(y) \div (1+\exp[y])$

Where:

P is the probability of live birth

y = -1.1774 + (age and duration effect) + (age and source of embryo effect) + (ICSI and cause effect) + (ICSI and cycle number effect) + (previous number of unsuccessful IVF attempts) + (previous obstetric history effect) + (hormonal preparation effect)*

There were a number of potential limitations and inconsistencies in the IVFPredict model that had to be accounted for in the health economic analysis:

- The outputs of IVFPredict do not always show a subsequent IVF attempt to have a lower probability of success than a previous attempt. In the absence of better patient selection with increasing cycles it would be expected that the pool of remaining infertile women would have a worsening average prognosis as the number of failed cycles increases. Therefore, in our analysis the probability of live birth in a cycle is constrained to not exceed the probability in a previous cycle.
- The model was based on retrospective routinely collected data which means patient selection and access to care were likely to affect outcomes.

* The values for these effects are in tables produced as supplementary material (Text S2) to the published paper which is available for download from: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000386

- The data used in IVFPredict were expressed 'per cycle' rather than 'per woman'. The latter would have been preferable for the development of the health economic model.
- The model was not designed to provide cumulative live births rates.
- The model did not consider the possibility of spontaneous conception between IVF treatments.
- Age was included as an ordinal scale rather than (and preferably) a continuous number, with age ranges of: 18 to 34 years; 35 to 37 years; 38 to 39 years; 40 to 42 years; 43 to 44 years; 45 to 50 years.
- The model has not been validated in another population.
- The model is almost exclusively based on couples who used double embryo transfer (DET).

Matching the Hunault and IVFPredict inputs.

The effectiveness of IVF compared to treatment alternatives was estimated using the two models outlined above. The variables included for predicting the success of the intervention and the success of expectant management were not identical. Therefore, the inputs were set to make the populations for the different models as closely matched as possible but additional assumptions were introduced in this process:

- Hunault output was always based on 'a couple receiving tertiary care' as it was assumed the population covered by the guideline would be under specialist care rather than primary care and to match IVFPredict which related to couples in tertiary care.
- The causes of infertility in Hunault and IVFPredict were not the same. Therefore, the following assumptions were made:
    - Male factor cause is characterised by a low sperm count in IVFPredict and is a dichotomous variable. However, in the Hunault model of expectant management a male factor cause is captured by a continuous variable for sperm motility. We assumed that 40% sperm motility or higher excluded a male factor cause in the Hunault model based on the World Health Organization (WHO) reference characteristics for human semen (Cooper et al., 2009). Where a diagnosis of low sperm count was used in IVFPredict (that is, male factor cause) a sperm motility of 20% was used in the Hunault model. The simplifying assumption was made that sub-optimal sperm motility (more precisely a sub-optimal value of 20%) is likely to be associated with a low sperm count in terms of its predicted impact on live birth rates. Neither model includes sperm morphology to define 'male factor cause'.
    - Tubal disease and severe endometriosis were each assumed to have zero chance of a live birth from expectant management. These were the two causes of infertility that could be modelled using IVFPredict. However, it was acknowledged that they would serve as paradigms for other conditions associated with no chance of spontaneous conception, such as azoospermia, which were not included in IVFPredict.
    - Unexplained cause and mild endometriosis were assumed to be equivalent in terms of treatment-independent live birth rates.
    - Ovulation disorders and 'cervical causes' of subfertility were not included in the analysis. IVF is not an appropriate treatment for women with ovulation disorders (see Chapter 8). 'Cervical causes' of infertility (such as cervical tachelectomy) are extremely rare and the GDG did not consider it necessary to include these in the model. This view was supported by the fact that the HFEA database which was used for the IVFPredict model had less than 100 women with this diagnosis (< 0.05%).

- Hunault defined obstetric history as having only two categories, namely primary (never been pregnant) or secondary (previously pregnant). However, IVFPredict defined three categories of obstetric history (no pregnancy, pregnancy but no birth and live birth).
- Within IVFPredict the source of embryo and medication could be varied. However, the model developed for this guideline was based on a population using their own eggs for IVF and where the medication used for ovulation induction would be gonadotrophins (used in over 98% of cases of IVF) (see Chapter 15). In addition, the Hunault did not include these variables. Therefore these factors were treated as 'fixed' in our analysis.

In addition to age, and largely based on IVFPredict, this model incorporated the cause of sub-fertility, duration of sub-fertility and pregnancy/obstetric history as predictors of live birth rates. These factors were used to define 198 clinical scenarios for analysis (6 x 11 x 3).

- Cause of sub-fertility (6)
  - Unexplained
  - Male factor treated without ICSI
  - Male factor treated with ICSI
  - Mild endometriosis
  - Severe endometriosis
  - Tubal disease

Whilst IVF can potentially be offered with and without ICSI for all causes, the 2004 guideline concluded that its use was only recommended for male factor causes. Endometriosis was sub-divided into mild and severe on the advice of the GDG, because it has an important bearing on the chances of pregnancy with expectant management. The model assumes that there is no chance of spontaneous pregnancy with expectant management when the cause of sub-fertility is tubal disease or severe endometriosis.

- Duration of sub-fertility (11)
  - From a minimum duration of 2 years sub-fertility through to a maximum of 12 years.
- Pregnancy history (3)
  - No previous IVF, no previous pregnancy (primary sub-fertility)
  - No previous IVF, previous pregnancy but no live birth
  - No previous IVF and previous live birth.

For each of the 198 clinical scenarios, the cost-effectiveness of IVF for each age group was determined by separately comparing the four treatment strategies from 20 years through to 45 years, which was considered by the GDG to represent a reasonable approximation of a woman's reproductive lifespan and the realistic upper age limit of conceiving using her own eggs. The actual starting age in any given scenario was determined by the duration of sub-fertility in that scenario given the simplifying assumption that sub-fertility could not begin prior to 18 years of age. Thus, for example, in clinical scenarios which used a duration of sub-fertility of 10 years, the cost effectiveness would be calculated for treatment from 28 to 45 years.

Quality adjusted life year (QALY) estimation

Utility values

Health state utilities are used to quantify health related quality of life and are ranked on a scale 0–1, with 0 being equivalent to death and 1 being a state of perfect health. Health state utilities measured over time can be used to generate QALYs by multiplying the duration in a particular health state by the utility associated with that state.

The QALY is the preferred measure of health outcome using NICE methods, primarily because it allows a comparison of the value for money of interventions which will be intended to improve many different dimensions of health-related quality of life. However, assisted reproductive treatments present difficulties for the QALY approach. For example, it has been stated that:

> "QALYs are intended to capture improvements in health among patients. They are not appropriate for placing a value on additional lives. Additional lives are not improvements in health; preventing someone's death is not the same as creating their life and it is not possible toimprove the quality of life of someone who has not been conceived by conceiving them." (Devlin and Parkin, 2003)

Or, in a similar vein:

> "Cost-utility analysis has little relevance to the management of infertility where lives are produced and not saved." (Collins et al., 2002)

This reasoning was accepted for the HE model and therefore any QALY gain in the analysis had to relate to the couple seeking treatment and not to a 'not yet conceived life'.

A health state utility decrement of 0.07 from being infertile has been reported recently in a UK economic evaluation of eSET versus DET (Scotland at al., 2011). Correspondence with the authors of this study provided the following explanation of how this utility decrement of 0.07 was identified. It came from a US study where the state of being infertile was assigned a profile – on the Health state Utilities Index Mark II (HUI2) – with a utility value of 0.82. This 0.82 was then subtracted from US population norms for the HUI2 (which is 0.89 for women of reproductive age) to give an estimated decrement of 0.07. Scotland et al. applied this decrement of 0.07 to the state of 'being infertile with the desire for a child' and assumed a reversal of this decrement for those achieving a live birth. While the decrement is not based on data values using UK general population time trade-off preferences (the approach favoured by NICE), it provides a rough estimate of the level of utility decrement that infertile women in the UK might be assigned on the EQ-5D measure of health outcome if it were to include a fertility dimension similar to the HUI2 instrument. However, relatively little has been published on QALY losses associated with infertility and there is considerable uncertainty about the actual health gain that would accrue from a live birth. Furthermore, Scotland and colleagues assumed utility stayed constant over a period of 20 years – the time horizon of the study – assuming that the 0.07 disutility decrement from being infertile would be lifelong and constant. This assumption may over-estimate the willingness to pay for a live birth if the disutility decrement from being infertile diminishes over time.

In the absence of any other published estimates identified in the literature, this approach was adopted to estimate the QALY gain for successful treatment. In the base case analysis the health state utility of the partner is not taken into account so it can plausibly be argued that the QALY gain from live birth is higher.

Sensitivity analysis addressed the implications of varying the change in health state utility arising from a live birth (see below).

An assumption of constant disutility over time was adopted for this model. This is because the GDG considered that, given the lack of studies on this issue, the added complexity of estimating a decrement over time to a value that is essentially unknown would not add to the analysis.

Discounting

In the cumulative approach used in the model the actual QALY gain of a birth in a given year was discounted at an annual discount rate of 3.5% from the time when the treatment decision is made. ONS 2007–09 life-tables were then used to determine the life expectancy over which this QALY gain is experienced but with future years until the end of life also discounted at a rate of 3.5% per annum.

For example, if a woman aged 24 at the time the treatment decision is made has a live birth in year 4 then the QALY from that birth is calculated as follows:

> QALY from achieving a live birth = $0.07 \div 1.035^3 = 0.063$
>
> Age of woman at birth = 27 years
>
> Remaining life expectancy = 55.7 years

$$\text{QALY gain} = \sum_{i=0}^{54} 0.063 \div (1.035)^{i} = 1.59 \text{ QALYs}$$

Adverse events

In addition to the QALY gain from a live birth, the model also takes into account potential QALY losses from OHSS. In the base case this is based on the mortality rate associated with OHSS with the discounted QALY loss from mortality calculated in a similar way as for live births, although OHSS will occur only in year 1 of the model with the exception of some cases for 3rd cycle eSET which takes place in year 2. In the base case analysis no QALY loss was attributed to OHSS morbidity because the effects tend to be relatively short term and in the case of mild OHSS it is often not considered clinically significant. However, the model does allow QALY losses to be attributed to mild, moderate and severe cases (see below).

In the base case analysis the health state utility of the partner is not taken into account, so it can be plausibly argued that the QALY gain from live birth is higher. Sensitivity analysis addressed the implications of varying the change in health state utility arising from a live birth (see below).

Cost effectiveness threshold

A key output in a cost effectiveness analysis is the incremental cost effectiveness ratio (ICER), the incremental costs per QALY in this case. However, in isolation this value does not give an indication as to whether that ratio represents good value for money (that is, whether it is cost effective). In order to determine whether this ICER is cost effective, the decision maker must have some idea concerning society's willingness to pay (WTP) for a QALY. As noted in the NICE Guidelines Manual "NICE has never identified an ICER above which interventions should not be recommended and below which they should". However, the guidance notes that when considering recommending treatments with an ICER greater than £20,000 per QALY threshold, justification must reflect:

- the degree of uncertainty around the ICER
- the presence of strong reasons that the analysis may inadequately capture health gain
- that the intervention may provide additional and substantial benefits other than those captured in the measurement of health gain.

The guidance notes that when considering recommending treatment with an ICER of greater £30,000 per QALY an even stronger case needs to be made with respect to the aforementioned points.

It could reasonably be argued that in the case of IVF the decision maker has a willingness to pay for a live birth which does not solely reflect improvements in health-related quality of life. If the decision maker has other objectives than QALY maximisation when providing IVF, then an approach based on a QALY will under estimate the decision maker's actual willingness to pay for a live birth. Therefore, to reflect this, an ICER of £30,000 per QALY was used as to assess the cost-effectiveness of IVF for this guideline.

The variables used to estimate net QALY gain are shown in Table 14.2.

Table 14.2 Variables used to estimate the QALY gain

Item	Value	Source	Notes
Health state utility from live birth	0.07	Scotland et al., 2011	The total QALY gain of a birth depends at what stage it occurs in a woman's reproductive life and the remaining years of life expectancy
Discount rate	3.5%	NICE (2009)	http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf - annual rate of discount on both costs and effects

Item	Value	Source	Notes
Mortality rate from OHSS	6:100,000	Braat et al., 2010	http://www.ncbi.nlm.nih.gov/pubmed/20488805
QALY loss from mild OHSS	0.00	Assumption	Can be varied as part of a sensitivity analysis
QALY loss from moderate OHSS	0.00	Assumption	Can be varied as part of a sensitivity analysis
QALY loss from severe OHSS	0.00	Assumption	Can be varied as part of a sensitivity analysis
WTP for a QALY	£30,000	NICE (2009)	An advisory threshold to make recommendations with respect to their cost effectiveness

QALY quality adjusted life year, OHSS ovarian hyperstimulation syndrome, WTP willingness to pay

Cancellation rates

It was assumed that a proportion of cycles get cancelled at various stages and these count as treatment failures in IVFPredict. A cancelled cycle incurs a lower cost and we used HFEA data to estimate the proportion of cycles cancelled at various stages, as shown in Table 14.3. These proportions are then used as the weights in calculating the mean treatment cost, which is a weighted average of the cost of completed and cancelled cycles.

Table 14.3 Cancellation rates (HFEA 2009 and 2010)

Age	Before egg collection	After egg collection	Frozen embryo transfer
18–36	4.7%	7.6%	6.1%
37–39	6.6%	8.0%	7.4%
40–42	8.0%	8.6%	8.8%
≥ 43	11.9%	12.6%	12.1%

Ovarian hyperstimulation syndrome (OHSS) rates

A published paper (Brinsden et al. 1995) was used to estimate the risks of mild, moderate and severe OHSS which would be used together with the cost of those adverse events to estimate the cost of IVF complications. These risks also determine the QALY loss from OHSS where a QALY loss from these outcomes is assumed. The OHSS risks used in the base case analysis are shown in Table 14.4.

Table 14.4 OHSS risk

Severity	Risk	Source	Notes
Mild	8.0%	Brinsden et al. 1995	8.0–23.0%
Moderate	3.5%	Brinsden et al. 1995	1–7%
Severe	1.0%	Brinsden et al. 1995	0.25–2.0%

Double embryo transfer compared with elective single embryo transfer

The outputs of IVFPredict reflect predominantly a DET strategy with the cycles on the HFEA database being almost exclusively DET. However, RCT evidence (see Chapter 15) suggests that an eSET strategy of one fresh embryo transfer followed by one frozen embryo transfer gives a similar success rate to a single DET cycle (Maartikinen et al., 2001; Lukassen et al., 2005). It should be noted that these RCTs were undertaken on narrow populations and the generalisibility of these findings is not

established. But they were extrapolated to the whole population as the best source of information available. Therefore, for the model, it was assumed that a cycle of DET was equivalent to an eSET cycle (comprising one fresh and one frozen embryo transfer) and therefore that the output from IVFPredict could be used for both DET and eSET strategies. In practice, the clinical situation will be more varied in terms of the number of embryos that will be available for freezing. On occasion, it may be possible to freeze more than one embryo for subsequent transfer or conversely there may be no embryos of good enough quality which can be used for a frozen transfer. The quality and quantity of available embryos will in part be determined by the woman's age.

An RCT comparing a fresh and frozen eSET cycle with a DET cycle (Maartikinen et al., 2001) reported that approximately 75% of all births using an eSET strategy occurred after the transfer of a fresh embryo. Thus 25% of live births would be expected to occur following a frozen transfer. This ratio was used in the model to estimate the proportion of women who would require frozen transfers as part of an eSET cycle.

It was assumed for eSET that there would be about 6 months between cycles which means that a 3rd cycle would occur in year 2. Therefore, the probability of success reflects the woman's older age and longer duration of sub-fertility. A DET cycle in the model consists of one transfer of two fresh embryos with the assumption that there would be about 4 months between cycles. Therefore all DET cycles are assumed to take place in the first year. For both eSET and DET it was assumed that, for causes where spontaneous pregnancy is possible, there would be some chance of a live birth arising from expectant management in the months between embryo transfers.

For the DET cycle all treatment is based on fresh cycles but in eSET the model includes a frozen cycle for those women who do not achieve a successful outcome with their fresh cycle. In line with the clinical recommendations in Chapter 15, the model assumes that eSET is the first-line approach for women aged 39 years and younger, and DET is the first-line strategy for with women aged 40–42 years if they have more than one embryo. However, it is unusual for women aged 40–42 years to have three or more embryos to use for a fresh DET cycle and, if necessary, a frozen DET cycle.

The data in Hunault and IVFPredict is not disaggregated into a singleton and twin probability. To estimate the twin probability from the live birth probability in a DET strategy we assumed that each embryo transferred had an equal chance of producing a live birth.

Y = live birth rate (output of IVFPredict)

P = probability of live birth per embryo

$Y = P^2 + 2P(1 - P)$

$\therefore 0 = 2P - P^2 - Y$

For each predicted live birth rate (Y), P can be estimated by solving this quadratic equation (P must lie between 0 and 1). The twin prediction probability is then simply P^2.

Costs

The costs inputs used in the model are shown in Table 14.5.

There were no NHS Reference costs that could be used for the purposes of this analysis. Therefore, cost inputs were derived from published UK sources or GDG estimates. The model allows IVF treatment to be provided with and without ICSI and clearly treatment costs represent a key part of the cost of each strategy. The model also estimates a cost for OHSS, an important adverse outcome of IVF.

Most costs are assumed to occur within the first year but there are costs for treatment and complications associated with a 3rd eSET cycle which takes place in the 2nd year and these are discounted at an annual rate of 3.5% in accordance with NICE guideline methods. The model assumes that DET cycles will be completed within the first year.

Although the NHS incurs costs associated with an ongoing IVF singleton pregnancy and birth, these were not incorporated into the analysis because they do not impose costs over and above those that would occur from natural conception. The assumption is that the children born from IVF would have been conceived spontaneously if this had been possible, incurring the same costs in pregnancy and

birth. Costs associated with pregnancy and birth arise from a different decision (a woman or couple's decision to conceive) and the services offered on the NHS (for example of antenatal, delivery and neo-natal care) are assumed to be cost effective. However, where a DET strategy is used, the risk of twin pregnancies increases compared with natural conception and twin pregnancies incur higher health service costs than singletons conceived using eSET or expectant management approaches. Therefore, the model includes an additional cost for twin pregnancy for the first year of life (Ledger et al., 2006). No other 'downstream' costs other than OHSS are included.

Table 14.5 IVF treatment and twin pregnancy costs

IVF treatment	Value	Source	Notes
IVF fresh cycle	£3123	Maheshwari et al., 2010	This Scottish study cited costs of IVF in 2007/08 prices of £2822 (age ≤ 35), £2940 (age 3–39) and £3097 (age ≥ 40) with these differences by age reflecting different drug therapy. These figures were updated to 2010/11 prices using the HCHS index and a weighted mean calculated based on HFEA cycle data for these age groups
IVF frozen cycle	£1343	Dixon et al., 2008	This English study cites a cost for the first frozen transfer of £1094 at 2003/04 prices. This was updated to 2010/11 prices using the HCHS index.
ICSI	£500	GDG	This value is a GDG consensus view of the NHS cost of ICSI on top of the baseline IVF cost. The GDG noted the following advertised additional prices for ICSI in a sample of private UK clinics:[*] £970[†] £735[‡] £650[§]
IVF fresh/cancelled pre-harvest	£1000	GDG	This value is a GDG consensus view of the NHS cost of a cancelled cycle before egg harvest. The GDG noted the following advertised refunds in a sample of private UK clinics : £2400[**] £2495[††] £2275[‡‡]
IVF fresh/cancelled post harvest	£2565	Maheshwari et al., 2010	This Scottish study cited costs of a cancelled IVF cycle in 2007/08 prices of £2326 (age ≤ 35 years), £2370 (age 36–39 years) and £2,608 (age ≥ 40 years) with these differences by age reflecting different drug therapy. These figures were updated to 2010/11 prices using the HCHS index and a weighted mean calculated based on HFEA cycle data for these age groups.

2013 Update

[*] Websites accessed 03/03/2012
[†] Source: http://www.northwestfertility.co.uk/fees.aspx
[‡] Source: http://www.leedsreproductivemedicine.co.uk/treatment-costs.html
[§] Source: http://www.gcrm.co.uk/downloads/Treatmentcosts.pdf
[**] Source: http://www.hsfc.org.uk/assets/docs/pricelists/2012-01-27_price-list_treatments.pdf
[††] Source: http://www.hertsandessexfertility.com/Treatment-Options/Fees/Payments-Cancellation.aspx
[‡‡] Source: http://www.northwestfertility.co.uk/fees.aspx

IVF treatment	Value	Source	Notes
IVF frozen cancelled	£800	GDG	This value was calculated by subtracting the average refund from the total IVF cost, as advertised by private UK clinics total cost: £530* £505†
OHSS mild	£236	Maheshwari et al., 2010	Updated to 2010/11 prices using the HCHS price index.
OHSS moderate	£1408	Maheshwari et al., 2010	Updated to 2010/11 prices using the HCHS price index.
OHSS severe	£3164	Maheshwari et al., 2010	Updated to 2010/11 prices using the HCHS price index.
Additional costs of a twin pregnancy	£7764	Ledger et al., 2006	Updated to 2010/11 prices using the HCHS price index. The analysis was based on the cost to the NHS per singleton, twin or triplet pregnancy resulting in a live newborn infant(s) surviving up to year one and included costs borne by the mother and the baby.

HCHS Hospital and community health services, HFEA Human Fertilisation and Embryology Authority, ICSI intracytoplasmic sperm injection, IVF in vitro fertilisation, OHSS ovarian hyperstimulation syndrome

14.4 Results

Findings of the base case analysis

In all, 198 clinical scenarios were analysed to evaluate which groups of women should have access to 1, 2 and 3 cycles of IVF. The full set of 198 base case analyses for eSET and DET strategies is presented in Appendix M. The general pattern of these results is that: DET is more cost-effective than eSET; and the cost effectiveness of IVF improves as duration of infertility and severity of condition increases.

Three example analyses are presented below for the purposes of illustration. In each analysis women/couples have a different set of exogenous clinical characteristics and for each set of characteristics the incremental cost effectiveness of additional IVF cycles is then evaluated according to the woman's age. Each analysis is presented for either eSET policy or DET policy.

Example analysis 1 (base case)

Scenario

Figure 14.2 shows the cumulative live birth rates for a woman aged 34 years with the following scenario:

- Duration of sub-fertility: 2 years
- Cause: tubal (no chance of natural/spontaneous conception)
- Pregnancy history: no previous pregnancy
- Strategy: eSET

* Source: http://www.carefertility.com/docs/locations/nottingham/nottingham-fees.pdf
† Source: http://www.northwestfertility.co.uk/fees.aspx

Figure 14.2 Cumulative live birth rates across the remaining reproductive life for a woman aged 34 years, with 2 years of sub-fertility of tubal cause and with no previous pregnancy*

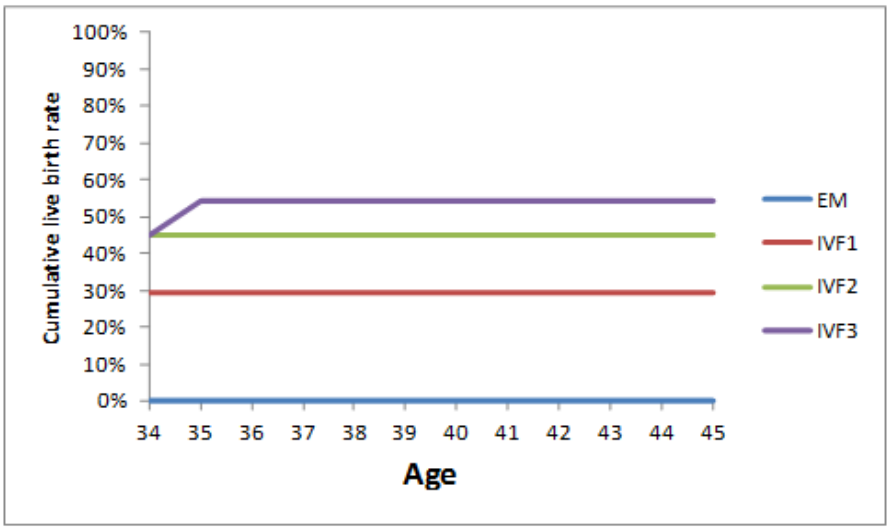


Table 14.6 shows how the cost effectiveness is determined for a woman age 34 years and the cost effectiveness results are summarised for women of all ages in Figure 14.3.

Table 14.6 Incremental cost-effectiveness ratios for women aged 34

Strategy	Cost	QALY	Incremental cost	Incremental QALY	ICER
EM	£0	0.00	-	-	-
IVF1	£4103	0.49	£4103	0.49	£8395
IVF2	£7050	0.75	£2948	0.26	£11,122
IVF3	£9288	0.90	£2238	0.14	£15,519

EM expectant management, ICER incremental cost effectiveness ratio, IVF in vitro fertilisation, QALY quality adjusted life year

* The kink in Figure 14.2 (see Figure 14.6 also) is because it is assumed that the third cycle of eSET would occur in year 2 of the model, i.e. 12 months after the first cycle. Any births as a result of a third eSET cycle would thus occur when the woman was 1-year older than when treatment commenced.

Figure 14.3 Cost-effective treatment thresholds for example analysis 1

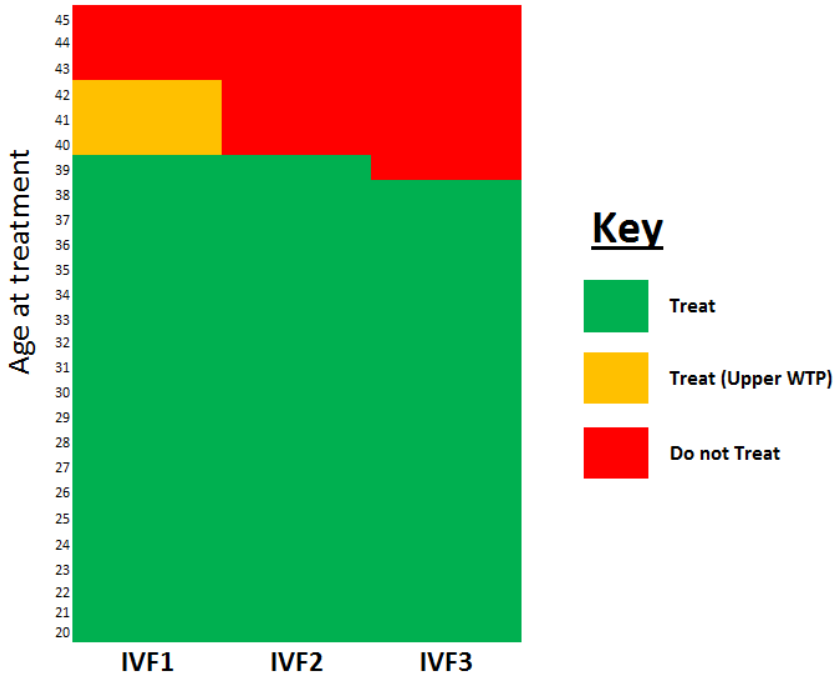


Figure 14.3 shows the cost effectiveness of both 1, 2 and 3 cycles of IVF with eSET, by age, for women who have been infertile for two years or more who have been diagnosed with tubal causes of infertility and therefore have no chance of natural/spontaneous conception. Treatment which is cost-effective at a £20,000 per QALY WTP threshold is denoted by green shading and is labelled "Treat" in the key. Treatment which is cost-effective at a £30,000 per QALY WTP threshold but not at a £20,000 per QALY is indicated by orange shading and is labelled "Treat (upper WTP)". Treatment which is not cost-effective at a £30,000 per QALY WTP threshold is shaded red and is labelled "Do not treat".

The chart suggests that for women aged 40–42 years, 1 cycle of IVF is cost effective. For women aged 39 years, 2 cycles of IVF is cost effective. For women aged 38 years and under, 3 cycles of IVF is cost effective. At a lower WTP threshold, IVF was no longer cost effective for 40-42 year olds.

Example analysis 2 (base case)

Scenario

Figure 14.4 shows the cumulative live birth rates for a woman aged 34 years with the following scenario:

- Duration of sub-fertility: 2 years
- Cause: tubal (no chance of natural/spontaneous conception)
- Pregnancy history: no previous pregnancy
- Strategy: DET

Figure 14.4 Cumulative live birth rates across the remaining reproductive life for a woman aged 34 years, with 2 years of sub-fertility of tubal cause and with no previous pregnancy

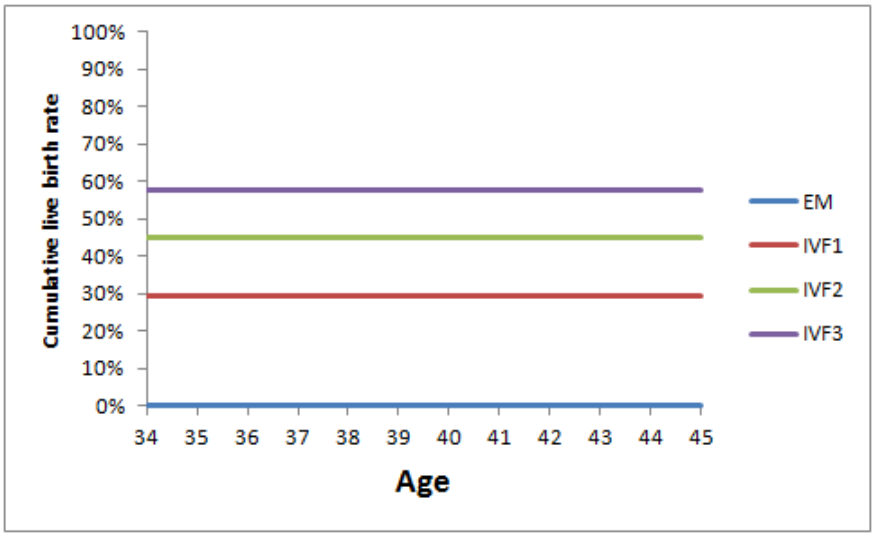


Table 14.7 then shows how the cost effectiveness is determined for a woman age 34 years and the cost effectiveness results are summarised for women of all ages in Figure 14.5.

Table 14.7 Incremental cost effectiveness ratios for women aged 34 years

Strategy	Cost	QALY	Incremental cost	Incremental QALY	ICER
EM	£0	0.000	-	-	-
IVF1	£3276	0.489	£3276	0.489	£6703
IVF2	£5533	0.754	£2257	0.265	£8515
IVF3	£7281	0.959	£1748	0.205	£8529

EM expectant management, ICER incremental cost effectiveness ratio, IVF in vitro fertilisation, QALY quality adjusted life year

Figure 14.5 Cost-effective treatment thresholds for example analysis 2

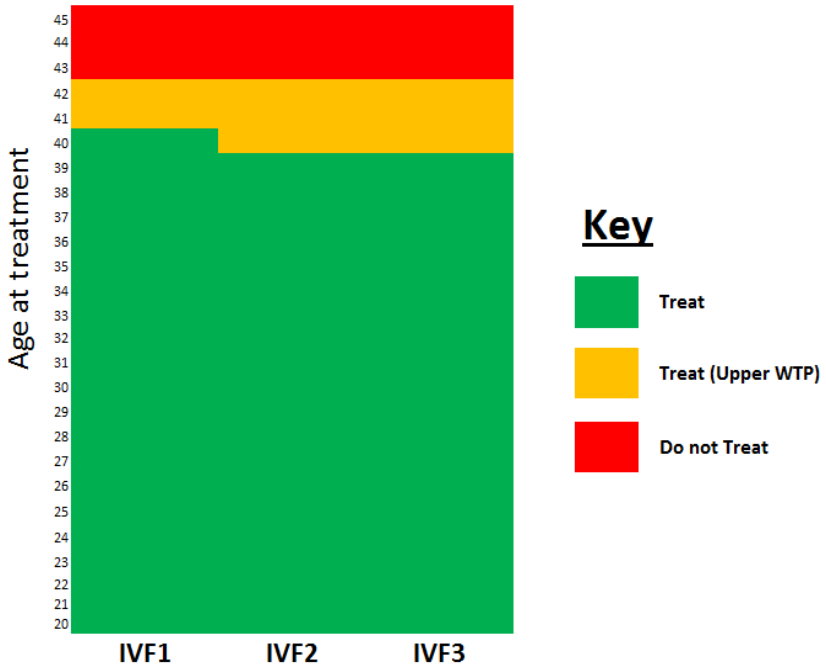


Figure 14.5 shows the cost effectiveness of both 1,2 and 3 cycles of IVF with DET, by age, for women who have been infertile for two years or more who have been diagnosed with tubal causes of infertility and therefore have no chance of natural/spontaneous conception. It suggests that IVF is cost-effective for all women aged 42 years and under. At a lower WTP threshold, IVF was no longer cost-effective for 41-42 year olds and only 1 cycle of IVF was cost-effective for women aged 40 years.

Example analysis 3 (base case)

Scenario

Figure 14.6 shows the cumulative live birth rates for a woman aged 34 years with the following scenario:

- Duration of sub-fertility: 2 years
- Cause: unexplained
- Pregnancy history: no previous pregnancy
- Strategy: eSET and DET

Figure 14.6 Cumulative live birth rates across the remaining reproductive life for a woman aged 34 years, with 2 years of sub-fertility of unexplained cause and with no previous pregnancy (eSET)

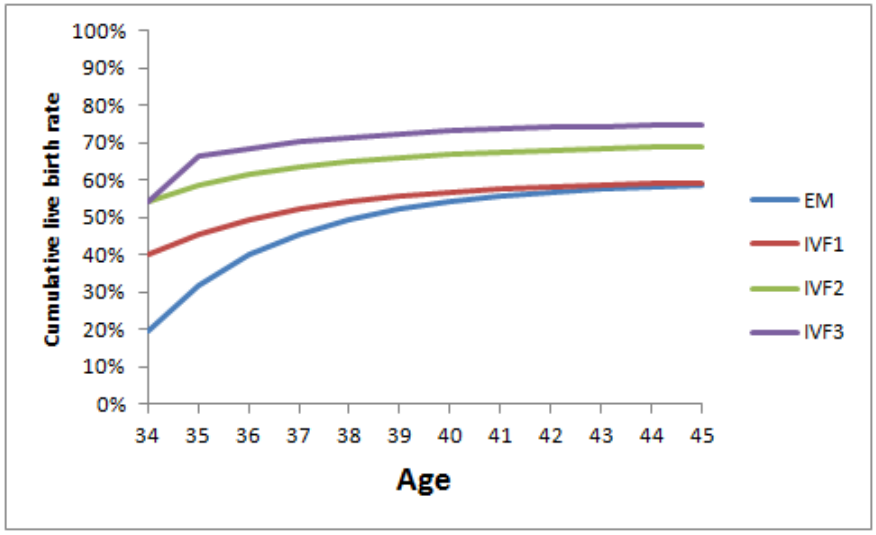


Table 14.8 then shows how the cost effectiveness is determined for a woman age 34 years and the cost effectiveness results are summarised for women of all ages in Figure 14.7.

Table 14.8 Incremental cost-effectiveness ratios for women aged 34 (eSET)

Strategy	Cost	QALY	Incremental cost	Incremental QALY	ICER
EM	£0	0.90	-	-	-
IVF1	£4037	0.95	n/a	n/a	Extended dominance
IVF2	£6655	1.12	n/a	n/a	Extended dominance
IVF3	£8491	1.22	£8491	0.32	£27,102

EM expectant management, ICER incremental cost effectiveness ratio, IVF in vitro fertilisation, QALY quality adjusted life year

Figure 14.7 Cost-effective treatment thresholds for example analysis 3

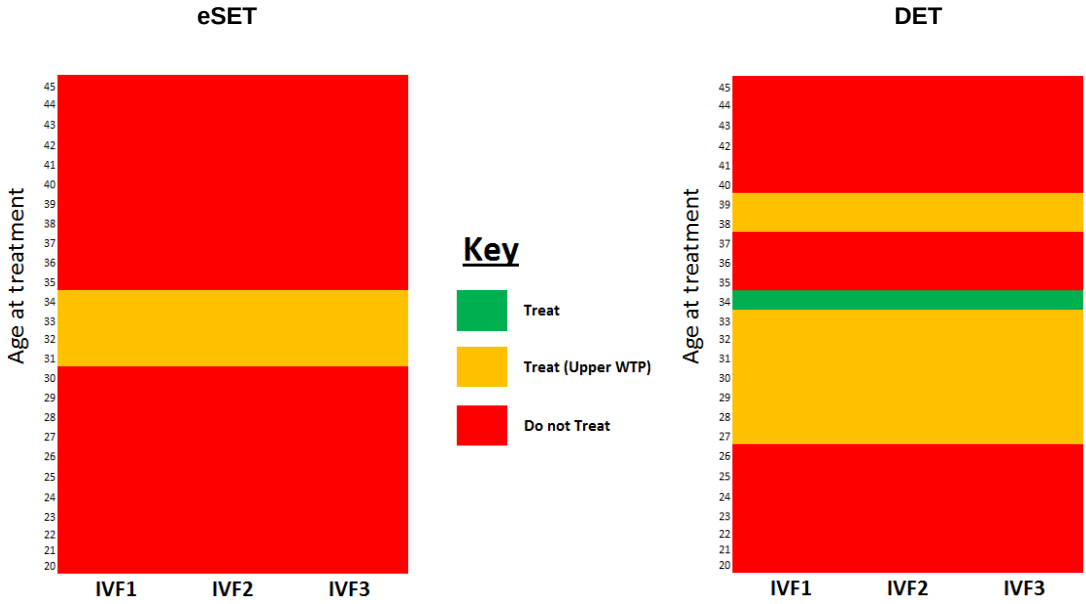


Figure 14.7 shows the cost effectiveness of 1, 2 and 3 cycles of IVF with eSET and DET, by age, for women with an unexplained cause of fertility for 2 years or more. Unlike the previous examples, women are assumed to have a chance of natural/spontaneous birth.

The left-hand chart suggests that 3 cycles of IVF using eSET is cost effective for women aged 31 to 34 years. For women not in that age band, IVF is not cost effective. At a lower WTP threshold, IVF is not cost effective for any age group.

The right-hand chart suggests that 3 cycles of IVF using DET is cost effective in women aged 27–34 years and 38–39 years, but for women not in these age bands IVF is not cost effective. At a lower WTP threshold, 3 cycles of IVF is cost effective for women aged 34 years only.

Sensitivity analysis

Sensitivity analysis was undertaken to assess the impact of changes to the variables in the prediction models.

Where there is a possibility of live birth arising from natural conception, there is uncertainty with respect to the effect size of IVF. In particular there are concerns that the Hunault model may have been developed in populations with 'less severe infertility' than that of the population of interest in the health economic model and that IVFPredict may not capture the ongoing improvement in IVF efficacy over time. For these reasons, the GDG believed that the effect size generated by the HE model may have been an under-estimate, especially in women aged 40 years and above. Therefore, in the sensitivity analysis the Hunault output was deflated to 80% of the calculated value in women aged 39 years and below and to 50% of the calculated value in women aged 40 years and above to reflect this. It was the opinion of some members of the GDG that the actual spontaneous conception rate in women aged 40 years and above could be even lower than this because of falling ovarian reserve,

Health state utility from live birth was varied using a threshold approach to assess the value that would be consistent with either maintaining or changing current practice

Sensitivity analyses were undertaken for all 198 scenarios for eSET and DET changing the Hunault prediction of live birth to 80% for women age 39 years and less and 50% for women aged 40 years and above and discounting QALYs at 1.5%. The results are presented in Appendix N for all scenarios.

Results for all clinical scenarios

The sensitivity analysis applied to all 198 scenarios show that the general pattern for women aged less than 40 years was that IVF became more cost effective when these changes to the live birth rate

and discount rates were factored into the model. For women aged over 40 years, the general pattern was that these changes to the parameters did not improve the cost effectiveness of IVF.

Results for specific example clinical scenarios

Three example scenarios of sensitivity analyses are presented below. The first analysis is based on women with unexplained infertility. The second and third examples are for male factor infertility, one analysis using eSET and the other using DET.

Sensitivity analysis 1

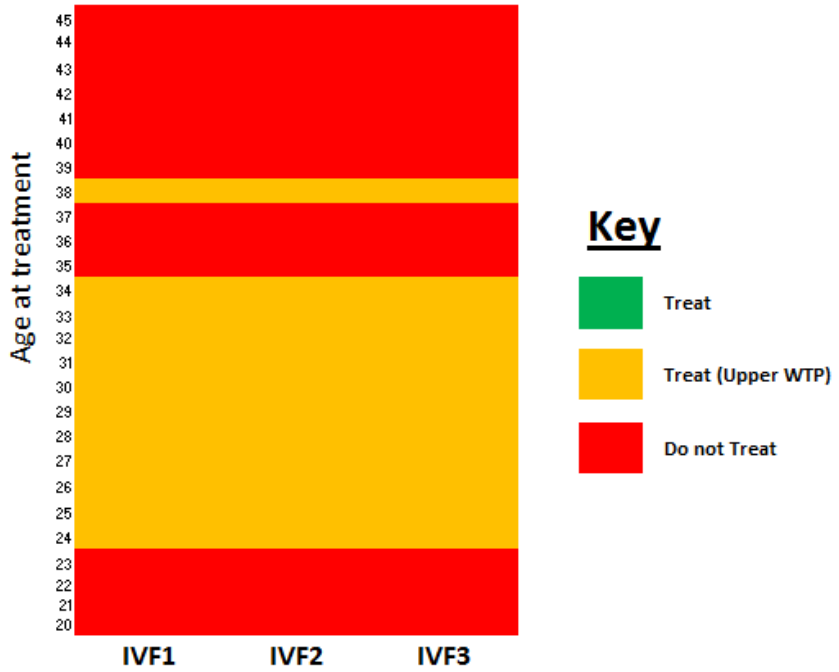
The base case analysis for example analysis 3 suggested that with eSET the current practice of offering IVF on the NHS to all women aged 23–39 might not be cost effective, at least when their duration of sub-fertility was 2 years.

Scenario

Figure 14.8 shows the results of this analysis for a policy of DET for the following clinical scenario:

- Duration of sub-fertility: 2 years
- Cause: unexplained
- Pregnancy history: no previous pregnancy
- Strategy: eSET
- Hunault deflator: 80% of predicted Hunault value (age ≤ 39 years); 50% of predicted value (age ≥ 40 years).

Figure 14.8 Cost-effective treatment thresholds for sensitivity analysis 1



This analysis suggests that the cost-effective conclusions for women with unexplained causes of infertility over 2 years or more are sensitive to the Hunault prediction values. Three cycles of IVF appear to be cost effective in many more age categories than in the equivalent base case analysis at a WTP threshold of £30,000 per QALY (Figure 14.7). If the health state utility was also increased by a small amount to 0.08 then IVF becomes cost effective for nearly all women aged 39 years and younger (not shown diagrammatically here) with the apparent age anomalies being likely artefacts of various aspects of the two models and the data on which they are based (see Section 14.5).

Sensitivity analysis 2

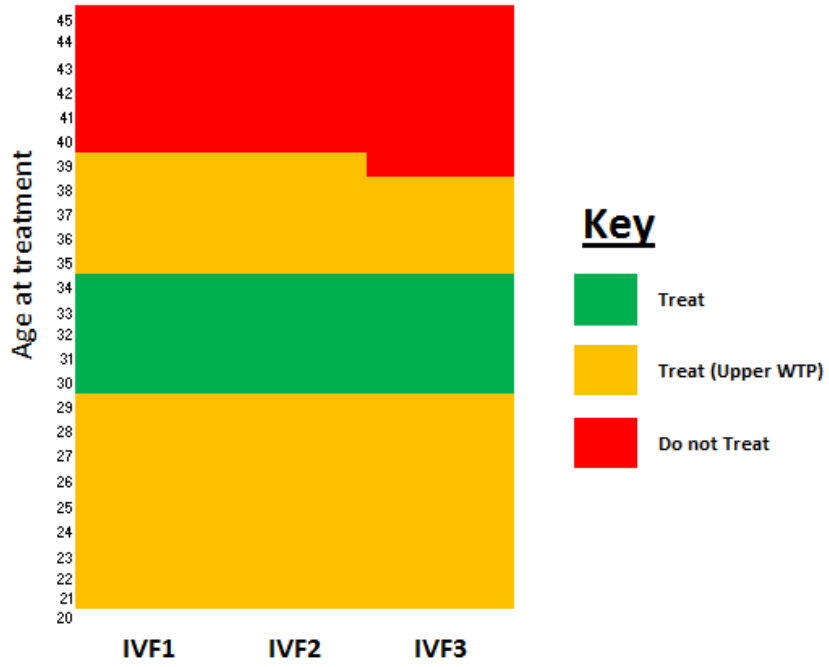
This example further illustrates that the cost effectiveness of IVF in women aged 39 and younger is sensitive to the prediction values generated by the model.

Scenario

Figure 14.9 shows the results of the following sensitivity analysis:

- Duration of sub-fertility 3 years
- Cause: male factor treated with ICSI
- Pregnancy history: no previous pregnancy
- Strategy: eSET
- Hunault deflator: 80% of predicted Hunault value (age ≤ 39 years); 50% of predicted value (age ≥ 40 years)

Figure 14.9 Cost-effective treatment thresholds for sensitivity analysis 2



This analysis suggests that for male factor causes of infertility over 3 years or more, 3 cycles of IVF with eSET can be considered to be cost effective in women aged 38 years and younger at a £30,000 per QALY WTP threshold. For women aged 39 years, the model suggests that 2 cycles of IVF can be considered to be cost effective. This lower number is because the model assumes that a third eSET cycle would commence a year later than the first.

Sensitivity analysis 3

The GDG believed that DET is a more acceptable strategy in older women because it is associated with lower rates of twin birth compared with DET in younger women (see Chapter 15). This sensitivity analysis is the same as for sensitivity analysis 2 but using DET rather than eSET. It assesses the sensitivity of the base case finding that IVF in women aged 40 years and above was not cost effective if a lower expectant management success was assumed.

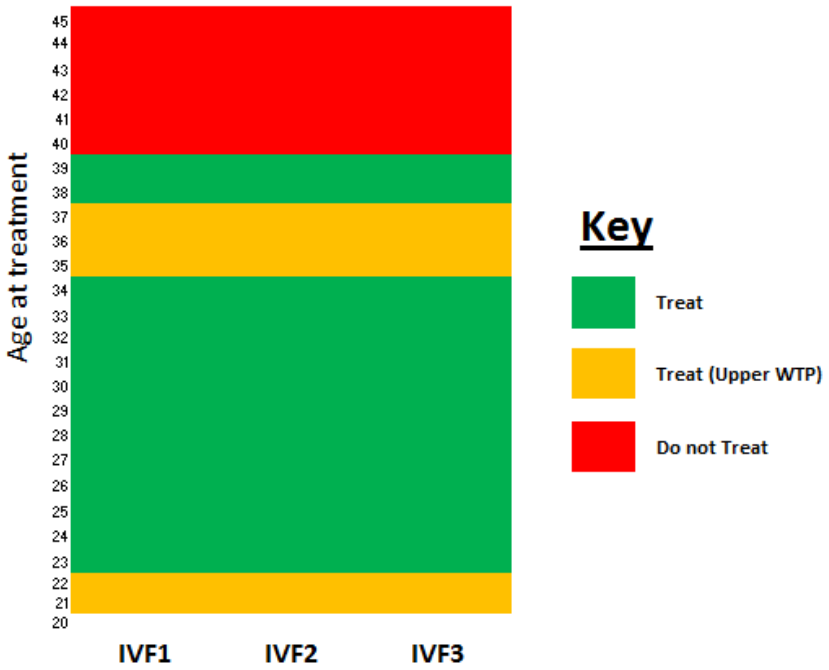
Scenario

Figure 14.10 shows the results of the following sensitivity analysis:

- Duration of sub-fertility: 3 years
- Cause: male factor treated with ICSI

- Pregnancy history: no previous pregnancy
- Strategy: DET
- Hunault deflator: 80% of predicted Hunault value (age ≤ 39 years); 50% of predicted value (age ≥ 40 years)

Figure 14.10 Cost-effective treatment thresholds for sensitivity analysis 3



This analysis suggests that for male factor causes of infertility over 3 years or more, assuming that the probability of live birth with expectant management was half of that predicted by the Hunault model, it would still not be cost effective to offer IVF to women aged 40 years and older. A threshold analysis suggested that the health state utility gain from a live birth would have to be increased to 0.116 before IVF could be considered cost effective in women aged 40–42 years, even with the higher IVF efficacy relative to expectant management assumed in this sensitivity analysis.

Threshold analysis

In the light of the above base case HE modelling and subsequent sensitivity analyses, the HE model suggests IVF is cost effective for women who have absolutely no chance of pregnancy ('absolute infertility') with expectant management and have never previously had IVF. Thus, a recommendation was drafted that women aged 40–42 years should be offered 1 full cycle of IVF if they had 'absolute infertility'; that is, no chance of spontaneous conception.

However, in their responses, stakeholders questioned the use of the term 'absolute infertility', stating that it was clinically impractical and requesting further clarification. Given these responses from stakeholders and the uncertainty of the HE model, a majority of the GDG agreed that the removal of the draft recommendation from the guideline would be reasonable. However, the NICE quality assurance panel highlighted that the stakeholder comments did not support a complete removal of the recommendation but rather were asking for clarification of the phrase 'absolute infertility'. Taking into account the stakeholder comments and quality assurance feedback, NICE convened a meeting of the GDG to further review the wording of the recommendation.

As a precursor to that discussion, NICE asked that a post-consultation theoretical threshold analysis was undertaken using the HE model to determine the probability of spontaneous pregnancy at which IVF became cost effective in women aged 40–42 years. This analysis was not based on any specific clinical scenario, but was instead a theoretical 'what-if' exercise. NICE wanted this analysis in order to

inform the post-consultation GDG discussion on the inclusion or exclusion of the recommendation on provision of IVF to women aged 40–42 years.

Table 14.9 shows the results of that analysis. The results are for a double embryo transfer as this is the only strategy the GDG recommended for women aged 40 years and over (see Chapter 15). As with the main model, all five clinical scenarios/diagnoses with differing durations of infertility are shown for 1, 2 and 3 cycles of IVF.

The figures show rates of conception with expectant management (natural conception) for women aged 40–42 years. The HE model suggests that if the mean conception rate using expected management for a clinical group (unknown infertility, mild endometriosis, severe endometriosis, tubal damage or male factor) is equal to or less than the figure shown in the table, then IVF would be cost effective. For example, women aged 41 years with unknown infertility of 2 years' duration would need an average expected underlying chance of live birth of 5% or less over their remaining reproductive life for up to 3 cycles of IVF to be cost effective. Cells in the table where no threshold rate of natural conception could be identified are marked 'n/a'. Cells marked 'never' indicate that it was never cost effective to offer up to this number of cycles of IVF.

Table 14.9: Theoretical upper threshold of natural conception for it to be cost effective to offer IVF in women aged 40–42 years

Cause	Duration of infertility (years)	One cycle			Two cycles			Three cycles		
		Threshold by age (years)			Threshold by age (years)			Threshold by age (years)		
		40	41	42	40	41	42	40	41	42
Unknown	2–3	5%	5%	5%	n/a	n/a	n/a	4%	5%	5%
	4–6	5%	5%	5%	n/a	n/a	n/a	4%	5%	5%
	7–9	3%	3%	4%	n/a	n/a	n/a	3%	3%	4%
	10–12	3%	3%	3%	n/a	n/a	n/a	2	2%	3%
Mild endometriosis	2–3	4%	4%	4%	n/a	n/a	n/a	3%	4%	4%
	4–6	4%	4%	4%	n/a	n/a	n/a	4%	4%	4%
	7–9	4%	4%	3%	n/a	n/a	n/a	2%	2%	2%
	10–12	3%	5%	3%	n/a	n/a	n/a	1%	1%	1%
Male factor: ICSI	2–3	5%	5%	5%	2%	2%	3%	1%	1%	1%
	4–6	5%	5%	5%	2%	2%	3%	1%	1%	1%
	7–9	4%	4%	4%	1%	1%	Never	Never	Never	Never
	10–12	4%	4%	4%	Never	Never	Never	Never	Never	Never
Tubal	2–3	2%	3%	3%	n/a	2%	n/a	2%	2%	2%
	4–6	3%	3%	3%	n/a	n/a	n/a	2%	2%	2%
	7–9	2%	2%	2%	Never	Never	Never	Never	Never	Never
	10–12	2%	2%	2%	Never	Never	Never	Never	Never	Never
Severe endometriosis	2–3	n/a	n/a	n/a	n/a	n/a	n/a	3%	3%	4%
	4–6	n/a	n/a	n/a	n/a	n/a	n/a	3%	4%	4%
	7–9	3%	3%	n/a	n/a	n/a	n/a	2%	2%	3%
	10–12	2%	2%	2%	1%	n/a	1%	1%	1%	1%

14.5 Conclusions

Base case results

Treatment with up to 3 cycles of IVF is cost effective for women under 39 years. IVF is not cost effective for specific sub-groups in the initial analysis, but becomes cost effective with very small adjustments to the live birth rate.

One or more cycles of IVF is not cost effective for women aged 40 to 42 years with unexplained, male factor or mild endometriosis causes. This result did not change under different assumptions about the benefit of treatment or the probability of spontaneous live birth. The base case analysis suggested that only women for whom IVF could have been cost effective were those with confirmed tubal cause of infertility (no chance of spontaneous conception) although the analysis did not include the cost effectiveness associated with the additional investigations necessary to identify these women.

IVF was not cost effective for women age 43 years or older.

Sensitivity analysis

The model suggests that the cost effectiveness of IVF can be sensitive to the value of health state utility and derived QALY from a live birth. This is important because not only is there considerable uncertainty with respect to what this value is and its temporal aspect, but it is quite likely that IVF is offered on the NHS for reasons other than QALY maximisation.

This analysis model also suggests, at least in women aged 39 years or younger, that cost effectiveness is sensitive to changes in the predicted output in the Hunault model. Only a relatively small reduction in this parameter is needed for 3 cycles of IVF to become cost effective for all women aged 39 years and younger.

In contrast, in women aged 40 years and older the cost effectiveness results are not particularly sensitive to changes in model inputs, with large increases needed in health state utility from live birth and/or heavily deflated expected management probabilities before IVF becomes cost effective in these groups.

Threshold analysis

In women aged 40 to 42 years, threshold analysis using the model suggested that, theoretically, it would be cost effective to provide IVF to any woman with a low probability of spontaneous pregnancy and not just those with ‘no chance of conception with expectant management’.

14.6 Discussion of the model

The health economic model is the first that attempts to incorporate QALYs, cumulative IVF success rates in different clinical settings, single (fresh and frozen) and double embryo transfers and a background chance of spontaneous conception. It therefore represents an advance on current health economic analysis in this area. The model has a number of limitations but it represents a synthesis of the current state of knowledge about the cost effectiveness of IVF using assumptions that the GDG considers reasonable for the NHS. As such it represents the best estimate for decision-makers currently considering the criteria for access to IVF on the NHS. Therefore, the results were used as a guide to inform the GDG’s deliberations rather than lead directly to recommendations. This section provides some further discussion on the strength and weaknesses of the modelling approach that has been adopted for this analysis.

Costs

This chapter lists the costs that have been included in the analysis and provides a rationale for the approach but alternative approaches could be used. So, for example, IVF might be considered as one step in the ‘production’ of a healthy baby. In the event of conception, the NHS would be expected to fund antenatal and delivery costs as well. Such costs have not been included in this analysis on the basis that the NHS is willing to fund these costs for women who conceive naturally, and therefore it can be argued that they are considered cost effective in their own right once conception is achieved.

To what extent 'downstream' costs should or should not be included is not a straightforward matter and arbitrary cut-offs can be made at various time points. IVF leading to live birth will incur costs to the NHS throughout the conceived individual's lifetime and not just during pregnancy and birth. It would not be rational to count these longer term costs without some consideration of the contribution or benefit that individual has to society. For this analysis for IVF, the QALY of the potential life is not considered because at the time of decision there is no QALY loss to a non-existent being if treatment is not offered. However, future 'downstream' costs do have that QALY as an end-point because they are then dealing with decisions affecting an existing life.

Live birth rates

There is considerable uncertainty with respect to cumulative live birth rates under each of the treatment strategies and the derived lifetime QALY that is gained as a result of a live birth. This model suggests, at least in women aged 39 years or younger, that cost effectiveness is sensitive to changes in the predicted output in the Hunault model. Only a relatively small reduction in this parameter was needed for 3 cycles of IVF to become cost effective for all women aged 39 years and younger. Therefore, the GDG concluded that this model does not provide strong evidence that current recommendations for treatment in women aged 39 years and younger should be overturned on cost-effectiveness grounds.

QALYs and the cost effectiveness threshold

There is perhaps an even more fundamental uncertainty in terms of what the decision-maker's actual willingness to pay for a live birth is if goals include objectives other than QALY maximisation. The utility value adopted in the model is an important area of parameter uncertainty in the model. The model suggests that the cost-effectiveness of IVF changes depending on the value of health state utility and derived QALY from a live birth.

Duration of fertility

The model shows that for unexplained infertility, male factor and mild endometriosis, cost effectiveness often increases with increased duration of sub-fertility. This is not because IVF achieves better success with increased duration but rather because duration has an even bigger negative impact on live birth rates from expectant management. Conversely, for tubal and severe endometriosis causes, cost effectiveness tends to decline with increased duration of sub-fertility. In these theoretical scenarios there are no live births with expectant management and declining cost effectiveness reflects diminishing IVF success rates with increased duration.

Primary and secondary fertility

The model also suggests that for unexplained infertility, male factor and mild endometriosis causes, IVF is more cost effective in women with primary sub-fertility, that is, those women never having had a previous pregnancy. Again, this is not because IVF produces more live births in this sub-group but rather because this marker for more severe sub-fertility has an even greater impact on diminishing the probability of live birth from expectant management. In women with secondary infertility the model suggests that it is more cost effective to treat those with a previous birth which is driven by the higher live birth rates predicted for this group in IVFPredict. However, it should be borne in mind that secondary infertility in the Hunault model does not distinguish between pregnancies leading to live birth or not and therefore the apparent difference in the health economic model may be an artefact of the different categorisation in the two prediction models.

Comparison of eSET and DET

Normally in an economic evaluation the cost effectiveness of all treatment alternatives should be compared in an incremental fashion. Although results have been presented for both eSET and DET, they have generally been compared with no treatment/expectant management and not with one another, although the data generated by the model would allow such a comparison. Sometimes, the results implicitly give the incremental analysis because where eSET is not cost effective then the relevant comparator for DET is no treatment/expectant management.

Where the treatment threshold diagrams suggest that both eSET and DET are cost effective strategies relative to no treatment, the analysis presented here does not address which of these strategies is to be preferred in women 39 years and younger. By assumption, cumulative live birth rates are almost identical but treatment costs are greater for eSET because a cycle consists of one

fresh transfer procedure and one frozen procedure compared with a single transfer procedure for DET. Against this treatment cost it is necessary to offset the additional human and financial costs of twin pregnancies with a DET strategy relative to eSET.

However, there has been a recent policy drive to reduce multiple births associated with IVF, such as the 'One at a time' initiative[*]. This is backed by the HFEA, the statutory UK regulator of IVF, which set a 15% target for multiple births for fertility clinics for April 2011[†] with a longer term target of no more than 10% multiple births. In order to achieve these targets there has to be a move to eSET and away from DET, especially in younger women where the embryo quality is high and the multiple pregnancy rates with DET are greater. Therefore, it was felt that in these younger groups a cost effectiveness comparison of eSET relative to DET would yield little in making guideline recommendations given the wider regulatory and policy constraints, although it was still important to assess whether eSET represented a cost-effective use of NHS resources. However, it is reasonable to consider DET in older women because the multiple birth rate from DET is lower and published studies have also suggested that its cost effectiveness relative to eSET improves with increasing age (Scotland et al., 2011).

Accuracy of tests used to identify people eligible for IVF

The HE model did not take into account the accuracy of tests used to identify the cause of infertility. The HE model assumed that diagnosis was correct, but in reality tests will give false-positive and false-negative results. This will mean ineligible patients will receive treatment and these costs have not been included in the HE analysis.

Matching of IVFPredict and Hunault models

The use of separate prediction models for IVF and expectant management meant that outputs had to be matched. Given the different structures of the models this has resulted in systemic differences that are based on how variables are matched rather than actual clinical differences between groups.

Age groupings used in IVFPredict

The age groupings used in the HFEA data underlying the IVFPredict model affects the interpretation of results, as it is unknown how cost effectiveness varies within these age groups. For example, the HFEA data includes a 40–42 years group: therefore, it is unknown how cost effectiveness varies within this group; that is, at 40, 41 or 42 years.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG considered that live full-term singleton birth was the primary outcome measure. When this was not available, live birth and multiple birth rates were used together as a proxy. In addition, the GDG stated that multiple birth rate was itself a proxy for a number of other adverse outcomes, such a prematurity, disability, perinatal mortality and maternal morbidity, all of which were higher with multiple births than with singleton births. Secondary outcomes included clinical pregnancy and OHSS.

Consideration of clinical benefits and harms

No formal evaluation of the clinical benefits was undertaken outside the economic model.

Consideration of health benefits and resource uses

The GDG outlined a number of issues that needed to be considered when interpreting the results of the health economic model and that needed to be investigated using sensitivity analysis (the results of which are presented in full in Appendix N).

Components of the model

Each component of the model was carefully discussed and agreed by the GDG:

- Inclusion of the contribution of spontaneous conception ('expectant management') over the reproductive life in most women who receive IVF was considered to be an important feature that had to be considered in the health economic model.

[*] See http://informahealthcare.com/doi/abs/10.1080/14647270802302629 and http://www.oneatatime.org.uk/
[†] See http://www.hfea.gov.uk/6458.html

- It was reasonable to include an adjustment to IVFPredict which meant that live birth rates of IVF cycles 2 and 3 could not be higher than IVF cycle 1.
- The rates of cancelled cycles with respect to the different stages of IVF had been provided by HFEA and the GDG felt that they were the best available. There was discussion in the GDG about the costs of cancelled cycles. The decision was taken to use a mean of the published refunds from IVF clinics for the pre-harvest cancellation and a published value for post-harvest cancellation as the best costs available.
- The published OHSS rates and costs for mild, moderate and severe forms of the condition were accepted by the GDG as reasonable for use in the HE model.
- The GDG acknowledged that the HE model could not cover every clinical setting but could only cover the most common. Thus, there are occasions where a frozen DET cycle would be available, or where there would be more than one frozen SET, neither of which is covered in the health economic model. However, the GDG felt that the two options used (fresh followed by thawed eSET and DET) would be the most commonly encountered in practice if the clinical recommendations, detailed in Chapter 15, were followed. Similarly, in the health economic model, ICSI is only used for male factor infertility, but in clinical practice this is not the only circumstance where ICSI might be used. For example, this guideline recommends that ICSI can be considered after a previous IVF treatment cycle which resulted in failed or very poor fertilisation. However, in the majority of cases ICSI would only be used for male factor infertility.
- The GDG members were aware that the limitations of the model meant that it could inform their thinking and discussions, but it could not be used directly to determine recommendations.
- The GDG did not feel it was realistic or helpful to make recommendations about each of the 198 clinical scenarios, preferring to use its overall conclusions about broader categories to inform a smaller number of recommendations.

Interpretation of the health economic model

This section describes the discussions that took place within the GDG in relation to making recommendations on access to IVF. Those discussions brought together the results of the health economic model and the wider clinical issues raised by the GDG.

Willingness to pay for a live birth

NICE does not have a defined willingness-to-pay threshold for a live birth. The GDG needed to adopt decision rules when deciding access to IVF treatment. In the absence of any evidence to inform the GDG, the first consultation draft reported two cost-effective thresholds; one for the access to treatment already offered in existing recommendations and a more stringent rule when considering access to IVF by groups not already covered by the existing guideline. This was based on the concept that more certainty should be required to increase access to NHS treatments than when confirming current recommendations.

Access to IVF by age

Lower age limit for IVF

The sensitivity analyses (for example sensitivity analysis 2) suggest that IVF is cost effective in women aged less than 23 years. Furthermore, the younger patient seeking help for fertility would be much more likely to be referred for IVF because of an underlying diagnosis, such as severe endometriosis, tubal damage or severe male factor. Therefore, in practice the cost effectiveness of treating women in this age group will often be better than that indicated by model scenarios where there is a chance of spontaneous conception.

Based on these arguments, the lower age limit for IVF was removed from the updated guideline.

IVF for women aged 23 to 39 years

The base case model suggests that 3 cycles of IVF is considered cost effective in women age 39 years and younger with at least 2 years of infertility, who had no chance of conceiving spontaneously.

Furthermore, sensitivity analysis suggested that funding 3 full cycles of IVF was cost effective in women age 39 years and younger in circumstances where there was a chance of conceiving spontaneously.

The analysis does not provide strong evidence that current recommendations for treatment in women aged 39 years and younger should be changed on cost effectiveness grounds. It supports the existing recommendation of 3 full cycles of IVF for all women eligible for IVF age 39 years and younger and thus the GDG did not feel there was any need to change the recommendation from the 2004 guideline for women in this age category.

IVF for women aged 40 to 42 years

For unexplained infertility, male factor or mild endometriosis causes, the HE model base case and sensitivity analysis suggest it is not cost effective to extend NHS treatment to women aged 40 to 42 years. However, the HE model suggests IVF is cost effective for women who have absolutely no chance of pregnancy ('absolute infertility') with expectant management and have never previously had IVF.

There was extensive debate and division of opinion within the GDG about whether a recommendation for the provision of IVF could be made for this age group.

The arguments against offering IVF were:

- The level of uncertainty within the HE model for this age group meant that it could not be used with any confidence to inform a recommendation.
- 'Absolute infertility' could not be defined by the GDG in terms of diagnostic criteria and therefore any recommendation could not be implemented in clinical practice.
- The overall message that would be sent by such a recommendation is that it is not unreasonable for women to defer pregnancy until they are aged 40 years and older. However, members of the GDG felt strongly this was not what was intended and highlighted that pregnancy at this age is associated with a reduced chance of a live birth and greater risks to both woman and baby.

The arguments in favour of making a recommendation were:

- It was felt that providing access to IVF for women aged 40 to 42 years would reflect the improvement in IVF success rates since the 2004 guideline. All the available data shows that the results of IVF have improved since 2004 and if the former approach of an overall 10% success rate as the threshold for cost effectiveness that was used in the 2004 guideline was applied in the same way in this update, then it could be argued that the recommendation should be to offer 3 cycles of IVF to women aged 40 to 42 years.
- Though it had limitations, the HE model did suggest that it could be considered cost effective to offer up to 3 cycles of IVF to some women aged 40 to 42 years.
- It was highlighted that HFEA data show that 19% of women having IVF are aged 40 years or older. Therefore, the reality was that women in this age group were seeking help and making decisions to have IVF.

In the public consultation version of the guidance, the GDG produced a draft recommendation that women aged 40 to 42 years should be offered 1 full cycle of IVF if they had 'absolute infertility', that is, no chance of spontaneous conception. The decision to offer 1 cycle was based on the interpretation of the HE model and the clinical belief that it would be futile in practice to offer any more than 1 cycle to women in this age group because of reduced ovarian reserve. Furthermore, it was agreed that it should be stipulated that these women should not previously have had IVF as the HE model was based on women not previously having treatment and also to avoid the unintended scenario of a woman having received 3 full cycles of IVF before she was aged 40 years being offered a fourth cycle of IVF after she reached her 40th birthday. However, in their responses stakeholders questioned the use of the term 'absolute infertility', stating it was clinically impractical and requested further clarification.

Given these responses from stakeholders and the uncertainty of the HE model, a majority of the GDG agreed that the removal of the draft recommendation from the guideline would be reasonable. However, the NICE quality assurance panel highlighted that the stakeholder comments did not support a complete removal of the recommendation but rather were asking for clarification of the phrase 'absolute infertility'. Taking into account the stakeholder comments and quality assurance feedback, NICE convened a meeting of the GDG to further review the wording of the recommendation. To facilitate this discussion, the results from the threshold analysis were presented. The threshold analysis (see threshold analysis results in Section 14.4) suggested that, in theory, for each cause of infertility, there was a range of values for the chance of spontaneous conception (from 0% to 5%) below which it would be cost effective to offer IVF. If a woman's chances of spontaneous conception were higher than those values then it would not be cost effective to offer IVF.

The GDG agreed that the results of the threshold analysis needed to be discussed but concluded that translating the results into clinical practice would not be possible. The GDG reasoned that there is no test which determines a woman's percentage chance of spontaneous conception as presented in the threshold analysis. Furthermore, an alternative approach of using clinical diagnoses as surrogates for women with a low percentage chance of spontaneous conception could not be used for two reasons: there was real variation in the degree of infertility associated with a single diagnosis; and there was variation in the classification of such conditions in clinical practice.

The GDG concluded that the limitations of both the HE model and threshold analysis meant neither could be used as a direct source of evidence, and that any recommendation for this age group would have to be based on clinical opinion.

One of the original aims of the HE model was to incorporate ovarian reserve testing as a predictor of success of IVF. However, this had not been possible as suitable evidence was not available. Nevertheless, it was noted that ovarian reserve testing is routinely used in clinical practice to investigate infertility and to determine the likely response to ovarian stimulation (see Chapter 6). Specifically, the GDG noted that these tests were used to determine if ovarian stimulation would be successful, but not the exact percentage probability of pregnancy. It was concluded that ovarian reserve testing could be used as the basis for a recommendation to offer IVF in this age group where falling ovarian reserve was the commonest cause of infertility. This would mean offering IVF to women with a demonstrable chance of success. Conversely, it should not be offered to those women in whom it was believed that IVF would not be successful.

At the end of the meeting the GDG concluded that

- there was a need for a recommendation highlighting the additional risks associated with pregnancy in women aged 40 to 42 years
- the recommendation including the term 'absolute infertility' should be removed
- a new recommendation for women aged 40 to 42 years should be produced based on a consensus of opinion and experience within the GDG rather than the HE analysis.

The final version of the reworded recommendation was agreed by the majority[*] of the GDG.

IVF for women aged 43 years or older

The clinical and health economic evidence was overwhelming in indicating that IVF should not be offered to women aged 43 years or older.

Quality of evidence

The evaluation of predictive models is not provided by the GRADE system. Therefore, separate quality assessment was undertaken based on the NICE criteria for prognostic studies and for systematic reviews. Based on these the evidence was judged to be of moderate to low quality.

A number of assumptions that had to be made in developing the model and the limitations of the source models (Hunault and IVFPredict) were discussed at length and are described above.

In order to address these limitations, sensitivity analysis was undertaken and GDG interpretation applied to the findings.

[*] Eight of the 11 members of the GDG agreed to the reworded recommendation.

Other considerations

The GDG members were able to agree about a number of recommendations that arose from the discussion on access to IVF.

They agreed that once a full cycle of IVF is started it should be completed, assuming there are frozen embryos to use if the fresh cycle was unsuccessful. This means that if the cycle is started when the woman is aged 39 years it can be completed in her 40th year because the egg which was used to produce the frozen embryo would have been collected when the woman was aged 39 years. Furthermore, the marginal cost of this additional frozen embryo transfer is small compared to the overall cost of the full cycle.

Whilst no clinical definition of 'no chance of pregnancy with expectant management and where IVF was the only effective treatment' could be agreed, the GDG did agree that in women younger than 40 years for whom, after investigation, there was a strong probability of 'no chance of pregnancy with expectant management and where IVF was the only effective treatment', for example with apparently occluded fallopian tubes, severe endometriosis or obstructive azoospermia, prompt referral for consideration of IVF should be recommended. In this group, with no or minimal chance of pregnancy through expectant management, it would not be cost effective or clinically rational for women to wait before IVF is offered.

The health economic model affirms the proposal in the original guideline that for most women eligible for IVF, 3 full cycles should be offered in the NHS. The GDG felt that it would be helpful for patients, health professionals and commissioners to make it clear what a full cycle comprised, as there is a variation in interpretation and definition in the NHS. The GDG unanimously agreed that, in most circumstances, a full cycle of IVF treatment should comprise one episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s), and made a recommendation accordingly.

As part of the discussion of this topic, the GDG acknowledged that the chance of success with IVF falls as the number of attempts increases, a fact which contributed to limiting the maximum number of full cycles that were offered to three. Therefore, the GDG felt that when considering a woman for IVF, the previous number of unsuccessful IVF cycles should be taken into account, irrespective of whether they were funded privately or by the NHS. Thus, for example, if a woman had had two previous unsuccessful IVF attempts she should only be entitled to one further attempt in the NHS.

The GDG wanted to highlight that no new fresh cycle would be started in a woman after her 40th birthday, even if this would form one of the three she would be eligible for when she was aged younger than 40 years. Therefore, it was essential that women should seek help for fertility problems as early as possible, especially given that a period of expectant management would often be required before IVF is started.

The GDG felt it was important to define what constituted a cancelled cycle in the context of the provision of IVF within the NHS. Again, there was unanimous agreement that a cancelled IVF cycle should be defined as one where an egg collection procedure is not undertaken. If an egg collection procedure is undertaken, this should count as a full cycle and one of the three that is offered and made a recommendation to this effect. As part of this discussion, however, the GDG acknowledged that although a cycle that was cancelled before egg collection was attempted should not count towards the '3 full cycles' in the NHS provision, clinicians needed to exercise judgement in respect of the response to previous stimulation, specifically when there was no ovarian response, as it did not make sense to continue attempting IVF in these circumstances.

Finally, the GDG agreed that it was essential that people were accurately and fully informed about the potential outcomes of IVF, including the fact that the chances of success with IVF decreased with age while the relative risks of adverse events increased.

ICSI

As suggested within the chapter on ICSI (Chapter 16), the use of ICSI should be restricted to the clinical indications suggested in Recommendation 170. Within this recommendation it suggests that ICSI can be offered to those for whom previous IVF cycles have failed. It should be noted that the evidence within that chapter shows that unless there is an indication for the use of ICSI, IVF is equally effective. Therefore the decision to offer ICSI after IVF failure should involve consideration of the added value that ICSI would have. For example, ICSI could be offered where the previous IVF cycle

demonstrates it may be of value (such as failure of the sperm to bind to the oocyte) or where the fertilisation rate is unexpectedly poor (a common value used is less than a 50% fertilisation rate).

Equalities

The people considered in this review were:

- people who have vaginal intercourse
- specific patient subgroups listed in the guideline Scope who may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychological problem
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
    - people who are preparing for cancer treatment who may wish to preserve their fertility.

A number of equality issues were discussed in relation to this section.

The first issue was age discrimination for accessing IVF. The 2004 guideline made recommendations on access to IVF purely based on a woman's age. For the update, multivariate analysis was used including a woman's age, cause of infertility, duration of infertility, previous obstetric history and previous failed attempts. The GDG was assured that this approach was robust and overcame concerns about recommendations being based purely on age. However, to allow the updated recommendations to be easy to use, they have been centred around age, namely ages 39 years and younger, 40 to 42 years and 43 years and over.

The GDG also discussed access to IVF for people who are preparing for cancer treatment. The GDG recommended the immediate referral for cryopreservation of material, using assisted reproduction treatments if required, for people with cancer, assuming that this does not adversely affect their cancer treatment. However, the GDG stated that the use of cryopreserved material would require assisted reproduction after cancer treatment had been successfully completed and therefore the relevant criteria from the main pathway would apply.

Finally, the GDG discussed what constituted equivalent expectant management for two groups of women (as already shown in Chapters 11 and 12):

- people having unprotected regular vaginal intervourse
- people in same-sex relationships where conception was being attempted by donor insemination (DI).

People having unprotected regular vaginal intercourse

Natural conception rates are shown in Figure 5.1. In summary, over 80% of couples where the women is age 39 years or younger will conceive within 12 months. The figure is over 85% where the woman is less than 35 years. If the couple continue to have unprotected regular intercourse for another 12 months, making 24 months in total, cumulative pregnancy success rates rise by about a further 15%.

The GDG noted that even after 2 years without a live birth, couples with unexplained infertility, mild endometriosis or mild male factor infertility still had a chance of natural conception. However, the additional cumulative success rates in the third year would be very small. Furthermore, they declined with the age of the woman. The GDG felt that this information should be explained early on to women with the diagnosis of unexplained infertility (see Figure 5.1). Thus, the GDG's conclusion was that after 2 years of unexplained infertility (including the 1 year before testing and diagnosis), IVF should be considered. The cost effectiveness of IVF under specific circumstances is considered elsewhere (see Chapter 13) but the GDG consensus view was that women with a diagnosis of unexplained

fertility should be told at the start of their 12 months of expectant management that they will be considered for IVF after a total of 2 years without conception. This provides women with unexplained infertility with a clear idea of the period of time they should continue with regular unprotected vaginal intercourse before IVF will be considered (although it will not necessarily be offered). The GDG view was that this would represent a positive approach and lessen the psychological consequences identified in the expectant management group in the trial reported here.

People in same-sex relationships where conception was being attempted by DI

Once, after assessment and investigation, the diagnosis of unexplained infertility, mild endometriosis or mild male factor infertility was made, the GDG felt that further attempts at conception should be made using IUI and donor sperm for a period of time. The GDG highlighted the cumulative success rates with ICI and IUI. Specifically, as reported in Chapter 5, the GDG noted that, after 6 cycles of DI the cumulative chances of successful conception from ICI or IUI in women who are 35 years or less were:

- over 40% for ICI using thawed semen (Federation CECOS et al., 1982)
- over 50% for ICI using fresh semen (van Noord-Zaadstra et al., 1991)
- over 60% for IUI using mainly thawed semen (HFEA data)

After a further 6 months (12 months in total) these figures rose to:

- over 60% for ICI using thawed semen (Federation CECOS et al., 1982)
- over 70% for ICI using fresh semen (van Noord-Zaadstra et al., 1991)
- over 80% for IUI using mainly thawed semen (HFEA data)

These additional cycles of IUI with donor sperm would be the same as expectant management in couples with unexplained infertility, mild endometriosis or mild male factor infertility having vaginal intercourse. The GDG discussed options for the number of cycles of IUI that should constitute an acceptable period of expectant management. The same issues were raised in this discussion as were covered in the discussion about determining when to refer people for assessment and possible treatment of their infertility (see Chapter 5). The GDG felt that the practical barriers (availability of sperm, human and financial cost and time) to undertaking IUI with donor sperm meant, in reality, that same-sex couples with unexplained infertility could not be expected to undergo 12 cycles of IUI in order to achieve numerical equivalence with people having vaginal intercourse with the same diagnosis having 12 months of expectant management.

In conclusion, if as a result of infertility assessment the diagnosis is made of unexplained infertility, mild endometriosis or mild male factor infertility, the GDG was of the opinion that the women in same-sex relationships should be advised to have a further 6 cycles of IUI with donor sperm (making a total of 12 cycles of DI in total) and that would constitute 'expectant management' for that group.

Recommendations

Number	Recommendation
127	When considering IVF as a treatment option for people with fertility problems, discuss the risks and benefits of IVF in accordance with the current Human Fertilisation and Embryology Authority (HFEA) code of practice. **[new 2013]**
128	Inform people that normally a full cycle of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), should comprise 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s). **[new 2013]**
129	In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles. **[new 2013]**

130 In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:

- they have never previously had IVF treatment
- there is no evidence of low ovarian reserve (see recommendation 50)
- there has been a discussion of the additional implications of IVF and pregnancy at this age. **[new 2013]**

131 Where investigations show there is no chance of pregnancy with expectant management and where IVF is the only effective treatment, refer the woman directly to a specialist team for IVF treatment. **[new 2013]**

132 In women aged under 40 years any previous full IVF cycle, whether self- or NHS-funded, should count towards the total of 3 full cycles that should be offered by the NHS. **[new 2013]**

133 Take into account the outcome of previous IVF treatment when assessing the likely effectiveness and safety of any further IVF treatment. **[new 2013]**

134 Healthcare providers should define a cancelled IVF cycle as one where an egg collection procedure is not undertaken. However, cancelled cycles due to low ovarian reserve should be taken into account when considering suitability for further IVF treatment. **[new 2013]**

2013 Update

15 Procedures used during in vitro fertilisation treatment

15.1 Introduction

In vitro fertilisation (IVF) involves the fertilisation of eggs with sperm outside the body. In general, it is used after other treatments have failed. Indications for its use include:

- Unsuccessful conception following:
    - a period of expectant management in people with unexplained infertility (see Chapter 11)
    - ovulation induction therapy (see Chapter 8)
    - treatment for an identified cause of male factor infertility (often in combination with intracytoplasmic sperm injection [ICSI]; see Chapters 7 and 15)
    - treatment for endometriosis (see Chapter 9)
    - IUI using partner or donor sperm (see Chapters 12 and 16)
    - treatment for tubal disease (see Chapter 10).
- Severe tubal disease.
- Severe male factor infertility (IVF with ICSI may be the preferred option; see Chapter 16).
- Failure of spermatogenesis following cancer treatment where cryopreserved semen has been unsuccessful at achieving conception with IUI.
- Ovarian failure caused by cancer treatment where eggs or embryos have been cryopreserved.
- Where oocyte donation is being used (see Chapter 18).

An IVF treatment cycle can comprise the following seven sequential stages. However, depending on the exact protocol being used, not all the stages are used:

- Pre-treatment (see Section 15.2). This is believed to have three potential functions:
    - improving the response to exogenous hormone therapy
    - minimising the risk of ovarian cyst formation, and
    - facilitating the scheduling of stimulated IVF cycles to ensure that the timing of oocyte recovery coincides with availability of clinical and laboratory staff.
- Down-regulation (see Section 15.3). This temporarily stops the pituitary gland from functioning which reduces the risk of a cycle being cancelled from early exposure to luteinising hormone (LH) which could disrupt normal follicle and oocyte development or stimulate premature release of the eggs before they can be retrieved surgically (‘harvested’) prior to insemination in the laboratory.

- Controlled ovarian stimulation (see Section 15.4). The aim of this stage is to produce a number of mature eggs which can be retrieved surgically prior to fertilisation in the laboratory.
- Ovulation trigger (see Section 15.5). At the end of the stimulation phase of an IVF cycle, a drug ('ovulation trigger') is used to mimic the natural endogenous LH surge which initiates the process of ovulation. The mature eggs are collected from the woman ('harvested') and fertilised with sperm in a laboratory.
- Oocyte and sperm retrieval (see Section 15.6). After triggering, mature oocytes are aspirated from the woman's ovaries for fertilisation in the laboratory. In addition, in some cases of male factor infertility the sperm has to be obtained directly from the testes (see also Chapter 7).
- Embryo replacement (see Section 15.7). Once the eggs have been fertilised, one or two of the resultant embryos are then placed back into the woman's uterus 2–3 days later, at the cleavage phase of embryo development. Longer laboratory culture times can be used with good quality eggs with intra-uterine replacement occurring after 5–6 days, at the blastocyst phase of development.
- Luteal phase support (see Section 15.8). After embryo replacement, drugs may be given to help support the early phase of pregnancy development. This is intended to mimic what happens in natural conception, where, once ovulation has occurred, the endometrium prepares to receive a fertilised embryo. This consists of a series of changes within it which are driven by progesterone produced by the corpus luteum in the ovary.

An IVF cycle may be stopped ('cancelled') at various points within the treatment process. A cycle will most often be cancelled either because the treatment presents a risk to the women (for example ovarian hyperstimulation syndrome [OHSS]) or because the woman has not responded to part of the treatment (for example ovarian stimulation), and this most frequently occurs during ovarian stimulation; that is, before oocyte retrieval. However, in some circumstance oocytes may be collected and frozen for later transfer. This may be construed as interruption of the fresh IVF cycle rather than cancellation as the intention is to transfer embryos at a later date.

In addition, there are two further variations of IVF which were developed in parallel using much of the same technology. However, they are no longer widely used:

- Gamete intrafallopian transfer (GIFT; see Section 15.9). In this procedure eggs, once collected, are transferred laparoscopically to the fallopian tube with prepared motile sperm to allow fertilisation to occur in vivo.
- Zygote intrafallopian transfer (ZIFT; see Section 15.9). In this procedure embryos, produced after fertilisation in vitro, are transferred laparoscopically to the fallopian tube.

This chapter reviews the evidence regarding the most effective treatment within each of these components of IVF.

15.2 Pre-treatment for IVF

Introduction

The success of IVF cycles depends on the ability to collect an adequate number of mature eggs. This involves a number of separate steps to stimulate the ovaries while making sure that the chances of spontaneous ovulation are minimised. Stimulation is usually undertaken using a gonadotrophin-releasing hormone (GnRH) agonist or antagonist along with gonadotrophin injections. An ovulation trigger is used to ensure that ooctye retrieval can be undertaken at a predictable time (see Section 15.5).

Sometimes pre-treatment with either a combined oral contraceptive pill, progestogen or ooestrogen is used before ovarian downregulation or stimulation. This is believed to improve the response to

exogenous hormone therapy, minimise the risk of ovarian cyst formation and facilitate scheduling of stimulation cycles to ensure that the timing of oocyte recovery coincides with availability of clinical and laboratory staff.

The evidence for the efficacy of this approach as part of IVF is reviewed in this section.

Review question

What is the effectiveness of pre-treatment as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?

Evidence profile

The guideline development group (GDG) agreed it was important to determine whether IVF protocols (with or without ICSI) that included pre-treatment with a combined oral contraceptive pill, progesterone or oestrogen are more effective than IVF without pre-treatment. They also wanted to establish whether there was a difference in the effectiveness of different types of pre-treatment.

The evidence is therefore presented in three profiles for this review:

- Pre-treatment compared with no pre-treatment in women receiving IVF treatment for the first time (Table 15.1).
- Pre-treatment compared with no pre-treatment in women with a previous low response to IVF treatment (Table 15.2).
- Comparison of different types of pre-treatment (Table 15.3).

Description of included studies

Pre-treatment compared with no pre-treatment (see Tables 15.1 and 15.2)

One Cochrane review (Smulders et al., 2010) and one randomised controlled trial (RCT) published subsequent to the review (Nyboe Andersen et al., 2011) compared women who received pre-treatment with women who did not receive pre-treatment as part of their IVF treatment. The Cochrane review (Smulders et al., 2010) included women who were receiving IVF treatment both for the first time and those with a previous low response to IVF treatment. Most of the comparisons in the Cochrane review included only one study and, as a result, there were small numbers of women in the review.

Comparison of different types of pre-treatment (Table 15.3)

One Cochrane review (Smulders et al., 2010) compared the effectiveness of different types of pre-treatment, namely the oral contraceptive pill, progesterone or oestrogen. Most of the comparisons included only one study and, as a result, small numbers of women.

Table 15.1 GRADE findings for pre-treatment compared with no pre-treatment in women receiving IVF treatment for the first time

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)					
1 (Smulders et al., 2010)	3/21 (14%) women	7/24 (29%) women	Peto OR 0.4 (0.1 to 1.7)	141 fewer per 1000 (from 248 fewer to 126 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone (agonist) vs. placebo or no treatment (agonist)					
1 (Smulders et al., 2010)	24/110 (22%) women	19/112 (17%) women	Peto OR 1.4 (0.7 to 2.6)	47 more per 1000 (from 46 fewer to 179 more)	Very low
Progesterone (antagonist) vs. placebo or no treatment (antagonist)					
1 (Smulders et al., 2010)	5/23 (22%) women	7/24 (29%) women	Peto OR 0.7 (0.2 to 2.5)	73 fewer per 1000 (from 219 fewer to 216 more)	Very low
Oestrogen (antagonist) vs. no treatment (antagonist)					
1 (Smulders et al., 2010)	3/25 (12%) women	7/24 (29%) women	Peto OR 0.4 (0.1 to 1.4)	163 fewer per 1000 (from 256 fewer to 76 more)	Very low
Clinical pregnancy					
Combined oral contraceptive (agonist protocol) vs. no pre-treatment (agonist protocol)					
1 (Smulders et al., 2010)	19/51 (37%) women	17/51 (33%) women	Peto OR 1.2 (0.5 to 2.7)	40 more per 1000 (from 124 fewer to 237 more)	Very low
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)					
2 (Nyboe Andersen et al., 2011 and Smulders et al., 2010)	142/629 (23%) women	195/626 (31%) women	RR 0.7 (0.6 to 0.9)	87 fewer per 1000 (from 40 fewer to 125 fewer)	Very low
Progesterone (agonist) vs. placebo or no treatment (agonist)					
1 (Smulders et al., 2010)	53/187 (28%) women	31/187 (17%) women	Peto OR 2.0 (1.2 to 3.2)	114 more per 1000 (from 27 more to 221 more)	Moderate
Progesterone (antagonist) vs. placebo or no treatment (antagonist)					
1 (Smulders et al., 2010)	7/23 (30%) women	11/24 (46%) women	Peto OR 0.5 (0.2 to 1.7)	149 fewer per 1000 (from 333 fewer to 130 more)	Low
Progesterone (no down-regulation) vs. placebo or no treatment (no down-regulation)					
1 (Smulders et al., 2010)	3/21 (14%) women	4/21 (19%) women	Peto OR 0.7 (0.1 to 3.6)	46 fewer per 1000 (from 159 fewer to 265 more)	Low

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Oestrogen (antagonist) vs. no treatment (antagonist)					
1 (Smulders et al., 2010)	20/72 (28%) women	22/67 (33%) women	Peto OR 0.8 (0.4 to 1.6)	50 fewer per 1000 (from 172 fewer to 114 more)	Very low
Adverse pregnancy outcome					
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol) (miscarriages and/or stillbirths)					
1 (Smulders et al., 2010)	35/420 (8%) women	29/427 (7%) women	Peto OR 1.3 (0.8 to 2.1)	16 more per 1000 (from 15 fewer to 66 more)	Very low
	Not reported per clinical pregnancy				
Progesterone (agonist) vs. placebo or no treatment (agonist) (miscarriages and/or stillbirths)					
1 (Smulders et al., 2010)	9/110 (8%) women	4/112 (4%) women	Peto OR 2.2 (0.7 to 6.7)	39 more per 1000 (from 10 fewer to 163 more)	Low
	Not reported per clinical pregnancy				
Progesterone (antagonist) vs. placebo or no treatment (antagonist) (miscarriages and/or stillbirths)					
1 (Smulders et al., 2010)	2/23 (9%) women	5/24 (21%) women	Peto OR 0.4 (0.1 to 1.9)	115 fewer per 1000 (from 188 fewer to 127 more)	Low
	2/7 (29%) pregnancies	5/11 (46%) pregnancies	Peto OR 0.5 (0.1 to 3.4)	156 fewer per 1000 (from 392 fewer to 283 more)	
Progesterone (no down-regulation) vs. placebo or no treatment (no down-regulation) (miscarriages and/or stillbirths)					
1 (Smulders et al., 2010)	1/21 (5%) women	1/21 (5%) women	Peto OR 1.0 (0.1 to 16.6)	0 fewer per 1000 (from 45 fewer to 405 more)	Low
	1/3 (33%) pregnancies	1/4 (25%) pregnancies	Peto OR 1.4 (0.1 to 30.5)	71 more per 1000 (from 227 fewer to 660 more)	

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Oestrogen (antagonist) vs. no treatment (antagonist) (miscarriages and/or stillbirths)					
1 (Smulders et al., 2010)	1/25 (4%) women	5/24 (21%) women	Peto OR 0.2 (0.0 to 1.2)	154 fewer per 1000 (from 198 fewer to 27 more)	Low
	Not reported per clinical pregnancy				
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)					
1 (Smulders et al., 2010)	2/21 (10%) women	1/24 (4%) women	Peto OR 2.3 (0.2 to 23.7)	50 more per 1000 (from 32 fewer to 465 more)	Low
	Not reported per clinical pregnancy				
Progesterone (antagonist) vs. placebo or no treatment (antagonist)					
1 (Smulders et al., 2010)	1/23 (4%) women	1/24 (4%) women	Peto OR 1.0 (0.1 to 17.2)	2 more per 1000 (from 39 fewer to 387 more)	Low
	1/7 (14%) pregnancies	1/11 (9%) pregnancies	Peto OR 1.6 (0.1 to 30.8)	50 more per 1000 (from 82 fewer to 664 more)	
Oestrogen (antagonist) vs. no treatment (antagonist)					
1 (Smulders et al., 2010)	0/25 (0%) women	1/24 (4%) women	Peto OR 0.1 (0.0 to 6.6)	36 fewer per 1000 (from 42 fewer to 180 more)	Low
	0/4 (0%) pregnancies	1/11 (9%) pregnancies	Peto OR 0.3 (0 to 21.5)	Not calculable	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence was reported					
Ovarian hyperstimulation syndrome (OHSS)					
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)					
1 (Smulders et al., 2010)	3/117 (3%) women	2/117 (2%) women	Peto OR 1.5 (0.3 to 8.8)	8 more per 1000 (from 13 fewer to 116 more)	Low
Oestrogen (antagonist protocol) vs. no pre-treatment (antagonist protocol)					
1 (Smulders et al., 2010)	0/16 (0%) women	0/6 (0%) women	Not calculable		Moderate
Congenital abnormalities					
No evidence reported					

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, IVF in vitro fertilisation, OHSS ovarian hyperstimulation syndrome, OR odds ratio

Table 15.2 GRADE findings for pre-treatment compared with no pre-treatment in women with a previous low response to IVF treatment

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)					
1 (Smulders et al., 2010)	8/27 (30%) women	5/27 (19%) women	Peto OR 1.8 (0.5 to 6.3)	107 more per 1000 (from 78 fewer to 402 more)	Very low
Clinical pregnancy					
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)					
1 (Smulders et al., 2010)	9/27 (33%) women	6/27 (22%) women	Peto OR 1.7 (0.5 to 5.6)	107 more per 1000 (from 91 fewer to 393 more)	Very low
Adverse pregnancy outcome					
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol) (miscarriages and/or stillbirths)					
1 (Smulders et al., 2010)	1/27 (4%) women	1/27 (4%) women	Peto OR 1.0 (0.1 to 16.4)	0 fewer per 1000 (from 35 fewer to 350 more)	Low
	1/9 (11%) pregnancies	1/6 (17%) pregnancies	Peto OR 0.6 (0.0 to 12.0)	53 fewer per 1000 (from 161 fewer to 540 more)	

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Combined oral contraceptive (antagonist protocol) vs. no pre-treatment (antagonist protocol)					
1 (Smulders et al., 2010)	2/27 (7%) women	1/27 (4%) women	Peto OR 2.0 (0.2 to 20.1)	34 more per 1000 (from 29 fewer to 399 more)	
	2/9 (22%) pregnancies	1/6 (17%) pregnancies	Peto OR 1.4 (0.1 to 16.8)	50 more per 1000 (from 145 fewer to 604 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
No evidence reported					
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, IVF in vitro fertilisation, OHSS ovarian hyperstimulation syndrome, OR odds ratio

Table 15.3 GRADE findings for comparison of different types of pre-treatment

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Combined oral contraceptive (antagonist) vs. progesterone (antagonist) (first treatment)					
1 (Smulders et al., 2010)	3/21 (14%) women	5/23 (22%) women	Peto OR 0.6 (0.1 to 2.8)	72 fewer per 1000 (from 183 fewer to 219 more)	Very low

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Combined oral contraceptive (antagonist) vs. oestrogen (antagonist) (first treatment)					
1 (Smulders et al., 2010)	3/21 (14%) women	3/25 (12%) women	Peto OR 1.2 (0.2 to 6.7)	23 more per 1000 (from 91 fewer to 357 more)	Very low
Progestogen (antagonist) vs. oestrogen (antagonist) (first treatment)					
1 (Smulders et al., 2010)	5/23 (22%) women	3/25 (12%) women	Peto OR 2.0 (0.4 to 8.9)	93 more per 1000 (from 63 fewer to 429 more)	Very low
Clinical pregnancy					
Combined oral contraceptive (antagonist) vs. progesterone (antagonist) (first treatment)					
1 (Smulders et al., 2010)	5/21 (24%) women	7/23 (30%) women	Peto OR 0.7 (0.2 to 2.7)	65 fewer per 1000 (from 228 fewer to 235 more)	Low
Combined oral contraceptive (antagonist) vs. oestrogen (antagonist) (first treatment)					
1 (Smulders et al., 2010)	5/21 (24%) women	4/25 (16%) women	Peto OR 1.6 (0.4 to 6.9)	76 more per 1000 (from 93 fewer to 408 more)	Low
Progestogen (antagonist) vs. oestrogen (antagonist) (first treatment)					
1 (Smulders et al., 2010)	7/23 (30%) women	4/25 (16%) women	Peto OR 2.2 (0.6 to 8.4)	138 more per 1000 (from 59 fewer to 457 more)	Low
Adverse pregnancy outcome					
Combined oral contraceptive (antagonist) vs. progesterone (antagonist) (miscarriages and/or stillbirths) (first treatment)					
1 (Smulders et al., 2010)	2/21 (10%) women	2/23 (9%) women	Peto OR 1.1 (0.1 to 8.4)	8 more per 1000 (from 74 fewer to 358 more)	Low
	2/5 (40%) pregnancies	2/7 (29%) pregnancies	Peto OR 1.6 (0.2 to 16.5)	105 more per 1000 (from 226 fewer to 583 more)	

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Combined oral contraceptive (antagonist) vs. oestrogen (antagonist) (miscarriages and/or stillbirths) (first treatment)					
1 (Smulders et al., 2010)	2/21 (10%) women	1/25 (4%) women	Peto OR 2.4 (0.2 to 24.8)	52 more per 1000 (from 30 fewer to 468 more)	Low
	2/5 (40%) pregnancies	1/4 (25%) pregnancies	Peto OR 1.8 (0.1 to 25.3)	128 more per 1000 (from 208 fewer to 644 more)	
Progestogen (antagonist) vs. oestrogen (antagonist) (miscarriages and/or stillbirths) (first treatment)					
1 (Smulders et al., 2010)	2/23 (9%) women	1/25 (4%) women	Peto OR 2.2 (0.2 to 22.2)	44 more per 1000 (from 31 fewer to 440 more)	Low
	2/7 (29%) pregnancies	1/4 (25%) pregnancies	Peto OR 1.2 (0.1 to 16.3)	32 more per 1000 (from 224 fewer to 595 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Combined oral contraceptive (antagonist) vs. progesterone (antagonist) (first treatment)					
1 (Smulders et al., 2010)	2/21 (10%) women	1/23 (4%) women	Peto OR 2.2 (0.2 to 22.6)	48 more per 1000 (from 34 fewer to 463 more)	Low
	2/5 (40%) pregnancies	1/7 (14%) pregnancies	Peto OR 3.5 (0.3 to 44.5)	227 more per 1000 (from 98 fewer to 738 more)	
Combined oral contraceptive (antagonist) vs. oestrogen (antagonist) (first treatment)					
1 (Smulders et al., 2010)	2/21 (10%) women	0/25 (0%) women	Peto OR 9.4 (0.6 to 156.7)	Not calculable	Low
	2/5 (40%) pregnancies	0/4 (0%) pregnancies	Peto OR 7.8 (0.4 to 154.3)	Not calculable	
Progestogen (antagonist) vs. oestrogen (antagonist) (first treatment)					
1 (Smulders et al., 2010)	1/23 (4%) women	0/25 (0%) women	Peto OR 8.1 (0.2 to 407.6)	Not calculable	Low
	1/7 (14%) pregnancies	0/4 (0%) pregnancies	Peto OR 4.8 (0.1 to 283)	Not calculable	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence was reported					

2013 Update

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Ovarian hyperstimulation syndrome (OHSS)					
No evidence was reported					
Congenital abnormalities					
No evidence was reported					
Patient satisfaction					
No evidence was reported					
Health related quality of life					
No evidence was reported					
Anxiety and/or depression					
No evidence was reported					

CI confidence interval, OHSS ovarian hyperstimulation syndrome, OR odds ratio

Evidence statements

Pre-treatment compared with no pre-treatment in women receiving IVF treatment for the first time

Live full-term singleton birth

There were no significant differences in the number of live full-term singleton births in women who received pre-treatment and those who did not receive pre-treatment, regardless of the pre-treatment or IVF protocol used.

Clinical pregnancy

In an agonist protocol (see Section 15.3), there were significantly more clinical pregnancies when progesterone was used for pre-treatment compared with no pre-treatment. In an antagonist protocol, there were significantly fewer clinical pregnancies when the combined oral contraceptive pill was used for pre-treatment, compared with no pre-treatment.

There were no significant differences in the number of clinical pregnancies in other pre-treatment protocols.

Adverse pregnancy outcome

There were no significant differences in the number of adverse pregnancy outcomes when comparing pre-treatment with no pre-treatment.

Multiple pregnancies

There were no significant differences in the number of multiple pregnancies when comparing pre-treatment with no pre-treatment.

Multiple births

There was no multiple birth data reported.

Ovarian hyperstimulation syndrome (OHSS)

There were no significant differences in the number of cases of OHSS when comparing pre-treatment with no pre-treatment.

Congenital abnormalities

There was no evidence reported for congenital abnormalities.

Patient satisfaction

There was no evidence reported regarding patient satisfaction.

Health related quality of life

There was no evidence reported regarding health related quality of life.

Anxiety and/or depression

There was no evidence reported for anxiety and/or depression.

Pre-treatment compared with no pre-treatment in women with a previous low response to IVF treatment

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births in low response women who received pre-treatment and those who did not receive pre-treatment as part of an antagonist protocol.

Clinical pregnancy

There was no significant difference in the number of clinical pregnancies when comparing the use of pre-treatment and no pre-treatment as part of an antagonist protocol in low response women.

Adverse pregnancy outcome

There was no significant difference in the number of adverse pregnancy outcomes when comparing pre-treatment with no pre-treatment as part of an antagonist protocol in low response women.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing pre-treatment with no pre-treatment as part of an antagonist protocol in low response women.

Multiple births

There was no multiple birth data reported.

OHSS

There were no significant differences in the number of cases of OHSS when comparing pre-treatment with no pre-treatment.

Congenital abnormalities

There was no evidence reported for congenital abnormalities.

Patient satisfaction

There was no evidence reported regarding patient satisfaction.

Health related quality of life

There was no evidence reported regarding health related quality of life.

Anxiety and/or depression

There was no evidence reported for anxiety and/or depression.

Comparison of different types of pre-treatment

Live full-term singleton birth

There were no significant differences in the number of live full-term singleton births when comparing different types of pre-treatment.

Clinical pregnancy

There were no significant differences in the number of clinical pregnancies when comparing different types of pre-treatment.

Adverse pregnancy outcome

There were no significant differences in the number of adverse pregnancy outcomes when comparing different types of pre-treatment.

Multiple pregnancies

There were no significant differences in the number of multiple pregnancies when comparing different types of pre-treatment.

Multiple births

There was no multiple birth data reported.

OHSS

There was no evidence reported for OHSS.

Congenital abnormalities

There was no evidence reported for congenital abnormalities.

Patient satisfaction

There was no evidence reported regarding patient satisfaction.

Health related quality of life

There was no evidence reported regarding health related quality of life.

Anxiety and/or depression

There was no evidence reported for anxiety and/or depression.

Health economics profile

This question was not identified for formal health economic evaluation. However, as discussed below, it was acknowledged that although the use of pre-treatment was associated with an increased cost, that cost was relatively small because of the low costs of the drugs involved. Furthermore, the use of pre-treatment to allow more predictable scheduling of the other components of IVF treatment might potentially offset any increased costs by avoiding the requirement to provide a 24 hour service 7 days per week.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG emphasised that pre-treatment is most commonly used to artificially control when menstruation will start, and therefore more accurately determine when IVF treatment can commence.

Although clinical pregnancies and live full-term singleton births are important outcomes relating to the use of any treatment during IVF, pre-treatment is used principally to more accurately schedule the start of the IVF procedure, rather than to increase clinical pregnancy and live full-term singleton birth rates.

The other outcomes in this review related to adverse effects of the treatments and are important to consider in order to fully inform couples of potential risks of treatment.

Consideration of clinical benefits and harms

The GDG view was that it was not possible to determine any clinical benefits or harms of pre-treatment using the available evidence.

Consideration of health benefits and resource uses

The actual cost of pre-treatment when compared solely against no treatment, and where there is no clear evidence of clinical benefit or harm, was considered by the GDG and was deemed significant. However, pre-treatment can be used to schedule IVF treatment so that the day of ovulation induction, oocyte retrieval and embryo transfer can be planned. This allows clinics to plan their work schedule to ensure that women receive the best care available. Scheduling treatment also enables clinics to save some of the costs that would be incurred from providing a service 7 days a week. The GDG felt the trade-off between these two costs was more in favour for the use of pre-treatment. The relative low cost of the pre-treatment drugs represented a saving compared with the significantly larger cost of running a service 7 days a week. Scheduling would also provide an added level of convenience.

The GDG acknowledged that is it biologically plausible that the use of the oral contraceptive pill for pre-treatment may reduce the risk of ovarian cyst formation, although this was not an outcome included in the current review. Such functional cyst formation can lead to cycle cancellation, and so reducing the risk of formation will most likely result in more completed cycles of IVF.

Quality of evidence

One systematic review and one randomised controlled trial were identified and the results reported from it were graded as very low quality due to the quality of the included studies. The GDG highlighted that the studies appeared to be underpowered for the outcomes they were investigating, and as a result the small sample size and low event rate meant that confidence intervals around estimates are extremely wide. This prevented the GDG from drafting recommendations based on the reported outcomes.

Other considerations

Further issues about IVF -scheduling

The GDG highlighted that pre-treatment is used to help control the woman's menstrual cycle to allow accurate scheduling of when IVF will begin. This is convenient for women and clinicians as they can ensure women receive scheduled care by planning their IVF treatment.

Pre-treatment is most often used to schedule GnRH antagonist cycles, although it can be used in long GnRH agonist protocols as well. Using pre-treatment as part of a GnRH antagonist cycle is more convenient for women as it negates the need for the lengthy down-regulation (or other regimens to avoid premature luteinising hormone surges) period that is required before GnRH agonist treatment. Omitting the long down-regulation period will reduce the time needed for each IVF cycle, and therefore reduce the number of women who relocate to other areas of the country during their treatment. This is an important consideration as this relocation can cause logistical and resource issues for women and their clinicians.

Equalities

The people considered in this review were

- People who have vaginal sexual intercourse.
- Specific patient subgroups listed in the guideline Scope that may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychological problem
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
- People who are preparing for cancer treatment who may wish to preserve their fertility.

There were no other specific issues that needed to be addressed with respect to any of these subgroups in the context of pre-treatment.

Key conclusions

The GDG stated that the main reason for using pre-treatment is the scheduling of IVF treatment, and that this is beneficial to women and their clinicians. The available evidence did not allow conclusions on clinical benefits or harms to be made.

Recommendations

Number	Recommendation
135	Advise women that using pre-treatment (with either the oral contraceptive pill or a progestogen) as part of IVF does not affect the chances of having a live birth. **[new 2013]**
136	Consider pre-treatment in order to schedule IVF treatment for women who are not undergoing long down-regulation protocols. **[new 2013]**

Number	Research recommendation
RR 27	What is the cost effectiveness of pre-treatment when used to schedule IVF treatment?

15.3 Down-regulation or other regimens to avoid premature luteinising hormone surges

Introduction

IVF treatment involves stimulating the ovaries with gonadotrophins with a view to producing a number of eggs which can be harvested when they are mature prior to insemination in the laboratory. It is important during the stimulation phase to avoid early exposure to luteinising hormone (LH), which could disrupt normal follicle and oocyte development or prompt release of the eggs before they can be retrieved surgically. Gonadotrophin-releasing hormone agonists (GnRHa) have been used as part of ovarian stimulation in IVF to block pituitary function temporarily, thus avoiding a premature LH surge which can lead to cycle cancellation. The use of GnRHa leads to an initial stimulatory phase, the 'flare-up' effect, followed by reversible inhibition of pituitary function. The resulting diminution in LH levels facilitates the development of a number of ovarian follicles and delays ovulation until circumstances are suitable for a planned egg collection procedure.

In more recent years GnRH antagonists have been used. These involve a shorter duration of use compared with the agonist long protocol and are started a few days after initiation of stimulation, continuing until administration of a drug to trigger ovulation.

GnRH agonists have been used in a number of different protocols. The most common is the 'long protocol' where the GnRH agonist is started at least 2 weeks before stimulation and continued until the ovulation trigger is given. Alternatively, a 'short protocol' is one where the GnRH agonist is started simultaneously with stimulation and continued until the day of the ovulation trigger. An 'ultra-short protocol' is one where stimulation commences 1 or 2 days after starting GnRH agonist, which itself is administered for 3 days. A stop protocol is one where a GnRH agonist is started 2 weeks prior to the start of ovarian stimulation but is stopped as soon as gonadotrophin treatment begins.

Review question

What is the effectiveness of down-regulation as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?

Evidence profile

The GDG believed there were three important aspects to this review question. The first was whether down-regulated cycles were more effective than non down-regulated cycles when used as part of an IVF or ICSI protocol. The second was whether antagonists or agonists provide the most effective form of down-regulation. The third was which agonist protocol was the most effective; that is, long, short, ultra-short or stop protocols.

Therefore, three profiles are presented:

- down-regulated compared with non down-regulated cycles (with or without clomifene citrate) (Table 15.4)
- antagonist down-regulated compared with agonist down-regulated protocols (Table 15.5)
- a comparison of different types of down-regulation protocol (including long, short, ultra-short and stop protocols) (Table 15.6).

Description of included studies

Down-regulated compared with non down-regulated cycles (with or without clomifene citrate) (Table 15.4)

Ten randomised controlled trials (RCTs) were included in this review (Antoine et al., 1990; Dhont et al., 1995; Grochowski et al., 1999; Harrison et al., 1994; van de Helder et al., 1990; Hojgaard et al., 2001; Long et al., 1995; Neveu et al., 1987; Polson et al., 1991; Weigert et al., 2002). Four studies compared down-regulated cycles with cycles that were not down-regulated and were stimulated with gonadotrophins only (Antoine et al., 1990; van de Helder et al., 1990; Neveu et al., 1987; Polson et al., 1991). Five studies compared down-regulated cycles with non down-regulated cycles in a protocol including clomifene citrate and gonadotrophins (Dhont et al., 1995; Grochowski et al., 1999; Harrison et al., 1994; Long et al., 1995; Weigert et al., 2002). One study compared patient satisfaction after down-regulated cycles with either unstimulated IVF or IVF without down-regulation and stimulated with clomifene citrate (Hojgaard et al., 2001)

Comparison of antagonist and agonist down-regulated protocols (Table 15.5)

One Cochrane review (Al-Inany et al., 2011) and four RCTs (Devesa et al., 2010; DiLuigi et al., 2011; Garcia-Velasco et al., 2011; and Tehraninejad et al., 2011) were included in this review.

Comparison of different types of down-regulation protocol (including long, short, ultra-short and stop protocols) (Table 15.6)

One Cochrane review was included in this review (Maheshwari et al., 2011).

Table 15.4 GRADE findings for comparison of down-regulated with non down-regulated cycles (with or without clomifene citrate)

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate)					
1 (Long et al., 1995)	1/36 (3%) women	4/36 (11%) women	RR 0.3 (0.0 to 2.1)	83 fewer per 1000 (from 108 fewer to 126 more)	Very low
Clinical pregnancy					
Down-regulation (without clomifene citrate) vs. no down-regulation (without clomifene citrate)					
4 (Antoine et al., 1990; Neveu et al., 1987; Polson et al., 1991; van de Helder et al., 1990)	59/270 (22%) women	20/178 (11%) women	RR 2.0 (1.2 to 3.2)	116 more per 1000 (from 29 more to 255 more)	Very low
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate)					
4 (Dhont et al., 1995; Grochowski et al., 1999, Long et al., 1995; Weigert et al., 2002)	128/455 (28%) women	128/471 (27%) women	RR 1.1 (0.8 to 1.5)[g]	14 more per 1000 (from 65 fewer to 122 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome					
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate) (miscarriage)					
1 (Long et al., 1995)	2/36 (6%) women	0/36 (0%) women	RR 5.0 (0.3 to 100.6)	Not calculable	Very low
	2/5 (40%) pregnancies	0/5 (0%) pregnancies	RR 5.0 (0.3 to 83.7)	Not calculable	
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate) (ectopic pregnancy)					
1 (Long et al., 1995)	0/36 (0%) women	1/36 (3%) women	RR 0.3 (0.0 to 7.9)	19 fewer per 1000 (from 28 fewer to 192 more)	Very low
	0/5 (0%) pregnancies	1/5 (20%) pregnancies	RR 0.3 (0.0 to 6.7)	134 fewer per 1000 (from 196 fewer to 1000 more)	
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate) (early pregnancy loss)					
2 (Harrison et al., 1994 and Weigert et al., 2002)	10/190 (5%) women	14/204 (7%) women	RR 0.8 (0.4 to 1.7)	16 fewer per 1000 (from 45 fewer to 47 more)	Very low
	7/41 (17%) pregnancies[i]	10/54 (19%) pregnancies[i]	RR 0.9 (0.4 to 2.2)[i]	15 fewer per 1000 (from 115 fewer to 224 more)[i]	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Down-regulation(without clomifene citrate) vs. no down-regulation (without clomifene citrate)					
1 (Antoine et al., 1990)	5/90 (6%) Women	0/90 (0%) women	RR 11.0 (0.6 to 196.0)	Not calculable	Very low
	5/19 (26%) pregnancies	0/11 (0%) pregnancies	RR 6.6 (0.4 to 109.1)	Not calculable	

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate)					
2 (Harrison et al., 1994; Grochowski et al., 1999)	8/210 (4%) women	10/214 (5%) women	RR 0.9 (0.2 to 3.1)[g]	7 fewer per 1000 (from 36 fewer to 100 more)	Very low
	3//38 (8%) pregnancies[j]	7/41 (17%) pregnancies[j]	RR 0.5 (0.1 to 1.7)[j]	92 fewer per 1000 (from 149 fewer to 113 more)[j]	
Multiple births (the number of babies born from a multiple pregnancy)					
Down-regulation (with clomifene citrate) vs. no down-regulation (with clomifene citrate)					
1 (Long et al., 1995)	2/3 (67%) babies	0/4 (0%) babies	RR 6.3 (0.4 to 96.5)	Not calculable	Very low
Ovarian hyperstimulation syndrome (OHSS)					
Down-regulation (with clomifene citrate)vs. no down-regulation (with clomifene citrate)					
2Grochowski et al., 1999; Weigert et al.,2002)	17/300 (6%) women	4/318 (1%) women	RR 4.2 (1.5 to 11.7)	41 more per 1000 (from 6 more to 135 more)	Low
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
Down-regulation(without clomifene citrate) vs. no down-regulation (with clomifene citrate)					
1 (Hojgaard et al., (2001)	60/64 (94%) women	139/141 (99%) women	RR 1.0 (0.9 to 1.0)	49 fewer per 1000 (from 108 fewer to 20 more)	Moderate
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, OHSS ovarian hyperstimulation syndrome, RR relative risk

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Table 15.5 GRADE findings for comparison of antagonist and agonist down-regulated protocols

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
GnRH antagonist vs. long course GnRH agonist					
2 (Al-Inany et al., 2011 and DiLuigi et al., 2011)	228/850 (27%) women	224/719 (31%) women	RR 0.9 (0.8 to 1.0)	31 fewer per 1000 (from 69 fewer to 16 more)	Very low
GnRH antagonist + OCP vs. long course GnRH agonist					
1 (Garcia-Velasco, 2011)	51/115 (44%) women	53/113 (47%) women	RR 1.0 (0.7 to 1.3)	23 fewer per 1000 (from 136 fewer to 122 more)	Very low
Clinical pregnancy					
GnRH antagonist vs. long course GnRH agonist (including low response)					
3 (Al-Inany et al., 2011; DiLuigi et al., 2011; Devesa et al., 2010; and Tehraninejad et al., 2011)	1091/4035 (27%) women	963/3111 (31%) women	RR 0.9 (0.8 to 1.0)	31 fewer per 1000 (from 9 fewer to 50 fewer)	Low
GnRH antagonist vs. long course GnRH agonist (low response only)					
1 (Al-Inany et al., 2011)	67/473 (14%) women	80/446 (18%) women	OR 0.7 (0.5 to 1.0)	45 fewer per 1000 (from 83 fewer to 3 more)	Very low
GnRH antagonist + OCP vs. long course GnRH agonist					
2 (Al-Inany et al., 2011, Garcia-Velasco, 2011)	293/761 (39%) women	312/703 (44%) women	RR 0.9 (0.8 to 1.0)	49 fewer per 1000 (from 93 fewer to 4 more)	Very low
Adverse pregnancy outcome					
GnRH antagonist vs. long course GnRH agonist (miscarriage)					
1 (Al-Inany et al., 2011)	92/2861 (3%) women	88/2040 (4%) women	OR 0.8 (0.6 to 1.0)	10 fewer per 1000 (from 19 fewer to 2 more)	Very low
	98/873 (11%) pregnancies	91/774 (12%) pregnancies	OR 1.0 (0.7 to 1.3)	4 fewer per 1000 (from 32 fewer to 31 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
GnRH antagonist + OCP vs. long course GnRH agonist (miscarriage)					
1 (Garcia-Velasco, 2011)	5/115 (4%) women	11/113 (10%) women	RR 0.5 (0.2 to 1.2)	54 fewer per 1000 (from 82 fewer to 23 more)	Low
	5/56 (9%) pregnancies	11/64 (17%) pregnancies	RR 0.5 (0.2 to 1.4)	83 fewer per 1000 (from 139 fewer to 69 more)	
GnRH antagonist vs. long course GnRH agonist					
1 (Tehraninejad et al., 2011)	18/150 (12%) women	9/150 (6%) women	RR 2.0 (0.9 to 4.3)	60 more per 1000 (from 4 fewer to 199 more)	Very low
	18/51 (35%) pregnancies	9/53 (17%) pregnancies	RR 2.1 (1.0 to 4.2)	183 more per 1000 (from 5 fewer to 542 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
GnRH antagonist + OCP vs. long course GnRH agonist					
1 (Garcia-Velasco, 2011)	15/115 (13%) women	18/113 (16%) women	RR 0.8 (0.4 to 1.5)	29 fewer per 1000 (from 91 fewer to 86 more)	Low
	15/56 (27%) pregnancies	18/64 (28%) pregnancies	RR 1.0 (0.5 to 1.7)	14 fewer per 1000 (from 132 fewer to 200 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence was reported					
Ovarian hyperstimulation syndrome (OHSS)					
GnRH antagonist vs. long course GnRH agonist					
1 (Al-Inany et al., 2011 and Tehraninejad et al., 2011)	110/3315 (3%) women	168/2402 (7%) women	RR 0.6 (0.4 to 0.8)	31 fewer per 1000 (from 15 fewer to 43 fewer)	Very low
Congenital abnormalities					
No evidence was reported					
Patient satisfaction					
No evidence was reported					
Health related quality of life					
No evidence was reported					

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Anxiety and/or depression					
No evidence was reported					

CI confidence interval, GnRH gonadotrophin-releasing hormone, OCP oral contraceptive pill, OHSS ovarian hyperstimulation syndrome, OR odds ratio, RR relative risk

Table 15.6 GRADE finding for comparison of different types of down-regulation protocol (including long, short, ultra-short and stop protocols)

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Long vs. short protocol					
1 (Maheshwari et al., 2011)	27/124 (22%) women	17/127 (13%) women	OR 1.8 (0.9 to 3.5)	84 more per 1000 (from 8 fewer to 217 more)	Very low
Long vs. ultra-short protocol					
1 (Maheshwari et al., 2011)	15/76 (20%) women	9/74 (12%) women	OR 1.8 (0.7 to 4.4)	76 more per 1000 (from 31 fewer to 255 more)	Very low
Long (luteal) vs. long (follicular)					
1 (Maheshwari et al., 2011)	17/96 (18%) women	13/127 (10%) women	OR 1.9 (0.9 to 4.1)	75 more per 1000 (from 12 fewer to 216 more)	Very low
Clinical pregnancy					
Long vs. short protocol					
1 (Maheshwari et al., 2011)	176/725 (24%) women	126/712 (18%) women	OR 1.5 (1.2 to 1.9)	66 more per 1000 (from 21 more to 116 more)	Very low
Long vs. ultra-short protocol					
1 (Maheshwari et al., 2011)	25/113 (22%) women	18/117 (15%) women	OR 1.6 (0.8 to 3.0)	67 more per 1000 (from 27 fewer to 203 more)	Very low
Long (luteal) vs. long (follicular)					
1 (Maheshwari et al., 2011)	66/281 (23%) women	64/288 (31%) women	OR 1.1 (0.7 to 1.6)[g]	12 more per 1000 (from 50 fewer to 90 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Long (continued GnRHa) vs. long (stop GnRHa)					
1 (Maheshwari et al., 2011)	21/132 (16%) women	26/132 (20%) women	OR 0.8 (0.4 to 1.4)	38 fewer per 1000 (from 106 fewer to 65 more)	Very low
Long (continued GnRHa) vs. long (reduced dose GnRHa)					
1 (Maheshwari et al., 2011)	58/156 (37%) women	57/155 (37%) women	OR 1.0 (0.6 to 1.6)	5 more per 1000 (from 96 fewer to 116 more)	Very low
Adverse pregnancy outcomes					
No evidence was reported					
Multiple pregnancies (the number of pregnancies with more than one fetus)					
No evidence was reported					
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence was reported					
Ovarian hyperstimulation syndrome (OHSS)					
No evidence was reported					
Congenital abnormalities					
No evidence was reported					
Patient satisfaction					
No evidence was reported					
Health related quality of life					
No evidence was reported					
Anxiety and/or depression					
No evidence was reported					

CI confidence interval, GnRHa gonadotrophin-releasing hormone agonist, OHSS ovarian hyperstimulation syndrome, OR odds ratio

Evidence statements

Down-regulated compared with non down-regulated cycles (with or without clomifene citrate)

Live full-term singleton birth

There was no evidence reported on the number of live full-term singleton births from studies that did not use clomifene citrate.

There was no significant difference in the number of live full-term singleton births resulting from down-regulated and non down-regulated cycles when clomifene citrate was used in the non down-regulated group.

Clinical pregnancy

When clomifene citrate was not used as part of the protocol, there were significantly more clinical pregnancies in down-regulated cycles when compared with non down-regulated cycles.

There was no significant difference in the number of clinical pregnancies resulting from down-regulated and non down-regulated cycles when both arms received clomifene citrate.

Adverse pregnancy outcome

There was no evidence reported on the number of adverse pregnancy outcomes from studies that did not use clomifene citrate.

There were no significant differences in the numbers of miscarriages, ectopic pregnancies or early pregnancy losses when comparing down-regulated and non down-regulated cycles when both arms received clomifene citrate.

Multiple pregnancies

There was no significant difference in the number of adverse pregnancy outcomes when comparing down-regulated and non down-regulated cycles in a study that did not use clomifene citrate.

There was no significant difference in the number of adverse pregnancy outcomes when comparing down-regulated and non down-regulated cycles in studies that used clomifene citrate.

Multiple births

There was no evidence reported on the number of multiple births from studies that did not use clomifene citrate.

There was no significant difference in the number of multiple births when comparing down-regulated and non down-regulated cycles in studies that used clomifene citrate.

OHSS

There was no evidence reported on the number of cases of OHSS from studies that did not use clomifene citrate.

There were significantly more cases of OHSS in down-regulated cycles when compared with non down-regulated cycles in studies that used clomifene citrate.

Congenital abnormalities

There was no evidence reported that compared congenital abnormalities in down-regulated and non down-regulated cycles.

Patient satisfaction

There was no significant difference in the number of women who were satisfied with their treatment when comparing down-regulated and non down-regulated cycles.

Health related quality of life

There was no evidence reported that assesses health related quality of life in down-regulated or non down-regulated cycles.

Anxiety and/or depression

There was no evidence that reported the number of women with anxiety and/or depression in down-regulated and non down-regulated cycles.

Comparison of antagonist and agonist down-regulation protocols

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births when comparing the use of GnRH antagonist with a long course GnRH agonist.

Clinical pregnancy

There were significantly more clinical pregnancies with a long GnRH agonist protocol than with GnRH antagonist. However, this difference did not remain significant when a sub-group analysis for ‘low response women’ was performed.

Adverse pregnancy outcome

There was no significant difference in the number of miscarriages or abortions when comparing the use of GnRH antagonist and long GnRH agonist protocols.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing the use of GnRH antagonist and long GnRH agonist protocols.

Multiple births

No evidence was reported that compared the number of multiple births with different down-regulation protocols.

OHSS

There were significantly more cases of OHSS in cycles that used a long GnRH agonist protocol when compared with those that received a GnRH antagonist protocol.

Congenital abnormalities

There was no evidence reported for the number of congenital abnormalities resulting from different down-regulation protocols.

Patient satisfaction

There was no evidence reported regarding patient satisfaction of different down-regulation protocols.

Health related quality of life

There was no evidence reported regarding health related quality of life from different down-regulation protocols.

Anxiety and/or depression

There was no evidence reported regarding anxiety and/or depression in women receiving different down-regulation protocols.

Comparison of different types of down-regulation protocol (including long, short, ultra-short and stop protocols)

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births when comparing long protocols with short or ultra-short protocols. There was also no significant difference between long protocols started in the luteal phase and long protocols started in the follicular phase of the woman's cycle.

Clinical pregnancy

There were significantly more clinical pregnancies with a long protocol compared with a short protocol.

There was no significant difference in the number of clinical pregnancies when comparing long with ultra-short or with stop protocols. There was also no significant difference between long protocols started in the luteal phase compared with long protocols started in the follicular phase, or between two long protocols with different doses of GnRH agonist.

Adverse pregnancy outcomes

There was no adverse pregnancy outcome data reported.

Multiple pregnancies

There was no multiple pregnancy data reported.

Multiple births

There was no multiple birth data reported.

OHSS

There was no OHSS data reported.

Congenital abnormalities

There was no evidence reported for congenital abnormalities.

Patient satisfaction

There was no evidence reported regarding patient satisfaction.

Health related quality of life

There was no evidence reported regarding health related quality of life.

Anxiety and/or depression

There was no evidence reported for anxiety and/or depression.

Health economics profile

No formal health economic review was undertaken.

Evidence to recommendations

Relative value placed on the outcomes considered

Clinical pregnancies and live singleton births are important outcomes which allow clinicians to inform people of their chances of conception and having a baby. The other outcomes in this review relate to side effects of the treatments and are important to consider in order to fully inform couples of potential risks of treatment.

Consideration of clinical benefits and harms

The evidence showed higher pregnancy rates in down-regulated IVF cycles compared with non down-regulated cycles. The GDG therefore recommended that down-regulation should be used as part of an IVF cycle.

Evidence showed higher pregnancy rates with the use of a long GnRH agonist protocol compared with an antagonist protocol, although down-regulation with agonists was also associated with higher rates of OHSS. In women who had had a previous low response to IVF treatment, there was no significant difference in the number of clinical pregnancies with the use of agonists compared with antagonists.

The GDG view was that clinicians need to be aware of the increased risk of OHSS with the use of GnRH agonists compared with the lower risks with the use of GnRH antagonists. The GDG acknowledged that the risk of OHSS is also dependent on which gonadotrophins and ovulation trigger are used during other parts of the IVF treatment cycle, and so it would not be appropriate to recommend against the use of GnRH agonists. However, there is a need to balance the increased chance of achieving a clinical pregnancy using GnRH agonist with the increased risk of OHSS. Therefore the GDG recommended the use of either GnRH agonist or GnRH antagonist for down-regulation, but emphasised that GnRH agonist should only be used in women with a low risk of OHSS.

Evidence showed higher clinical pregnancy rates associated with long down-regulation protocols compared with short down-regulation protocols. However, there was no difference in the number of live full-term singleton births and a comparison of adverse outcomes was not reported. The GDG acknowledge that there are some groups of women for whom a short GnRH agonist protocol is more appropriate than a long protocol, for example women who are likely to respond poorly to IVF treatment. The GDG members did not, therefore, want to recommend against using a short protocol in all situations, although they agreed that the long protocol should remain the standard approach. Hence they recommended that, when the use of a GnRH agonist is appropriate, it is used as part of long down-regulation protocol. They chose not to recommend against using a short protocol, and instead drafted a research recommendation regarding the efficacy of short protocols in poor responders.

Consideration of health benefits and resource uses

Although the cost of one dose of GnRH agonist is lower than one dose of GnRH antagonist, the GDG acknowledged that GnRH agonist is used for a longer portion of the IVF protocol than GnRH antagonist. Therefore, the GDG view was that more GnRH agonist is used to achieve the same down-regulation effect as GnRH antagonist, and so the difference in cost between the two is not likely to be large.

Quality of evidence

The evidence was graded as moderate to very low quality, depending on the outcome being reported. The main reasons were poor allocation concealment and a lack of reported power calculations. In

addition, studies may have been underpowered for many of the reported outcomes, as shown by the wide confidence intervals around point estimates.

The GDG acknowledged that there are few new studies investigating the use of down-regulation compared with no down-regulation as it is an accepted part of current practice.

Other considerations

Clomifene

The GDG highlighted that some of the studies that compared down-regulation with no down-regulation studies used clomifene citrate, which is no longer widely used in UK practice.

Antagonists compared with agonists

Using a long down-regulation GnRH agonist protocol is the preferred approach by clinicians as it obviates the need for pre-treatment. The use of a GnRH antagonist with pre-treatment (such as the oral contraceptive pill), allows IVF treatment to be scheduled (see Section 15.2). The ability to schedule treatment is of benefit to both women and their healthcare team. The GDG acknowledged that recommending the use of GnRH antagonist over GnRH agonist would represent a substantial change in current UK practice, which uses a GnRH agonist as part of the standard long down-regulation IVF protocol. The GDG believed that the evidence for the efficacy of GnRH antagonists is not convincing enough to recommend their use in place of GnRH agonists, but acknowledged that their use is important in women who are at a higher risk of OHSS.

Poor responders

The GDG acknowledged that alternatives to long protocols may be preferred in women who are poor responders as there was no significant difference in clinical pregnancy rates between agonist and antagonist protocols for these women.

Equalities

The people considered in this review were:

- People who have vaginal intercourse.
- Specific patient subgroups listed in the guideline Scope that may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychological problem
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
- People who are preparing for cancer treatment who may wish to preserve their fertility.

There were no other specific issues that needed to be addressed with respect to any of these subgroups in the context of down-regulation.

Key conclusions

IVF cycles that use down-regulation result in more clinical pregnancies than non-down regulated cycles.

The use of GnRH agonist results in more clinical pregnancies than the use of GnRH antagonist, but is associated with an increased of OHSS. There are more clinical pregnancies with the use of a long GnRH agonist protocol compared with a short GnRH agonist protocol, but there is no difference in the number of live full-term singleton births. Therefore the use of GnRH antagonist protocols should be considered in women who are at a higher risk of OHSS.

Recommendations

Number	Recommendation
137	Use regimens to avoid premature luteinising hormone surges in gonadotrophin-stimulated IVF treatment cycles. **[new 2013]**
138	Use either gonadotrophin-releasing hormone agonist down-regulation or gonadotrophin-releasing hormone antagonists as part of gonadotrophin-stimulated IVF treatment cycles. **[new 2013]**
139	Only offer gonadotrophin-releasing hormone agonists to women who have a low risk of ovarian hyperstimulation syndrome. **[new 2013]**
140	When using gonadotrophin-releasing hormone agonists as part of IVF treatment, use a long down-regulation protocol. **[new 2013]**

Number	Research recommendation
RR 28	What is the effectiveness of short down-regulation protocols in poor responders?

15.4 Controlled ovarian stimulation in IVF

Introduction

The aim of controlled ovarian stimulation in IVF is to produce a number of mature eggs which can be retrieved surgically prior to fertilisation in the laboratory. Stimulation is achieved with gonadotrophins. A number of formulations are available. The choice is between human menopausal gonadotrophin (hMG), which is produced from the urine of menopausal women and contains follicle-stimulating hormone (FSH) and luteinising hormone (LH), and a variety of urinary gonadotrophins including purified FSH (p-FSH) and highly purified FSH (hp-FSH) containing mainly FSH. More recently, recombinant DNA technology has been used to produce recombinant FSH (rFSH) which contains no LH. rFSH is not derived from human sources and has minimal batch-to-batch variability.

These gonadotrophins have been used in different protocols and in varying doses, and sometimes in combination with clomifene citrate. Some IVF clinics have used clomifene citrate for ovarian stimulation either on its own or in combination with GNRH antagonists. There have also been clinics and patients who have favoured IVF in an unstimulated cycle with the anticipation of only collecting a mature single egg and thus lessening the likelihood of OHSS.

This section reviews the evidence of the efficacy of these different approaches to ovarian stimulation.

Review question

What is the effectiveness of the following strategies as part of an ovarian stimulation protocol in women undergoing IVF or ICSI treatment:

- stimulation with gonadotrophins
- ‘milder’ stimulation
- adjuvant growth hormone and di-hydro-epi-androsterone (DHEA) treatment for women with a previous poor response?

Evidence profile

The GDG believed there were several important topics to be addressed within this review question. One of these topics is the 'standard' practice of stimulation with gonadotrophins, and includes comparing the effectiveness of urinary and recombinant gonadotrophins. Another topic is alternative approaches to standard ovarian stimulation, including unstimulated or natural cycle IVF, reduced doses of FSH/rFSH and stimulation with clomifene citrate. The final topic within this review is the use of adjuvant therapies throughout IVF treatment (with or without ICSI) for poor responders, including growth hormone and DHEA.

To address these topics, the following comparisons are presented:

- unstimulated IVF compared with stimulated IVF (Table 15.7)
- urinary compared with recombinant gonadotrophins (Table 15.8)
- specific recombinant compared with specific urinary gonadotrophins (Table 15.9)
- Urinary compared with urinary gonadotrophins and recombinant compared with recombinant gonadotrophins (Table 15.10)
- dosages of FSH/rFSH for ovarian stimulation (Table 15.11)
- unstimulated IVF compared with stimulation with clomifene citrate and/or gonadotrophins (no IVF/ICSI) (Table 15.12)
- GnRH agonist and gonadotrophins IVF/ICSI cycles compared with clomifene citrate and gonadotrophins (plus GnRH antagonist) IVF/ICSI cycles (Table 15.13)
- adjuvant growth hormone for women with a previous low response (Table 15.14)
- adjuvant DHEA for women with a previous low response (Table 15.15).

Description of included studies

Unstimulated IVF compared with stimulated IVF (Table 15.7)

Four RCTs (Ingerslev et al., 2001; MacDougall et al., 1994; Morgia et al., 2004; Ragni et al., 2000,) and one questionnaire study (Hojgaard et al., 2001) were included in this review. Two rRCTs compared IVF cycles stimulated with clomifene citrate with unstimulated IVF cycles (Ingerslev et al., 2001; MacDougall et al., 1994) and two others compared IVF cycles stimulated with GnRH agonist and FSH with unstimulated cycles in low response women (Morgia et al., 2004; Ragni et al., 2000). The Hojgaard et al. (2001) study compared patient satisfaction in women who received IVF cycles stimulated with GnRH agonist and gonadotrophins with those who received either natural cycle or clomifene citrate stimulated IVF. This study was a follow-up of the women in the Ingerslev et al. (2001) study.

Comparison of recombinant gonadotrophins with urinary gonadotrophins (Table 15.8)

This review was undertaken to establish whether, as a group of drugs, the outcomes of IVF/ICSI cycles stimulated with urinary gonadotrophins differed from those stimulated with recombinant gonadotrophins. This review included one large Cochrane review (van Wely et al., 2011), which contained 42 RCTs in its comparisons.

Specific recombinant compared with specific urinary gonadotrophins (Table 15.9)

This review was undertaken to establish whether specific types of urinary gonadotrophins are as effective (in terms of IVF/ICSI cycle outcomes) as specific types of recombinant gonadotrophins. The review included one Cochrane review (van Wely et al., 2011) and 19 RCTs that were not included in the Cochrane review (Aboulghar et al., 2010; Ashrafi et al., 2011; Battaglia et al., 2000; Blockell et al., 2009; Check et al., 2008; Coelingh Bennink et al., 1998; De Placido et al., 2001; Devesa et al., 2010; Drakakis et al., 2005; Drakakis et al., 2009; Gholami et al., 2010; Gomes et al., 2007; Kahn et al., 1999; Loutradis et al., 2003; Pacchiarotti et al., 2010; Raga et al., 1999; Selman et al., 2010; Sohrabvand et al., 2010; Tanbo et al., 2001).

The Cochrane review compared rFSH with hMG/highly purified hMG (hp-hMG), with p-FSH and with hp-FSH (van Wely et al., 2011).

Of the individual RCTs, one study compared rFSH with hMG (Gomes et al., 2007) and five studies compared rFSH with rFSH plus hMG (Check et al., 2008; De Placido et al., 2001; Devesa et al., 2010; Drakakis et al., 2009; Loutradis et al., 2003; and Sohrabvand et al., 2010). One study compared rFSH + recombinant LH (rLH) with urinary human menopausal gonadotrophin (uhMG) (Pacchiarotti et al., 2010).

Two studies compared rFSH with human follicle-stimulating hormone (hFSH) (Gholami et al., 2010; Selman et al., 2010), one study compared rFSH with hp-FSH (Aboulghar et al., 2010), one study compared rFSH with rFSH plus hFSH (Selman et al., 2010), and one study compared rFSH plus hFSH with hFSH (Selman et al., 2010). One study compared rFSH plus hp-FSH with hp-FSH (Battaglia et al., 2000). Four studies compared rFSH with urinary follicle-stimulating hormone (uFSH) (Coelingh Bennink et al., 1998; Kahn et al., 1999; Raga et al., 1999; Tanbo et al., 2001).

One study compared rFSH with human chorionic gonadotrophin (hCG) (Gomes et al., 2007) and three studies compared rFSH with rFSH plus hCG (Ashrafi et al., 2011; Blockell et al., 2009; Check et al., 2008). One study compared rFSH plus hCG with rFSH plus rLH (Drakakis et al., 2009).

Comparisons of urinary gonadotrophins with other urinary gonadotrophins and recombinant gonadotrophins with other recombinant gonadotrophins (Table 15.10)

Sixteen RCTs were included in this review (Balasch et al., 1996; Balasch et al., 2001; Barrenetxea et al., 2008; Dunerin et al., 2008; Ferraretti et al., 2004; Gomes et al., 2007; Griesinger et al., 2005; Kovacs et al., 2010; Ku et al., 2003; Levi-Setti et al., 2006; Marrs et al., 2004; Matorras et al., 2009; NyboeAndersen et al., 2008; Pezzuto et al., 2010; Quigley et al., 1988; Tarlatzis et al., 2006).

One study compared hCG with hMG (Gomes et al., 2007) and one study compared hFSH with hMG (Quigley et al., 1988). One study compared p-FSH with p-FSH plus hMG (Balasch et al., 1996) and two studies compared hpFSH with hpFSH plus hMG (Balasch et al., 1996; Ku et al., 2003). Five studies compared recombinant human follicle-stimulating hormone (rhFSH) with rhFSH plus rLH (Balasch et al., 2001; Barrenetxea et al., 2008; Matorras et al., 2009; Marrs et al., 2004; Tarlatzis et al., 2006) and one study compared rhFSH plus recombinant human luteinising hormone (rhLH) with rhLH (Dunerin et al., 2008). Eight studies compared rFSH with rFSH plus rLH (Caserta et al., 2011; Fabregues et al., 2011; Ferraretti et al., 2004; Griesinger et al., 2005; Kovacs et al., 2010; Levi-Setti et al., 2006; NyboeAndersen et al., 2008; Pezzuto et al., 2010).

Dosages of FSH/rFSH for ovarian stimulation (Table 15.11)

Sixteen RCTs were identified for this review (Cavagna et al., 2006; De Jong et al., 2000; Harrison et al., 2001; Hoomans et al., 2002; Klinkert et al., 2005; Koundouros et al., 2008; Latin-American Puregon IVF study group, 2001; Out et al., 1999; Out et al., 2000; Out et al., 2001; Out et al., 2004; Popovic-Todorovic et al., 2003; Tan et al., 2005; Wikland et al., 2001; Yong et al., 2005; Zhu et al., 2009).

Thirteen studies compared fixed doses of rFSH (Cavagna et al., 2006; De Jong et al., 2000; Harrison et al., 2001; Hoomans et al., 2002; Klinkert et al., 2005; Latin-American Puregon IVF study group, 2001; Out et al., 1999; Out et al., 2000; Out et al, 2001.; Out et al, 2004.; Tan et al, 2005.; Wikland et al., 2001; Yong et al., 2005). Five studies compared a dose of 100 international units (IU) rFSH with 200 IU rFSH (De Jong et al., 2000; Hoomans et al., 2002; Out et al., 1999; Out et al., 2001; Tanet al., 2005). Three studies compared a dose of 150 IU rFSH with a dose of 200 IU rFSH (Cavagna et al., 2006; Harrison et al., 2001; Out et al., 2004). Two studies compared a dose of 150 IU rFSH with 225 IU rFSH (Wikland et al., 2001; Yong et al., 2005) and two studies compared a dose of 150 IU rFSH with 250 IU rFSH (Latin-American Puregon IVF study group, 2001; Out et al., 2000). One study compared a dose of 150 IU rFSH with 300 IU rFSH (Klinkert et al., 2005) and one study compared a dose of 300 IU rFSH with 400 IU rFSH (Harrison et al., 2001).

Three studies compared variable doses of FSH or rFSH (Koundouros et al., 2008; Popovic-Todorovic et al., 2003; Zhuet al., 2009). One study compared a low dose step-up with a step-down protocol (Koundouros et al., 2008) and one study compared two low dose step-up protocols (Zhu et al., 2009).

One study compared an individualised dose of between 100 IU and 250 IU rFSH with a fixed dose of 150 rFSH (Popovic-Todorovic et al., 2003).

Unstimulated IVF compared with stimulation with clomifene citrate and/or gonadotrophins (no IVF/ICSI) (Table 15.12)

No RCTs were found that were relevant to this review.

GnRH agonist plus gonadotrophins IVF/ICSI cycles compared with clomifene citrate plus gonadotrophins (plus GnRH antagonist) IVF/ICSI cycles (Table 15.13)

Seven randomised controlled studies (Dhont et al., 1995; Grochowski et al., 1999; Harrison et al., 1994; Karimzadeh et al., 2010; Lin et al., 2006; Long et al., 1995; Weigert et al., 2002) and one questionnaire study (Hojgaard et al., 2001) were included in this review. Four studies compared a GnRH agonist plus hMG protocol with clomifene citrate plus hMG (Dhont et al., 1995; Grochowski et al., 1999; Harrison et al., 1994; Long et al., 1995). Two studies compared the same protocols, but with the addition of a GnRH antagonist in the clomifene citrate arm (Lin et al., 2006; Karimzadeh et al., 2010). One study compared a GnRH agonist plus rFSH protocol with clomifene citrate plus rFSH and rLH plus corticosteroid (Weigert et al., 2002). The questionnaire study compared patient satisfaction in women who received GnRH agonist plus gonadotrophins with those who received natural cycle IVF or IVF stimulated with clomifene citrate alone (Hojgaardet al., 2001).

Adjuvant growth hormone in IVF/ICSI protocols for women with a previous low response (Table 15.14)

One Cochrane review (Duffy et al., 2010) and two RCTs (Suikkari et al., 1996; Owen et al., 1991) that reported on the addition of growth hormone to IVF/ICSI protocols for women with a previous low response were included in this review. The two rRCTs were included in the Cochrane review, but for different outcomes. The Cochrane review included a small number of studies, and therefore a small number of women.

Adjuvant DHEA for women with a previous low response (Table 15.15)

One RCT (Wiser et al., 2010) that reported on the addition of DHEA to IVF/ICSI protocols for women with a previous low response was included in this review.

Table 15.7 GRADE findings for comparison of unstimulated IVF with stimulated IVF

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
CC + hCG vs. natural cycle IVF + hCG					
1 (MacDougall et al., 1994)	2/16 (13%) women	0/14 (0%) women	RR 4.4 (0.2 to 84.8)	Not calculable	Very low
Clinical pregnancy					
CC + hCG vs. natural cycle IVF + hCG					
2 (Ingerslev et al.,2001, MacDougall et al., 1994)	22/84 (26%) women	4/78 (5%) women	RR 4.7 (1.8 to 12.2)	188 more per 1000 (from 40 more to 576 more)	Very low
GnRH agonist + FSH vs. natural cycle IVF + hCG (low response)					
2 (Morgia et al., 2004; Ragni et al., 2000)	9/77 (12%) women	9/66 (14%) women	RR 0.9 (0.4 to 2.1)	16 fewer per 1000 (from 86 fewer to 143 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome					
No evidence reported					
Multiple pregnancies (the number of pregnancies with more than one fetus)					
CC + hCG vs. natural cycle IVF + hCG					
1 (Ingerslev et al., 2001)	2/68 (3%) women	0/64 (0%) women	RR 4.7 (0.2 to 96.3)	Not calculable	Low
	2/20 (10%) pregnancies	0/4 (0%) pregnancies	RR 1.2 (0.07 to 21.1)	Not calculable	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
No evidence reported					
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
GnRH agonist + FSH/hMG + hCG vs. natural cycle or CC stimulated IVF + hCG					
1 (Hojgaard et al., 2001)	60/64 (94%) women	139/141 (99%) women	RR 1.0 (0.9 to 1.0)	49 fewer per 1000 (from 108 fewer to 20 more)	Moderate
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CC clomifene citrate, CI confidence interval, FSH follicle-stimulating hormone, GnRH gonadotrophin-releasing hormone, hCG human chorionic gonadotrophin, hMG human menopausal gonadotrophin, IVF in vitro fertilisation, OHSS ovarian hyperstimulation syndrome, RR relative risk

Table 15.8 GRADE findings for comparison of urinary compared with recombinant gonadotrophins

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
rFSH vs. urinary gonadotrophins					
1 (Van Wely et al., 2011)	894/3796 (24%) women	868/3543 (24%) women	OR 1.0 (0.9 to 1.1)	9 fewer per 1000 (from 29 fewer to 11 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy					
rFSH vs. urinary gonadotrophins					
1 (Van Wely et al., 2011)	1353/4864 (28%) women	1301/4618 (28%) women	OR 1.0 (0.9 to 1.1) [d]	4 fewer per 1000 (from 21 fewer to 14 more)	Very low
Adverse pregnancy outcome					
rFSH vs. urinary gonadotrophins (miscarriage)					
1 (Van Wely et al., 2011)	192/3329 (6%) women	166/3334 (5%) women	OR 1.2 (0.9 to 1.4)	8 fewer per 1000 (from 20 fewer to 5 more)	Very low
	Not reported per clinical pregnancy				
Multiple pregnancies (the number of pregnancies with more than one fetus)					
rFSH vs. urinary gonadotrophins					
1 (Van Wely et al., 2011)	232/3150 (7%) women	260/3179 (8%) women	OR 0.9 (0.8 to 1.1)	8 fewer per 1000 (from 20 fewer to 5 more)	Low
	232/906 (26%) pregnancies	260/989 (26%) pregnancies	OR 1.0 (0.8 to 1.2)	6 fewer per 1000 (from 43 fewer to 35 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence was reported					
Ovarian hyperstimulation syndrome (OHSS)					
rFSH vs. urinary gonadotrophins					
1 (Van Wely et al., 2011)	92/3994 (2%) women	73/3746 (2%) women	OR 1.2 (0.9 to 1.6)	4 more per 1000 (from 2 fewer to 12 more)	Very low
Congenital abnormalities					
No evidence was reported					
Patient satisfaction					
No evidence was reported					
Health related quality of life					
No evidence was reported					
Anxiety and/or depression					
No evidence was reported					

CI confidence interval, hCG human chorionic gonadotrophin, OHSS ovarian hyperstimulation syndrome, OR odds ratio, rFSH recombinant follicle-stimulating hormone

Table 15.9 GRADE findings for comparison of specific recombinant with specific urinary gonadotrophins

Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
rFSH vs. hMG/hp-hMG					
1 (Van Wely et al., 2011)	359/1604 (22%) women	406/1593 (25%) women	OR 0.8 (0.7 to 1.0)[a]	32 fewer per 1000 (from 2 fewer to 57 fewer)	Very low
rFSH vs. pFSH					
1 (Van Wely et al., 2011)	171/825 (21%) women	103/605 (17%) women	OR 1.3 (1.0 to 1.7)	36 more per 1000 (from 4 fewer to 85 more)	Very low
rFSH vs. hp-FSH					
1 (Van Wely et al., 2011)	364/1367 (27%) women	359/1345 (27%) women	OR 1.0 (0.9 to 1.2)	4 more per 1000 (from 20 fewer to 28 more)	Very low
rFSH vs. uFSH					
1 (Kahn et al., 1999)	49/147 (33%) women	38/115 (33%) women	RR 1.0 (0.7 to 1.4)	3 more per 1000 (from 96 fewer to 142 more)	Very low
rFSH vs rFSH + hCG					
2 (Blockell et al., 2009; Check et al., 2008)	14/57 (24.6%)	17/55 (30.9%)	RR 0.8 (0.4 to 1.5)	65 fewer per 1000 (from 176 fewer to 139 more)	Very low
rFSH vs. rFSH + hMG					
1 (Sohrabvand et al., 2010)	6/32 (19%) women	6/32 (19%) women	RR 1 (0.4 to 2.8)	0 fewer per 1000 (from 120 fewer to 332 more)	Very low
Clinical pregnancy					
rFSH vs. hMG/hp-hMG					
2 (Gomes et al., 2007; and Van Wely et al., 2011)	507/1917 (26%) women	563/1892 (30%) women	RR 0.9 (0.8 to 1.0)b	33 fewer per 1000 (from 6 fewer to 57 fewer)	Very low
rFSH vs. hCG					
1 (Gomes et al., (2007)	3/17 (18%) women	6/17 (35%) women	RR 0.5 (0.2 to 1.7)	176 fewer per 1000 (from 300 fewer to 240 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
rFSH + rLH vs. uhMG					
1 (Pacchiarotti et al., 2010)	15/62 (24%) women	17/60 (28%) women	RR 0.9 (0.5 to 1.6)	42 fewer per 1000 (from 150 fewer to 156 more)	Very low
rFSH + hCG vs. rFSH + rLH					
1 (Drakakis et al., 2009)	16/60 (27%) women	6/60 (10%) women	RR 2.7 (1.1 to 6.4)	167 more per 1000 (from 12 more to 535 more)	Very low
rFSH vs. pFSH					
1 (Van Wely et al., 2011)	244/891 (27%) women	150/669 (22%) women	OR 1.3 (1.0 to 1.7)	49 more per 1000 (from 5 more to 99 more)	Very low
rFSH vs. hp-FSH					
2 (Aboulghar et al., 2010 and Van Wely et al., 2011)	627/2115 (30%) women	615/2116 (29%) women	RR 1.0 (0.9 to 1.1)	9 more per 1000 (from 17 fewer to 38 more)	Very low
rFSH vs. uFSH					
4 (Coelingh Bennink et al., 1998; Kahn et al., 1999; Raga et al., 1999; Tanbo et al., 2001)	105/292 (36%)	74/219 (33%)	RR 1.1 (0.8 to 1.4)	24 more per 1000 (from 54 fewer to 118 more)	Very low
rFSH vs. hFSH					
2 (Gholami et al., 2010; Selman et al., 2010)	42/118 (35%)	47/122 (38%)	RR 0.9 (0.7 to 1.3)	27 fewer per 1000 (from 127 fewer to 112 more)	Very low
rFSH vs. rFSH + hFSH					
1 (Selman et al., 2010)	21/65 (32%) women	27/63 (43%) women	RR 0.8 (0.5 to 1.2)	107 fewer per 1000 (from 223 fewer to 81 more)	Very low
rFSH + hFSH vs. hFSH					
1 (Selman et al., 2010)	27/63 (43%) women	23/60 (38%) women	RR 1.1 (0.7 to 1.7)	46 more per 1000 (from 103 fewer to 276 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
rFSH + hp-FSH vs. hp-FSH					
1 (Battaglia et al., 2000)	5/20 (25%) women	2/18 (11%) women	RR 2.3 (0.5 to 10.2)	139 more per 1000 (from 56 fewer to 1000 more)	Very low
rFSH vs. rFSH + hMG					
6 (Check et al., 2008; De Placido et al., 2001; Devesa et al., 2010; Drakakis et al., 2005; Loutradis et al., 2003; Sohrabvand et al., 2010)	146/496 (29%) women	66/253 (26%) women	RR 1.0 (0.8 to 1.3)	5 fewer per 1000 (from 65 fewer to 73 more)	Very low
rFSH vs. rFSH + hCG					
1 (Ashrafi et al., 2011)	14/27 (52%) women	26/51 (51%) women	RR 1.0 (0.7 to 1.6)	10 more per 1000 (from 178 fewer to 306 more)	Moderate
Adverse pregnancy outcome					
rFSH vs. uFSH (abortions before 12 weeks after hCG administration)					
1 (Coelingh Bennink et al., 1998)	10/105 (10%) women	6/67 (9%) women	RR 1.1 (0.4 to 2.8)	5 more per 1000 (from 53 fewer to 160 more)	Low
	10/32 (31%) pregnancies	6/19 (32%) pregnancies	RR 1.0 (0.4 to 2.3)	3 fewer per 1000 (from 180 fewer to 407 more)	
rFSH vs. hFSH (miscarriage)					
2 (Gholami et al., 2010; Selman et al., 2010)	5/118 (4%) women	6/122 (5%) women	RR 0.9 (0.3 to 2.7)	7 fewer per 1000 (from 36 fewer to 86 more)	Very low
	5/42 (12%) pregnancies	6/47 (13%) pregnancies	RR 0.9 (0.3 to 2.8)	9 fewer per 1000 (from 88 fewer to 234 more)	

Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. rFSH + hFSH (abortion)					
1 (Selman et al., 2010)	3/65 (5%) women	4/63 (6%) women	RR 0.7 (0.2 to 3.1)	17 fewer per 1000 (from 53 fewer to 135 more)	Low
	3/21 (14%) pregnancies	4/27 (15%) pregnancies	RR 1.0 (0.2 to 3.9)	6 fewer per 1000 (from 113 fewer to 422 more)	
rFSH + hFSH vs. hFSH (abortion)					
1 (Selman et al., 2010)	4/63 (6%) women	3/60 (5%) women	RR 1.3 (0.3 to 5.4)	13 more per 1000 (from 35 fewer to 222 more)	Low
	4/27 (15%) pregnancies	3/23 (13%) pregnancies	RR 1.1 (0.3 to 4.6)	18 more per 1000 (from 94 fewer to 464 more)	
rFSH vs rFSH + hCG (miscarriage)					
1 (Blockeel et al., 2009)	3/35 (9%) women	3/35 (9%) women	RR 1 (0.2 to 4.6)	0 fewer per 1000 (from 67 fewer to 310 more)	Very low
	Not reported per clinical pregnancy				
rFSH vs rFSH + hCG (ectopic pregnancy)					
1 (Blockeel et al., 2009)	1/35 (3%) women	0/35 (0%) women	RR 3 (0.1 to 71.2)	Not calculable	Very low
	Not reported per clinical pregnancy				
rFSH vs. rFSH + hMG (abortion)					
1 (De Placido et al., 2001)	2/23 (8%) women	1/20 (5%) women	RR 1.7 (0.2 to 17.8)	37 more per 1000 (from 42 fewer to 839 more)	Very low
	2/8 (25%) pregnancies	1/10 (10%) pregnancies	RR 2.5 (0.3 to 22.9)	150 more per 1000 (from 73 fewer to 1000 more)	

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Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. hCG (miscarriage)					
1 (Gomes et al., 2007)	1/17 (6%) women	3/17 (18%) women	RR 0.3 (0.0 to 2.9)	118 fewer per 1000 (from 169 fewer to 334 more)	Very low
	1/3 (33%) pregnancies	3/6 (50%) pregnancies	RR 0.7 (0.1 to 4.0)	165 fewer per 1000 (from 445 fewer to 1000 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
rFSH vs. rFSH + hMG					
1 (Check et al., 2008)	2/22 (9%) women	2/20 (10%) women	RR 0.9 (0.1 to 5.9)	9 fewer per 1000 (from 86 fewer to 486 more)	Very low
	2/7 (29%) pregnancies	2/10 (20%) pregnancies	RR 1.4 (0.3 to 7.9)	86 more per 1000 (from 148 fewer to 1000 more)	
rFSH vs. rFSH + hCG					
1 (Ashrafi et al., 2011)	4/27 (15%) women	3/51 (6%) women	RR 2.5 (0.6 to 10.4)	89 more per 1000 (from 23 fewer to 555 more)	Moderate
	4/14 (29%) pregnancies	3/26 (12%) pregnancies	RR 2.5 (0.6 to 9.5)	171 more per 1000 (from 42 fewer to 985 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
rFSH vs. hMG/hp-hMG					
1 (Van Wely et al., 2011)	27/1604 (2%) women	27/1593 (2%) women	OR 1.0 (0.6 to 1.7)	0 fewer per 1000 (from 7 fewer to 12 more)	Very low
rFSH vs. pFSH					
1 (Van Wely et al., 2011)	24/855 (3%) women	9/635 (1%) women	OR 1.8 (0.9 to 3.6) z	11 more per 1000 (from 1 fewer to 35 more)	Very low

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Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
rFSH vs. hp-FSH					
1 (Van Wely et al., 2011)	41/1535 (3%) women	37/1518 (2%) women	OR 1.1 (0.7 to 1.8)	3 more per 1000 (from 7 fewer to 18 more)	Very low
rFSH vs. rFSH + hCG					
1 (Ashrafi et al., 2011)	4/27 (15%) women	0/54 (0%) women	RR 17.7 (0.9 to 316.9)	Not calculable	Low
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, FSH follicle-stimulating hormone, pFSH purified follicle-stimulating hormone, highly purified follicle-stimulating hormone, rFSH recombinant follicle-stimulating hormone, rh-FSH recombinant human follicle-stimulating hormone, hMG human menopausal gonadotrophin, rLH recombinant luteinizing hormone , rh-LH recombinant human luteinizing hormone, hCG human chorionic gonadotropin, RR relative risk

[a] this result was significantly in favour of hMG at 2 decimal places

[b] this result was significantly in favour of hMG at 2 decimal places

Table 15.10 GRADE findings for comparisons of urinary with urinary gonadotrophins and recombinant with recombinant gonadotrophins

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
rhFSH vs. rhFSH + rhLH					
2 (Matorras et al., 2009; Tarlatzis et al., 2006)	15/125 (12%) women	18/118 (15%) women	RR 0.8 (0.2 to 3.2) [g]	32 fewer per 1000 (from 122 fewer to 339 more)	Very low
rhFSH vs. hMG					
1 (Quigley et al., 1988)	4/48 (8%) women	2/50 (4%) women	RR 2.1 (0.4 to 10.9)	43 more per 1000 (from 24 fewer to 394 more)	Low

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy					
pFSH vs. pFSH + hMG					
1 (Balasch et al., 1996)	13/92 (14%) women	11/96 (12%) women	RR 1.2 (0.6 to 2.6)	26 more per 1000 (from 48 fewer to 184 more)	Very low
hp-FSH vs. hp-FSH + hMG					
2 (Balasch et al., 1996; and Ku et al., 2003)	22/149 (15%) women	23/148 (16%) women	RR 1.0 (0.4 to 2.5) [g]	6 more per 1000 (from 87 fewer to 233 more)	Very low
rhFSH vs. rhFSH + rhLH					
6 (Balasch et al., 2001; Barrenetxea et al., 2008; Fabregues et al., (2011); Marrs et al., 2004; Matorras et al., 2009; Tarlatzis et al., 2006)	148/462 (32%) women	157/513 (31%) women	RR 1.1 (0.8 to 1.4) [g]	15 more per 1000 (from 67 fewer to 125 more)	Very low
rhFSH + rhLH vs. rhLH					
1 (Dunerin et al., 2008)	24/75 (32%) women	23/71 (32%) women	RR 1.0 (0.6 to 1.6)	3 fewer per 1000 (from 123 fewer to 188 more)	Very low
rFSH vs. rFSH + rLH					
7 (Caserta et al., 2011; Ferraretti et al., (2004; Griesinger et al., 2005; Kovacs et al., 2010; Levi-Setti et al., 2006; NyboeAndersen et al., 2008; Pezzuto et al., 2010)	183/957 (19%) women	221/951 (23%) women	RR 0.8 (0.6 to 1.1)	49 fewer per 1000 (from 100 fewer to 28 more)	Very low
hCG vs. hMG					
1 (Gomes et al., 2007)	6/17 (35%) women	6/17 (35%) women	RR 1 (0.4 to 2.5)	0 fewer per 1000 (from 212 fewer to 522 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome					
pFSH vs. pFSH + hMG (clinical abortion)					
1 (Balasch et al., 1996)	2/92 (2%) women	2/96 (2%) women	RR 1.0 (0.2 to 7.3)	1 more per 1000 (from 18 fewer to 130 more)	Very low
	2/13 (15%) pregnancies	2/11 (18%) pregnancies	RR 0.9 (0.1 to 5.1)	27 fewer per 1000 (from 156 fewer to 738 more)	
Hp-FSH vs. hp-FSH + hMG (clinical abortion)					
1 (Balasch et al., 1996)	2/123 (2%) women	4/129 (3%) women	RR 0.5 (0.1 to 2.8)	15 fewer per 1000 (from 28 fewer to 56 more)	Very low
	2/16 (13%) pregnancies	4/21 (19%) pregnancies	RR 0.7 (0.1 to 3.2)	65 fewer per 1000 (from 164 fewer to 410 more)	
rFSH vs. rFSH + rLH (abortion)					
1 (Ferraretti et al., 2004)	1/45 (2%) women	2/41 (5%) women	RR 0.5 (0.0 to 4.8)	26 fewer per 1000 (from 47 fewer to 187 more)	Very low
	1/11 (9%) women	2/22 (9%) women	RR 1 (0.1 to 9.9)	0 fewer per 1000 (from 82 fewer to 805 more)	
rFSH vs. rFSH + rLH (miscarriage before 12 weeks)					
1 (Griesinger et al., 2005)	3/65 (5%) women	8/62 (13%) women	RR 0.4 (0.1 to 1.3)	83 fewer per 1000 (from 116 fewer to 37 more)	Very low
	Not reported per clinical pregnancy				
rhFSH vs. rhFSH + rhLH (miscarriage)					
1 (Fabregues et al., 2011)	4/62 (7%) women	6/125 (5%) women	RR 1.3 (0.4 to 4.6)	16 more per 1000 (from 29 fewer to 172 more)	Low
	4/22 (18%) pregnancies	6/31 (19%) pregnancies	RR 0.9 (0.3 to 2.9)	12 fewer per 1000 (from 135 fewer to 375 more)	

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rhFSH + rhLH vs. rhLH (miscarriage)					
1 (Tarlatzis et al., 2006)	4/57 (7%) women	3/55 (5%) women	RR 1.29 (0.3 to 5.5)	16 more per 1000 (from 38 fewer to 245 more)	Low
	4/14 (29%) pregnancies	3/9 (33%) pregnancies	RR 0.9 (0.3 to 3.0)	47 fewer per 1000 (from 250 fewer to 653 more)	
hCG vs. hMG (miscarriage)					
1 (Gomes et al., 2007)	3/17 (18%) women	0/17 (0%) women	RR 7 (0.4 to 126.0)	Not calculable	Very low
	3/6 (50%) pregnancies	0/6 (0%) pregnancies	RR 7 (0.4 to 111.9)	Not calculable	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
rhFSH vs. rhFSH + rhLH					
1 (Fabruegues et al., 2011)	6/62 (10%) women	6/125 (5%) women	RR 2.0 (0.7to 6.0)	49 more per 1000 (from 15 fewer to 240 more)	Low
	6/22 (27%) pregnancies	6/31 (19%) pregnancies	RR 1.41 (0.52 to 3.8)	79 more per 1000 (from 93 fewer to 542 more)	
rFSH vs. rFSH + rLH					
1 (NyboeAndersen et al., 2008)	16/261 (6%) women	20/265 (8%) women	RR 0.8 (0.4 to 1.5)	14 fewer per 1000 (from 43 fewer to 40 more)	Very low
	16/88 (18%) pregnancies	20/83 (24%) pregnancies	RR 0.8 (0.4 to 1.4)	60 fewer per 1000 (from 140 fewer to 84 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Ovarian hyperstimulation syndrome (OHSS)					
pFSH vs. pFSH + hMG					
1 (Balasch et al., 1996)	1/92 (1%) women	2/96 (2%) women	RR 0.5 (0.1 to 5.7)	10 fewer per 1000 (from 20 fewer to 97 more)	Very low
hp-FSH vs. hp-FSH + hMG					
1 (Balasch et al., 1996)	2/123 (2%) women	3/129 (2%) women	RR 0.7 (0.1 to 4.1)	7 fewer per 1000 (from 20 fewer to 72 more)	Very low
rFSH vs. rFSH + rLH					
1 (Caserta et al., 2011)	6/521 (1%) women	1/518 (0.2%) women	RR 6.0 (0.7 to 49.4)	10 more per 1000 (from 1 fewer to 93 more)	Low
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, FSH follicle-stimulating hormone, pFSH purified follicle-stimulating hormone, highly purified follicle-stimulating hormone, rFSH recombinant follicle-stimulating hormone, rh-FSH recombinant human follicle-stimulating hormone, hMG human menopausal gonadotrophin, rLH recombinant luteinizing hormone , rh-LH recombinant human luteinizing hormone, hCG human chorionic gonadotropin, RR relative risk

Table 15.11 GRADE findings for comparison of dosages of FSH/rFSH for ovarian stimulation

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decreased to 150 IU/day for three days) (low response)					
1 (Koundouros et al., 2008)	13/75 (17%) women	11/75 (15%) women	RR 1.2 (0.6 to 2.5)	26 more per 1000 (from 63 fewer to 216 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
150 IU rFSH vs. 225 IU rFSH					
1 (Yong et al., 2003)	7/60 (12%) women	9/63 (14%) women	RR 0.8 (0.3 to 2.1)	26 fewer per 1000 (from 97 fewer to 150 more)	Very low
Clinical pregnancy					
150 IU rFSH vs. 200 IU rFSH					
3 (Cavagna et al., 2006; Harrison et al., 2001; Out et al., 2004)	79/318 (24%)	73/319 (22%)	RR 1.1 (0.8 to 1.4)	18 more per 1000 (from 41 fewer to 98 more)	Very low
100 IU rFSH vs. 200 IU rFSH					
5 (De Jong et al., 2000; Hoomans et al., 2002; Out et al., 1999; Out et al., 2001; Tan et al., 2005)	93/460 (20%) women	92/455 (20%) women	RR 1 (0.8 to 1.3)	0 fewer per 1000 (from 47 fewer to 59 more)	Very low
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decreased to 150 IU/day for three days) (low response)					
1 (Koundouros et al., 2008)	18/75 (24%) women	20/75 (27%) women	RR 0.9 (0.5 to 1.6)	27 fewer per 1000 (from 128 fewer to 149 more)	Very low
300 IU rFSH vs. 400 IU rFSH					
1 (Harrison et al., 2001)	2/24 (8%) women	2/24 (8%) women	RR 1 (0.2 to 6.5)	0 fewer per 1000 (from 71 fewer to 461 more)	Very low
150 IU rFSH vs. 300 IU rFSH					
1 (Klinkert et al., 2005)	3/26 (11%)	1/26 (3%)	RR 3.0 (0.3 to 27.0)	77 more per 1000 (from 26 fewer to 1000 more)	Very low
150 IU rFSH vs. 250 rFSH					
2 (Latin-American, 2001; Out et al., 2000)	44/268 (16%) women	42/276 (15%) women	RR 1.1 (0.7 to 1.6)	12 more per 1000 (from 41 fewer to 90 more)	Low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Individual dose (100 to 250 IU) rFSH vs. 150 IU rFSH					
1 (Popovic-Todorovic et al., 2003)	48/131 (37%) women	32/131 (24%) women	RR 1.5 (1.0 to 2.2)	122 more per 1000 (from 7 more to 288 more)	Very low
150 IU rFSH vs. 225 IU rFSH					
1 (Wikland et al., (2001)	21/60 (35%) women	24/60 (40%) women	RR 0.9 (0.6 to 1.4)	48 fewer per 1000 (from 180 fewer to 156 more)	Very low
Low dose FSH (between 37.5 IU and 75 IU) vs. standard dose FSH (between 112.5 IU and 225 IU)					
1 (Zhu et al., 2009)	33/60 (57%) women	31/60 (60%) women	RR 1.1 (0.8 to 1.5)	31 more per 1000 (from 124 fewer to 253 more)	Very low
Adverse pregnancy outcome					
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decrease of 150 IU/day for three days) (low response) (miscarriage)					
1 (Koundouros et al., 2008)	7/75 (9%) women	9/75 (12%) women	RR 0.8 (0.3 to 2.0)	26 fewer per 1000 (from 83 fewer to 118 more)	Very low
	7/18 (39%) pregnancies	9/20 (45%) pregnancies	RR 0.9 (0.4 to 1.8)	63 fewer per 1000 (from 266 fewer to 378 more)	
100 IU rFSH vs. 200 IU rFSH (miscarriage)					
2 (Hoomans et al., 2002; Out et al.,2001)	3/254 (1%) women	10/255 (4%) women	RR 0.3 (0.1 to 1.1)	27 fewer per 1000 (from 36 fewer to 2 more)	Very low/Low
	3/49 (6%) pregnancies	10/45 (22%) pregnancies	RR 0.3 (0.1 to 0.9)	162 fewer per 1000 (from 18 fewer to 204 fewer)	
150 IU rFSH vs. 250 rFSH (extra-uterine pregnancy)					
1 (Latin-American Puregon IVF study group, 2001)	1/201 (1%) women	0/203 (0%) women	RR 3.0 (0.1 to 73.9)	Not calculable	Moderate
	1/34 (3%) pregnancies	0/33 (0%) pregnancies	RR 2.9 (0.1 to 69.1)	Not calculable	

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
100 IU rFSH vs. 200 IU rFSH (ectopic pregnancy and/or miscarriage)					
2 (Outet al., 1999; Tan et al., 2005)	13/198 (7%) women	5/193 (3%) women	RR 2.2 (0.5 to 10.8) [r]	32 more per 1000 (from 14 fewer to 254 more)	Very low /Moderate
	10/16 (63%) pregnancies	2/23 (9%) pregnancies	RR 7.2 (1.8 to 28.5)	538 more per 1000 (from 70 more to 1000 more)	
150 IU rFSH vs 200 rFSH (miscarriage and/or ectopic pregnancy)					
1 (Out et al., 1999)	8/132 (6%) women	9/132 (7%) women	RR 0.9 (0.4 to 2.2)	8 fewer per 1000 (from 44 fewer to 84 more)	Low
	8/41 (20%) pregnancies	9/32 (28%) pregnancies	RR 0.7 (0.3 to 1.6)	87 fewer per 1000 (from 197 fewer to 169 more)	
Individual dose (100 to 250 IU) rFSH vs. 150 IU rFSH (biochemical pregnancy, abortion, or extrauterine pregnancy)					
1 (Popovic-Todorovic et al., 2003)	11/131 (8%) women	15/131 (11%) women	RR 0.7 (0.4 to 1.5)	31 fewer per 1000 (from 74 fewer to 62 more)	Very low
	11/48 (23%) pregnancies	15/32 (47%) pregnancies	RR 0.5 (0.3 to 0.9)	239 fewer per 1000 (from 37 fewer to 347 fewer)	
150 IU rFSH vs. 225 IU rFSH (miscarriage or extrauterine pregnancies)					
1 (Wiklandet al., 2001)	6/60 (10%) women	9/60 (15%) women	RR 0.7 (0.3 to 1.8)	49 fewer per 1000 (from 113 fewer to 114 more)	Very low
	6/21 (28.6%) pregnancies	9/24 (37.5%) pregnancies	RR 0.8 (0.3 to 1.8)	90 fewer per 1000 (from 251 fewer to 292 more)	
150 IU rFSH vs. 225 IU rFSH (miscarriage)					
1 (Yong et al., 2003)	1/60 (2%) women	1/63 (2%) women	RR 1.1 (0.1 to 16.4)	1 more per 1000 (from 15 fewer to 245 more)	Very low
	Not reported per clinical pregnancy				

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decrease of 150 IU/day for three days) (low response)					
1 (Koundouros et al., 2008)	4/74 (5%) women	5/75 (7%) women	RR 0.8 (0.2 to 2.9)	13 fewer per 1000 (from 51 fewer to 127 more)	Very low
	4/18 (22%) pregnancies	5/20 (20%) pregnancies	RR 0.9 (0.3 to 2.8)	28 fewer per 1000 (from 180 fewer to 452 more)	
100 IU rFSH vs. 200 IU rFSH					
1 (Hoomans et al., 2002)	9/163 (6%) women	9/167 (5%) women	RR 1.0 (0.4 to 2.5)	1 more per 1000 (from 31 fewer to 82 more)	Very low
	9/32 (28%) pregnancies	9/30 (30%) pregnancies	RR 0.9 (0.4 to 2.0)	18 fewer per 1000 (from 171 fewer to 312 more)	
150 IU rFSH vs. 300 IU rFSH					
1 (Klinkert et al.,2005)	0/26 (0%) women	0/26 (0%) women	Not calculable	Not calculable	Very low
	0/3 (0%) pregnancies	0/1 (0%) pregnancies	Not calculable	Not calculable	
150 IU rFSH vs. 250 rFSH					
1 (Latin-American Puregon IVF study group, 2001)	16/201 (8%) women	9/203 (4%) women	RR 1.8 (0.8 to 4.0)	35 more per 1000 (from 8 fewer to 132 more)	Moderate
	16/34 (47%) pregnancies	9/33 (27%) pregnancies	RR 1.7 (0.9 to 3.3)	199 more per 1000 (from 30 fewer to 638 more)	
150 IU rFSH vs. 225 IU rFSH					
2 (WIkland et al., 2001; Yong et al., 2003)	5/120 (4%)	8/123 (7%)	RR 0.6 (0.2 to 1.9)	23 fewer per 1000 (from 51 fewer to 58 more)	Very low
	5/28 (18%)	8/33 (24%)	RR 0.8 (0.3 to 2)	61 fewer per 1000 (from 175 fewer to 242 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple births (the number of babies born from a multiple pregnancy out of the total number of babies born)					
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decreased to 150 IU/day for three days) (low response)					
1 (Koundouros et al., 2008)	8/21 (38%) babies	10/21 (48%) babies	RR 0.8 (0.4 to 1.6)	95 fewer per 1000 (from 290 fewer to 295 more)	Very low
Ovarian hyperstimulation syndrome (OHSS)					
150 IU FSH vs. 200 IU FSH					
2 (Cavagna et al., 2006; and Out et al., 2004)	8/172 (5%) women	10/168 (6%) women	RR 0.8 (0.3 to 2.0)	12 fewer per 1000 (from 40 fewer to 57 more)	Very low
Low dose step-up FSH (75 IU/day for 6 days, increased by 37.5 IU/day thereafter) vs. step-down FSH (225 IU/day for 3 days then decreased to 150 IU/day for three days) (low response)					
1 (Koundouros et al., 2008)	3/75 (4%) women	8/75 (11%) women	RR 0.4 (0.1 to 1.4)	66 fewer per 1000 (from 96 fewer to 38 more)	Very low
100 IU rFSH vs. 200 IU rFSH					
3 (Hoomans et al. 2002; Out et al., 2001; Tan et al. 2005)	8/351 (2%) women	9/350 (3%) women	RR 1.0 (0.3 to 4.0)	0 fewer per 1000 (from 19 fewer to 76 more)	Very low
150 IU rFSH vs. 300 IU rFSH					
1 (Klinkert et al., 2005)	0/26 (0%) women	0/26 (0%) women	Not calculable	Not calculable	Very low
150 IU rFSH vs. 250 rFSH					
1 (Latin-American Puregon IVF study group, 2001)	5/201 (3%) women	8/203 (4%) women	RR 0.6 (0.2 to 2.0)	15 fewer per 1000 (from 31 fewer to 35 more)	Moderate
150 IU rFSH vs. 225 IU rFSH					
1 (Yong et al., 2003)	0/60 (0%) women)	4/63 (6%) women	RR 0.1 (0.0 to 2.1)	56 fewer per 1000 (from 63 fewer to 71 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Low dose FSH (between 37.5 IU and 75 IU) vs. standard dose FSH (between 112.5 IU and 225 IU)					
1 (Zhu et al.,2009)	4/60 (7%) women	12/60 (20%) women	RR 0.3 (0.1 to 1.0)	134 fewer per 1000 (from 4 fewer to 178 fewer)	Very low
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, FSH follicle-stimulating hormone, rFSH recombinant follicle-stimulating hormone, IU international units, RR relative risk

Table 15.12 GRADE findings for comparison of unstimulated IVF with stimulation with clomifene citrate and/or gonadotrophins (no IVF/ICSI)

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
No evidence reported					
Clinical pregnancy					
No evidence reported					
Adverse pregnancy outcome					
No evidence reported					
Multiple pregnancies (the number of pregnancies with more than one fetus)					
No evidence reported					
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
No evidence reported					
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

Table 15.13 GRADE findings for comparison of GnRH agonist plus gonadotrophins IVF/ICSI cycles with clomifene citrate plus gonadotrophins (plus GnRH antagonist) IVF/ICSI cycles

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
GnRH agonist + hMG vs. CC + hMG					
1 (Long et al., 1995)	1/36 (3%) women	4/36 (11%) women	RR 0.3 (0.0 to 2.1)	83 fewer per 1000 (from 108 fewer to 126 more)	Very low
GnRH agonist + hMG/FSH vs. CC + hMG + GnRH antagonist					
1 (Lin et al., 2006)	21/60 (35%) women	22/60 (37%) women	RR 1.0 (0.6 to 1.5)	18 fewer per 1000 (from 150 fewer to 198 more)	Very low
Clinical pregnancy					
GnRH agonist + hMG vs. CC + hMG					
3 (Dhont et al.,1995; Grochowski et al., 1999; Long et al., 1995)	87/315 (27.6%)	74/317 (23.3%)	RR 1.2 (0.8 to 1.7) [h]	44 more per 1000 (from 44 fewer to 173 more)	Very low
GnRH agonist + gonadotrophins vs. CC + hMG + GnRH antagonist					
2 (Karimzadeh and Lin, 2006)	55/160 (34%) women	62/160 (39%) women	RR 0.9 (0.7 to 1.2)	43 fewer per 1000 (from 132 fewer to 70 more)	Very low
GnRH agonist + rFSH vs. CC + rFSH + rLH + corticosteroid					
1Weigert et al., 2002)	41/140 (29%) women	54/154 (35%) women	RR 0.8 (0.6 to 1.2)	56 fewer per 1000 (from 140 fewer to 60 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome					
GnRH agonist + hMG vs. CC + hMG (miscarriage)					
1 (Long et al., 1995)	2/36 (6%) women	0/36 (0%) women	RR 5.0 (0.3 to 100.6)	Not calculable	Very low
	2/5 (40%) pregnancies	0/5 (0%) pregnancies	RR 5.0 (0.3 to 83.7)	Not calculable	
GnRH agonist + hMG vs. CC + hMG (ectopic)					
1 (Long et al., 1995)	0/36 (0%) women	1/36 (3%) women	RR 0.3 (0.0 to 7.9)	19 fewer per 1000 (from 28 fewer to 192 more)	Very low
	0/5 (0%) pregnancies	1/5 (20%) pregnancies	RR 0.3 (0.0 to 6.7)	134 fewer per 1000 (from 196 fewer to 1000 more)	
GnRH agonist (triptorelin) + hMG vs. CC + hMG (pregnancy loss)					
1 (Harrison et al., 1994)	3/50 (6%) women	4/50 (8%) women	RR 0.8 0.2 to 3.2)	20 fewer per 1000 (from 66 fewer to 174 more)	Low
	Not reported per clinical pregnancy				
GnRH agonist (buserelin) + hMG vs. CC + hMG (pregnancy loss)					
1 (Harrison et al., 1994)	3/50 (6%) women	4/50 (8%) women	RR 0.8 (0.2 to 3.2)	20 fewer per 1000 (from 66 fewer to 174 more)	Low
	Not reported per clinical pregnancy				
GnRH agonist + hMG/FSH vs. CC + hMG + GnRH antagonist (abortion or stillbirth)					
1 (Lin et al., 2006)	3/60 (5%) women	3/60 (5%) women	RR 1 (0.2 to 4.8)	0 fewer per 1000 (from 40 fewer to 188 more)	Low
	3/24 (13%) pregnancies	3/25 (12%) pregnancies	RR 1.0 (0.2 to 4.7)	5 more per 1000 (from 92 fewer to 439 more)	

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
GnRH agonist + rFSH vs. CC + rFSH + rLH + corticosteroid (early pregnancy losses)					
1 (Weigert et al., 2002)	7/140 (5%) women	10/154 (6%) women	RR 0.8 (0.3 to 2.0)	15 fewer per 1000 (from 45 fewer to 63 more)	Very low
	7/41 (17%) pregnancies	10/54 (19%) pregnancies	RR 0.9 (0.4 to 2.2)	15 fewer per 1000 (from 115 fewer to 224 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
GnRH agonist + hMG vs. CC + hMG					
1 (Grochowski et al., 1999)	7/164 (4%) women	3/160 (2%) women	RR 2.3 (0.6 to 8.7)	24 more per 1000 (from 7 fewer to 143 more)	Very low
	7/41 (17%) pregnancies	3/38 (8%) pregnancies	RR 2.2 (0.6 to 7.8)	92 more per 1000 (from 32 fewer to 534 more)	
GnRH agonist (triptorelin) + hMG vs. CC + hMG					
1(Harrison et al., 1994)	5/50 (10%) women	3/50 (6%) women	RR 1.7 (0.4 to 6.6)	40 more per 1000 (from 35 fewer to 336 more)	Low
	Not reported per clinical pregnancy				
GnRH agonist (buserelin) + hMG vs. CC + hMG					
1(Harrison et al., 1994)	5/50 (10%) women	3/50 (6%) women	RR 1.7 (0.4 to 6.6)	40 more per 1000 (from 35 fewer to 336 more)	Low
	Not reported per clinical pregnancy				
Multiple births (the number of babies born from a multiple pregnancy)					
GnRH agonist + hMG vs. CC + hMG					
1 (Long et al., 1995)	2/3 (67%) babies	0/4 (0%) babies	RR 6.3 (0.4 to 96.5)	Not calculable	Very low
Ovarian hyperstimulation syndrome (OHSS)					
GnRH agonist + hMG vs. CC + hMG					
1 (Grochowski et al., 1999)	5/160 (3%) women	41/164 (25%) women	RR 0.1 (0.1 to 0.3)	220 fewer per 1000 (from 172 fewer to 237 fewer)	Low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
GnRH agonist + gonadotrophins vs. CC + hMG + GnRH antagonist					
2(Karimzadeh and Lin, 2006)	9/160 (6%) women	1/160 (1%) women	RR 6.3 (1.2 to 35)	33 more per 1000 (from 1 more to 212 more)	Low
GnRH agonist + rFSH vs. CC + rFSH + rLH + corticosteroids					
1 (Weigert et al.,2002)	12/140 (9%) women	4/154 (3%) women	RR 3.3 (1.1 to 10.0)	60 more per 1000 (from 2 more to 234 more)	Low
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
GnRH agonist + FSH/hMG vs. natural cycle or CC stimulated IVF					
1 (Hojgaard et al., 2001)	60/64 (94%) women	139/141 (99%) women	RR 1.0 (0.9 to 1.0)	49 fewer per 1000 (from 108 fewer to 20 more)	Moderate
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CC clomifene citrate, CI confidence interval, FSH follicle-stimulating hormone, GnRH gonadotropin-releasing hormone, hCG human chorionic gonadotropin, hMG human menopausal gonadotrophin, IU international units, LH luteinizing hormone, RR relative risk

Table 15.14 GRADE findings for comparison of adjuvant growth hormone for women with a previous low response

Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Growth hormone + GnRH agonist + FSH and/or hMG + hCG vs. GnRH agonist + FSH and/or hMG + hCG					
1 (Duffy et al., 2010)	6/23 (26%) women	0/15 (0%) women	OR 5.8 (0.7 to 50.4) [d]	Not estimable	Low

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Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
Clinical pregnancy					
Growth hormone + GnRH agonist + FSH and/or hMG + hCG vs. GnRH agonist + FSH and/or hMG + hCG					
1 (Duffy et al., 2010)	19/62 (31%) women	8/54 (15%) women	OR 2.6 (1.0 to 6.5)	163 more per 1000 (from 0 more to 728 more)	Low
Adverse pregnancy outcome					
No evidence reported					
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Growth hormone + GnRH agonist + FSH + hCG vs. placebo + GnRH agonist + FSH + hCG (using 4 IU GH group only)					
1 (Suikkari et al., 1996)	1/10 (10%) women	0/6 (0%) women	RR 1.9 (0.1 to 40.6)	Not estimable	Very low
	1/2 (50%) pregnancies	0/0 (0%) pregnancies	Not estimable		
Growth hormone + GnRH agonist + FSH + hCG vs. placebo + GnRH agonist + FSH + hCG (using 12 IU GH group only)					
1 (Suikkari et al., 1996)	0/6 (0%) women	0/6 (0%) women	Not estimable		Low
	0/0 (0%) pregnancies	0/0 (0%) pregnancies	Not estimable		
Growth hormone + hMG + GnRH agonist + hCG + hCG vs. placebo + hMG + GnRH agonist + hCG + hCG					
1(Owen et al., 1991)	2/13 (15%) women	0/12 (0%) women	RR 4.6 (0.3 to 87.9)	Not estimable	Very low
	2/4 (50%) pregnancies	0/1 (0%) pregnancies	RR 2 (0.2 to 25.8)	Not estimable	
Multiple births (the number of babies born from a multiple pregnancy)					
Growth hormone + GnRH agonist + FSH + hCG vs. placebo + GnRH agonist + FSH + hCG (using 4 IU GH group only)					
1 (Suikkari et al., 1996)	1/2 (50%) babies	0/0 (0%) babies	Not estimable		Low
Growth hormone + hMG + GnRH agonist + hCG + hCG vs. placebo + hMG + GnRH agonist + hCG + hCG					
1 (Owen et al., 1991)	4/6 (67%) babies	0/1 (0%) babies	RR 2.6 (0.2 to 30.2)	Not estimable	Very low
Ovarian hyperstimulation syndrome (OHSS)					
No evidence was reported					
Congenital abnormalities					
No evidence was reported					

Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
Patient satisfaction					
No evidence was reported					
Health related quality of life					
No evidence was reported					
Anxiety and/or depression					
No evidence was reported					

CC clomifene citrate, CI confidence interval, FSH follicle-stimulating hormone, GnRH gonadotropin-releasing hormone, hCG human chorionic gonadotropin, hMG human menopausal gonadotrophin, IU international units, LH luteinizing hormone, RR relative risk

Table 15.15 GRADE findings for comparison of adjuvant DHEA for women with a previous low response

Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
DHEA + GnRH agonist + rFSH + rhCG + progesterone vs. GnRH agonist + rFSH + rhCG + progesterone					
1 (Wiser et al., 2010)	6/17 (35%) women	1/16 (6%) women	RR 5.7 (0.8 to 41.9)	291 more per 1000 (from 15 fewer to 1000 more)	Very low
Clinical pregnancy					
DHEA + GnRH agonist + rFSH + rhCG + progesterone vs. GnRH agonist + rFSH + rhCG + progesterone					
1 (Wiser et al., 2010)	7/17 (41%) women	3/16 (19%) women	RR 2.2 (0.7 to 7.1)	225 more per 1000 (from 60 fewer to 1000 more)	Very low
Adverse pregnancy outcome					
DHEA + GnRH agonist + rFSH + rhCG + progesterone vs. GnRH agonist + rFSH + rhCG + progesterone (abortion)					
1 (Wiser et al., 2010)	1/17 (6%) women	2/16 (13%) women	RR 0.5 (0.1 to 4.7)	66 fewer per 1000 (from 119 fewer to 462 more)	Very low
	1/7 (14%) pregnancies	2/3 (67%) pregnancies	RR 0.2 (0.0 to 1.6)	527 fewer per 1000 (from 647 fewer to 373 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
No evidence reported					

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Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
No evidence reported					
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

DHEA dehydroepiandrosterone, GnRH gonadotropin-releasing hormone, rFSH recombinant follicle-stimulating hormone, rhCG recombinant human chorionic gonadotropin, RR relative risk

Evidence statements

Unstimulated IVF compared with stimulated IVF (Table 15.7)

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births when comparing stimulated with natural cycle IVF.

Clinical pregnancy

There were significantly more clinical pregnancies when comparing clomifene citrate stimulated cycles to natural cycle IVF. There was no significant difference in the number of clinical pregnancies when comparing GnRH agonist and gonadotrophin with natural cycle IVF in low response women.

Adverse pregnancy outcome

No evidence was reported on adverse pregnancy outcomes in stimulated compared with non stimulated IVF or ICSI cycles.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing clomifene citrate stimulated cycles with natural cycle IVF.

Multiple births

There was no evidence reported on births from multiple pregnancies when comparing stimulated and non stimulated IVF cycles.

OHSS

There was no evidence reported on the number of cases of OHSS when comparing stimulated and non stimulated IVF cycles.

Congenital abnormalities

There was no evidence reported on the number of congenital abnormalities when comparing stimulated and non stimulated IVF cycles.

Patient satisfaction

There was no significant difference in patient satisfaction when comparing women who received GnRH agonist with gonadotrophins with a group of women who received either natural cycle or clomifene citrate stimulated IVF. It was not possible to separate out the women who received natural cycle IVF.

Health related quality of life

There was no evidence reported regarding the health related quality of life when comparing stimulated and non stimulated IVF cycles.

Anxiety and/or depression

There was no evidence comparing the number of women with anxiety and/or depression in stimulated and non stimulated IVF cycles.

Comparison of recombinant gonadotrophins with urinary gonadotrophins (Table 15.8)

This profile compares recombinant gonadotrophins with urinary gonadotrophins as a concept. All of the studies used rFSH in one arm of the trial. The included studies may use one or more types or urinary gonadotrophin as a comparator; for example rFSH compared with hMG or pFSH.

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births after rFSH compared with after urinary gonadotrophins.

Clinical pregnancy

There was no significant difference in the number of clinical pregnancies after rFSH compared with after urinary gonadotrophins.

Adverse pregnancy outcome

There was no significant difference in the number of adverse pregnancy outcomes after rFSH compared with after urinary gonadotrophins.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies after rFSH compared with after urinary gonadotrophins.

Multiple births

There was no evidence reported on the number of births from multiple pregnancies after rFSH compared with after urinary gonadotrophins.

OHSS

There was no significant difference in the number of cases of OHSS after rFSH compared with after urinary gonadotrophins.

Congenital abnormalities

There was no evidence reported on the number of congenital abnormalities after rFSH compared with after urinary gonadotrophins.

Patient satisfaction

There was no evidence reported regarding patient satisfaction after rFSH compared with after urinary gonadotrophins.

Health related quality of life

There was no evidence reported regarding health related quality of life after rFSH compared with after urinary gonadotrophins.

Anxiety and/or depression

There was no evidence reported on the number of women with anxiety and/or depression after rFSH compared with after urinary gonadotrophins.

Comparison of specific recombinant with specific urinary gonadotrophins (Table 15.9)

This profile compares specific recombinant gonadotrophins with specific urinary gonadotrophins; for example rFSH compared with uFSH.

Live full-term singleton birth

There were significantly more live full-term singleton births with the use of hMG or hphMG compared with rFSH.

There was no significant difference in the number of live full-term singleton births for any other comparisons.

Clinical pregnancy

There were significantly more clinical pregnancies after hMG or hp-hMG compared to after rFSH and there were significantly more clinical pregnancies after rFSH compared to after rFSH and rLH.

There was no significant difference in the number of clinical pregnancies for any other comparisons.

Adverse pregnancy outcome

There was no significant difference in the number of adverse pregnancy outcomes when comparing specific recombinant gonadotrophins with specific urinary gonadotrophins.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing specific recombinant gonadotrophins with specific urinary gonadotrophins.

Multiple births

There was no evidence reported on the number of births from multiple pregnancies after specific recombinant gonadotrophins compared with specific urinary gonadotrophins.

OHSS

There was no significant difference in the number of cases of OHSS after specific recombinant gonadotrophins compared with specific urinary gonadotrophins.

Congenital abnormalities

There was no evidence reported on the number of congenital abnormalities after specific recombinant gonadotrophins compared with specific urinary gonadotrophins.

Patient satisfaction

There was no evidence reported regarding patient satisfaction after specific recombinant gonadotrophins compared with specific urinary gonadotrophins.

Health related quality of life

There was no evidence reported regarding health related quality of life after specific recombinant gonadotrophins compared with specific urinary gonadotrophins.

Anxiety and/or depression

There was no evidence reported on the number of women with anxiety and/or depression after specific recombinant gonadotrophins compared with specific urinary gonadotrophins.

Comparisons of urinary gonadotrophins with other urinary gonadotrophins and recombinant gonadotrophins with other recombinant gonadotrophins (Table 15.10)

This profile compares different types of urinary gonadotrophins with each other, and different types of recombinant gonadotrophins with each other, for example rhFSH with rhFSH and rhLH, or rFSH with rFSH and rLH.

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births when comparing rhFSH with rhFSH plus rhLH, or with hMG.

Clinical pregnancy

There was no significant difference in the number of clinical pregnancies when comparing different types of urinary gonadotrophin to each other, or when comparing rFSH with rFSH and rLH.

Adverse pregnancy outcome

There was no significant difference in the number of adverse pregnancy outcomes when comparing different types of urinary gonadotrophin with each other, or when comparing rFSH with rFSH plus rLH.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing rFSH with rFSH plus rLH or when comparing rhFSH with rhFSH plus rhLH.

Multiple births

No evidence was reported that compared the number of births from multiple pregnancies after different urinary gonadotrophins, or different recombinant gonadotrophins.

OHSS

There was no significant difference in the number of cases of OHSS when comparing pFSH with pFSH plus hMG, when comparing hpFSH with hpFSH and hMG, or when comparing rFSH with rFSH and rLH.

Congenital abnormalities

No evidence was reported that compared the number of congenital abnormalities after different urinary gonadotrophins, or different recombinant gonadotrophins.

Patient satisfaction

No evidence was reported that compared patient satisfaction after different urinary gonadotrophins, or different recombinant gonadotrophins.

Health related quality of life

No evidence was reported on health related quality of life after different urinary gonadotrophins, or different recombinant gonadotrophins.

Anxiety and/or depression

No evidence was reported that compared the number of women with anxiety and/or depression after different urinary gonadotrophins, or different recombinant gonadotrophins.

Dosages of FSH/rFSH for ovarian stimulation (Table 15.11)

This profile aimed to compare different dosages of FSH to determine the most effective dose.

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births with a low dose step up protocol and a step down protocol in low response women. There was also no significant difference in the number of live full-term singleton births after 150 IU FSH compared with 225 IU FSH.

Clinical pregnancy

There was no significant difference in the number of clinical pregnancies when comparing different doses of FSH/rFSH.

Adverse pregnancy outcome

Mixed results were reported for adverse pregnancy outcomes as reported per pregnancy. Some studies reported significantly more miscarriages per pregnancy with 200 IU rFSH compared with 100 IU rFSH, but another reported significantly more ectopic pregnancies and/or miscarriages with 100 IU rFSH compared with 200 IU rFSH. One study reported that there were significantly more biochemical pregnancies, abortions or extrauterine pregnancies per pregnancy when using a pre-determined dose of 150 IU rFSH rather than a dose individualised to the woman. There were no significant differences in the number of miscarriages and/or ectopic pregnancies when comparing different doses of FSH/rFSH.

There was no significant difference in the number of adverse pregnancy outcomes per woman when comparing different doses of FSH/rFSH.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing different doses of FSH/rFSH.

Multiple births

There was no significant difference in the number of babies born from multiple pregnancies when comparing different doses of FSH/rFSH.

OHSS

One study reported significantly more cases of OHSS when using a standard dose of between 112.5 IU and 225 IU of FSH compared with using a lower dose between 37.5 IU and 75 IU of FSH.

There was no significant difference in the number of cases of OHSS when comparing other doses of FSH/rFSH.

Congenital abnormalities

No evidence was reported that compared the number of congenital abnormalities after different doses of FSH/rFSH.

Patient satisfaction

No evidence was reported that compared patient satisfaction after different doses of FSH/rFSH.

Health related quality of life

No evidence was reported that compared health related quality of life after different doses of FSH/rFSH.

Anxiety and/or depression

No evidence was reported that compared the number of women with anxiety and/or depression after different doses of FSH/rFSH.

Unstimulated IVF compared with stimulation with clomifene citrate and/or gonadotrophins (no IVF/ICSI) (Table 15.12)

No RCTs were found that compared unstimulated IVF/ICSI with clomifene citrate or gonadotrophin stimulated cycles (without IVF/ICSI).

GnRH agonist plus gonadotrophins IVF/ICSI cycles compared with clomifene citrate plus gonadotrophins (plus GnRH antagonist) IVF/ICSI cycles (Table 15.13)

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births when comparing GnRH agonist plus gonadotrophin with clomifene citrate plus gonadotrophin, with or without GnRH antagonist.

Clinical pregnancy

There was no significant difference in the number of clinical pregnancies when comparing GnRH agonist plus gonadotrophin with clomifene citrate plus gonadotrophin, with or without GnRH antagonist or corticosteroids.

Adverse pregnancy outcome

There was no significant difference in the number of adverse pregnancy outcomes when comparing GnRH agonist and gonadotrophin with clomifene citrate and gonadotrophin, with or without GnRH antagonist or corticosteroids.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing GnRH agonist v gonadotrophin with clomifene citrate and gonadotrophin.

Multiple births

There was no significant difference in the number of babies born from multiple pregnancies when comparing GnRH agonist and gonadotrophin with clomifene citrate and gonadotrophin.

OHSS

There were significantly more cases of OHSS when comparing clomifene citrate and gonadotrophin with GnRH agonist and gonadotrophin. However, when GnRH antagonist or corticosteroids was added to the clomifene citrate protocol, the number of cases of OHSS was significantly lower that the number of cases of OHSS with GnRH agonist and gonadotrophin.

Congenital abnormalities

No evidence was reported on congenital abnormalities when comparing GnRH agonist and gonadotrophins with clomifene citrate and gonadotrophins.

Patient satisfaction

There was no significant difference in the number of women satisfied with their treatment when comparing those that received GnRH agonist and gonadotrophins and those that received either natural cycle or clomifene citrate stimulated IVF.

Health related quality of life

No evidence was reported on health related quality of life when comparing GnRH agonist and gonadotrophins with clomifene citrate and gonadotrophins.

Anxiety and/or depression

No evidence was reported on the number of women with anxiety and/or depression when comparing GnRH agonist plus gonadotrophins with clomifene citrate plus gonadotrophins.

Adjuvant growth hormone in IVF/ICSI protocols for women with a previous low response (Table 15.14)

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births when comparing protocols that include growth hormone with those that do not.

Clinical pregnancy

There was no significant difference in the number of clinical pregnancies when comparing protocols that include growth hormone with those that do not.

Adverse pregnancy outcome

No evidence was reported on adverse pregnancy outcomes when comparing protocols that include growth hormone with those that do not.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing protocols that include growth hormone with those that do not.

Multiple births

There was no significant difference in the number of births from multiple pregnancies when comparing protocols that include growth hormone with those that do not.

OHSS

No evidence was reported on the number of cases of OHSS when comparing protocols that include growth hormone with those that do not.

Congenital abnormalities

No evidence was reported on the number of congenital abnormalities when comparing protocols that include growth hormone with those that do not.

Patient satisfaction

No evidence was reported on patient satisfaction when comparing protocols that include growth hormone with those that do not.

Health related quality of life

No evidence was reported on health related quality of life when comparing protocols that include growth hormone with those that do not.

Anxiety and/or depression

No evidence was reported on anxiety and/or depression when comparing protocols that include growth hormone with those that do not.

Adjuvant DHEA for women with a previous low response (Table 15.15)

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births when comparing protocols that include DHEA with those that do not.

Clinical pregnancy

There was no significant difference in the number of clinical pregnancies when comparing protocols that include DHEA with those that do not.

Adverse pregnancy outcome

There was no significant difference in the number of adverse pregnancy outcomes when comparing protocols that include DHEA with those that do not.

Multiple pregnancies

No evidence was reported on the number of multiple pregnancies when comparing protocols that include DHEA with those that do not.

Multiple births

No evidence was reported on the number of births from multiple pregnancies when comparing protocols that include DHEA with those that do not.

OHSS

No evidence was reported on the number of cases of OHSS when comparing protocols that include DHEA with those that do not.

Congenital abnormalities

No evidence was reported on the number of congenital abnormalities when comparing protocols that include DHEA with those that do not.

Patient satisfaction

No evidence was reported on patient satisfaction when comparing protocols that include DHEA with those that do not.

Health related quality of life

No evidence was reported on health related quality of life when comparing protocols that include DHEA with those that do not.

Anxiety and/or depression

No evidence was reported on anxiety and/or depression when comparing protocols that include DHEA with those that do not.

Health economics profile

No specific health economic analysis was undertaken for this question, as work focused on comparing IVF with expectant management.

Evidence to recommendations

Relative value placed on the outcomes considered

Clinical pregnancies and live full-term singleton births are important outcomes which allow clinicians to inform couples of their chances of conception and having a baby. The other outcomes in this review relate to side-effects of the treatments and are important to consider in order to fully inform couples of potential risks of treatment.

Consideration of clinical benefits and harms

Stimulation compared with natural cycle

The available evidence shows that natural cycles result in lower clinical pregnancy rates than stimulated cycles. The GDG therefore made a recommendation that ovarian stimulation should be used as part of an IVF protocol.

Choice of agent

The GDG acknowledged that there was no overwhelming evidence in favour of a particular recombinant or urinary product, and that some urinary products are in short supply or are no longer available. It therefore recommended that either urinary or recombinant gonadotrophins can be used.

FSH dose

The GDG considered that the evidence on FSH dosage shows that there is unlikely to be a difference in harms or benefits, but concluded that the evidence does not provide sufficiently detailed information on how dosage should change with clinical factors, such as age and response to previous treatment. The majority of studies included in this review altered the dose of FSH given to women during the duration of the study, preventing a true comparison of exact dosages to be made. The GDG made a recommendation to emphasise that doses of gonadotrophins should be individualised depending on the circumstances of the woman involved. It also recommended a maximum dose of FSH based on GDG members' current practice, expert opinion and clinical experience, as there is no evidence that higher doses increase the chances of a clinical pregnancy or live full-term singleton birth.

OHSS

The GDG acknowledged that, compared with unstimulated IVF, there is an increased risk of OHSS when ovarian stimulation takes place, but concluded that the benefits of ovarian stimulation over natural cycle IVF in terms of increased clinical pregnancy and live full-term singleton birth rates outweigh this risk. However, the GDG agreed that it is important to continue to assess the risk of OHSS throughout IVF treatment using ultrasound monitoring.

As the use of an ovulation trigger further increases the risk of OHSS, the GDG believed it was necessary to make a recommendation on when the risk of OHSS is too high to continue with IVF treatment. No RCT data was identified that could inform the GDG's discussion on this, and so a consensus method was used to determine the GDG's clinical practice and experience. The consensus method enabled the GDG to make a recommendation of when the risk of OHSS is regarded as too high and therefore ovulation should not be triggered.

Adjuvant treatments

The GDG believed that some women are currently receiving growth hormone or other adjuvant treatments, despite there being insufficient evidence for an increase in live birth or clinical pregnancy rates. The evidence shows there is little evidence regarding the potential adverse effects of these treatments, and so the GDG recommended that they are not used as adjuvant treatment during IVF procedures.

Consideration of health benefits and resource uses

Given there was no consistent difference in the benefits of the various types of ovarian stimulation, cost has to be taken into account. It has been noted that the use of urinary products is cheaper than their recombinant counterparts. However, the availability and quality of urinary products can vary and the costs of the recombinant agents may be lower in the future. Because of this, and in light of the evidence showing no difference in clinical effectiveness between urinary and recombinant products, the GDG did not believe it was possible to recommend the use of one class of product over the other.

Quality of evidence

The evidence was graded as moderate to very low quality depending on the outcome being reported. The main reasons were poor allocation concealment and a lack of reported power calculations. In addition, studies may have been underpowered for many of the reported outcomes, as shown by the wide confidence intervals around point estimates.

There was a lack of evidence for women who have had a previous low response to ovarian stimulation, and so no specific recommendations were made for them.

Other considerations

Patient preference for natural cycle IVF

The GDG acknowledged that some couples express a preference for unstimulated IVF. The current evidence suggests that natural cycle IVF is less effective than stimulated IVF, as it results in lower pregnancy rates. The GDG recommended that, when discussing IVF treatment options, clinicians inform women of the lower pregnancy rates resulting from natural cycle IVF.

Equalities

The people considered in this review were:

- People who have vaginal intercourse.
- Specific patient subgroups listed in the guideline Scope that may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychological problem
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
- People who are preparing for cancer treatment who may wish to preserve their fertility.

There were no other specific issues that needed to be addressed with respect to any of these subgroups in the context of ovarian stimulation as part of IVF.

Recommendations

Number	Recommendation
141	Use ovarian stimulation as part of IVF treatment. **[new 2013]**
142	Use either urinary or recombinant gonadotrophins for ovarian stimulation as part of IVF treatment. **[new 2013]**
143	When using gonadotrophins for ovarian stimulation in IVF treatment: • use an individualised starting dose of follicle-stimulating hormone, based on factors that predict success, such as: o age o BMI o presence of polycystic ovaries o ovarian reserve • do not use a dosage of follicle-stimulating hormone of more than 450 IU/day. **[new 2013]**
144	Offer women ultrasound monitoring (with or without oestradiol levels) for efficacy and safety throughout ovarian stimulation. **[new 2013]**
145	Inform women that clomifene citrate-stimulated and gonadotrophin-stimulated IVF cycles have higher pregnancy rates per cycle than 'natural cycle' IVF. **[2013]**
146	Do not offer women 'natural cycle' IVF treatment. **[2013]**
147	Do not use growth hormone or dehydroepiandrosterone (DHEA) as adjuvant treatment in IVF protocols. **[new 2013]**

2013 Update

Number	Research recommendations
RR 29	What is the clinical and cost effectiveness of ovarian stimulation with clomifene citrate compared to GnRH agonist and gonadotrophins?
RR 30	Is the use of adjuvant DHEA in poor responders clinically effective?
RR 32	What is the clinical and cost effectiveness of highly purified gonadotrophins compared to other gonadotrophins?

15.5 Triggering ovulation in IVF

Introduction

At the end of the stimulation phase of an IVF cycle, a drug ('ovulation trigger') is used to mimic the endogenous LH surge in a natural menstrual cycle which initiates the process of ovulation. For many years hCG (urinary or recombinant [uhCG, rhCG]) has been used but recombinant LH and GnRH have also been used in recent years.

This section reviews the evidence of the efficacy of these triggering options.

Oocyte maturation – human chorionic gonadotrophin

Human chorionic gonadotrophin has been used as a surrogate LH surge to induce final oocyte maturation before oocyte retrieval in assisted reproduction.

An RCT found no significant differences between rhCG and uhCG in clinical pregnancy rate (33% with rhCG versus 24.7% with uhCG) and live birth rate (27% with rhCG versus 23% with uhCG) and OHSS incidence (7.2% with rhCG versus 6.4% with uhCG).[854] [Evidence level 1b]

Another RCT showed no significant differences between 250 micrograms and 500 micrograms of rhCG and uhCG in clinical pregnancy rate (35.1% versus 36% versus 35.9%), live births (87.9% versus 84.4% versus 84.8%) or OHSS incidence (3.25% versus 9% versus 3.1%).[855] [Evidence level 1b]

Monitoring of stimulated cycles

In assisted reproduction, the purpose of monitoring ovarian response is to ensure safe practice in reducing the incidence and severity of OHSS, and to optimise the timing of luteinisation before oocyte retrieval.

An average number of three-ultrasound-scan monitoring is commonly practiced: at the start of ovarian stimulation in GnRH agonist-controlled cycle, to assess at day seven to nine and to determine timing of hCG administration at days 11 to 14. The extent of monitoring is reduced in GnRH antagonist controlled cycles.[856] [Evidence level 3]

One RCT (n = 114) found no significant differences between ultrasonic ovulation control with hormone determination versus ultrasound alone in pregnancy rate per embryo transfer (27.2% versus 29.5%) and OHSS rate (5.3% versus 7%) in women undergoing GnRHa-hMG during IVF embryo-transfer for the first time.[857] [Evidence level 1b]

One RCT (n = 279) found no significant differences between cycle monitoring using both serum oestradiol and ultrasound versus ultrasound alone in clinical pregnancy rate (34.3% versus 31.4%) and OHSS rates (4.9% versus 4.1%) in normal responders undergoing GnRHa-rFSH during IVF-embryo-transfer.[858] [Evidence level 1b]

A non-RCT (n = 206) found no significant differences between ultrasound with hormonal determination versus ultrasound alone in clinical pregnancy rate (22.9% versus 23.4%), live birth rate (14.3% versus 14.8%) and OHSS rate (1.04% versus 0.9%) in women undergoing GnRHa-hMG/hCG during IVF-embryo-transfer.[859] [Evidence level 2a]

Ovarian hyperstimulation syndrome

OHSS is an iatrogenic and potentially life-threatening complication of superovulation. The incidence of OHSS varies between 0.6% and 10% in IVF cycles. The severe form of the condition occurs in 0.5–2% of IVF cycles[860]

Several risk factors have been associated with the development of OHSS:[861]

- young age (less than 30 years)
- lean physique
- polycystic ovary syndrome
- high serum oestradiol (greater than 2500 pg/ml or 9000 pmol/l)
- rapidly increasing oestradiol levels (greater than 75% from previous day)
- size and number of follicles and ultrasonographic ovarian 'necklace sign' of multiple small
- follicles
- hCG administration
- number of oocytes retrieved (greater than or equal to 20)
- multiple pregnancy.

Criteria for classifying the severity of OHSS are:

- Mild:
    - abdominal bloating, mild pain
    - ovarian size usually less than 8 cm*
- Moderate:
    - increased abdominal discomfort accompanied by nausea, vomiting and/or diarrhoea
    - ultrasound evidence of ascites
    - ovarian size usually 8–12 cm*
- Severe:
    - clinical ascites, sometimes hydrothorax
    - haemoconcentration (haematocrit greater than 45%, white blood cell count greater than 15000/ml)
    - oliguria with normal serum creatinine
    - liver dysfunction
    - anasarca
    - ovarian size usually greater than 12 cm*
- Critical:
    - tense ascites
    - haematocrit greater than 55%, white blood cell count greater than 25000/ml
    - oliguria with elevated serum creatinine

* Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration. Nevertheless, recording ovarian measurements of ovarian size is not currently considered useful as a prognostic indicator nor as an indicator of the stage of the disease.[861]

- o renal failure
- o thromboembolic phenomenon
- o ovarian size usually greater than 12 cm.*

Prevention

There is no evidence to support the superiority of either hMG or rFSH[517] (OR 1.60, 95% CI 0.60 to 4.3) or urinary preparations[518] (OR 1.36, 95% CI 0.79 to 2.33) in preventing OHSS. [Evidence level 1a]

Cycle cancellation

Cancellation of a treatment cycle is a strategy that has been considered if ovarian ultrasound reveals a large number of developing follicles and/or serum oestradiol levels are excessively high. The principle behind this decision is to withhold the ovulatory trigger (hCG). In cycles where GnRH agonists have not been used, this may not completely prevent early-onset OHSS as a natural LH surge may still occur.[862]

Coasting

Coasting involves discontinuation of gonadotrophins in cycles with an excessive response and delaying hCG administration, while continuing GnRH agonist administration in the presence of ultrasound and endocrine monitoring.[863] It is an alternative to cycle cancellation in situations where there is a substantial risk of OHSS associated with high serum oestradiol levels above 2500 pg/ml (9000 pmol/l). The aim is to allow FSH levels to drop, thus inhibiting granulosa-cell proliferation and subsequent availability for luteinisation. The patient is monitored until the oestradiol level falls below a safe limit (< 2500 pg/ml or 9000 pmol/l). Although shown to be effective in observational studies, there is insufficient evidence to advocate the use of coasting in routine practice. It can potentially reduce the number of oocytes recovered and may even compromise pregnancy rates. A systematic review on the role of coasting for the prevention of OHSS identified only one RCT. Compared with elective unilateral follicular aspiration (elective aspiration of excess ovarian follicles), there was no convincing benefit associated with the use of coasting (OR 0.76, 95% CI 0.18 to 3.24).[864] [Evidence level 1a]

Elective cryopreservation of all embryos (see section 15.6)

Following oocyte recovery in assisted reproductive treatments, fresh embryo transfer may be deferred if there are excessive numbers of follicles and oocytes recovered (for example, more than 20). All embryos are cryopreserved and electively replaced at a later date. The idea is to prevent a conception cycle and, hence, late-onset OHSS. A systematic review has found that there is insufficient evidence to support routine cryopreservation in cases with a high risk of OHSS (OR 5.33, 95% CI 0.51 to 56.24 for elective cryopreservation versus intravenous albumin; OR 0.12, 95% CI 0.01 to 2.29 for elective cryopreservation versus fresh embryo transfer).[865] [Evidence level 1a]

Luteal-phase support (see section 15.8)

A systematic review has confirmed the effectiveness of routine luteal phase support after embryo transfer in IVF cycles involving the use of gonadotrophin-releasing hormone agonists.[866] [Evidence level 1a] The use of hCG in this situation can aggravate OHSS and progesterone should be the preparation of choice in high-risk women.[867]

Prophylactic albumin administration

It has been suggested that administration of intravenous albumin around the time of oocyte recovery could be used as a preventative measure in the high-risk woman. The exact mode of action of albumin is unknown but it is thought to bind to vasoactive substances involved in the pathogenesis of OHSS. It also increases the intravascular oncotic pressure, thereby preventing loss of water from the intravascular compartment.[861] A systematic review[868] reported that the use of intravenous albumin at the time of oocyte retrieval significantly reduced the incidence of severe OHSS in high-risk women undergoing IVF (OR 0.28, 95% CI 0.11 to 0.73). [Evidence level 1a] However, the optimal timing and dose of albumin are unclear, as is its effect on implantation. There are also growing concerns about

* Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration. Nevertheless, recording ovarian measurements of ovarian size is not currently considered useful as a prognostic indicator nor as an indicator of the stage of the disease.[861]

the possibility of febrile reactions, anaphylactic shock and the potential risk of virus and prion transmission.[869] The systematic review,[868] suggested that 18 women at risk would need to be treated with albumin infusion in order to prevent a single case of severe OHSS. This needs to be taken into account in the context of clinical decision making.

The alternative to albumin is infusion of hydroxyethyl starch solution, which is a plasma colloidal substitute. It may be a safer, cheaper and effective method that needs evaluation in an RCT, and there are concerns about its interaction with the blood-coagulation system.[870]

Role of follicular aspiration

Recovery of immature oocytes (which can then be cultured in vitro and subsequently used for IVF) has been suggested as a means of preventing OHSS when hCG is withheld.[871] Follicular aspiration alone cannot be relied on to avert the development of OHSS or to arrest clinical deterioration in a pre-existing case. Despite this, practitioners are known to attempt meticulous puncture and aspiration of all stimulated follicles at time of oocyte recovery in the belief that this interferes with the mechanisms leading to production of the ovarian mediators of OHSS.[861]

Other methods of prevention

In a prospective randomised trial,[875] ovarian electro diathermy in women with polycystic ovaries before IVF was compared with IVF alone. There was no significant difference in the incidence of OHSS in women treated by ovarian diathermy or not. [Evidence level 1b]

Treatment

Treatment of OHSS is mainly supportive.[862] Multidisciplinary local protocols involving gynaecologists, anaesthetists and haematologists should be generated and strictly followed. The condition is self-limiting and resolution parallels the decline in serum hCG levels (about seven days in nonpregnant women and 10–20 days in pregnant women). Mild OHSS is usually benign and resolves with the onset of the first period. Moderate to severe cases need hospital admission and monitoring. The principles of care include appropriate specialist involvement, circulatory support using intravenous fluids, maintenance of renal function, thromboprophylaxis and drainage of third space accumulation.

Review question

Which is the most effective ovulation trigger to use as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?

Evidence profile

This review was undertaken to establish whether there is a difference in the clinical effectiveness of the most commonly used forms of ovulation trigger.

The evidence was presented in one profile:

- Comparison of different types of agents used to trigger ovulation in an IVF cycle (see Table 15.16).

Description of included studies

Two Cochrane reviews (Youssef et al., 2011a; Youssef et al., 2011b) and three RCTs (Papanikolaou et al., 2010; Papanikolaou et al., 2011; Segal et al., 1992) were included in the review. One Cochrane review and one of the trials compared rhCG and uhCG (Youssef et al., 2011a and Papanikolaou et al., 2010) and the same Cochrane review also compared rhLH with uhCG (Youssef et al., 2011a). The other Cochrane review and two of the trials compared GnRH agonist with hCG (Papanikolaou et al., 2011; Segal et al., 1992; Youssef et al., 2011b).

Table 15.16 GRADE findings for comparison of different types of trigger

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
rhCG vs uhCG					
2 (Youssef et al., 2011a; Papanikolaou et al., 2010)	205/565 (36%) women	221/573 (39%) women	RR 1.1 (0.9 to 1.3)	31 more per 1000 (from 27 fewer to 96 more)	Very low
rhLH vs uhCG					
1 (Youssef et al., 2011a)	27/144 (19%) women	27/136 (20%) women	OR 0.9 (0.5 to 1.8)	11 fewer per 1000 (from 86 fewer to 97 more)	Very low
GnRH agonist vs. hCG					
2 (Youssef et al., 2011b; Papanikolaou et al., 2010)	51/270 (19%) women	85/262 (32%) women	RR 0.5 (0.3 to 0.9) [k]	162 fewer per 1000 (from 23 fewer to 237 fewer)	Very low
Clinical pregnancy					
rhCG vs uhCG					
2(Youssef et al., 2011a; Papanikolaou et al., 2010)	263/708 (37%) women	192/617 (31%) women	RR 1.2 (1.0 to 1.4)	62 more per 1000 (from 12 more to 121 more)	Very low
rhLH vs uhCG					
1 (Youssef et al., 2011a)	36/144 (25%) women	36/136 (27%) women	OR 0.9 (0.5 to 1.6)	14 fewer per 1000 (from 102 fewer to 98 more)	Very low
GnRH agonist vs. hCG					
3 (Youssef et al., 2011; Papanikolaou et al., 2010; and Segal et al. (1992)	108/482 (22%) women	138/480 (29%) women	RR 0.7 (0.5 to 1.0)[k]	80 fewer per 1000 (from 138 fewer to 3 fewer)	Very low
Adverse pregnancy outcome					
rhCG vs uhCG (miscarriage)					
1 (Youssef et al., 2011a)	26/599 (4%) women	32/507 (6%) women	OR 0.7 (0.4 to 1.2)	20 fewer per 1000 (from 37 fewer to 9 more)	Very low
	Not reported per clinical pregnancy				

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Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rhCG vs uhCG (abortion)					
1 (Papanikolaou et al., 2010)	1/59 (2%) women	2/60 (3%) women	RR 0.5 (0.1 to 5.5)	16 fewer per 1000 (from 32 fewer to 149 more)	Low
	1/27 (4%) pregnancies	2/18 (11%) pregnancies	RR 0.3 (0.0 to 3.4)	74 fewer per 1000 (from 108 fewer to 268 more)	
rhLH vs uhCG (miscarriage)					
1 (Youssef et al., 2011b)	44/368 (12%) women	22/345 (6%) women	OR 1.9 (1.1 to 3.2)	56 more per 1000 (from 10 more to 124 more)	Low
	Not reported per clinical pregnancy				
rhLH vs uhCG (miscarriage)					
1 (Youssef et al., 2011a)	9/144 (6%) women	9/136 (7%) women	OR 0.9 (0.4 to 2.4)	4 fewer per 1000 (from 41 fewer to 82 more)	Very low
	Not reported per clinical pregnancy				
GnRH agonist vs hCG (pregnancy loss)					
1 (Papanikolaou et al., 2011)	1/18 (6%) women	2/17 (12%) women	RR 0.5 (0.1 to 4.7)	62 fewer per 1000 (from 112 fewer to 440 more)	Very low
	1/4 (25%) pregnancies	2/4 (50%) pregnancies	RR 0.5 (0.1 to 3.6)	250 fewer per 1000 (from 465 fewer to 1000 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
No evidence reported					
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
rhCG vs uhCG					
1 (Youssef et al., 2011a)	11/324 (3%) women	6/225 (3%) women	OR 1.3 (0.5 to 4.1)	7 more per 1000 (from 14 fewer to 61 more)	Low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
rhLH vs uhCG					
1 (Youssef et al., 2011a)	15/144 (10%) women	17/136 (13%) women	OR 0.8 (0.4 to 1.7)	21 fewer per 1000 (from 72 fewer to 70 more)	Very low
GnRH agonist vs. hCG					
1 (Youssef et al., 2011b)	0/266 (0%) women	7/238 (3%) women	OR 0.1 (0.0 to 0.8)	28 fewer per 1000 (from 29 fewer to 1 fewer)	Low
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, GnRH gonadotropin-releasing hormone, hCG human chorionic gonadotropin, uhCG urinary human chorionic gonadotropin, rhCG recombinant human chorionic gonadotropin, RR relative risk, rh-LH recombinant human luteinizing hormone.

Evidence statements

Live full-term singleton birth

There were significantly more live full-term singleton births when hCG was used to trigger ovulation compared with GnRH agonist.

There was no significant difference in the number of live full-term singleton births when comparing rhCG with uhCG and rhLH with uhCG.

Clinical pregnancy

There were significantly more clinical pregnancies with the use of uhCG compared with rhCG, and with the use of hCG compared with GnRH agonist.

There was no significant difference in the number of clinical pregnancies when comparing rhLH with uhCG.

Adverse pregnancy outcomes

There was no significant difference in the number of miscarriages per woman or per pregnancy with the use of GnRH agonist compared with hCG. There was no significant difference in the number of pregnancy losses per pregnancy or per woman when comparing GnRH agonist with hCG.

There was no significant difference in the number of miscarriages or abortions when comparing rhCG with uhCG, or in the number of miscarriges when comparing rhLH with uhCG.

Multiple pregnancies

No evidence was reported regarding the number of multiple pregnancies associated with using different ovulation triggers.

Multiple births

No evidence was reported regarding the number of babies born from multiple pregnancies associated with using different ovulation triggers.

OHSS

There were significantly more cases of OHSS with the use of hCG when compared with the use of GnRH agonist.

There was no significant difference in the number of cases of OHSS when comparing rhCG with uhCG, or when comparing rhLH with uhCG.

Congenital abnormalities

No evidence was reported regarding the number of congenital abnormalities associated with using different ovulation triggers.

Patient satisfaction

No evidence was reported regarding the patient satisfaction associated with using different ovulation triggers.

Health related quality of life

No evidence was reported regarding health related quality of life associated with different ovulation triggers.

Anxiety and/or depression

No evidence was reported regarding the number of women with anxiety and/or depression associated with using different ovulation triggers.

Health economics profile

No specific health economic analysis was undertaken for this question, as work focused on comparing IVF with expectant management.

Evidence to recommendations

Relative value placed on the outcomes considered

Live singleton births and clinical pregnancies are important outcomes which allow clinicians to inform couples of their chances of conception and having a baby. The other outcomes in this review relate to side-effects of the treatments and are important to consider in order to fully inform couples of potential risks of treatment.

Consideration of clinical benefits and harms

The evidence showed that hCG was associated with more live births and clinical pregnancies than GnRH agonist. Although the evidence showed that, when compared with GnRH agonist, hCG resulted in more cases of OHSS, the GDG acknowledged that the absolute number of cases was low. The GDG was also aware that there is uncertainty regarding luteal phase support when using GnRH agonist as a trigger. Based on the increased number of clinical pregnancies and live births, as well as considering the role of luteal phase support, the GDG recommended the use of hCG to trigger ovulation.

The evidence showed no difference between the use of uhCG compared with rhCG in terms of live full-term singleton births, pregnancy rates or OHSS. There were significantly more clinical pregnancies with the use of uhCG compared with rhCG, although that GDG acknowledged that the significance is borderline. The GDG acknowledged that some urinary products are in short supply or are no longer available. It therefore recommended that either urinary or recombinant hCG can be used to trigger ovulation.

The evidence did not suggest that there is a difference in the clinical benefits or harms of rLH compared with hCG. However, the doses used in the three studies included in the Cochrane review started at 5,000 IU and as the only licensed rLH currently available in the UK is provided in 75 IU ampoules, over 66 ampoules would be needed to achieve the dosages reported in the studies. The GDG believed that this was impractical in a clinical setting.

The GDG acknowledged that there is a risk of OHSS occurring throughout the IVF cycle, and in particular when ovulation is triggered. It therefore recommended that women are monitored with ultrasound throughout the cycle, and that clinics have protocols in place for preventing, diagnosing and managing OHSS.

Consideration of health benefits and resource uses

Given there were no large absolute differences in benefits between the treatment options, except for GnRH agonists compared with hCG, cost and availability have to be considered. There is no evidence of a large systematic difference in cost between products, although local variation does occur.

Given there is no consistent difference in the benefits of the various types of ovarian stimulation, cost has to be taken into account. It has been noted that the use of urinary products is cheaper than their recombinant counterparts; however, the availability and quality of urinary products can vary. Because of this, and in light of the evidence showing no difference in clinical effectiveness between urinary and recombinant products, the GDG did not believe it was possible to recommend the use of one class of product over the other.

Quality of evidence

The evidence was graded as low to very low quality depending on the outcome being reported. The main reasons were poor reporting of allocation concealment, method of randomisation and a lack of reported power calculations. In addition, studies may have been underpowered for many of the reported outcomes, as shown by the wide confidence intervals around point estimates.

Other considerations

UK practice

The GDG highlighted that hCG is the standard method trigger used in the UK. In addition, there is ongoing discussion in relation to the use of urinary hCG, given that rhCG is available.

OHSS

The GDG stated that the risk of OHSS can be reduced by not using an ovulation trigger.

Equalities

The people considered in this review were:

- People who have vaginal intercourse.
- Specific patient subgroups listed in the guideline Scope that may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychological problem
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
- People who are preparing for cancer treatment who may wish to preserve their fertility.

There were no other specific issues that needed to be addressed with respect to any of these subgroups in the context of triggering ovulation.

Recommendations

Number	Recommendation
148	Offer women human chorionic gonadotrophin (urinary or recombinant) to trigger ovulation in IVF treatment. **[new 2013]**
149	Offer ultrasound monitoring of ovarian response as an integral part of the IVF treatment cycle. **[2013]**
150	Clinics providing ovarian stimulation with gonadotrophins should have protocols in place for preventing, diagnosing and managing ovarian hyperstimulation syndrome. **[2004]**

Number	Research recommendation
RR 32	Further research is needed to determine whether interventions, such as prophylactic albumin treatment, administered at the time of egg collection are effective in reducing the risk of OHSS. This research should include issues related to timing and dose?

15.6 Oocyte and sperm retrieval in IVF

Introduction

Following triggering, all mature oocytes are aspirated from the woman's ovaries for fertilization in the laboratory. Retrieval can either be done under direct vision laparoscopically or by ultrasound.

In most cases, sperm for IVF is easily obtained from the male partner by masturbation. However, in some cases of male factor infertility the sperm has to be obtained directly from the testes (see Chapter 7). Again, in such circumstances specific procedural issues need to be addressed.

These procedural aspects of gamete retrieval for IVF are discussed in this section.

Conscious sedation and anaesthesia or analgesia

It is accepted that transvaginal oocyte retrieval is unpleasant and painful. It is therefore important to provide effective anaesthesia or analgesia to minimise adverse effects and to minimise toxic effects on embryo cleavage rates and pregnancy rates. No technique of anaesthesia, analgesia or sedation is free from adverse effects. Whatever technique is used, it is essential that it should conform to the recognised standards of practice and guidance on the safe use of sedative drugs for patients undergoing health procedures as published by the Academy of Royal Medical Colleges.[876] [Evidence level 4]

A narrative review of anaesthesia methods used for transvaginal retrieval of oocytes found that general anaesthetics can traverse into the follicular fluid and may be detrimental to cleavage rates of embryo and pregnancy rate. Epidural anaesthesia avoids many of the adverse effects of general anaesthesia and it may shorten recovery time. However, it requires the expertise of an anaesthetist. Local anaesthesia (paracervical block) or no anaesthesia can cause unnecessary discomfort. Conscious sedation requires less-specialised equipment, causes relatively few complications and is well-tolerated, although there is a theoretical risk of agents contaminating the follicular fluid.[877] [Evidence level 2b–3]

Conscious sedation versus placebo

An RCT showed significantly higher median vaginal pain and abdominal pain levels in women given paracervical block and placebo as compared with paracervical block and conscious sedation. However, there was no significant difference in pregnancy rates per cycle.[878] [Evidence level 1b]

Another RCT found significantly higher anxiety levels and vaginal and abdominal pain levels in women given placebo when compared with women given premedication with anxiolytic during oocyte retrieval.[879] [Evidence level 1b]

Patient-controlled analgesia

An RCT showed no significant difference in mean pain score and patient satisfaction rate between fentanyl administration via a patient-controlled analgesia delivery system versus administration by a physician. However, significantly more fentanyl was used in the patient-controlled analgesia group.[880] [Evidence level 1b] Another RCT reported no difference in patient satisfaction with conventional intravenous analgesia compared with patient-controlled inhalational isodesox during oocyte recovery, although the mean pain score was higher in the group receiving isodesox. There was no difference in fertility outcomes between the two groups.[881] [Evidence level 1b] Patient-controlled sedation using propofol or alfentanil was also reported to provide less pain relief for patients than physician-administered sedation using diazepam and pethidine during transvaginal ultrasound-guided oocyte retrieval. Fertility outcomes were similar in the two groups.[882] [Evidence level 1b]

Conscious sedation versus general anaesthesia

An RCT found significantly higher mean pain score with conscious sedation using midazolam and ketamine when compared with general anaesthesia using fentanyl and propofol, although the higher pain score with sedation was not sufficiently high to render it unacceptable to women. There was no difference between the two groups in pregnancy rate per embryo transfer (22.7% with sedation versus 23.8% with general anaesthesia). The mean number of embryos transferred was significantly higher in the sedation group (2.8 versus 1.9). Patient satisfaction did not differ between the two groups.[883] [Evidence level 1b]

Intravenous midazolam and remifentanil and intravenous propofo and fentanyl were reported to be similar in providing effective sedation during oocyte retrieval for IVF procedures. However, a significant proportion of women (13%) given intravenous midazolam and remifentanil found the experience unpleasant due to awareness during the surgical procedure and said they would not accept conscious sedation for the same procedure in the future. All of the women given propofol and fentanyl were satisfied and said they would accept conscious sedation again.[884] [Evidence level 1b]

Exposure to the intravenous anaesthetic drug propofol was not reported to have a detrimental effect on oocyte quality.[885] [Evidence level 3]

A cohort study (n = 202) compared the effects of general anaesthesia with conscious sedation on oocyte retrieval and IVF outcome. This study found that significantly more oocytes were collected in the general anaesthesia group compared with the sedation group but there were no differences in cleavage and pregnancy rates between the two groups (23.6% with general anaesthesia versus 31.3% with conscious sedation).[886] [Evidence level 2b] Epidural anaesthesia was reported to be effective in pain control when compared with intravenous sedation in an IVF programme. The pregnancy rates were similar in the two groups.[887] [Evidence level 2b] Clinical pregnancy rates and delivery rates were lower following oocyte retrieval performed under general anaesthesia using nitrous oxide compared with epidural and local anaesthesia.[888] [Evidence level 2b] A meta-analysis of three RCTs and one case–control study reported no difference in pregnancy rates (pooled OR 0.71, 95% CI 0.47 to 1.08) between general anaesthesia and locoregional anaesthesia in patients undergoing laparoscopic oocyte retrieval.[889] Meta-analysis of the three RCTs showed similar results (OR 0.84, 95% CI 0.28 to 2.56) [Evidence level 1a]

A 1997 survey of UK fertility centres found that many different techniques were used for anaesthesia in IVF programmes.[890] [Evidence level 3] A recent survey reported that 84% and 16% of IVF clinics used intravenous sedation and general anaesthesia, respectively, for transvaginal oocyte retrieval.[891] [Evidence level 3] There was wide variation in personnel present during the procedure, the use of drugs, the degree of monitoring and the availability of emergency drugs. This wide variation in current practice within the UK highlighted the need for adoption of national guidelines for safe use of sedation

in women undergoing IVF treatment. A set of guidelines with recommendations for good practice for sedation in assisted reproduction treatments has since been developed.[892] [Evidence level 4]

Follicle flushing

Follicle flushing is traditionally employed during transvaginal ultrasound-directed oocyte recovery for IVF in the belief that flushing allows a larger number of oocytes to be collected that would otherwise be missed if aspiration alone were used.

An RCT (n = 36) reported similar oocyte recovery rate using a single-lumen needle without flushing or a double-lumen needle with flushing at ovum pick up. Administration of hCG occurred when the dominant follicle reached 18 mm in diameter in the presence of an appropriate oestradiol level. The number of follicles at the time of hCG administration was not reported. Operating time may be longer with follicle flushing.[893] [Evidence level 1b]

Another RCT (n = 34) showed no significant differences between follicular aspiration with flushing and follicular aspiration only in mean number of oocytes retrieved (7.0 versus 8.5), fertilisation rate (64% versus 60%) and ongoing pregnancy rate (17% versus 19%). This trial included women who had developed at least three follicles that had attained a diameter of 18 mm with corresponding oestradiol levels at the time of hCG administration. Significantly longer time was required for the procedure of flushing.[894] [Evidence level 1b]

A further RCT found no significant differences between follicular aspiration with flushing and follicular aspiration only in mean number of oocytes retrieved (9 versus 11), fertilisation rate (60% versus 55.6%) and clinical pregnancy rate per woman (26% versus 24%; RR 0.92, 95% CI 0.47 to 1.82). This trial excluded women who had developed less than four or more than 25 follicles that were wider than 14 mm on the day of hCG administration. Significantly longer time and higher doses of pethidine were required for the procedure of flushing.[895] [Evidence level 1b]

The use of follicle flushing in women with less than three follicles has not been evaluated but it may be useful for ensuring that oocyte yield is maximised.

Sperm recovery

Spermatozoa can be retrieved from both the epididymis and the testis using a variety of techniques with the intention of achieving pregnancies for couples where the male partner has obstructive or nonobstructive azoospermia. Sperm recovery is also used in ejaculatory failure and where only non-motile spermatozoa are present in the ejaculate (see chapter 7) Ejaculatory failure is not uncommon on the day of egg collection and is usually caused by anxiety.

Surgically collected sperm in azoospermia are immature (because they have not traversed the epididymus) and have low fertilising ability with standard IVF. It is therefore necessary to use ICSI. Sperm recovery for ICSI has made it possible for infertile men to father children who are genetically their own.

Surgical techniques for sperm retrieval from the epididymis or the testis include:

- percutaneous epididymal sperm aspiration (PESA)
- testicular sperm aspiration (TESA), which is also described as testicular fine needle aspiration (TEFNA)
- testicular sperm extraction (TESE) from a testicular biopsy
- microsurgical epididymal sperm aspiration (MESA).

In obstructive azoospermia, sperm can usually be obtained from the epididymis (PESA or MESA) and from the testis (TESA or TESE). In some men, sperm can be recovered from naturally occurring spermatoceles by percutaneous puncture.

In nonobstructive azoospermia, sperm needs to be obtained directly from the testis by aspiration (TESA) or biopsy (TESE). The chance of finding sperm is reduced. PESA and TESA can be performed under local anaesthesia in an outpatient clinic.[896,897] PESA does not jeopardise future epididymal sperm retrieval.[898]

A systematic review that includes one RCT (n = 59) compared MESA to epididymal micropuncture with perivascular nerve stimulation techniques and aspiration in men with obstructive azoopsermia such as congenital bilateral absence of vas deferens (CBAVD). MESA achieved lower pregnancy (OR 0.19, 95% CI 0.04 to 0.83) and fertilisation rates (OR 0.16, 95% CI 0.05 to 0.48). Caution is required in the interpretation of this trial as the method of randomisation used was not reported clearly, nor was there any dropout or loss to follow-up reported.[899] [Evidence level 1a]

PESA and TESA are two alternatives to MESA. MESA is more invasive, costly and technically more difficult but may be performed at the same time as correction of epididymal obstruction. In order to avoid subsequent scrotal surgery, cryopreservation of supernumerary spermatozoa during MESA should be undertaken.[900] Facilities for genetic screening with a view to referral to preimplantation genetic diagnosis should be available in any sperm retrieval programme.[901]

The best method of extracting spermatozoa from the testicular tissue in nonobstructive azoospermia is uncertain. The relative merits of TESA and TESE using small (5-mm), multiple or large (10–15-mm) diameter biopsies is unknown.[902–906] Compared with TESE, TESA has a reduced rate of sperm recovery but is less invasive.[907–910] [Evidence level 3]

Failure rates of retrieval

Reported failure rates of sperm retrieval vary with study and with technique (see Table 13.1). A further complication is added by the inconsistent method of reporting (for example, per attempt, per patient, or per couple).

In nonobstructive azoospermia, testicular size, plasma FSH levels and testicular histology are related to spermatogenesis but they cannot be relied upon to exclude the presence of any spermatozoa within the testis.[901,903,911–919] The quality of the sperm retrieved vary widely among aetiological groups, but are of no value in predicting fertilisation or pregnancy rates, or the embryo cleavage rate following PESA/ICSI cycles.[920]

Table 15.18 Failure rates of sperm retrieval

Azoospermia	Procedure	Quoted failure rate
Obstructive	MESA	1.7% of men (1/59)[921]
		22% of men (2/9)[922]
	PESA[a]	17% of initiated cycles (30/181)[898]
		15.8% of initiated cycles (43/234)[896]
		11% in men with CBAVD (7/62) and 5% in men with failed reversed vasectomy (3/60)[923]
	TESA	0% of men (1/197)[924]
Non-obstructive	TESE	13% of men (2/15)[925]
		19.7% of men (39/159)[921]
		38% of men (6/16)[911]
		8% of men (10/124)[926]
		57% of men (21/37)[903]
	TESA	66% of men (34/51)[924]

CBAVD congenital bilateral absence of vas deferens, microsurgical epididymal sperm aspiration MESA, PESA percutaneous epididymal sperm aspiration, TESA testicular sperm aspiration, TESE testicular sperm extraction

a These studies may include some of the same men

Clinical outcomes of using surgically recovered sperm (success rates of epididymal, testicular or ejaculate spermatozoa)

Epididymal and testicular spermatozoa yield similar fertilisation, cleavage and ongoing pregnancy rates using ICSI[927,928] and are both successful for establishing pregnancies.[915,922] Some authors report

these success rates as being lower than those achieved by spermatozoa from the ejaculate. One study[929] found that the normal fertilisation rate was significantly higher with ejaculated spermatozoa than with epididymal or testicular spermatozoa but no differences were observed with regard to embryo quality, the percentages of transfer after ICSI and the clinical pregnancy rates in the three groups of women. However, another study[898] showed that the outcome of PESA–ICSI treatment compares favourably with that of ICSI using ejaculated spermatozoa. One study[896] also found that the results of PESA–TESA were similar to ejaculate sperm. [Evidence level 3]

Another study[930] found that the normal fertilisation rates with testicular and MESA spermatozoa did not differ significantly from each other but, with testicular spermatozoa, the rate was significantly lower than that obtained with ejaculated spermatozoa and ICSI in matched couples. [Evidence level 3] Spermatozoa can be retrieved from the testis in couples in whom epididymal aspiration failed.[901,928,931] When spermatozoa cannot be recovered by one technique another one can be employed, for example, TESE after MESA.[922] Testicular spermatozoa can be successful in achieving fertilisation and pregnancies for couples in whom epididymal aspiration failed.[901,916] However, some studies report fertilisation or pregnancy rates lower than those achieved with epididymal spermatozoa. For example, one study[901] found a transfer rate lower with TESE than with epididymal spermatozoa but there was little difference in pregnancy rate using epididymal or testicular spermatozoa. Also, the spermatozoa could not be frozen and saved for use in future cycles. PESA, MESA or TESE and ICSI are effective in men with CBAVD and in those with failed reversal of vasectomy.[923,928,932] [Evidence level 3]

Variation in outcome using testicular sperm in nonobstructive azoospermia compared with obstructive azoospermia has been demonstrated by various studies.[933–935] Results in nonobstructive azoospermia are generally inferior.

Testicular sperm cryostorage

Cryopreservation of spermatozoa does not negatively influence the outcome. Various studies have shown that the fecundity rate, clinical pregnancy rate, overall rate of clinical pregnancy rate per embryo transfer or clinical abortions after ICSI using cryopreserved or fresh surgically retrieved spermatozoa are not significantly different.[901,927,936] In one study,[901] the only significant factor appeared to be the age of the woman. [Evidence level 3] Using cryopreserved testicular sperm (cryo-TESE) for ICSI is an effective and successful approach for the treatment of severe testicular insufficiency.[921] Because cryopreservation of spermatozoa has many additional advantages (for example, in comparison to the use of native testicular sperm with the necessity of repetitive testicular biopsies), it is routine in the performance of MESA–ICSI and TESE–ICSI.[921,927] Testicular tissue which is intentionally obtained well before any planned ICSI cycle and cryopreserved could then serve as an efficacious sperm source in a subsequent ICSI cycle. This approach should be an alternative to repeated testicular tissue sampling and the availability of spermatozoa is assured before the initiation of ovulation induction. This tissue can be harvested at the same time as diagnostic biopsy, thereby minimising the number of surgical procedures.[937]

A retrospective consecutive case series[938] compared the results of ICSI with fresh and with frozen-thawed epididymal spermatozoa obtained after MESA in 162 couples suffering from infertility because of CBAVD, failed microsurgical reversal for vasectomy or postinfectious epididymal obstruction, irreparable epididymal obstruction, ejaculatory duct obstruction or anejaculation. Overall, 176 MESA procedures were performed in the male partners, followed by 275 ICSI procedures with either fresh (n = 157) or frozen-thawed (n = 118) epididymal spermatozoa. The overall pregnancy rate (as indicated by raised hCG levels) per ICSI cycle was significantly lower when frozen-thawed epididymal spermatozoa were used (26.3% versus 39.5%). However, no significant differences were found either in clinical or ongoing pregnancy rates, or in implantation rates, and there were no differences in pregnancy outcome. [Evidence level 3] In men suspected of having obstructive azoospermia with no work-up or an incomplete one, MESA was preferred as a method for sperm recovery because a full scrotal exploration can be performed and, whenever indicated, a vasoepididymostomy may be performed concomitantly. Recovery of epididymal spermatozoa for cryopreservation during a diagnostic procedure is a valid option in these patients since ICSI may be performed later or even in another centre using the frozen-thawed epididymal spermatozoa without jeopardising the ICSI success rate. In a retrospective study[939] the authors aimed to determine whether fertilisation and implantation rates after ICSI with fresh or frozen-thawed testicular spermatozoa were comparable. They found that the fertilisation rate after ICSI with frozen-thawed testicular spermatozoa was

significantly lower than with fresh testicular spermatozoa (71% versus 79%), the pregnancy rate was similar for both groups (38% and 27%), the implantation rate per transferred embryo was significantly lower in the frozen-thawed rather than in the fresh testicular sperm group (9% versus 25%), and the live birth rate per transferred embryo was higher in the group in which fresh testicular spermatozoa were used (19% versus 8%). [Evidence level 3]

A retrospective analysis of consecutive ICSI cycles[940] compared the outcome of ICSI with fresh and frozen-thawed testicular spermatozoa in patients with nonobstructive azoospermia. No statistically significant differences were noted in any parameters examined between ICSI cycles with fresh or cryopreserved testicular spermatozoa from the same nine men and comparing all ICSI cycles performed (two-pronuclear fertilisation, embryo cleavage rates, implantation rates and clinical pregnancy rate). The delivery or ongoing pregnancy rate using fresh sperm was better but the difference was not statistically significant. Cumulative clinical pregnancy rates and ongoing pregnancy rates per testicular sperm extraction procedure were 36% and 24%, respectively. [Evidence level 3]

Assisted hatching

Assisted hatching has been proposed as a method to disrupt the zona pellucida, which may facilitate and enhance implantation and pregnancy rates. A narrative review of four RCTs and three non-randomised controlled trials found considerable heterogeneity in study methodology, populations selected, indications and techniques of assisted hatching. It reported that assisted hatching might be suggested for women aged over 38 years, those with elevated day-three serum FSH and repeated IVF failures. Data from this review did not support generalised assisted hatching for all patients.[941] [Evidence level 1b–2a]

The four RCTs from the previous review[941] were included in a systematic review of 23 RCTs (2572 women) assessing the impact of assisted hatching on live birth, clinical pregnancy and implantation rates.942 [Evidence level 1a] This review showed that assisted hatching had no significant effect on live birth rate (OR 1.21, 95% CI 0.82 to 1.78; based on six RCTs, n = 523 women). However, there was an increase in clinical pregnancy rate with assisted hatching (OR 1.63, 95% CI 1.27 to 2.09, based on 19 RCTs, n =2 175 women). This effect may be increased in a subgroup of women who had previously had one or more cycles of IVF or ICSI that did not result in a live birth (OR 2.33, 95% CI 1.63 to 3.34, based on four RCTs, n = 666 women). However, these results should be interpreted with caution because of the poor methodological quality of the included trials, with unclear methods of randomisation in 13 trials and inadequate concealment of allocation in 23 trials.

A recent Cochrane review (Das et al., 2010) has suggested that assisted hatching has no significant effect on live birth.

Multiple gestation

Monoamniotic multiple gestation may be increased in zona-manipulated cycles. The potential obstetric risks and complications of zona manipulation should be discussed with couples. In an anonymous survey of 42 IVF centres in the USA,[943] 143 pregnancies were ascertained from zona-manipulated cycles (ICSI, subzonal sperm injection, zona drilling and mechanical assisted hatching). A multiple gestation frequency of 16.1% was reported. There were five monoamniotic twin gestations (all of which resulted in live births), four being from manipulated cycles and one being from a non-manipulated cycle. There has also been one case report of conjoined twins in a triplet pregnancy after IVF and assisted hatching.[944] [Evidence level 3]

Recommendations

Number	Recommendation
151	Women undergoing transvaginal retrieval of oocytes should be offered conscious sedation because it is a safe and acceptable method of providing analgesia. **[2004]**
152	The safe practice of administering sedative drugs published by the Academy of Medical Royal Colleges should be followed. **[2004]**

153	Women who have developed at least 3 follicles before oocyte retrieval should not be offered follicle flushing because this procedure does not increase the numbers of oocytes retrieved or pregnancy rates, and it increases the duration of oocyte retrieval and associated pain. **[2004]**
154	Surgical sperm recovery before ICSI may be performed using several different techniques depending on the pathology and wishes of the man. In all cases, facilities for cryopreservation of spermatozoa should be available. **[2004]**
155	Assisted hatching is not recommended because it has not been shown to improve pregnancy rates. **[2004]**

Number	Research recommendation
RR 34	Further research is needed to evaluate the effects of assisted hatching on live birth rates and long-term consequences for children born as a result of assisted hatching.

15.7 Embryo transfer strategies

Introduction

The aim of IVF is for a woman to have a healthy baby delivered safely at term, without increasing the woman's risks. However, IVF is associated with a risk of multiple pregnancy and this represents the greatest source of harm for both mothers and babies. Thus, a decision must be made between transferring more embryos to increase the chance of having at least one live born baby and transferring a single embryo to reduce the chance of having a multiple birth.

This decision is based on a number of factors, such as the number of embryos that are available, the age of the woman, the quality of the embryos and the type of subfertility involved. However, it is also influenced by the state of IVF technology and expertise. HFEA data shows that overall live full-term singleton birth rates with IVF have improved from 17% per cycle in 1992 to 29% in 2006.

The same HFEA data shows that about one in four IVF pregnancies resulting in live birth babies were multiple pregnancies. In other words, two out of five (or 40%) live born babies from IVF were from multiple pregnancies. These figures contrast with the statistics for spontaneously conceived pregnancies in which an incidence of one in 80 (approximately 1%) pregnancies being multiple pregnancies and one out of 40 (approximately 2%) live born babies coming from multiple pregnancies. The incidence of multiple births with IVF predominantly varies with whether one or two embryos are replaced. As a result, elective single embryo transfer (eSET) is increasingly promoted as an alternative to double embryo transfer (DET), which is the most commonly used strategy in the UK, in order to reduce the rate of multiple births. This 'single embryo strategy' comprises the transfer of a single fresh embryo and the freezing of any 'spare' embryos for subsequent thaw and transfer if the fresh transfer was unsuccessful.

In addition, there is a trend to extend the culture of embryos to day 5 or 6 (blastocyst) rather than the conventional day 2 or 3 (cleavage) which is thought to improve the chances of a live full-term singleton birth.

This section reviews the evidence of the efficacy of these different embryo transfer strategies.

Table 15.18 Multiple births as a proportion of total births by age group and number of embryos transferred (single cycles)

Age group (years)	eSET			DET		
	Singleton birth	Multiple births	Multiples as proportion of total births	Singleton birth	Multiple births	Multiples as proportion of total births
Under 35	848	7	0.8%	5720	2607	22.0%
35–37	268	5	1.9%	3211	1010	31.8%
38–39	80	1	1.2%	1700	385	22.7%
40–42	28	0	0%	661	94	14.2%
43–44	2	0	0%	68	3	4.4%
Over 44	0	0	0%	1	0	0%

DET double embryo transfer, eSET elective single embryo transfer

In the UK the HFEA has adopted a target in order to limit the number of multiple births per clinic per year. In 2012 this was set at 10% of all births per clinic per year, with the aim of reducing this to 10% in the future. This allows each clinic to determine the mix of eSET and DET it uses based on the technology and expertise it has available. In addition, the HFEA has mandated that only two embryos may be transferred per cycle in women aged under 40. The British Fertility Society and The Association of Clinical Embryologists have produced guidelines on eSET (Cutting et al., 2008). These guidelines highlight that a cumulative fresh and thawed embryo strategy should be taken into account when planning IVF, and that a woman's age and quality of available embryos need to be considered when deciding if eSET should be used.

This review examines:

- The effectiveness of different embryo transfer strategies.
- In addition, a formal consensus survey was undertaken within the GDG to decide in which clinical situations which embryo transfer strategy would be most effective.

Embryo transfer techniques

Use of ultrasound

Ultrasound-guided embryo transfer is a complex intervention. Four RCTs[945–948] and four quasiRCTs[949–952] comparing ultrasound-guided embryo transfer versus clinical touch embryo transfer were identified. [Evidence level 1b–2a]

We performed a meta-analysis using data from all eight studies. This showed a significant increase in pregnancy rates with routine ultrasound-guided embryo transfer (pooled OR 1.46, 95% CI 1.25 to 1.70, n = 3358 embryo transfers). When the quasi-RCTs were excluded, there was still a significant increase in pregnancy rates with routine ultrasound-guided embryo transfer (pooled OR 1.42, 95% CI 1.17 to 1.73, n = 2051 embryo transfers). Overall, the meta-analyses suggest that use of ultrasound at the time of embryo transfer increases pregnancy rates. However, there was clinical heterogeneity among different groups of women and in the specific role of ultrasound in each trial. [Evidence level 1a]

Type of catheter

Seven RCTs have been identified comparing a number of different catheters.[958–964] The results of these trials suggest that the choice of embryo transfer catheter can affect pregnancy rates. In particular, data from large trials suggest that certain types of soft catheter are more effective that other types of catheter. [Evidence level 1b] Data from the various studies could not be aggregated due to significant clinical heterogeneity and differences between individual catheters.

Endometrial thickness

Endometrial thickness and endometrial pattern are the two anatomical parameters suggested to evaluate the endometrium by ultrasound. The role of endometrial thickness as a single factor in predicting pregnancy following IVF is controversial. A narrative review of 27 cohort and observational studies found insufficient data for an association between endometrial thickness and the probability of conception during IVF cycles. The mean endometrial thicknesses for conception and non-conception cycles were similar, ranging from 8.6 mm to 12.0 mm. There was also no case in which the endometrial thickness was less than 5 mm which resulted in pregnancy (based on 1605 cycles in 13 studies).[965] [Evidence level 2b–3] In such circumstances, the IVF cycle should be abandoned and consideration given to preparing the endometrium with exogenous hormones before a frozen embryo replacement cycle. Implantation and pregnancy rates were reported to be significantly reduced in women with an endometrial thickness of greater than 14 mm on the day of hCG administration in an IVF programme.[966] [Evidence level 2b] One study reported that reduced endometrial thickness had only a marginal effect on the probability of achieving a pregnancy rates with assisted reproduction.[967] [Evidence level 2b]. However, no significant correlation was found between endometrial volume and thickness and occurrence of pregnancy during IVF treatment in two studies.[968] [Evidence level 3] [969] [Evidence level 2b]

Bed rest versus no bed rest

One RCT (n = 182) found no significant difference in pregnancy rate per embryo transfer between 20 minutes of bed rest versus 24-hours of bed rest following embryo transfer (24% versus 23.6%), spontaneous miscarriage rate (19% versus 18%) and multiple pregnancy rate (14% versus 13.6%).[970] [Evidence level 1b] Another RCT (n = 211) assessed the role of fibrin sealant for embryo transfer and found no significant difference in implantation and pregnancy rates when both study and control groups were instructed to routine activities without any bed rest after embryo transfer. There was no group that was assigned to bed rest.[971] [Evidence level 3]

Review question

What is the effectiveness and safety of different embryo/blastocyst transfer strategies in relation to both:

- number of embryos (comparing single with double)
- timing of transfer (comparing cleavage with blastocyst stage).

Description of included studies

In total 17 RCTs met the inclusion criteria for either the number of embryos question or the timing of transfer question (Gerris et al., 1999; Rienzi et al., 2002; Van der Auwera et al., 2002; Hreinsson et al., 2004; Bungum et al., 2003; Thurin et al., 2004; van Montfoort et al., 2006; Papanikolaou et al., 2006; Martikainen et al., 2001; Kolibianakis et al., 2004; Gardner et al., 2004; Lukassen et al., 2004; Coskun et al., 2000; Emilaini et al., 2003; Gardner et al., 1998; Papanikolaou et al., 2005; Zech et al., 2007). In addition, one meta-analysis of RCTs using individual patient data was included (McLernon et al., 2011). The quality ranged from moderate to very low depending on the study and the outcome being assessed.

In all studies the best quality embryos were transferred, and any unused embryos were cryopreserved. All the studies reported results from the fresh cycles, with one study also reporting relevant data on subsequent frozen cycles (Martikainen et al., 2001).

Evidence from RCTs provides the best quality information on the effectiveness of different embryo transfer strategies. However, questions remain about whether the results can be applied to women not represented in the studies, especially those in older age groups, and what criteria should be used for determining how many embryos to transfer. Therefore, further information was reviewed based on large routinely collected datasets or multi-centre observational or comparative studies.

Seven observational studies were included and are summarised below (Luke et al., 2010; Wang et al., 2010a; Wang et al., 2010b; Scotland et al., 2011; Roberts et al., 2010; Sazonova et al., 2011; Kallen et al., 2010). The complexity and variation in reporting meant that results could not be meta-analysed or tabulated. The quality of these studies ranged from low to very low quality.

Evidence profile

Numbers of embryos

RCTs

Six RCT studies in seven publications (Gerris et al., 1999; Lukassen et al., 2004; Martikainen et al., 2001; Thurin et al., 2004; van Montfoort et al., 2006; Fiddelers et al., 2006; Gardner et al., 2004) compared single embryo transfer with double embryo transfer. Six studies compared cleavage-stage single embryo transfer with double embryo transfer and one study (Gardner et al., 2004) also compared blastocyst-stage single embryo transfer with double embryo transfer. A meta-analysis of individual patient data includes all the above studies except Gardner et al., 2004. In addition, data from three unpublished studies was included (McLernon et al., 2011).

Table 15.19 GRADE findings for comparison of numbers of embryos transferred

Number of studies	Number of patients/women		Effect		Quality
	Intervention (SET)	Comparator (DET)	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Cumulative (fresh + frozen-thawed)					
1 (Martikainen et al., 2001)	29/74 (39.2%)	36/70% (51.4%)	OR 0.61 (0.31 to 1.18)	122 fewer per 1000 (from 267 fewer to 41 more)	Very low
Cumulative (fresh + frozen-thawed) – Blastocyst stage					
No evidence reported					
Fresh cycle – Cleavage stage					
5 (Lukassen et al., 2005; Thurin et al.,2004; Martikainen et al., 2001; Gerris et al., 1999; Fiddelers et al., 2006)	169/638 (26.5%)	282/635 (44.4%)	OR 0.44 (0.31 to 0.62)	184 fewer per 1000 (113 fewer to 246 fewer)	Very low
Fresh cycle – Blastocyst stage					
No evidence reported					
Frozen cycle – Cleavage stage					
1 (Martikainen et al., 2001)	7/54 (13%)	8/38 (21.1%)	OR 0.56 (0.18 to 1.70)	81 fewer per 1000 (from 165 fewer to 101 more)	Very low
Cleavage or blastocyst					
1 (McLernon et al., 2011)	181/683 (26.5%)	285/683 (41.7%)	OR 0.50 (0.40 to 0.63)	-	Low

Number of studies	Number of patients/women		Effect		Quality
	Intervention (SET)	Comparator (DET)	Relative (95% CI)	Absolute (95% CI)	
Cleavage or blastocyst					
1 (McLernon et al., 2011)	158/181 (87.3%)	169/284 (59.5%)	OR 4.93 (2.98 to 8.18)	-	Moderate
Clinical pregnancy					
Cleavage stage					
5 (Lukassen et al., 2005; Thurin et al., 2004; Martikainen et al., 2001; Gerris et al., 1999; van Montfoort et al., 2006)	202/638 (31.7%)	315/635 (50%)	OR 0.46 [0.37, 0.58]	184 fewer per 1000 (from 133 fewer to 229 fewer)	Very low
Blastocyst stage					
1 (Gardner et al., 1998)	14/23 (60.9%)	19/25 (76%)	OR 0.49 (0.14 to 1.70)	152 fewer per 1000 (from 453 fewer to 83 more)	Very low
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Cleavage stage					
5 (Lukassen et al., 2005; Thurin et al., 2004; Martikainen et al., 2001; Gerris et al., 1999; van Montfoort et al., 2006)	3/638 (0.5%)	82/635 (12.9%)	OR 0.04 [0.01 to 0.11]	123 fewer per 1000 (from 113 fewer to 128 fewer)	Very low
Blastocyst stage					
1 (Gardner et al., 1998)	0/23 (0%)	9/25 (36.0%)	OR 0.04 (0.00 to 0.68)	338 fewer per 1000 (from 83 fewer to 360 fewer)	Low
Cleavage or blastocyst					
1 (McLernon et al., 2011)	3/181 (1.7%)	84/285 (29.5%)	OR 0.07 (0.03 to 0.17)	-	Moderate
Multiple births					
No evidence reported					

Number of studies	Number of patients/women		Effect		Quality
	Intervention (SET)	Comparator (DET)	Relative (95% CI)	Absolute (95% CI)	
Preterm delivery					
Cleavage stage					
3 (Lukassen et al., 2005; Thurin et al., 2004; Martikainen et al., 2001)	18/458 (3.9%)	66/454 (14.5%)	OR 0.24 (0.14 to 0.41)	106 fewer per 1000 (from 80 fewer to 122 fewer)	Low
Blastocyst stage					
No evidence reported					
Cleavage or blastocyst stages					
1 (McLeron et al., 2011)	14/181 (7.7%)	69/284 (24.3%)	OR 0.26 (0.14 to 0.48)	-	Moderate
Adverse pregnancy outcome (miscarriage, ectopic pregnancy, extra uterine pregnancy) – Cleavage stage					
4 (Lukassen et al., 2005 ;Thurin et al., 2004; Martikainen et al., 2001; van Montfoort et al., 2006)	46/612 (7.5%)	54/608 (8.9%)	OR 0.84 (0.55 to 1.26)	13 fewer per 1000 (from 38 fewer to 21 more)	Very low
Adverse pregnancy outcome – Blastocyst stage					
No evidence reported					

CI confidence interval, SET single embryo transfer, DET double embryo transfer, OR odds ratio.

Observational studies

Five observational studies were included in the review (Wang et al., 2010a; Luke et al., 2010; Scotland et al., 2011; Roberts et al., 2010; Sazonova et al., 2011). All these studies compared the live full-term singleton birth rates resulting from SET or DET, and three of the studies also examined the multiple pregnancy rates. The complexity of the analysis and heterogeneity of presentation meant that results could not be reported in a GRADE format.

Australian and New Zealand Assisted Reproduction Database

The first observational study was based on data from the Australian and New Zealand Assisted Reproduction Database (1 January 2004 to 31 December 2007) regarding 34,035 cycles where embryo transfer took place out of 44,869 that were started. The study examined variation in risk-adjusted outcomes depending on woman's age, stage of embryo development, number of embryos transferred and number of embryos available for transfer (Wang et al., 2010a). The quality of this study was low (bias had been addressed and there was no inconsistency, no indirectness and low imprecision).

Table 15.20 shows how live birth rates (number of live births as proportion of number of transfers) varied according to the embryo transfer strategy that was being employed. The authors examined the effect of woman's age and stage of embryo development on live birth rates. In addition, the authors made a distinction between situations where the women had enough embryos available to select how many were transferred and which were frozen ('selective'), and situations where all embryos created

were transferred ('unselected'). The study found that live birth rates decreased with increasing age of the woman, and that blastocyst transfers were more successful than cleavage. The study also found no difference between SET or DET when an elective strategy was being used. The study did not report on multiple births.

Table 15.20 Rate ratio (using SSET BL as comparator) of live birth by group of embryo transfers, woman's age and stage of embryo transfer. Results are adjusted for clinic, cause of infertility, previous pregnancy of more than 20 weeks and type of fertilisation(Wang etal., 2010a).

Embryo transfer	Live birth rate (%)	Rate ratio (95% CI)	Adjusted rate ratio (95% CI)
Women aged < 35 years			
SSET BL	46.2	1 (reference)	1 (reference)
USSET BL	31.2	0.67 (0.60–0.76)	0.68 (0.60–0.76)
SDET BL	44.1	0.95 (0.76–1.19)	0.99 (0.79–1.24)
USDET BL	33.2	0.72 (0.58–0.89)	0.72 (0.58–0.89)
SSET CL	33.6	0.73 (0.68–0.78)	0.77 (0.70–0.85)
USSET CL	20.6	0.44 (0.40–0.50)	0.47 (0.42–0.53)
SDET CL	42.4	0.92 (0.85–0.99)	1.00 (0.90–1.11)
USDET CL	30.3	0.66 (0.59–0.73)	0.71 (0.62–0.81)
Women aged 35–39 years			
SSET BL	37.1	1 (reference)	1 (reference)
USSET BL	21.2	0.57 (0.49–0.68)	0.57 (0.48–0.67)
SDET BL	41.3	1.12 (0.90–1.39)	1.11 (0.89–1.38)
USDET BL	25.3	0.68 (0.56–0.83)	0.69 (0.57–0.84)
SSET CL	24.4	0.66 (0.59–0.74)	0.67 (0.60–0.75)
USSET CL	13.2	0.36 (0.30–0.41)	0.36 (0.31–0.42)
SDET CL	29.8	0.80 (0.72–0.90)	0.82 (0.73–0.91)
USDET CL	21.1	0.57 (0.50–0.65)	0.58 (0.50–0.66)
Women aged ≥ 40 years			
SSET BL	22.7	1 (reference)	1 (reference)
USSET BL	8.6	0.38 (0.24–0.60)	0.40 (0.25–0.64)
SDET BL	26.1	1.15 (0.74–1.79)	1.09 (0.70–1.70)
USDET BL	13	0.57 (0.39–0.84)	0.56 (0.38–0.82)
SSET CL	9.3	0.41 (0.27–0.62)	0.50 (0.31–0.81)
USSET CL	3.8	0.17 (0.11–0.25)	0.20 (0.13–0.30)
SDET CL	14	0.62 (0.44–0.86)	0.75 (0.50–1.12)
USDET CL	7.8	0.34 (0.24–0.49)	0.40 (0.27–0.59)

BL blastocyst, Cl cleavage, DET double embryo transfer, S selective (same as elective), SET single embryo transfer, US unselected (all available embryos transferred) (Wang et al., 2010a)

US Society of Reproductive Technology (SART) database

The second observational study was based on data from 69,028 transfer cycles undertaken between 2004 and 2006 and recorded on the US Society of Assisted Reproductive Technology (SART) database. The study examined how live birth rates varied by age and number of embryos transferred where women had enough embryos available to 'electively' choose SET or DET (Luke et al., 2010). The study quality was low as no distinction was made between blastocyst and cleavage embryos though bias had been addressed, and there was no inconsistency, no indirectness and low imprecision.

Table 15.21 shows the relationship between the woman's age and the number of embryos transferred and live birth rates. This shows that eDET results in higher live birth rates than eSET in all age groups.

Table 15.21 Live birth rate by woman's age and number of embryos transferred (%) (Luke et al., 2010)

Woman's age	All transfers	Number of embryos transferred				Across groups comparison (*P*-value)
		1	2	3	4	
Number of cycles	69,028	3037	42,396	17,480	6115	
< 30 years	52.6%	47.0%	53.6%	50.4%	46.5%	= 0.001
30–34 years	51.6%	46.2%	53.4%	48.0%	44.7%	< 0.0001
35–39 years	45.2%	39.9%	47.8%	42.8%	42.6%	< 0.0001
> 40 years	30.7%	22.0%	33.4%	31.2%	29.5%	= 0.02

Table 15.22 shows that 36% of all DET cycles resulted in multiple births (or 53% of all children born) compared with 2% in SET. Where three or more embryos were transferred, triplets or higher order births comprised about 6% of the live births.

Table 15.22 Live birth (%) by number of embryos transferred (Luke et al., 2010)

	All transfers	Number of embryos transferred				Across groups comparison (*P*-value)
		1	2	3	4	
Number of cycles	32,819	3037	42,396	17,480	6115	
Singleton	63.4%	98.0%	63.0%	59.7%	60.4%	< 0.0001
Twins	34.2%	2.0%	36.1%	34.5%	33.5%	-
Triplets	2.3%	0%	0.9%	5.8%	6.1%	-

Table 15.23 shows the risk-adjusted odd ratios for the outcomes by the number of embryos transferred. Live births were 34% higher with DET than SET. However, the risk-adjusted figures show that singleton births were lower in DET compared with SET, and the ratio of multiple pregnancies was more than 27 times higher.

Table 15.23 Live birth (%) and odds ratios (95% CIs) for multiple birth by number of embryos transferred; adjusted for age, ethnicity, type of infertility (Luke et al., 2010)

Outcome by number of embryos transferred	OR (95% CI)	Adjusted OR (95% CI)
Pregnancy		
1	1.00 (-)	1.00 (-)
2	1.35 (1.25 – 1.45)	1.33 (1.23 – 1.43)
3	1.02 (0.95 – 1.10)	1.08 (1.00 – 1.17)
4	0.87 (0.80 – 0.95)	1.00 (0.91 – 1.09)
Live birth (singleton and multiple)		
1	1.00 (-)	1.00 (-)
2	1.37 (1.27 – 1.48)	1.34 (1.25 – 1.45)
3	1.03 (0.95 – 1.10)	1.11 (1.03 – 1.20)
4	0.81 (0.74 – 0.88)	0.99 (0.90 – 1.08)
Singleton live birth		
1	1.00	1.00
2	0.64 (0.60 – 0.69)	0.63 (0.59 – 0.68)
3	0.48 (0.44 – 0.52)	0.48 (0.45 – 0.52)
4	0.41 (0.37 – 0.45)	0.42 (0.38 – 0.46)
Multiple live birth		
1	1.00 (-)	1.00 (-)
2	27.7 (18.8 – 40.8)	27.4 (18.6 – 40.4)
3	25.6 (17.3 – 37.7)	29.1 (19.8 – 43.0)
4	21.0 (14.2 – 31.1)	28.6 (19.3 – 42.4)

CI confidence interval, OR odds ratio

Scottish IVF clinics

The third study included 6153 women undergoing treatment at one of three Scottish IVF clinics, between January 1997 and June 2007 (Scotland et al., 2011). The study compared the live birth, singleton birth and multiple birth rates between eSET and DET, and how this varied in three age bandings. The results are summarised in Table 15.24. There were significantly higher live birth rates with DET for all three age groups, but no differences in full-term live birth rates at 32 years and 36 years. The study also showed that DET transfers were associated with significantly lower percentage of singleton births (at 32 years and 36 years) and that multiple births were ten times higher for all three age groups. Finally, the study reported that disability and perinatal death rates were twice as likely with DET compared with eSET. The quality of this study was low (bias had been addressed, but there was no inconsistency, no indirectness and low imprecision).

Table 15.24 Cumulative outcomes following up to three fresh treatment cycles with eSET or DET (with associated frozen cycles) (Scotland et al., 2011)

Woman's age	**32 years**		**36 years**		**39 years**	
Transfer strategy	**eSET**	**DET**	**eSET**	**DET**	**eSET**	**DET**
Live births (%)	50.4	58.5*	40.5	47.4*	29.4	37.1*
Term live births (%)	45.4	46.8	36.4	38.6	26.5	30.9*
Singleton live births (%)	48.9*	40.2	39.3*	34.3	28.7	28.7
Twin live births (%)	2.5	27.6*	2.3	23.4*	1.9	19.1*
Disability (per 1000 births)	7.5	14.0*	6.0	10.5*	4.3	7.7*
Perinatal death (per 1000 births)	5.0	10.6*	4.0	8.0*	2.9	5.8*

DET double embryo transfer, eSET elective single embryo transfer

*significant at $P = 0.05$

NIHR Technology Appraisal Data

The fourth study examined the feasibility of introducing an eSET policy in the UK (Roberts et al., 2010). The study included primary data on 23,582 cycles (17,857 fresh, 5725 frozen) from 11,767 women from five centres and secondary data from 139,848 cycles from 84,349 women treated in 84 centres from 2000 to 2005 provided by the HFEA. The quality of this study was low (bias had been addressed, but there was no inconsistency, no indirectness and low imprecision).

The study identified a number of factors (the woman's age, the number of embryos available and the quality of embryos available) that were predictive of the outcome (live full-term singleton births and multiple births) following IVFand could be used to predict the outcome of eSET. Using these factors a number of scenarios were developed to determine which criteria would need to be used in order to achieve different rates of twin births (ranging from 25% to 0%).

The analysis showed that adopting an eSET policy to reduce multiple births is always associated with a reduction in live birth rates but that selection criteria can be used to mitigate this. Table 12.25 outlines the criteria for SET that would be needed for a given overall twin rate target. In all cases, live birth rates would be lower than if DET continued to be used alone.

The study also showed that cumulative fresh and thawed embryo transfer could be as effective as double embryo transfer as long as cryopreservation resulted in at least 70% of embryos being viable after thawing.

Table 15.25 Numbers of patients needed to receive SET in order to achieve a range of twin target rates for selection using patient characteristics. The predictions for selection using a random approach to achieve a given twin rate are also shown for comparison (Roberts et al., 2010)

Policy	**Couples using SET (%)**	**Estimated live births (%)**	**Estimated twin rate (%)**
All DET	0	24.3	25
Random allocation to SET	68.3	19.0	10
Age alone (< 33.3 years)	51.8	19.8	10
Age (< 34.3 years) and at least one top-quality (grade 3 or 4, growth rate 0.95–1.15 doublings per day) embryo	48.2	19.9	10
All SET	100	16.5	0

DET double embryo transfer, SET single embryo transfer

Swedish National Database

The fifth study investigated the obstetric outcomes after IVF with either SET or DET in comparison with the general population (Sazonova et al., 2011). The study included data on 13,544 children born from IVF and 587,009 children not born from IVF in Sweden. The quality of this study was very low (bias had been addressed, but there was no inconsistency, or indirectness as the study did not directly compare SET and DET, and low imprecision).

Although the study did not directly compare outcomes from SET and DET these can be calculated based on the data provided. These show increased odds of preterm births (OR 2.77, 95% CI 2.50 to 3.07), low birth weight (< 2500 g: OR 3.25, 95% CI 2.90 to 3.65) and peri/neonatal death (OR 2.01, 95% CI 1.15 to 3.50) with DET compared with SET. Furthermore, the authors found that when multiple births were excluded from the analysis, there was no difference in outcomes for SET or DET.

Table 15.26 Perinatal outcomes for IVF SET and DET (including singletons and multiples) children compared non-IVF children in the general population. General population is reference standard of 1.00 (Sazonova, 2011)

Outcome	SET		DET	
	OR (95% CI)	AOR *(95% CI)	OR (95% CI)	AOR* (95% CI)
Born < 28 weeks	2.26 (1.72 to 2.97)	1.45 (1.04 to 2.03)	3.13 (2.40 to 4.08)	1.85 (1.37 to 2.50)
Born < 32 weeks	1.76 (1.48 to 2.10)	1.13 (0.93 to 1.38)	3.88 (3.40 to 4.44)	2.26 (1.92 to 2.65)
Born < 37 weeks	1.42 (1.31 to 1.54)	1.06 (0.97 to 1.16)	3.93 (3.69 to 4.17)	2.78 (2.58 to 2.99)
Birth weight < 1500 g	1.96 (1.63 to 2.36)	1.23 (0.99 to 1.51)	3.75 (3.23 to 4.35)	2.16 (1.81 to 2.57)
Birth weight < 2500 g	1.43 (1.30 to 1.57)	0.87 (0.79 to 0.97)	4.77 (4.48 to 5.08)	3.16 (2.93 to 3.42)
Small for gestational age	1.38 (1.23 to 1.56)	0.98 (0.86 to 1.12)	2.82 (2.56 to 3.11)	1.95 (1.74 to 2.20)
Apgar 5 < 7	1.25 (1.04 to 1.51)	0.96 (0.78 to 1.18)	1.89 (1.59 to 2.25)	1.34 (1.09 to 1.64)
Peri/neonatal mortality	1.20 (0.78 to 1.85)	1.11 (0.68 to 1.81)	2.42 (1.71 to 3.41)	1.92 (1.26 to 2.92)

AOR adjusted odds ratio, DET double embryo transfer, OR odds ratio, SET single embryo transfer

*Adjusted ORs for year of birth, maternal age, parity, smoking, BMI and years on involuntary childlessness.

Timing of transfer

RCTs

Eleven RCT studies (Rienzi et al., 2002; Van der Auwera et al., 2002; Hreinsson et al., 2004; Bungum et al., 2003; Papanikolaou et al., 2006; Kolibianakis et al., 2004; Coskunet al., 2000; Emilaini et al., 2003; Gardner et al., 1998; Papanikolaou et al., 2005; Zech et al., 2007) compared cleavage-stage embryo transfer with blastocyst transfer. In five studies two or more embryos were used in both arms and blastocyst was compared with cleavage-stage embryo transfer (Coskun et al., 2000; Emiliani et al., 2003; Gardner et al., 1998; Karaki et al., 2002; Papanikolaou et al., 2005). One study (Papanikolaou, 2006) compared single embryo transfer at the cleavage stage with single embryo transfer at the blastocyst stage. One study compared single blastocyst with single cleavage-stage embryo transfer (Zech et al., 2007).

Table 15.27 GRADE findings for comparison of timing of embryo transfer

Number of studies	Number of patients/women		Effect		Quality
	Intervention (Day 2 – 3)	Comparator (Day 5 – 6)	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Cumulative					
No evidence reported					
Fresh cycle					
DET					
4 (Van der Auwera et al., 2002; Rienzi et al, 2002; Emiliani et al., 2003; Papanikolaou et al., 2005)	121/287 (42.2%)	140/282 (49.6%)	OR 0.74 (0.53 to 1.04)	75 fewer per 1000 (from 153 fewer to 10 more)	Very low
SET					
1 (Papanikolaou et al., 2006)	38/176 (21.6%)	56/175 (32%)	OR 0.59 (0.36 to 0.95)	103 fewer per 1000 (from 11 fewer to 175 fewer)	Moderate
Frozen cycle					
No evidence reported					
Clinical pregnancy					
DET					
7 (Van der Auwera et al., 2002; Rienzi et al., 2002; Emiliani et al., 2003; Papanikolaou et al., 2005; Hreinsson et al., 2004; Bungum et al., 2003; Coskun et al., 2000)	219/525 (41.7%)	232/507 (45.8%)	OR 0.86 (0.67 to 1.1)	37 fewer per 1000 (from 96 fewer to 24 more)	Very low
Clinical pregnancy – SET					
2 (Papanikolaou et al., 2006; Zech et al., 2007)	64/275 (23.3%)	100/303 (33%)	OR 0.62 (0.43 to 0.89)	96 fewer per 1000 (from 25 fewer to 155 fewer)	Moderate

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Number of studies	Number of patients/women		Effect		Quality
	Intervention (Day 2 – 3)	Comparator (Day 5 – 6)	Relative (95% CI)	Absolute (95% CI)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
DET					
7 (Kolibianakis et al., 2004; Van der Auwera et al., 2002; Rienzi et al., 2002; Emiliani et al., 2003; Papanikolaou et al., 2005; Hreinsson et al., 2004; Bungum et al., 2003)	72/658 (10.9%)	78/633 (12.3%)	OR 0.9 (0.64 to 1.27)	11 fewer per 1000 (from 41 fewer to 28 more)	Very low
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Preterm delivery					
No evidence reported					
Adverse pregnancy outcome (ectopic pregnancy, extrauterine pregnancy, miscarriage)					
DET					
7 (Kolibianakis et al., 2004; Van der Auwera et al., 2002; Rienzi et al., 2002; Emiliani et al., 2003; Papanikolaou et al., 2005; Hreinsson et al., 2004; Bungum et al., 2003)	51/658 (7.8%)	67/633 (10.6%)	OR 0.72 (0.49 to 1.05)	27 fewer per 1000 (from 51 fewer to 5 more)	Very low
SET					
2 (Papanikolaou et al., 2006; Zech et al., 2007)	29/275 (10.5%)	26/303 (8.6%)	OR 1.23 (0.7 to 2.15)	18 more per 1000 (from 24 fewer to 82 more)	Low

CI confidence interval, DET double embryo transfer, OR odds ratio, SET single embryo transfer

Observational studies

Two observational studies were reviewed that compared the timing of embryo transfers (Wang et al., 2010b; Kallen et al., 2010).

Australian and New Zealand Assisted Reproduction Database

The first observational study was based on data from 150,376 IVF cycles undertaken between 2002 and 2006 and recorded on the Australian and New Zealand Assisted Reproduction Database. The study examined variation on risk-adjusted live birth rates depending on the timing of embryo transfer (Wang et al., 2010b).

The study found that the transfer of fresh blastocyst embryos was significantly better than fresh cleavage or any form of frozen embryos. When using thawed embryos, blastocysts developed from thawed cleavage embryos produced the best outcomes (see Table 15.28).

Table 15.28 Odds ratio of live delivery of different stages of embryo (Wang et al., 2010b)

	Live birth rate (%)	OR (95% CI)	AOR (95% CI).
All embryos transfer cycles			
Fresh cleavage	21.7	0.71 (0.69 to 0.74)	0.67 (0.64 to 0.69)
Fresh blastocyst	27.9	1.00 (reference)	1.00 (reference)
Thawed cleavage	15.2	0.46 (0.44 to 0.48)	0.46 (0.44 to 0.48)
Blastocyst from thawed cleavage	22.0	0.73 (0.66 to 0.80)	0.71 (0.64 to 0.79)
Thawed blastocyst	16.3	0.50 (0.47 to 0.54)	0.50 (0.47 to 0.54)
Thawed cycles only			
Thawed cleavage	15.2	0.64 (0.58 to 0.70)	0.63 (0.57 to 0.70)
Blastocyst from thawed cleavage	22.0	1.00 (reference)	1.00 (reference)
Thawed blastocyst	16.3	0.69 (0.62 to 0.77)	0.71 (0.64 to 0.79)

AOR adjusted odds ratio, OR odds ratio

Swedish National Database

The second study compared adverse outcomes associated with blastocyst (n = 1311 babies from 1190 women) and cleavage stage (n = 12,562 babies from 11,548 women) embryo transfers undertaken between 2002 and 2007 in Sweden (Kallen et al., 2010).

Table 15.29 shows the risk-adjusted odds of prematurity and congenital malformation were statistically higher in blastocysts compared with cleavage transfers.

Table 15.29 Adverse outcomes associated with blastocyst and cleavage embryo transfers (Kallen et al., 2010)

Outcome	Blastocyst		Cleavage		AOR	95% CI
	Number	Total cycles	Number	Total cycles		
Born < 32 weeks	18	1071	142	10,513	1.44	0.87 to 2.40
Born < 37 weeks	97	1071	757	10,513	1.35	1.07 to 1.71
Any congenital malformation	90	1311	645	12,562	1.43	1.14 to 1.81
Severe	61	1311	509	12,562	1.33	1.01 to 1.75
Cardiovascular malformation	20	1311	177	12,562	1.18	0.94 to 1.90

AOR adjusted odds ratio, CI confidence interval

Evidence statements

Number of embryos transferred

Live full-term singleton birth – full term – cumulative (cleavage stage)

Very low quality evidence from one study showed no significant difference in cumulative rates of live births when comparing fresh transfer of a single embryo plus subsequent frozen transfers against fresh transfer of two embryos plus subsequent frozen transfers.

Live full-term singleton birth – full term – cumulative (blastocyst stage)

There was no reported evidence.

Live full-term singleton birth – full term – cumulative (cleavage or blastocyst stage)

Low quality evidence from one study showed that cumulative fresh and thawed single embryo transfer could be as effective as double embryo transfer as long as the cryopreservation resulted in at least 70% of embryos being viable after thawing.

Live full-term singleton birth – fresh cycle (cleavage stage)

Very low quality evidence from five studies showed a significantly higher rate of live births from fresh cycles when one transfer of two embryos was compared with one transfer of a single embryo.

Live full-term singleton birth – fresh cycle (bBlastocyst stage)

Low quality evidence from one observational study showed that there was no difference in live birth rates between eSET and DET when elective blastocyst transfer was undertaken.

Live full-term singleton birth – frozen cycle (cleavage stage)

Very low quality evidence from one study showed no significant difference in live births from frozen cycles when one transfer of two embryos was compared with one transfer of a single embryo.

Live full-term singleton birth – frozen cycle (blastocyst stage)

There was no reported evidence.

Live full-term singleton birth – fresh cycle (cleavage or blastocyst stage)

Moderate quality evidence from one study showed that live full-term singleton births were significantly more likely to occur using SET than using DET.

Very low quality evidence from five studies showed that eSET resulted in lower live birth rates per transfer than DET, but where blastocysts or a cumulative fresh and thawed embryo strategy are used there is no difference between SET and DET.

Clinical pregnancy (cleavage stage)

Very low quality evidence from five studies showed there were significantly more clinical pregnancies when one transfer of two embryos was compared with one transfer of a single embryo.

Clinical pregnancy (blastocyst stage)

Very low quality evidence from one study involving small numbers showed no significant difference in the number of clinical pregnancies when one transfer of two embryos was compared with one transfer of a single embryo.

Multiple pregnancy (cleavage stage)

Very low quality evidence from five studies showed there was a significantly higher rate of multiple pregnancy when one transfer of two embryos was compared with one transfer of a single embryo.

Multiple pregnancy (blastocyst stage)

Low quality evidence from one study showed there was a significantly higher number of multiple pregnancies when one transfer of two embryos was compared with one transfer of a single embryo.

Multiple pregnancy (cleavage or blastocyst stage)

Very low quality evidence from five studies showed that eSET results in significantly lower multiple pregnancy rates than DET.

Preterm delivery (cleavage stage)

Low quality evidence from three studies showed there were significantly more preterm deliveries when one transfer of two embryos was compared with one transfer of a single embryo.

Preterm delivery (blastocyst stage)

There was no reported evidence.

Preterm delivery (blastocyst or cleavage stage)

Very low quality evidence from one study showed that preterm births were significantly more likely if DET was used compared with SET.

Adverse pregnancy outcome (cleavage stage)

Very low quality evidence from five studies showed there was no significant difference in the numbers of other adverse pregnancy outcomes (excluding multiple pregnancy and pre-term births) when one transfer of two embryos was compared with one transfer of a single embryo.

Adverse pregnancy outcome (blastocyst stage)

There was no reported evidence.

Adverse pregnancy outcome (blastocystor cleavage stage)

Low and very low quality evidence from two oberservational studies showed that DET resulted in significantly higher rates of disability and perinatal death compared with SET.

Timing of transfer

Live full-term singleton birth – full term – cumulative

There was no reported evidence.

Live full-term singleton birth – fresh cycle (DET)

Very low quality evidence from four studies showed no significant difference in the rate of live births from transfer at either the blastocyst or the cleavage stages using two fresh embryos.

Live full-term singleton birth – fresh cycle (SET)

Moderate quality evidence from one study showed a significantly higher number of live births from transfer of a single fresh blastocyst compared with a single fresh cleavage-stage embryo.

Live full-term singleton birth – frozen cycle (SET or DET)

Low quality evidence from one study showed significantly higher live birth rates with blastocyst transfers developed from thawed cleavage embryos compared with frozen cleavage or blastocyst transfers.

Clinical pregnancy (DET)

Very low quality evidence from seven studies showed there was no significant difference in the number of clinical pregnancies when double blastocyst stage transfer was compared with double cleavage stage transfer.

Clinical pregnancy (SET)

Moderate quality evidence from two studies showed there were significantly more clinical pregnancies with a single blastocyst stage transfer compared with a single cleavage stage transfer.

Multiple pregnancy (DET)

Very low quality evidence from seven studies showed there was no significant difference in multiple pregnancy when double blastocyst stage transfer was compared with double cleavage stage transfer.

Multiple pregnancy (SET)

Low quality evidence from one study showed there was no significant difference in the number of multiple pregnancies when single blastocyst stage transfer was compared with single cleavage stage transfer.

Preterm delivery (SET or DET)

Low quality evidence from one observational study found higher rates of preterm birth resulting from blastocyst compared with cleavage embryo transfers.

Adverse pregnancy outcome (DET)

Very low quality evidence from seven RCT studies showed there was no significant difference in the number of adverse pregnancy outcomes when double blastocyst stage transfer was compared with double cleavage stage transfer.

Adverse pregnancy outcome (SET)

Low quality evidence from one study showed there was no significant difference in the number of adverse pregnancy outcomes when single blastocyst stage transfer was compared with single cleavage stage transfer.

Adverse pregnancy outcome (SET or DET)

Very low quality evidence from one observational study showed higher rates of adverse events after blastocyst embryo transfer compared to cleavage embryo transfer.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG considered that live full-term singleton birth was the primary outcome measure. When this was not available the multiple birth rate was substracted from the total live births to give an approximation of the singleton births. In addition, the GDG stated that multiple birth rate was itself a proxy for a number of other adverse outcomes, such as prematurity, disability and perinatal mortality, all of which are higher with multiple compared with singleton births. Secondary outcomes included clinical pregnancy and preterm birth. The GDG was also interested in cumulative live birth rates as this demonstrates the overall effectiveness of any embryo transfer strategy as the majority of women having IVF will require more than 1 cycle of embryo transfer.

Consideration of clinical benefits and harms

The GDG members agreed that the RCT and observational evidence presented was consistent with their clinical experience of current practice.

The GDG was aware that the terminology often used in regional embryo transfer strategies can lead to inconsistency between treatment centres, where phrases such a 'top grade and quality' are used to different degrees to describe embryos and blastocyst grading. The GDG therefore moved to recommend a standard that can be used to underpin the grading of blastocysts and embryos within the recommendations made in this review. While there are grading standards for blastocysts available, there is no agreed system for judging embryo quality, a point that is fundamental to the implementation of the recommendations the GDG made on decisions regarding DET and SET. Therefore the GDG chose to adopt the forthcoming Association of Clinical Embryologists (ACE/UK) National External Quality Assessment Service (NEQAS) for Reproductive Science Embryo and Blastocyst Grading schematic, a standard that will incorporate pre-existing blastocyst grading systems with a new embryo grading schematic. Further information can be found at the UK NEQAS Reproductive Science – Embryo Morphology webpage.

The GDG highlighted that few studies reported on live full-term singleton birth rates or on the cumulative live birth rate associated with fresh and thawed single embryo transfer strategy. The GDG stated that the recommendations had to take into account the fact that women often underwent several cycles of embryo transfer. However, the GDG considered that the available evidence was sufficient to make recommendations on the number and timing of embryo transfer.

The evidence showed that single embryo transfer resulted in higher live full-term singleton birth rates and significantly lower multiple birth rates compared with double embryo transfers. The evidence showed that blastocyst transfer was associated with higher live full-term singleton birth rates and similar multiple birth rates compared with transfer at the cleavage stage. However, the GDG highlighted that extending embryo culture from cleavage to the blastocyst stage resulted in fewer embryos being available for transfer. As a result, in situations where few cleavage embryos were available it might be considered preferable to undertake transfer at this stage rather than risk no embryos being available after extending the culture period and subjecting the woman to ovarian stimulation and egg retrieval to no avail. Furthermore, the GDG highlighted that the available evidence showed that where freezing was of a suitable standard, replacement of frozen–thawed embryos had similar outcomes to embryos replaced during natural cycles and hormone-

supplemented cycles. Therefore, the GDG concluded that an embryo transfer strategy should apply to both fresh and frozen embryos within any cycle.

Consensus survey of GDG

The GDG discussed a number of factors that could influence the success of any embryo transfer strategy and could be included in a decision-making process:

- the woman's age
- the woman's obstetric and gynaecological history
- the number of previous failed IVF attempts
- the woman's ovarian response or reserve
- the number of embryos created
- the quality of the embryos, including blastocysts.

Where donor eggs are used the age of the donor has to be taken into account.

The GDG concluded that any recommendation on embryo transfer should take into account specific combinations of these factors. It was not possible to reach a conclusion on all the combinations in the GDG setting. Therefore it was decided to use a formal consensus survey of the GDG to determine which embryo transfer strategy would be applied in a variety of clinical settings (see Chapter 3). This information could then be used as the basis for recommendations and, where necessary, further discussion within the GDG.

Initially a table was outlined based an algorithm outlined by Cutting et al., 2008 (see Table 15.30). The algorithm included women's age, number of failed IVF cycles and the number and the quality of embryos. In total, there were 27 different clinical scenarios. In addition, the survey contained a number of questions and statements related to embryo transfers, such as the need for information provision to couples about the risks of multiple births.

Three rounds of voting were then undertaken where GDG members were asked to apply the evidence they had been presented with alongside their own judgement to the clinical scenarios outlined in the table. The survey and voting were all undertaken electronically. Results and comments were combined and anonymised before being returned to the GDG. A detailed description of the methodology used is shown in Chapter 3. The initial table was simplified over the three rounds as consensus allowed clinical scenarios to be combined and the simplified table was used in the final recommendation. Furthermore, as the strategy was based on three full cycles of IVF and the algorithm outlined by Cutting et al, 2008 was based on a single cycle, the GDG varied the embryo transfer strategy used in each cycle in order to maximise the chances of achieving a live full-term singleton birth.

Table 15.30 shows the results of the three rounds of voting. The results show that it was mainly in situations where women aged under 40 years had no top quality embryos available or had a number of previous failed IVF cycles that there was no consensus on which embryo transfer strategy should be used. In women under 40 years with top quality embryos available and/or in their first or second IVF cycle, single embryo transfer (SET) was the preferred option. In women 40 years or older the preferred option was usually double embryo transfer (DET).

The results were then written up into draft recommendations which the GDG discussed and voted on at a GDG meeting.

Table 15.30 Results of consensus survey for embryo transfer strategies

Cycle	Women's age (years)	Number and grade of embryos available at cleavage stage	SET	DET
1st cycle: no previous IVF cycles	36 or under	Embryos (2 plus) available but none are top grade	~√	
		1 to 3	√	
		4 plus	√	
	37–39	Embryos (2 plus) available but none are top grade	=	
		1 to 3	√	
		4 plus	√	
	40–42	Embryos (2 plus) available but none are top grade		√
		1 to 3	=	
		4 plus	~√	
2nd cycle: 1 previous failed full cycle of IVF	36 or under	Embryos (2 plus) available but none are top grade	=	
		1 to 3	√	
		4 plus	√	
	37–39	Embryos (2 plus) available but none are top grade	=	
		1 to 3	=	
		4 plus	√	
	40 - 42	Embryos (2 plus) available but none are top grade		√
		1 to 3		~√
		4 plus	=	
3rd cycle: 2 previous failed full cycle of IVF	36 or under	Embryos (2 plus) available but none are top grade	=	
		1 to 3	=	
		4 plus	=	
	37–39	Embryos (2 plus) available but none are top grade		~√
		1 to 3	=	
		4 plus	=	
	40–42	Embryos (2 plus) available but none are top grade		√
		1 to 3		√
		4 plus		√

DET double embryo transfer, IVF in vitro fertilisation, SET single embryo transfer

√ consensus ≥70% agreement or disagreed with an embryo transfer strategy

~√ 'near consensus' 60–69% agreement

= no consensus 50–59% agreement

Summary

Taking into account the clinical factors and the relative success of embryo transfer strategies, the GDG considered that either a single embryo transfer or single blastocyst transfer strategy provided the chance of a live full-term singleton birth in women aged under than 40 years with blastocyst transfer being more succeful than embryo transfer. However, the GDG considered that in women

using their own eggs who were 40 years or older or who had a number of previous failed attempts at IVF, double embryo transfer with cleavage embryos should be considered as the risk of multiple pregnancy was reduced in these groups and the quality of available embryos was often lower.

Consideration of health benefits and resource uses

The GDG highlighted that the health risks to children born following assisted conception would be reduced by avoidance of multiple pregnancy, including risk of stillbirth, neonatal death and disability in the children and risk of complications to the mother. The transfer of a single embryo with freezing of supernumerary embryos to maximise the cumulative pregnancy rate from a 'full cycle' will reduce health risks to the women undergoing ovarian stimulation and egg harvest, and reduce drug costs, but increase laboratory costs. More embryo transfer procedures would be required using elective single embryo transfer to achieve live birth.

Furthermore, the evidence showed that single embryo transfer would require a woman to have more transfers than a double embryo transfer in order to achieve a live birth. The GDG also highlighted that extending the culture of embryos to blastocyst stage requires more laboratory time. However, these additional resources are offset by the lower obstetric, neonatal and paediatric resources needed as a result of lower multiple birth rates. These issues are further discussed in Chapter 14.

Quality of evidence

The quality of the studies reviewed varied from moderate to very low depending on the outcome being assessed.

Other considerations

The GDG highlighted that before IVF is started that a woman's previous medical and obstetric history must be taken into account when determining what, if any, is the safest embryo transfer strategy. The GDG gave the following examples of situations where single embryo transfer should be considered:

- congenital heart disease
- chronic renal failure
- hypertension
- diabetes
- previous premature delivery
- previous caesarean section.

Equalities

The people considered in this review were

- People who have vaginal intercourse.
- Specific patient subgroups listed in the guideline Scope that may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychological problem
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
- People who are preparing for cancer treatment who may wish to preserve their fertility.

There were no other specific issues that needed to be addressed with respect to any of these subgroups in the context of embryo transfer strategies.

Recommendations

Number	Recommendation
156	Women undergoing IVF treatment should be offered ultrasound-guided embryo transfer because this improves pregnancy rates. **[2004]**
157	Replacement of embryos into a uterine cavity with an endometrium of less than 5 mm thickness is unlikely to result in a pregnancy and is therefore not recommended. **[2004]**
158	Women should be informed that bed rest of more than 20 minutes' duration following embryo transfer does not improve the outcome of IVF treatment. **[2004]**
159	Evaluate embryo quality, at both cleavage and blastocyst stages, according to the Association of Clinical Embryologists (ACE) and UK National External Quality Assessment Service (UK NEQAS) for Reproductive Science Embryo and Blastocyst Grading schematic (see appendix O). **[new 2013]**
160	When considering the number of fresh or frozen embryos to transfer in IVF treatment: • For women aged under 37 years: o In the first full IVF cycle use single embryo transfer. o In the second full IVF cycle use single embryo transfer if 1 or more top-quality embryos are available. Consider using 2 embryos if no top-quality embryos are available. o In the third full IVF cycle transfer no more than 2 embryos. • For women aged 37–39 years: o In the first and second full IVF cycles use single embryo transfer if there are 1 or more top-quality embryos. Consider double embryo transfer if there are no top-quality embryos. o In the third full IVF cycle transfer no more than 2 embryos. • For women aged 40–42 years consider double embryo transfer. **[new 2013]**
161	For women undergoing IVF treatment with donor eggs, use an embryo transfer strategy that is based on the age of the donor. **[new 2013]**
162	No more than 2 embryos should be transferred during any one cycle of IVF treatment. **[2013]**
163	Where a top-quality blastocyst is available, use single embryo transfer. **[new 2013]**
164	When considering double embryo transfer, advise people of the risks of multiple pregnancy associated with this strategy. **[new 2013]**
165	Offer cryopreservation to store any remaining good-quality embryos after embryo transfer. **[new 2013]**
166	Advise women who have regular ovulatory cycles that the likelihood of a live birth after replacement of frozen–thawed embryos is similar for embryos replaced during natural cycles and hormone-supplemented cycles. **[2013]**

Number	Research recommendation
RR 33	Further research is needed on long term outcomes of children, and whatever is missing from the health economics

2013 Update

RR 34 Further research is needed to improve embryo selection to facilitate single embryo transfers.

Why this is important

In current IVF practice it is common to transfer more than one embryo in order to maximise the chance of pregnancy. As detailed in the guideline, this practice has inherent risks, especially multiple pregnancy and its consequences. Embryo selection for transfer is based on the developmental stage and morphological grading criteria assessed in the laboratory. These features are indicative of implantation potential though the predictive accuracy is relatively poor. However, if prediction of implantation could be improved, this would facilitate embryo selection for single embryo transfer rather than double embryo transfer.

15.8 Luteal phase support after IVF

Introduction

In a normal menstrual cycle, once ovulation has occurred, the endometrium prepares to receive a fertilised embryo. This consists of a series of changes within it which are driven by progesterone produced by the corpus luteum in the ovary.

During IVF, GnRH agonists or antagonists are used to ensure that the pituitary gland is desensitised, such that it does not produce follicle stimulating hormone (FSH) and luteinising hormone (LH), which act on the ovary to cause maturation and release of oocytes (see 'Down-regulation', Section 15.3). This allows the use of exogenous hormones to achieve controlled ovarian stimulation and ensures that the maximum number of mature eggs can be collected at a pre-scheduled time.

However, use of these hormones to block the activity of the pituitary gland can result in inadequate production of progesterone by the ovaries which may decrease the chance of an embryo implanting or embedding in the endometrium.

Thus, it has been felt that in IVF the luteal phase needs to be supported by means of progesterone, human chorionic gonadotropin (hCG) (which stimulates progesterone production) or gonadotropin-releasing hormone (GnRH) agonists. This review aims to determine which luteal phase support protocol (if any) increases the chances of a clinical pregnancy and live full-term singleton birth.

A number of other agents have been promoted as being useful in luteal phase support and were mentioned during the scoping phase for the Guideline update; these include low dose aspirin, heparin, prednisoline, immunoglobulins and/or fat emulsions. The pre-scoping search and review did not identify any RCT evidence suggesting benefit from any of these interventions. Furthermore, it was highlighted that these are not part of conventional care in the UK, and therefore they were not included in the final scope for the guideline update.

Progesterone versus no support in non-downregulated cycles

A 1988 meta-analysis of five RCTs found no significant difference between luteal-phase progesterone support in non-downregulated IVF cycles and no such support in pregnancy rate (OR 1.25, 95% CI 0.93 to 1.66) in women undergoing IVF or GIFT after ovarian stimulation with clomifene and hMG.[972] [Evidence level 1a]

Human chorionic gonadotrophin versus no treatment/human chorionic gonadotrophin versus progesterone in downregulated cycles

A meta-analysis of 18 RCTs showed significantly higher pregnancy rate per cycle in women treated with hCG compared with no treatment (OR 1.9, 95% CI 1.3 to 3.1, based on five RCTs) when used with GnRH agonist.[866] [Evidence level 1a] A significantly higher pregnancy rate per cycle was also found in groups treated with intramuscular or oral progesterone (progestagen) compared with no treatment (OR 1.2, 95% CI 1.0 to 1.7, based on eight RCTs). In three RCTs that compared hCG luteal

support with intramuscular or oral progesterone, pregnancy rate per cycle was significantly higher in women treated with hCG compared with progesterone (OR 2.0, 95% CI 1.1 to 3.9). However, this effect was to due a difference in the effectiveness of hCG and oral (rather than intramuscular) progesterone. There was no significant difference in spontaneous abortion rate between women given luteal support or no support (OR 0.8, 95% CI 0.4 to 1.7, based on seven RCTs). The overall incidence of OHSS with hCG was 5% (n = 220) versus 0% (n = 193) with progesterone or no treatment.[866] [Evidence level 1a]

Another meta-analysis[973] of 30 RCTs showed that intramuscular hCG significantly improved clinical pregnancy rate when compared with no treatment (RR 2.72, 95% CI 1.56 to 4.90, based on four RCTs). Intramuscular progesterone significantly improved clinical pregnancy rate (RR 2.38, 95% CI 1.36 to 4.27, based on three RCTs), ongoing pregnancy rate (RR 3.8, 95% CI 1.42 to 11.38, based on three RCTs) and delivery rate (RR 5.50, 95% CI 1.25 to 35.53, based on one RCT) when used with long GnRH agonist protocol. Intramuscular hCG significantly improved clinical pregnancy rate (RR 8.36, 95% CI 1.44 to 173.74, based on four RCTs) and ongoing pregnancy rate (RR 7.43, 95% CI 1.22 to 156.64, based on four RCTs) when compared with oral progesterone used in a short GnRH agonist protocol.[973] [Evidence level 1a]

The same meta-analysis reported that intramuscular progesterone significantly improved clinical pregnancy rate (RR 1.33, 95% CI 1.02 to 1.75, based on five RCTs) and delivery rate (RR 2.06, 95% CI 1.48 to 2.88, based on two RCTs) when compared with vaginal progesterone. There were no significant differences in fertility outcomes when comparing: vaginal progesterone with no treatment; different doses of progesterone; intramuscular progesterone with oral progesterone; intramuscular hCG with oral progesterone in both long and short GnRH agonist protocols; intramuscular hCG with intramuscular progesterone; ooestrogen plus progesterone with progesterone only in long GnRH agonist protocols; hCG plus progesterone with vaginal progesterone in long and short GnRH agonist protocols; intramuscular progesterone plus ooestrogen with hCG. Given the increased risk of OHSS associated with hCG use, progesterone was favoured for luteal-phase supplementation with addition of ooestrogen.[973] [Evidence level 1a]

The review did not consider patient satisfaction. However in one of the RCTs, 4/30 women discontinued treatment because of their inability to administer intramuscular progesterone.

The two meta-analyses show inconsistency in the relative effectiveness of the different drugs and routes of administration for luteal support. Although the meta-analyses involved a total of 18 and 30 RCTs, respectively, most of the detailed comparisons were based on meta-analyses of very few RCTs.

Patient satisfaction was assessed as part of a non-randomised multicentre study conducted in the USA.[974] [Evidence level 3] Women were asked to report their preferences between vaginal progesterone and intramuscular progesterone; 94% of the women found vaginal progesterone easier to use, and 84% preferred vaginal progesterone to intramuscular progesterone.

Review question

What is the effectiveness of luteal phase support as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?

Evidence profile

The GDG believed that there are three separate aspects of luteal phase support to consider in this review. The first is whether luteal phase support is more effective than no support. The second is whether there is one type of support that is more effective than others. The third is whether the length of luteal phase support affects the clinical effectiveness of the support.

Therefore, the evidence is presented in three profiles, comparing:

- luteal phase support with no luteal phase support (see Table 15.31)
- types of support (see Table 15.32)
- length of luteal phase support (see Table 15.33).

Description of included studies

One Cochrane review (van der Linden et al., 2011) was included in the current review. The Cochrane review included 13 randomised trials in its comparison of luteal phase support with no luteal phase support. Five of the included studies compared hCG to placebo or no treatment, and the remaining seven studies compared progesterone to placebo or no treatment.

Comparison of types of luteal phase support (Table 15.32)

One Cochrane review (van der Linden et al., 2011) and one additional RCT (Ata et al., 2010) were included in the current review. The Cochrane review included 23 RCTs in its comparison of different types of luteal phase support. Fourteen of the studies compared progesterone to progesterone plus hCG, and the remaining nine studies compared progesterone to progesterone plus oestrogen. The Ata et al. (2010) study compared progesterone to oestrogen in a GnRH agonist protocol.

Length of luteal phase support (Table 15.33)

Three rRCTs were included in this review (Goudge et al., 2010; Kyrou et al., 2011; Nyboe et al., 2002). One study compared progesterone from the day of oocyte retrieval for 5 to 6 weeks with progesterone from day of embryo transfer for 11 days after either a GnRH agonist or GnRH antagonist protocol (Goudge et al., 2010). Another study compared progesterone given from the day of embryo transfer until the day of a positive hCG test (2 weeks) with progesterone given from the day of embryo transfer until three weeks after hCG test (5 weeks) after a GnRH agonist protocol (Nyboe et al., 2002). The third study compared progesterone until 16 days after embryo transfer with progesterone until 7 weeks of gestation after a GnRH antagonist protocol (Kyrou et al., 2011).

Table 15.31 GRADE findings for comparison of luteal phase support with no luteal phase support

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Any type of support vs. placebo/no support					
1 (van der Linden et al., 2011)	18/117 (15%) women	5/77 (7%) women	OR 2.8 (1.1 to 6.9)	95 more per 1000 (from 6 more to 259 more)	Very low
Progesterone vs. placebo/no support					
1 (van der Linden et al., 2011)	15/104 (14%) women	2/52 (4%) women	OR 3.0 (1.0 to 8.6)	67 more per 1000 (from 1 more to 217 more)	Very low
hCG vs. placebo					
1 (van der Linden et al., 2011)	3/13 (23%) women	3/25 (12%) women	OR 2.3 (0.4 to 14)	115 more per 1000 (from 72 fewer to 533 more)	Very low
Clinical pregnancy					
Any type of support vs. placebo/no support					
1 (van der Linden et al., 2011)	181/831 (22%) women	117/756 (16%) women	OR 1.6 (1.2 to 2.0)	66 more per 1000 (from 25 more to 114 more)	Low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone vs. placebo/no support					
1 (van der Linden et al., 2011)	106/470 (23%) women	52/371 (14%) women	OR 1.8 (1.3 to 2.6)	90 more per 1000 (from 34 more to 158 more)	Low
Support with hCG vs. placebo support					
1 (van der Linden et al., 2011)	75/361 (21%) women	65/385 (17%) women	OR 1.3 (0.9 to 1.9)	40 more per 1000 (from 14 fewer to 108 more)	Very low
Adverse pregnancy outcome					
Any type of support vs. placebo/no support (miscarriage)					
1 (van der Linden et al., 2011)	14/271 (5%) women	12/294 (4%) women	OR 1.3 (0.6 to 2.8)	10 more per 1000 (from 17 fewer to 65 more)	Very low
	14/59 (24%) pregnancies	10/51 (20%) pregnancies	OR 1.27 (0.5 to 3.1)	40 more per 1000 (from 84 fewer to 235 more)	
Support with progesterone vs. placebo (miscarriage)					
1 (van der Linden et al., 2011)	10/207 (5%) women	9/218 (4%) women	OR 1.2 (0.5 to 3.0)	7 more per 1000 (from 21 fewer to 73 more)	Very low
	10/43 (23%) pregnancies	7/34 (21%) pregnancies	OR 1.2 (0.4 to 3.4)	24 more per 1000 (from 112 fewer to 260 more)	
Support with hCG vs. placebo (miscarriage)					
1 (van der Linden et al., 2011)	4/64 (6%) women	3/76 (4%) women	OR 1.5 (0.3 to 6.9)	18 more per 1000 (from 26 fewer to 180 more)	Very low
	4/16 (25%) pregnancies	3/17 (18%) pregnancies	OR 1.6 (0.3 to 8.1)	76 more per 1000 (from 114 fewer to 458 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Support with progesterone vs. placebo support					
1 (van der Linden et al., 2011)	1/12 (8%) women	0/22 (0%) women	OR 17 (0.3 to 1027.3)	Not calculable	Very low
	Not reported by clinical pregnancy				

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
Support with hCG vs. placebo support					
1 (van der Linden et al., 2011)	30/193 (16%) women	8/194 (4%) women	OR 3.6 (1.9 to 7.1)	93 more per 1000 (from 32 more to 192 more)	Low
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, hCG human chorionic gonadotropin, OR odds ratio

Table 15.32 GRADE findings for comparison of types of support

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Progesterone vs. hCG					
1 (van der Linden et al., 2011)	4/96 (4%) women	11/107 (10%) women	OR 0.4 (0.1 to 1.2)	58 fewer per 1000 (from 87 fewer to 16 more)	Very low
Progesterone vs. oestrogen					
1 (Ata et al., 2010)	11/30 (37%) women	10/30 (33%) women	RR 1.1 (0.6 to 2.2)	33 more per 1000 (from 150 fewer to 397 more)	Very low
Progesterone vs. progesterone + hCG					
1 (van der Linden et al., 2011)	3/70 (4%) women	5/62 (8%) women	OR 0.5 (0.1 to 2.2)	37 fewer per 1000 (from 70 fewer to 79 more)	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone vs. progesterone + oestrogen					
1 (van der Linden et al., 2011)	11/50 (22%) women	10/50 (20%) women	OR 1.1 (0.4 to 2.9)	20 more per 1000 (from 103 fewer to 224 more)	Very low
Clinical pregnancy					
Progesterone vs. hCG					
1 (van der Linden et al., 2011)	285/943 (30%) women	248/852 (29%) women	OR 1.1 (0.9 to 1.3)	12 more per 1000 (from 30 fewer to 59 more)	Very low
Progesterone vs. oestrogen					
1 (Ata et al., 2010)	16/30 (53%) women	14/30 (47%) women	RR 1.1 (0.7 to 1.9)	65 more per 1000 (from 145 fewer to 420 more)	Very low
Progesterone vs. progesterone + hCG					
1 (van der Linden et al., 2011)	169/540 (31%) women	173/540 (32%) women	OR 1.0 (0.7 to 1.3)	9 fewer per 1000 (from 62 fewer to 50 more)	Very low
Progesterone vs. progesterone + oestrogen					
1 (van der Linden et al., 2011)	312/664 (47%) women	237/546 (43%) women	OR 0.8 (0.6 to 1.0)	54 fewer per 1000 (from 112 fewer to 7 more)	Very low
Adverse pregnancy outcome					
Progesterone vs hCG (miscarriage)					
1 (van der Linden et al., 2011)	21/381 (6%) women	16/389 (4%) women	OR 1.3 (0.7 to 2.6)	13 more per 1000 (from 12 fewer to 59 more)	Very low
	21/134 (16%) pregnancies	16/113 (14%) pregnancies	OR 1.1 (0.6 to 2.3)	16 more per 1000 (from 57 fewer to 133 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone vs oestrogen (miscarriage)					
1 (Ata et al., 2010)	4/30 (13%) women	2/30 (7%) women	RR 2 (0.4 to 10.1)	67 more per 1000 (from 40 fewer to 607 more)	Very low
	4/16 (25%) pregnancies	2/14 (14%) pregnancies	RR 1.8 (0.4 to 8.2)	107 more per 1000 (from 89 fewer to 1000 more)	
Progesterone vs. progesterone + hCG (miscarriage)					
1 (van der Linden et al., 2011)	4/70 (6%) women	4/62 (7%) women	OR 0.9 (0.2 to 3.7)	7 fewer per 1000 (from 50 fewer to 137 more)	Very low
	4/13 (31%) pregnancies	4/13 (31%) pregnancies	OR 1 (0.2 to 5.1)	0 fewer per 1000 (from 226 fewer to 387 more)	
Progesterone vs. progesterone + oestrogen (miscarriage)					
1 (van der Linden et al., 2011)	95/649 (15%) women	58/497 (12%) women	OR 1.0 (0.7 to 1.4)	5 fewer per 1000 (from 38 fewer to 38 more)	Very low
	82/267 (31%) pregnancies	43/161 (27%) pregnancies	OR 1.0 (0.6 to 1.5)	10 fewer per 1000 (from 90 fewer to 89 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Progesterone vs. hCG					
1 (van der Linden et al., 2011)	1/70 (1%) women	3/77 (4%) women	OR 0.4 (0.1 to 2.9)	23 fewer per 1000 (from 37 fewer to 66 more)	Very low
	1/13 (8%) pregnancies	3/15 (20%) pregnancies	OR 0.4 (0.1 to 3.1)	113 fewer per 1000 (from 188 fewer to 233 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone vs. progesterone + hCG					
1 (van der Linden et al., 2011)	1/70 (1%) women	3/62 (5%) women	OR 0.3 (0.0 to 2.3)	32 fewer per 1000 (from 46 fewer to 56 more)	Very low
	1/13 (8%) women	3/13 (23%) women	OR 0.3 (0.0 to 2.6)	143 fewer per 1000 (from 219 fewer to 206 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
Progesterone vs. hCG					
1 (van der Linden et al., 2011)	30/524 (6%) women	46/484 (10%) women	OR 0.6 (0.4 to 0.9)	39 fewer per 1000 (from 6 fewer to 60 fewer)	Low
Progsterone vs. progesterone + hCG					
1 (van der Linden et al., 2011)	18/359 (5%) women	37/354 (11%) women	OR 0.5 (0.3 to 0.8)	55 fewer per 1000 (from 20 fewer to 75 fewer)	Low
Progesterone vs. progesterone + oestrogen					
1 (van der Linden et al., 2011)	0/29 (0%) women	2/30 (7%) women	OR 0.1 (0.0 to 2.2)	57 fewer per 1000 (from 66 fewer to 70 more)	Very low
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, hCG human chorionic gonadotropin, OR odds ratio

Table 15.33 GRADE findings for comparisons for length of luteal phase support

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton birth					
Progesterone daily on day of oocyte retrieval until pregnancy confirmation with ultrasound (5 to 6 weeks) vs. progesterone daily on day of embryo transfer until pregnancy test (11 days)					
1 (Goudge et al., 2010)	20/46 (44%) women	13/51 (26%) women	RR 1.7 (1.0 to 3.0)	181 more per 1000 (from 10 fewer to 517 more)	Very low
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks)					
1 (Nyboe et al., 2002)	86/150 (57%) women	94/153 (61%) women	RR 0.9 (0.8 to 1.1)	43 fewer per 1000 (from 141 fewer to 74 more)	Low
GnRH agonist from 21st day of preceding cycle until 12th day after ET vs. GnRH agonist from 21st day of preceding cycle until trigger administration					
1 (Isikoglu et al., 2007)	34/90 (38%) women	32/91 (35%) women	RR 1.1 (0.7 to 1.6)	25 more per 1000 (from 95 fewer to 204 more)	Very low
Clinical pregnancy					
Progesterone daily on day of oocyte retrieval until pregnancy confirmation with ultrasound (5 to 6 weeks) vs. progesterone daily on day of embryo transfer until pregnancy test (11 days)					
1 (Goudge et al.,2010)	29/46 (63%) women	32/51 (63%) women	RR 1 (0.7 to 1.4)	0 fewer per 1000 (from 163 fewer to 226 more)	Very low
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks)					
1 (Nyboe et al., 2002)	133/150 (89%)women	139/153 (91%)women	RR 1.0 (0.9 to 1.1)	18 fewer per 1000 (from 91 fewer to 45 more)	Low
Progesterone until 16 days after embryo transfer vs. progesterone until 7 weeks of gestation					
	90/100 (90%) women	83/100 (83%) women	RR 1.1 (1.0 to 1.2)	66 more per 1000 (from 25 fewer to 174 more)	Very low

2013 Update

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Adverse pregnancy outcome					
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks) (miscarriage)					
1 (Nyboe et al., 2002)	22/300 (7%)women	18/306 (6%)women	RR 1.3 (0.7 to 2.3)	15 more per 1000(from 18 fewer to 75 more)	Very low
	Not reported per clinical pregnancy				
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks) (ectopic pregnancy)					
1 (Nyboe et al., 2002)	0/150 (0%)women	2/153 (1%)women	RR 0.2 (0.0 to 4.2)	10 fewer per 1000 (from 13 fewer to 42 more)	Very low
	Not reported per clinical pregnancy				
Progesterone until 16 days after embryo transfer vs. progesterone until 7 weeks of gestation (abortion)					
1 (Kyrou et al., 2011)	17/100 (17%) women	22/100 (22%) women	RR 0.8 (0.4 to 1.4)	51 fewer per 1000 (from 123 fewer to 81 more)	Very low
	17/90 (19%) pregnancies	22/83 (27%) pregnancies	RR 0.7 (0.4 to 1.3)	77 fewer per 1000 (from 156 fewer to 66 more)	
Progesterone until 16 days after embryo transfer vs. progesterone until 7 weeks of gestation (ectopic)					
1 (Kyrou et al., 2011)	1/100 (1%) women	4/100 (4%) women	RR 0.3 (0.0 to 2.2)	30 fewer per 1000 (from 39 fewer to 48 more)	Very low
	1/90 (1%) pregnancies	4/83 (5%) pregnancies	RR 0.2 (0.0 to 2.0)	37 fewer per 1000 (from 47 fewer to 49 more)	
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Progesterone daily on day of oocyte retrieval until pregnancy confirmation with ultrasound (5 to 6 weeks) vs. progesterone daily on day of embryo transfer until pregnancy test (11 days)					
1 (Goudge et al.,2010)	4/46 (9%) women	12/51 (24%) women	RR 0.4 (0.1 to 1.1)	148 fewer per 1000 (from 205 fewer to 16 more)	Very low
	4/29 (14%) pregnancies	12/39 (31%) pregnancies	RR 0.5 (0.2 to 1.3)	169 fewer per 1000 (from 258 fewer to 77 more)	

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks)					
1(Nyboe et al., 2002)	37/150 (25%)women	39/153 (26%)women	RR 1.0 (0.7 to 1.4)	8 fewer per 1000 (from 87 fewer to 110 more)	Very low
	37/133 (28%) pregnancies	39/139 (28%) pregnancies	RR 1.0 (0.7 to 1.5)	3 fewer per 1000 (from 90 fewer to 126 more)	
Progesterone until 16 days after embryo transfer vs. progesterone until 7 weeks of gestation					
1 (Kyrou et al., 2011)	9/100 (9%) women	7/100 (7%) women	RR 1.3 (0.5 to 3.3)	20 more per 1000 (from 35 fewer to 162 more)	Very low
	9/90 (10%)pregnancies	7/83 (8%) pregnancies	RR 1.2 (0.5 to 3.0)	16 more per 1000 (from 46 fewer to 172 more)	
Multiple births (the number of babies born from a multiple pregnancy)					
Progesterone daily on day of oocyte retrieval until pregnancy confirmation with ultrasound (5 to 6 weeks) vs. progesterone daily on day of embryo transfer until pregnancy test (11 days)					
1 (Goudge et al.,2010)	8/28 (29%) babies	24/37 (65%) babies	RR 0.4 (0.2 to 0.8)	363 fewer per 1000 (from 110 fewer to 499 fewer)	Very low
Progesterone from day of embryo transfer until day of positive hCG test (2 weeks) vs. progesterone from day of embryo transfer until three weeks after positive hCG test (5 weeks)					
1 (Nyboe et al., 2002)	64/150 (43%) babies	64/158 (41%) babies	RR 1.1 (0.8 to 1.4)	20 more per 1000 (from 77 fewer to 150 more)	Low
Ovarian hyperstimulation syndrome (OHSS)					
No evidence reported					
Congenital abnormalities					
No evidence reported					
Patient satisfaction					
No evidence reported					
Health related quality of life					
No evidence reported					
Anxiety and/or depression					
No evidence reported					

CI confidence interval, hCG human chorionic gonadotropin, RR relative risk

Evidence statements

Luteal phase support compared with no luteal phase support (Table 15.31)

Live full-term singleton birth

There were significantly more live full-term singleton births in women who had received some form of luteal phase support compared with women who did not receive any luteal phase support.

When a subgroup analysis was undertaken by type of luteal phase support drug, the difference in the number of live full-term singleton births was significantly higher after progesterone compared with after placebo. There was no significant difference in the number of live full-term singleton births when comparing luteal phase support with hCG with support with placebo.

Clinical pregnancy

There were significantly more clinical pregnancies with some form of support than with no support.

When a subgroup analysis was performed for different luteal phase support drugs, progesterone resulted in significantly more clinical pregnancies than placebo or no support. There was no significant difference in the number of clinical pregnancies when comparing the use of hCG with no support.

Adverse pregnancy outcomes

There were no significant differences in the number of adverse pregnancy outcomes when comparing support with no support.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing support with progesterone with no support.

Multiple births

There was no evidence reported that compared the number of births from multiple pregnancies in women who received luteal phase support with those who did not.

OHSS

There were significantly more cases of OHSS when comparing support with hCG with no support.

Congenital abnormalities

There was no evidence reported that compared the number of congenital abnormalities in the babies of women who received luteal phase support with those who did not.

Patient satisfaction

There was no evidence reported that compared the satisfaction of women who received luteal phase support with those who did not.

Health related quality of life

There was no evidence reported that compared the health related quality of life in women who received luteal phase support with those who did not.

Anxiety and/or depression

There was no evidence reported that compared the number of women with anxiety and/or depression among those that received luteal phase support with those who did not.

Comparison of types of luteal phase support (Table 15.32)

Live full-term singleton birth

There were no significant differences in the number of live full-term singleton births when comparing the most commonly used different types of luteal phase support protocols.

Clinical pregnancy

There were no significant differences in the number of clinical pregnancies when comparing the most commonly used different types of luteal phase support protocols.

Adverse pregnancy outcomes

There were no significant differences in the number of adverse pregnancy outcomes when comparing different types of support.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing support with progesterone to support with hCG, or to support with progesterone plus hCG.

Multiple births

No evidence was reported regarding the number of births from multiple pregnancies after different types of luteal phase support.

OHSS

There were significantly more cases of OHSS in women receiving hCG when compared with progesterone or with progesterone plus hCG. There was no significant difference in the number of cases of OHSS when comparing the use of progesterone alone with progesterone plus oestrogen.

Congenital abnormalities

No evidence was reported regarding the number of congenital abnormalities after different types of luteal phase support.

Patient satisfaction

No evidence was reported regarding patient satisfaction after different types of luteal phase support.

Health related quality of life

No evidence was reported regarding the number health related quality of life after different types of luteal phase support.

Anxiety and/or depression

No evidence was reported regarding the number of women with anxiety and/or depression after different types of luteal phase support.

Length of luteal phase support (Table 15.33)

Live full-term singleton birth

There was no significant difference in the number of live full-term singleton births when comparing different lengths of luteal phase support.

Clinical pregnancy

There was no significant difference in the number of clinical pregnancies when comparing different lengths of luteal phase support.

Adverse pregnancy outcome

There was no significant difference in the number of adverse pregnancy outcomes when comparing different lengths of luteal phase support.

Multiple pregnancies

There was no significant difference in the number of multiple pregnancies when comparing different lengths of luteal phase support.

Multiple births

There were significantly more babies born from multiple pregnancies after 11 days of luteal phase support compared with after 5 to 6 weeks of luteal phase support.

OHSS

No evidence was reported regarding the number of women with OHSS after different lengths of luteal phase support.

Congenital abnormalities

No evidence was reported regarding the number of congenital abnormalities after different lengths of luteal phase support.

Patient satisfaction

No evidence was reported regarding patient satisfaction after different lengths of luteal phase support.

Health related quality of life

No evidence was reported regarding health related quality of life after different lengths of luteal phase support.

Anxiety and/or depression

No evidence was reported regarding the number of women with anxiety and/or depression after different lengths of luteal phase support.

Health economics profile

No formal economic assessment was undertaken.

Evidence to recommendations

Relative value placed on the outcomes considered

Live singleton births and clinical pregnancies are important outcomes which allow clinicians to inform couples of their chances of conception and having a baby. The other outcomes in this review relate to side-effects of the treatments and are important to consider in order to fully inform couples of potential risks of treatment.

Consideration of clinical benefits and harms

Luteal phase support compared with no support

There is evidence that luteal phase support with progesterone is associated with significantly more live full-term singleton births and clinical pregnancies than placebo or no support. The GDG therefore recommended that progesterone is used for luteal phase support.

Choice of drugs

There was no significant difference in the number of clinical pregnancies and live full-term singleton births when comparing the different types of drugs that are used for luteal phase support. However, the evidence showed that using hCG for luteal phase support was associated with an increased risk of OHSS compared with the use of progesterone. The GDG therefore recommended that hCG is not used for luteal phase support.

Duration of support

Offering luteal phase support for an extended period of time did not appear to result in more clinical benefits, or to cause more harm, than a short period of luteal phase support. However, the evidence reported in this area is limited. The GDG noted that it is biologically plausibile for luteal phase support to be effective for up to 8 weeks after embryo transfer, after which time the pregnancy is self-supporting. The GDG's clinical view is that luteal phase support is often offered for up to 8 weeks after embryo transfer. The GDG therefore recommend that women should be informed that there is no evidence for continuing luteal phase support beyond 8 weeks.

Consideration of health benefits and resource uses

Although no formal health economic evaluation was undertaken for this question, the GDG recommended the use of progesterone for luteal phase support, this was considered to be a relatively low-cost option.

Quality of evidence

The evidence was graded as low to very low quality depending on the outcome being reported. The main reasons were poor reporting of allocation concealment, method of randomisation and a lack of reported power calculations. In addition, studies may have been underpowered for many of the reported outcomes, as shown by the wide confidence intervals around point estimates.

The GDG highlighted that most of the evidence comparing support with no support is over 20 years old and that new research is unlikely to be conducted as luteal phase support is accepted to be an essential part of IVF treatment.

Other considerations

Endogenous luteal phase support

The GDG members took into consideration the point at which a pregnancy is self-supporting and therefore does not require additional sources of support. They considered whether a distinction needs to be made between routine luteal phase support and luteal phase support after pregnancy has been confirmed.

Method of down-regulation

Luteal phase support is relevant to cycles that are down-regulated with GnRH agonist. The role of luteal phase support in GnRH antagonist cycles is less clear.

Equalities

The people considered in this review were:

- People in same sex relationships who have vaginal intercourse.
- Specific patient subgroups listed in the guideline Scope that may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, or who have been advised not to, have vaginal intercourse
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
- People who are preparing for cancer treatment who may wish to preserve their fertility.

There were no specific issues with respect to luteal phase support in IVF that needed to be addressed with respect to any of these subgroups.

Recommendations

Number	Recommendation
167	Offer women progesterone for luteal phase support after IVF treatment. **[new 2013]**
168	Do not routinely offer women human chorionic gonadotrophin for luteal phase support after IVF treatment because of the increased likelihood of ovarian hyperstimulation syndrome. **[2013]**
169	Inform women undergoing IVF treatment that the evidence does not support continuing any form of treatment for luteal phase support beyond 8 weeks' gestation. **[new 2013]**

Number	Research recommendation
RR 35	Further research is needed to compare the effectiveness (including patient satisfaction) of different drugs and routes of administration for luteal support during in vitro fertilisation.
RR 36	Further research is needed to assess the efficacy of adjuvant luteal phase support treatments such as low-dose aspirin, heparin, prednisoline, immunoglobulins and/or fat emulsions.

Why this is important

These interventions are starting to be used in clinical practice in the absence of any RCT evidence of benefit, and even where there is RCT evidence of no benefit. Their use has potential dangers to the treated women. In cases where women are advised to continue taking the preparations until the end of the first trimester there is the additional potential for teratogenicity. Immunoglobulins are also very expensive. It is important that the clinical efficacy of these agents is formally established so that clear statements about whether they should be recommended or are contraindicated can be made.

15.9 Gamete intrafallopian transfer and zygote intrafallopian transfer

Gamete intrafallopian transfer

Gamete intrafallopian transfer (GIFT) is a technique which has been developed alongside IVF using much of the same technology, but where eggs, once collected, are transferred laparoscopically to the fallopian tube with prepared motile sperm to allow fertilisation to occur in vivo. GIFT is not now widely used because of the need for a laparoscopy. It has been most commonly used in the management of people with unexplained male factor fertility problems, and where transcervical embryo transfer is impossible.

We did not find any RCTs that compared GIFT with no treatment in couples with unexplained infertility.

One RCT compared GIFT with stimulated and unstimulated IUI in woman with unexplained infertility. It found higher pregnancy rates with GIFT (OR 0.12, 95% CI 0.02 to 0.20 with GIFT versus OR 0.018, 95% CI 0 to 0.05 with IUI plus OS; versus OR 0.018, 95% CI 0 to 0.05 with IUI in spontaneous cycle).[812] [Evidence level 1b]

Another RCT compared GIFT and conventional infertility treatments in couples with female infertility excluding tubal factors. Overall, it showed higher pregnancy rates in the group receiving GIFT but in the subgroup of woman with unexplained infertility (number of women not specified) there was no significant difference in pregnancy rates per cycle (23.6% with GIFT versus 36.8% with conventional treatments).813 [Evidence level 1b]

The third RCT (n = 39) compared GIFT with ovarian stimulation in couples with unexplained infertility or failure of donor insemination. It found no significant difference in pregnancy rates between the two interventions in those women with unexplained infertility (8% with GIFT versus 13% with ovarian stimulation; RR 0.63, 95% CI 0.10 to 3.98).[814] [Evidence level 1b]

A small RCT (n = 13) found no significant difference between GIFT and IVF in terms of pregnancy rates (33% with GIFT versus 28.5% with IVF) in couples with male factor fertility problems.[815] [Evidence level 1b]

Zygote intrafallopian transfer

ZIFT is a technique that is not widely practised; it has been developed alongside IVF using much of the same technology. When transcervical embryo transfer is impossible, laparoscopic transfer of embryos to the fallopian tube after fertilisation in vitro offers an alternative route.

A meta-analysis of six RCTs (458 women, 548 cycles) found no significant difference in pregnancy rates between women undergoing ZIFT and IVF and embryo transfer for all causes of infertility exluding tubal factors (OR 0.99; 95% CI 0.62 to 1.57). There was a trend towards a two-fold greater chance of having an ectopic pregnancy in ZIFT than in IVF (OR 2.05; 95% CI 0.21 to 20.22)[816] [Evidence level 1a]

The dominant adverse effect of female age on the success of IVF, GIFT and ZIFT has been highlighted in two cross-sectional studies, with a higher cycle cancellation rate and pregnancy loss

rate associated with older women with unexplained infertility undergoing assisted reproduction.[817,818] [Evidence level 3]

Recommendations

Number	Recommendation
170	There is insufficient evidence to recommend the use of gamete intrafallopian transfer or zygote intrafallopian transfer in preference to IVF in couples with unexplained fertility problems or male factor fertility problems. **[2004]**

16 Intracytoplasmic sperm injection

16.1 Introduction

Intracytoplasmic sperm injection (ICSI), an extension to conventional in vitro fertilisation (IVF) treatment, can be applied in cases where there is low sperm number, motility or morphology, or a combination of these parameters. ICSI can also be used in cases where sperm have been retrieved surgically from the epididymis or testicular tissue and in cases where the polyspermy rate from IVF has been unexpectedly and unacceptably high. Although the injection of motile and morphologically normal sperm is the most common route (following immotilisation), immotile sperm can also be used where no motile sperm is seen in a sperm sample but where viability of the sperm can be confirmed.

16.2 Indications for intracytoplasmic sperm injection

A review of the activities of European centres performing ICSI between 1993 to 1994 showed that the fertilisation rates achieved with ejaculated, epididymal and testicular spermatozoa were 64%, 62.5% and 52%, respectively.[975] Approximately 90% of couples had an embryo transfer and 19–22% of them achieved a viable pregnancy, irrespective of the origin of the spermatozoon. [Evidence level 3]

Use in oligozoospermia and other causes of poor semen quality

A systematic review[976] of ten randomised controlled trials (RCTs) compared ICSI with other types of IVF technique (eight compared ICSI with conventional IVF, one compared ICSI with subzonal sperm injection and one compared ICSI with additional IVF). The review showed that for couples with normal semen there was no difference in pregnancy rate or fertilisation rates per retrieved oocyte or between IVF and ICSI. However, there was a slight benefit of ICSI over IVF when fertilisation rate per inseminated oocyte was considered (combined odds ratio [OR] 1.42, 95% confidence interval [CI] 1.17 to 1.72). For couples with borderline semen (concentration 10–20 million/ml, motility 30–50%, morphology 4–14% normal forms) ICSI results in higher fertilisation rates, whatever the denominator, compared with conventional IVF (combined OR 3.79, 95% CI 2.97 to 4.85 per oocyte retrieved, combined OR 3.90, 95% CI 2.96 to 5.15 per oocyte inseminated). Couples with very poor semen (concentration less than 10 million/ml, motility less than 30%, morphology less than 4% normal forms) will have better fertilisation outcomes with ICSI than with subzonal sperm injection or additional IVF; however, there were only two RCTs that considered couples with very poor semen quality. [Evidence level 1a]

An RCT reported lower ongoing pregnancy rates with ICSI compared with conventional IVF (10.8% with ICSI versus 25.7% with IVF) in cases of moderate teratozoospermia (as defined by a minimum concentration of 5 million/ml and morphology of 4–20%). The mean number of embryos per transfer was 2.2.[977] [Evidence level 1b]

An RCT (n = 73) compared ICSI with IVF using a standard insemination gradient and IVF with a high insemination gradient in couples with male infertility defined by abnormal semen. The unit of randomisation was sibling oocytes. There was a significant difference between standard IVF and ICSI in overall fertilisation rate per oocytes injected (37.4% with IVF versus 64.3% with ICSI; relative risk [RR] 1.7, 95% CI 1.4 to 2.1) but no significant difference between IVF with high insemination gradient and ICSI (59.6% with high insemination gradient/IVF versus 67.6% with ICSI; RR 1.13, 95% CI 0.99 to 1.29). Pregnancy outcomes were not measured.[978] [Evidence 1b] A meta-analysis of this trial and eight other RCTs, including three RCTs from the previous systematic review,[976] showed that ICSI

significantly improved the probability of fertilisation in couples with male subfertility (RR 1.9; 95% CI 1.4 to 2.5) when compared with IVF; however, 3.1 ICSI cycles may be needed to avoid one complete fertilisation failure after conventional IVF (95% CI 1.7 to 12.4).[978] [Evidence level 1a]

It has been reported in case series studies that despite severe semen impairment such as cryptozoospermia, total astheno- or teratozoospermia, fertilisation failure after ICSI was mainly caused by immotile sperm,[979] poor sperm morphology[980] and poor quality oocytes.[981] [Evidence level 3]

Use in azoospermia

Obstructive azoospermia

A case series study reported that aspiration of sperm by microsurgical epididymal sperm aspiration (MESA), testicular sperm aspiration (TESA) and testicular sperm extraction (TESE) was 100% successful in men with obstructive azoospermia before ICSI with a pregnancy rate of 41%.[982] [Evidence level 3] Another case series study reported an ongoing pregnancy rate of 42% per couple and 26% per treatment cycle after 39 ICSI procedures in 24 couples with obstructive azoospermia using similar sperm retrieval techniques.[931] [Evidence level 3]

Nonobstructive azoospermia

A case series study (n = 15) reported a two-pronuclear fertilisation rate of 48% and an ongoing pregnancy rate of 25% (3 of 12 embryo replacements) in men with azoospermia due to testicular failure.[925] [Evidence level 3]

Inferior outcome in nonobstructive azoospermia relative to obstructive azoospermia has been demonstrated in three case series studies.[915,933,935] [Evidence level 3]

ICSI clinical pregnancy rates with epididymal spermatozoa in obstructive azoospermia were not significantly different from those achieved using testicular spermatozoa in men with nonobstructive azoospermia, although fertilisation rates with epididymal spermatozoa were higher (57% versus 81%).[983] [Evidence level 3] A case series reported that although fertilisation rate after ICSI with testicular spermatozoa in non-obstructive azoospermia is significantly lower than in obstructive azoospermia, pregnancy and embryo implantation rates are similar.[939] [Evidence level 3] Another case series reported significantly lower fertilisation and pregnancy rates from ICSI with testicular sperm from men with nonobstructive azoospermia, compared with men with obstructive azoospermia.[984] [Evidence level 3] Both case series reported significantly higher fertilisation rates with testicular spermatozoa in obstructive azoospermia than those with nonobstructive azoospermia.[939,984] [Evidence level 3]

Use in couples with failed fertilisation

ICSI is offered to couples with previously failed fertilisation in IVF cycles, with good results.[985] However, the outcome of ICSI may depend on its indications. Case series studies have found that ICSI is better for treating severe male factor infertility than for treating previously failed fertilisation in an IVF cycle when the male has otherwise normal sperm parameters.[986–989] [Evidence level 3] Others found that none of the sperm parameters of the original semen analysis were associated with the outcome of ICSI cycles[990] and that pregnancy and fertilisation rates did not differ between men who had previously failed fertilisation in conventional IVF, men with moderately poor semen quality, men with semen parameters of 1–10 million/ml, and men with less than 1 million/ml.[980] Another case series[991] showed that clinical pregnancy and delivery rates did not differ between groups with prior failed fertilisation, prior poor fertilisation or sperm parameters unsuitable for IVF and no difference was found in three basic sperm parameters between those men who produced a pregnancy and those who did not, although the fertilisation rate was higher in men with more adequate sperm parameters. [Evidence level 3]

Poor ICSI results may be due to the coexistence of oocyte defects not bypassed by ICSI.[986,989] A number of studies have found a significant negative correlation between female age and pregnancy results,[773,990,991] especially after the age of 35 years.[992] This may be because of low oocyte yield or poor oocyte quality associated with increased female age and shows that ICSI does not always overcome female factors. A comparative study of factors influencing ICSI outcomes reported a significant correlation between the occurrence of pregnancy with female age (90th quantile: 38 years),

number of oocytes retrieved (tenth quantile: five oocytes) and number of oocytes injected (tenth quantile: four oocytes). Sperm origin (epididymal or testicular), status (freshed or thawed), male partner's age and serum follicle-stimulating hormone (FSH) had no significant effect on implantation, pregnancy per embryo transfer or spontaneous miscarriage rates.[993] [Evidence level 3]

One study[994] examined how fertilisation failure after ICSI might impact upon ICSI treatments. This study suggested that fertilisation failure in one ICSI cycle does not preclude successful fertilisation and delivery in a later ICSI treatment cycle. [Evidence level 3]

Use in couples with non-male subfertility

A systematic review of one RCT (n = 415) reported no difference in pregnancy rates (OR 1.40, 95% CI 0.95 to 2.20) between ICSI and IVF in couples with non-male subfertility.[995] [Evidence level 1a] The RCT did not report live birth rates or miscarriage rates.[996]

Evidence to recommendations

Although ICSI was not reviewed within the 2013 guideline update, to improve the implementation of the recommendation the guideline development group (GDG) has included a note of clarification on the indications of when to use ICSI.

ICSI should be offered as part of the first IVF cycle where there is a clear indication for its use (for example azoospermia) or where there are severe deficits in semen quality, normally determined using World Health Organization (WHO) semen criteria (WHO, 2010).

ICSI can also be offered to a potentially wider group in whom previous IVF cycles have failed. It should be noted that the evidence within this chapter shows that unless there is an indication for the use of ICSI, IVF is equally effective. Therefore the decision to offer ICSI after IVF failure should involve consideration of the added value that ICSI would have. For example, ICSI could be offered where the previous IVF cycle demonstrates it may be of value (such as failure of the sperm to bind to the oocyte) or where the fertilisation rate is unexpectedly poor (a common value used is less than a 50% fertilisation rate).

2013 Update

Recommendations

Number	Recommendation
171	The recognised indications for treatment by ICSI include: • severe deficits in semen quality • obstructive azoospermia • non-obstructive azoospermia. In addition, treatment by ICSI should be considered for couples in whom a previous IVF treatment cycle has resulted in failed or very poor fertilisation. **[2004]**

16.3 Genetic issues and counselling

The likelihood of genetic abnormalities (such as chromosomal abnormalities) is greater in men with nonobstructive azoospermia than in men with obstructive azoospermia. The clinical features of obstructive and nonobstructive azoospermia and congenital bilateral absence of vas deferens (CBAVD) are important to elicit. For example, in nonobstructive azoospermia testis volumes are lower and a diagnosis of CBAVD can only be made on clinical examination. Therefore, couples should undergo appropriate clinical examination and laboratory investigations.

The need for proper clinical assessment is further supported by the increased risk of testicular cancer in infertile men. A case–control study[997] evaluated the association between subfertility in men and the subsequent risk of testicular cancer and found a reduced risk of testicular cancer associated with paternity (RR 0.63, 95% CI 0.47 to 0.85), although a higher number of children than expected was not associated with a corresponding protective effect. These associations were similar for seminoma and

nonseminoma and were not influenced by adjustment for potential confounding factors. [Evidence level 3] Although the general cure rate in patients with testicular cancer is high, not only is spermatogenesis already so severely impaired before treatment that fertility is lower than in healthy men but radiotherapy and chemotherapy both induce dose-dependent impairment of spermatogenesis (see Chapter 19). Recovery of spermatogenesis after treatment may take longer than five years in some patients.[998] These men, therefore, need counselling about their reproductive function with respect to semen cryopreservation, chance of recovery of spermatogenesis, fertility, and the possible need for androgen replacement.[998] Effective counselling depends upon understanding the illness itself, the context of men's lives, the assault upon the sense of self, the impact on intimate relationships and treatment options and psychosexual effects.[999] Infertility after testicular cancer can be treated effectively with IVF or ICSI.[1000] For example, one study[1001] obtained an ongoing pregnancy rate of 57% per cycle. [Evidence level 3]

Male infertility due to severe oligozoospermia and azoospermia has been associated with a number of genetic factors, including numerical and structural chromosomal abnormalities,[1002] microdeletions of the Y chromosomes[1003,1004] and mutations in the cystic fibrosis transmembrane conductance regulator gene, commonly associated with congenital vas deferens abnormalities.[1005,1006] [Evidence level 3]

Chromosomal abnormalities have been detected in 2.1–8.9% of men attending infertility clinics,[1007] compared with 1% of the general male population.[1008] In couples undergoing ICSI, chromosomal abnormalities have been reported in 2.0–3.3% of male partners and 3.3–5.4% of female partners.[1009,1010] [Evidence level 3] Higher prevalence of chromosomal abnormalities in the male rather than the female partner of couples referred for ICSI has also been reported.[1008,1011,1012] [Evidence level 3] Genetic abnormality was identified in 24% of men with extreme oligozoospermia and azoospermia in couples requesting ICSI.[1013] [Evidence level 3] Sperm of azoospermic men, when compared with ejaculated spermatozoa of healthy men, has been reported to have a higher incidence of chromosomal abnormalities, of which sex chromosome aneuploidy was the most prominent.[1014,1015] [Evidence level 3] Application of ICSI in these couples can result in offspring with an enhanced risk of genetic abnormalities and possibly decreased fertility. Genetic testing and counselling is indicated for these couples before ICSI is considered. However, chromosome studies should be undertaken in both members of the couple before ICSI.

A number of clinical syndromes that present with normal virilisation have also been shown to have a genetic origin. These include cystic fibrosis and CBAVD. Cystic fibrosis is the most common autosomal recessive condition in northern Europeans and 97–98% of males with cystic fibrosis are infertile.[1016] CBAVD leads to obstructive azoospermia in otherwise normal men and is responsible for approximately 2% of male infertility.[1]

When these conditions are known or suspected, or in Kartagener syndrome or primary ciliary dyskinesia, appropriate genetic counselling and testing should be offered.

A review[1017] found that 13.7% of men with azoospermia and 4.6% of men with oligozoospermia had an abnormal karyotype. In men with azoospermia, sex chromosome abnormalities (for example, 47XXY, mosaics of 46XY/47XXX) were present in 1.9 to 22.1%, while autosomal abnormalities were found in only 0.6 to 3.7% of such men. Among oligozoospermic men, sex and autosomal abnormalities are found in 0.9 to 3.6% and 0.9 to 4.9%, respectively. [Evidence level 3] Robertsonian and reciprocal translocations occur most frequently but their roles in the aetiology of oligozoospermia are not clear, since the spermatogenic defect in these men can vary from severe impairment to almost normal spermatogenesis. Where the indication for ICSI is a severe deficit of sperm quality or nonobstructive azoospermia, the male partner's karyotype should be established.

The Y chromosome is an important carrier of genetic information for the control of spermatogenesis. Microdeletion of the azoospermic factor region of the Y chromosome occur in 1–29% of oilgozoospermic and azoospermic men.1018 The prevalence is higher in azoospermic than oligospermic men.[1019] [Evidence level 3] One comparative study found a significantly lower fertilisation rate in Y-deleted men when compared with a control group without this genetic disorder who underwent ICSI (55%, 95% CI 41 to 69% versus 71%, 95% CI 67 to 74%; $P < 0.01$), but no significant differences in pregnancy, implantation or live birth rates were found.1018 [Evidence level 3] The presence of Y deletions was reported to have no impact on fertilisation and pregnancy rates in one case-series study.[1020] [Evidence level 3]

Several screening programmes have confirmed the common occurrence of microdeletions in the Yq part of the chromosome among men with otherwise unexplained oligo- or azoospermia.[1021,1022] [Evidence level 3] De novo microdeletions in Yq that are not present in fathers' or brothers' chromosomes have been reported with a prevalence of between 3% and 18% of men studied.[1016] [Evidence level 3] They cause the azoospermic or oligozoospermic phenotype and are likely to be passed on to the sons of these infertile men if ICSI is carried out.[1023,1024]

Testing for Y chromosome microdeletions should not be regarded as a routine investigation before ICSI. A recent survey among staff working in UK fertility clinics found that despite some benefits, screening for sperm aneuploidy is not a common practice. The benefits are that screening would enable couples to make informed decisions about the genetic repercussions of ICSI before treatment and would also facilitate a larger research study to assess the safety of ICSI. However, there are counter arguments that most couples would have ICSI regardless of results and that sex chromosome abnormalities are clinically not severe enough to worry about in this context.[1025] [Evidence level 3]

Recommendations

Number	Recommendation
172	Before considering treatment by ICSI, people should undergo appropriate investigations, both to establish a diagnosis and to enable informed discussion about the implications of treatment. **[2004, amended 2013]**
173	Before treatment by ICSI consideration should be given to relevant genetic issues. **[2004]**
174	Where a specific genetic defect associated with male infertility is known or suspected couples should be offered appropriate genetic counselling and testing. **[2004]**
175	Where the indication for ICSI is a severe deficit of semen quality or non-obstructive azoospermia, the man's karyotype should be established. **[2004]**
176	Men who are undergoing karyotype testing should be offered genetic counselling regarding the genetic abnormalities that may be detected. **[2004]**
177	Testing for Y chromosome microdeletions should not be regarded as a routine investigation before ICSI. However, it is likely that a significant proportion of male infertility results from abnormalities of genes on the Y chromosome involved in the regulation of spermatogenesis, and couples should be informed of this. **[2004]**

16.4 Intracytoplasmic sperm injection versus IVF

There are no RCTs comparing ICSI with IVF (or other interventions) where semen quality is so poor that IVF would not achieve fertilisation. It is accepted that ICSI is the only treatment option in those circumstances. The role of ICSI where IVF can be expected to give a reasonable fertilisation rate has been investigated using RCTs.

A systematic review of ten RCTs compared ICSI versus IVF, ICSI versus additional IVF and ICSI versus subzonal sperm injection in couples with mild–moderate male factor infertility, unexplained infertility and tubal subfertility.[976] [Evidence level 1a] In couples with normal semen (three RCTs), there was no significant difference in fertilisation per oocyte retrieved or in pregnancy rate between ICSI and IVF. One RCT examined pregnancy rates per embryo transfer in couples with borderline semen[1026] and found no significant difference in pregnancy rates between ICSI and IVF. ICSI was associated with an increased fertilisation rate per oocyte retrieved (OR 3.79, 95% CI 2.97 to 4.85) and per oocyte injected (OR 3.90, 95% CI 2.96 to 5.15) for borderline semen (three RCTs). For couples with very poor semen (two RCTs), ICSI versus subzonal sperm injection significantly increased fertilisation rate per oocyte injected (33% with ICSI versus 16% with subzonal sperm injection, OR 2.59, 95% CI 1.11 to 6.04) and ICSI versus additional IVF significantly increased fertilisation rate per

oocyte injected (63% with ICSI versus 0% with additional IVF, OR 13.77, 95% CI 7.96 to 23.82). No trials compared pregnancy rates between ICSI and IVF for couples with poor semen quality.[976] [Evidence level 1a]

Although the evidence for this recommendation has not been updated for the 2013 edition of the guideline, it should be noted for clarification that in the absence of male factors (see Recommendation 170), ICSI is not proven to confer a benefit in terms of increased pregnancy rates and should not be offered in the first treatment cycle.

Recommendations

Number	Recommendation
178	Couples should be informed that ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF. **[2004]**

Number	Research recommendation
RR 37	Further research is needed to evaluate the effect of intracytoplasmic sperm injection on live birth or pregnancy rates in couples where the male partner has poor semen quality

16.5 Cost effectiveness of intracytoplasmic sperm injection

The cost effectiveness models for ICSI treatment are described in detail in Appendix M. We found no live birth rates for ICSI and so the cost effectiveness models were based upon the same clinical effectiveness rates as IVF but with additional costs. The cost per live birth for couples undergoing ICSI using the baseline cost of ICSI treatment (£2,936, including drugs) and an OHSS incidence rate of 0.2% was £14,029. At a lower cost per ICSI treatment (£1,936, excluding drugs) the cost per live birth was £9,056.

17 Donor insemination

17.1 Introduction

2013 Update

Donor insemination is used in situations where a male partner is infertile or in same-sex couples. In the UK the process is regulated by the Human Fertilisation and Embryology Authority (HFEA) which has established age criteria for donors, requires genetic screening tests before donation and prohibits payments. The process involves a fertile male donating sperm at a clinic which the clinic then stores for later use. When a person wants to use donated sperm within a medical setting, standard assisted reproduction technology (ART) techniques are used. In theory, the semen can be either fresh or thawed, though in the UK most regulated units will only use thawed semen to allow for the results of investigations of the donor to be obtained.

This chapter reviews the evidence of the clinical effectiveness of this procedure.

17.2 Clinical indications for donor insemination

Male infertility affects about 25% of all infertile couples.[1] Until ICSI became available, the main technique for treating male factor infertility where azoospermia or severe abnormalities of semen quality were present was insemination with donated sperm. The need to prevent transmission of sexually transmitted diseases (including HIV)[1027] by donor insemination has led to the mandatory quarantine of donor sperm for six months by cryopreservation prior to its use in the UK,[1028] [Evidence level 3–4] despite the fact that pregnancy rates are significantly higher when fresh sperm is used compared with cryopreserved sperm.[1029] [Evidence level 1b] Donor insemination is also indicated where the male partner is likely to pass on an inheritable genetic condition, an infection such as HIV or if severe rhesus incompatibility has been a problem because of the male partner's homozygous status.

Evidence to recommendations

2013 Update

Donor insemination was not included within the updated scope of 2013 guideline. However, the guideline development group (GDG) noted that in some men with azoopsernia, semen can be surgically extracted and be used in intracytoplasmic sperm injection (ICSI) procedures. The GDG wished to clarify that Recommendation 178 does not list the clinical indications for when donor insemination should be offered; instead, it lists when donor insemination can be considered as an option (where the evidence shows it is effective).

Recommendations

Number	Recommendation
179	The use of donor insemination is considered effective in managing fertility problems associated with the following conditions: • obstructive azoospermia • non-obstructive azoospermia • severe deficits in semen quality in couples who do not wish to undergo ICSI. **[2004, amended 2013]**

180	Donor insemination should be considered in conditions such as: • where there is a high risk of transmitting a genetic disorder to the offspring • where there is a high risk of transmitting infectious disease to the offspring or woman from the man • severe rhesus isoimmunisation. **[2004, amended 2013]**

17.3 Information and counselling

ICSI is often preferred to donor insemination in severe male factor infertility because the resulting child is genetically related to both parents when treatment is successful.[1030] [Evidence level 3] The views of the couple in question should help decide what treatment is suitable for them and additional counselling may be required in order to help them answer this question. Some couples choose donor insemination primarily because they object to the invasive nature of assisted reproduction treatments or through fear of potential genetic risks with ICSI. Conversely, when a couple has not achieved a successful pregnancy with ICSI, they may want to proceed to donor insemination as an alternative treatment. However, the most common motivation for choosing donor insemination was that IVF–ICSI was not financially affordable, therefore a balanced view of treatment options can only really be given when both ICSI and donor insemination are easily available to the couple.[1030] [Evidence level 3]

Implication counselling is particularly important when donor gametes are considered, both for the donor and the recipient couple.[218,1031] [Evidence level 4]

Recommendations

Number	Recommendation
181	Couples should be offered information about the relative merits of ICSI and donor insemination in a context that allows equal access to both treatment options. **[2004]**
182	Couples considering donor insemination should be offered counselling from someone who is independent of the treatment unit regarding all the physical and psychological implications of treatment for themselves and potential children. **[2004]**

17.4 Screening of sperm donors

The HFEA Code of Practice requires clinics to take all reasonable steps to avoid transmission of serious genetic disorders stating a mandatory upper age limit of 45 years for sperm donors. It is also mandatory that pre- and post-test information and counselling are provided and appropriate advice and support given to donors by an appropriately trained person or a genetic counsellor.[218,1031] [Evidence level 4]

The Association of Biomedical Andrologists (ABA), Association of Clinical Embryologists (ACE), British Andrology Society (BAS), British Fertility Society (BFS) and Royal College of Obstetricians and Gynaecologists (RCOG) have published a joint working party set of guidelines on the selection and screening of semen donors specifically to protect the offspring of donor insemination treatment from heritable genetic disorders and to protect the recipient women from infection (BFS joint working party, 2008). The joint working party guidelines suggest an upper age limit of 40 years for sperm donors. The joint working party guidelines recommend that sperm donors are screened for karyotyping of chromosomal abnormalities, autosomal recessive conditions (such as beta-thalassaemia, sickle-cell disease and Tay–Sachs disease), bacterial infections and rhesus antigens. These guidelines also recommend the exclusion of sperm donors who are seropositive for HIV, hepatitis B virus, hepatitis C virus, syphilis, C. trachomatis and cytomegalovirus.

Serological testing for HIV will not detect early infection in the first 6–12 weeks, when the individual has not yet seroconverted. Potential recipients of donated sperm should therefore be informed that an HIV test in the donor does not absolutely exclude the transmission of HIV. With hepatitis B, hepatitis C, syphilis and cytomegalovirus, positive serology does not necesaarily indicate an ongoing risk of infection. The suitability as sperm donors of people who are seropositive for hepatitis B, hepatitis C, syphilis or cytomegalovirus should, therefore, be considered in relation to their history of treatment, subsequent follow-up and change in serological titre level.

The prevalence of sexually transmitted diseases in potential semen donors in an urban area of Canada was found to be 34.5% (n = 29).[1032] [Evidence level 3] A follow-up infection rate of 22.2% was found in this study. These results suggest that a high prevalence of sexually transmissible infections is present in potential semen donors and that new infections are common during the follow-up period. Six confirmed cases and two possible cases of donor insemination-associated AIDS were reported in an American surveillance study which also identified self-insemination with unscreened sperm as the most likely source of risk of new infections associated with donor insemination.[1033] [Evidence level 3]

Recommendations

Number	Recommendation
183	Units undertaking semen donor recruitment and the cryopreservation of donor spermatozoa for treatment purposes should follow the 'UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors' (2008)* describing the selection and screening of donors. **[2004, amended 2013]**
184	All potential semen donors should be offered counselling from someone who is independent of the treatment unit regarding the implications for themselves and their genetic children, including any potential children resulting from donated semen. **[2004]**

17.5 Assessment of the woman

In order for donor insemination to be effective, the female partner must be ovulating and have at least one patent tube. Treatment-independent pregnancy rates of 3.2% over 24 months have been reported (0.0% in the azoospermic group and 7.6% in the nonazoospermia group) in a group of infertile couples requiring donor insemination.[1034] [Evidence level 3] Before the use of frozen-thawed semen, donor insemination with fresh semen resulted in cycle fecundity rates that approached natural conception.[1035–1037] [Evidence level 3]

An observational study (n = 305 couples, 1131 cycles) found that in couples using IUI with donor semen, there was a significant correlation between successful outcomes and the first treatment cycle, number of mature follicles, time of insemination, insemination after ovulation had occurred, and female age under 30 years.[1038] [Evidence level 3]

Other factors that affect donor insemination success rates are female age and previous success with donor insemination. Female fecundity declines after the age of 30 years or 35 years, depending upon the population studied, and more cycles are needed to achieve conception.[22,1039–1043] [Evidence level 2b–3] Previous success with donor insemination is associated with quicker conception with subsequent donor insemination attempts.[1035,1040] [Evidence level 3]

Before treatment with donor insemination begins, a history should have been taken from the female partner confirming regular menstrual cycles and a mid-luteal phase progesterone assessment should be made in order to confirm ovulation. If the female partner is oligo- or anovulatory, this can be corrected with an appropriate treatment, which initially is likely to be an anti-oestrogen such as

* This recommendation has been updated to reflect a new guideline issued by the joint working party of Association of Biomedical Andrologists (ABA), Association of Clinical Embryologists (ACE), British Andrology Society (BAS), British Fertility Society (BFS) and Royal College of Obstetricians and Gynaecologists (RCOG).

clomifene. Recognition of such a condition requiring treatment is important, as pregnancy rates in women with treated ovulatory dysfunction approach those with no other infertility factors, although conception may take more cycles.[1036,1045,1046] [Evidence level 3]

Tubal assessment using HSG or laparoscopy should be performed before treatment in women with a history that is suggestive of tubal damage. Tubal disease will reduce the likelihood of success and cycle fecundability with donor insemination.[1036,1046] However, a low incidence of abnormal HSG findings (2.8%) has been reported in asymptomatic ovulatory women with no history of pelvic disease.[1047] This significantly decreased fecundity in the first six cycles of treatment. No corresponding study using laparoscopy has been reported. [Evidence level 3]

Recommendations

Number	Recommendation
185	Before starting treatment by donor insemination (for conditions listed in recommendations 179 and 180) it is important to confirm that the woman is ovulating. Women with a history that is suggestive of tubal damage should be offered tubal assessment before treatment. **[2004, amended 2013]**
186	Women with no risk factors in their history should be offered tubal assessment after 3 cycles if treatment by donor insemination (for conditions listed in recommendations 179 and 180) has been unsuccessful. **[2004, amended 2013]**

17.6 Intrauterine insemination versus intracervical insemination

A systematic review[1048] of 12 randomised controlled trials (RCTs) compared intrauterine injection (IUI) with intracervical insemination using fresh and frozen donor sperm. The overall pregnancy rate per cycle was 18% in the IUI group versus 5% in the intracervical insemination group. When frozen semen was used, IUI significantly increased pregnancy rate per cycle (odds ratio [OR] 2.63, 95% confidence interval [CI] 1.85 to 3.73) and per woman (OR 3.86, 95% CI 1.81 to 8.25) in clomifene citrate cycles and in gonadotrophin cycles (OR 2.17, 95% CI 1.35 to 3.49 and OR 2.72, 95% CI 1.37 to 5.40, respectively). However, no significant difference was found in IUI or intracervical insemination when fresh semen was used (OR 0.90, 95% CI 0.36 to 2.24).[1048] [Evidence level 1a] The cost of using IUI has been estimated to be 1.5–2.0 times greater than intracervical insemination,[1049] mostly because of the additional sperm preparation required.

A meta-analysis of seven RCTs (included in the previous systematic review[1048]) found significant higher fecundability rate with IUI compared with intracervical insemination using frozen sperm (OR 2.4, 95% CI 1.5 to 3.8).[1050] [Evidence level 1a]

Recommendations

Number	Recommendation
187	Couples using donor sperm should be offered intrauterine insemination in preference to intracervical insemination because it improves pregnancy rates. **[2004]**

17.7 Unstimulated versus stimulated donor insemination

Ovarian stimulation leads to an increased number of multiple pregnancies, which should be avoided wherever possible. HFEA data showed a multiple birth rate of 1.9% per treatment cycle (67/3354) in

2000 and 1.8% per treatment cycle (54/3024) in 2001 in couples receiving donor insemination using stimulated treatment cycles.[743] [Evidence level 3]

Some female partners in couples where donor insemination is indicated may have additional infertility factors. Female partners of azoospermic men seem to conceive more quickly with donor insemination than female partners of men with abnormal semen quality,[1041,1045,1046,1051,1052] [Evidence level 3] suggesting that in the latter case unexplained female factors are contributing to the couple's subfertility. Therefore, there will be cases where unstimulated donor insemination is initially unsuccessful. To reduce multiple pregnancies and their attendant risks, it would be reasonable to try six cycles of unstimulated donor insemination initially in regularly ovulating women. There is no evidence from RCTs to support this recommendation.

Recommendations

Number	Recommendation
188	Women who are ovulating regularly should be offered a minimum of 6 cycles of donor insemination (for conditions listed in recommendations 179 and 180) without ovarian stimulation to reduce the risk of multiple pregnancy and its consequences. **[2004, amended 2013]**

18 Oocyte donation

18.1 Introduction

Gamete donation was restricted to sperm donation until techniques of oocyte collection were developed for in vitro fertilisation (IVF). The first pregnancies achieved with donated eggs were reported in the mid-1980s (Trounson et al., 1983). In the context of fertility treatment, oocyte donation is the process by which a fertile woman allows several of her oocytes to be aspirated, usually following ovarian stimulation, and used to enable another woman, who is infertile due to ovarian failure (World Health Organization [WHO] Group III), to conceive with IVF. As with sperm donation, the process is regulated in the UK by the Human Fertilisation and Embryology Authority (HFEA). Stringent screening is applied to gamete donors (British Fertility Society [BFS] working party, 2008). Success rates are related to the age and fertility status of the donor rather than the recipient (Steiner and Paulson, 2006).

This chapter reviews the evidence of the clinical effectiveness of this procedure.

18.2 Indications for oocyte donation

Premature ovarian failure

The major indication for use of donor oocytes is premature ovarian failure, either primary or secondary. Causes of premature ovarian failure that are potentially amenable to oocyte donation include surgical oophorectomy, irreversible gonadal damage after certain regimens of chemotherapy or radiotherapy, Turner syndrome and other chromosomal disorders causing gonadal dysgenesis. In addition, oocyte donation might be employed to avoid the risk of transmission of a genetic disorder in cases in which the carrier status of both partners is known.

Donor oocyte IVF success rates were reported to be similar in women with or without primary ovarian failure, despite recognisable differences in recipient age and degree of male factor infertility.[1061] [Evidence level 2b]

Women with markedly diminished ovarian reserve should be counselled on their low chances of conception using their own gametes, even with assisted reproduction, and should be offered the options of donor oocytes or adoption.[1062] [Evidence level 4] Egg donation is the most successful technique for producing pregnancy in perimenopausal women.[1063] [Evidence level 4] Early menopause due to the exhaustion of the ovarian follicles occurs in approximately 1% of women before the age of 40 years and, when there is little remaining follicular capacity, ovum donation may represent the best chance of a successful pregnancy.[1064] [Evidence level 3] While oocyte donation for women with premature menopause has become widely accepted within the UK, the use of oocyte donation to achieve pregnancy after the start of natural menopause (typically between the ages of 45 years and 55 years) remains controversial.

Turner syndrome

Spontaneous pregnancies among women with Turner syndrome are associated with a high risk of miscarriage and an inceased risk of trisomy 21 in the offspring.[1149,1065,1066] [Evidence level 3] Oocyte donation offers women with ovarian failure due to Turner syndrome the chance of pregnancy and live birth. Pretreatment screening is essential to exclude phenotypic manifestations of the syndrome that might jeopardise successful pregnancy, including aortic dilation and cardiac lesions.[1067] An observational study (n = 29) assessing the factors influencing outcomes of oocyte donation in women with Turner syndrome reported a pregnancy rate of 41.2% per treatment cycle (n = 68 cycles; 50 fresh cycles and 18 frozen cycles) of embryo or zygote transfer (27 embryo transfer and 41 gamete intrafallopian transfer [GIFT]) The implantation rate was 17.1% per embryo transferred. The

recipient's age, chromosomal constitution and associated uterine or tubal anomaly had no influence on the treatment outcome. The implantation and pregnancy rates were significantly higher in subsequent than initial cycles (22.6% versus 9.99%; 51.3% versus 27.6%). An endometrial thickness of = 6.5 mm was an important predictor of pregnancy but the endometrial echo pattern failed to predict the outcome. The number of oocytes fertilised affected the pregnancy rate irrespective of the number of embryos transferred. The implantation and pregnancy rates were significantly higher when fresh rather than frozen-thawed embryos were transferred (20.3% versus 8.2%; 48% versus 22.2%) but the route of transfer was of no statistical importance.[1068] [Evidence level 3]. Pregnancy rates in women with Turner syndrome following oocyte donation were similar to those in women with other causes of primary ovarian failure.[1069] [Evidence level 3]. Another observational study (n = 18) reported a clinical pregnancy rate of 46% for fresh embryo transfer and implantation rate of 30% among women with Turner syndrome treated in an oocyte donation programme. This was similar to the corresponding rates among oocyte recipients with primary ovarian failure in general. However, the miscarriage rate was high, at 40%, and so was the risk of cardiovascular and other complications such as hypertension and pre-eclampsia. This suggested that a careful assessment before and during follow-up of pregnancy and transfer of one embryo at a time to avoid additional complications caused by multiple pregnancy are important considersations.[1070] [Evidence level 3]

One cohort study (n = 53) reported that women with Turner syndrome had a significantly higher rate of biochemical pregnancies (22.7% versus 4.3%), a lower clinical pregnancy rate (22.7% versus 33.3%), a significantly higher rate of early abortions (60% versus 8.7%) and a significantly lower rate of deliveries per pregnancy (20.0% versus 73.1%) compared women without Turner syndrome following oocyte donation, suggesting that those with Turner syndrome may have an inherent endometrial abnormality affecting receptivity in oocyte donation.[1071] [Evidence level 2b]

Ovarian failure following chemotherapy or radiotherapy

Anticancer treatment can cause ovarian failure and women face limited options for fertility preservation. Cryopreservation of oocytes has had very limited success; currently its use before chemotherapy is not a feasible option. However, cryopreservation of embryos is possible and another solution is oocyte donation followed by IVF.[1072] Success following oocyte donation has been reported in women who had previously received chemotherapy or radiotherapy. Two cases of normal live births with embryos from donated oocytes have been reported in women (aged 36 years and 33 years) who have been treated with bone marrow transplantation following total body irradiation and cyclophosphamide for leukaemia.[1073,1074] [Evidence level 3] A successful live birth was achieved with oocyte donation in one woman following radical surgery (with uterine conservation) and chemotherapy for ovarian cancer.[1075] [Evidence level 3]

In vitro fertilisation failure

Oocyte donation has also been advocated in certain cases of repeated failure of IVF, particularly those in which oocyte quality is compromised, although unexplained failure of fertilisation has also been treated using this method.

An observational study (n = 32 couples, 119 cycles) reported a pregnancy rate of 24.5% per cycle following oocyte donation in women with previously failed IVF treatment. Variables found to have an effect on oocyte donation outcome included the number of previous natural conceptions and live births, and the IVF fertilisation rate. However, increasing female age did not affect outcome.[1076] [Evidence level 3] Pregnancy rates of 33.3% per started cycle and 38.4% per embryo transfer were reported in another study (n = 15 couples, 15 cycles) in women following oocyte donation by ICSI in women with previous failed IVF.[1077] [Evidence level 3]

Genetic disorders

Heritable genetic diseases can be avoided with the use of donor oocytes. A case series study used donor oocytes from anonymous, matched, fertile donors in four women with heritable genetic disorders and found that use of donor oocytes was a practical, successful, and currently available technique for the prevention of genetic disorders.[1078] [Evidence level 3]

Recommendations

Number	Recommendation
189	The use of donor oocytes is considered effective in managing fertility problems associated with the following conditions: • premature ovarian failure • gonadal dysgenesis including Turner syndrome • bilateral oophorectomy • ovarian failure following chemotherapy or radiotherapy • certain cases of IVF treatment failure. Oocyte donation should also be considered in certain cases where there is a high risk of transmitting a genetic disorder to the offspring. **[2004]**

18.3 Screening of oocyte donors

A cross-sectional study (n = 73) found that 11% of volunteer oocyte donors were inappropriate for donation because of their genetic history or genetic testing results. Cystic fibrosis mutations were identified in 7%, abnormal karyotype in 3.5% and autosomal dominant skeletal dysplasia in 1.4%.[1079] [Evidence level 3]

Younger donors were reported to provide a significant higher pregnancy success rates for recipients (59.1%, 45.9%, 30.5%, 30.9% and 27.3% for the age groups 20–22 years, 26–28 years, 32–34 years and over 38 years, repectively), suggesting that age should be a major factor in selecting prospective donors.[1080] [Evidence level 3]. Limiting oocyte donors to women under 35 years of age[218,1031,1081,1082] and under 34 years old[1083] to decrease the risk of aneuploid offspring has been suggested. [Evidence level 3–4]

The French national federation of centres for the study and preservation of human eggs and sperm analyses the genetic control of oocyte donors and sperm donors. One study[1084] reported an analysis of 98 female donors and 1609 male donors. In all, 2% of women donors were excluded after genetic screening discussion and 2% were excluded following karyotype. Results for male donors were similar: 3.2% were excluded for genetic reasons (2.6% after genetic screening discussion and 0.6% following karyotype). The risk factor presence level was 27.8% on average but varied considerably from one centre to another. Diseases most commonly encountered were: allergies, cardiovascular disorders and ophthalmological disorders.

Given the high prevalence of cystic fibrosis, which is the most common autosomal recessive disorder in northern Europeans, the HFEA[218] recommends screening both egg and sperm donors for carrier status in cystic fibrosis and Tay–Sachs, and also screening for cytomegalovirus and HIV (see Section 6.5). All licensed clinics are now required to inform couples whether or not a donor has been tested for cystic fibrosis and of the risks for any child who may be born from fertility treatment. The HFEA encourages clinics to offer testing to couples. If donors agree to be tested for cystic fibrosis, they should be offered genetic counselling and be provided with information about the implications for themselves and their family if they were found to be carriers. Regarding screening for other infectious diseases, the HFEA recommends that the guidelines of the joint working party of the Association of Biomedical Andrologists (ABA), Association of Clinical Embryologists (ACE), British Andrology Society (BAS), British Fertility Society (BFS) and Royal College of Obstetricians and Gynaecologists (RCOG) for egg and embryo donors should be followed (BFS joint working party, 2008).

Recommendations

Number	Recommendation
190	Before donation is undertaken, oocyte donors should be screened for both infectious and genetic diseases in accordance with the 'UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors' (2008)*. **[2004, amended 2013]**

18.4 Oocyte donation and 'egg sharing'

Oocyte donation

'Shared' oocyte donation can be an efficient use of precious resource of human oocytes. In a retrospective analysis of a programme using 'shared' anonymous oocyte donation (n = 249 donor cycles, 241 retrievals), the efficacy of 'shared' oocyte donation between two phenotypically matched recipients has been shown to provide a high delivery rates per donor retrieval (95.4%).[1086] [Evidence level 3] However, the number of treatment cycles undertaken in the UK using donated oocytes remains small, due to the practical difficulty of recruiting volunteer donors willing to undergo the time consuming and painful processes of pituitary downregulation, superovulation and transvaginal oocyte collection. Volunteers must undergo adequate counselling concerning the possible risks of the procedures, including the surgical risk of oocyte retrieval and the putative link between superovulation with gonadotrophins and the risk of ovarian cancer in later life.

The professional counselling of prospective donors with respect to the results of tests and the implications of test results with respect to their future medical and reproductive health are important parts of providing good care. In one study,1087 only 50% of women wishing to participate in oocyte donation were considered suitable candidates; 50% of these women were scheduled an entry interview on completion of the formal medical, genetic and psychological screening process and 18% of those actually interviewed were denied entry. [Evidence level 3]

Concerns about complications and logistic factors such as travel and time commitment involved were major reasons for non-donation in a survey of women on anonymous oocyte donation.[1088] [Evidence level 3] A survey of UK licensed centres reported that nearly all have experienced difficulty in obtaining a sufficient supply of donated oocytes. Seventy-five percent of potential donors changed their mind about donating after receiving information on the procedures involved. There is also a shortage of both oocyte and semen donors from specific ethnic groups.[1089] [Evidence level 3]

For many volunteer donors, guaranteeing anonymous oocyte donation plays a crucial role in their decision to donate.[1090] In the UK, nonidentifying information on the donor is recorded by statute in assisted reproduction with gamete donation. This may be made available eventually to the resulting children. One study analysed forms from the HFEA completed by all donors at one IVF unit and found that 94% of oocyte donors did not respond to the question asking for a brief description of themselves, leaving only profession and interests as information to be given to the child in the future. There was a significant difference between the known and anonymous responders.[1091] [Evidence level 3]

A survey of a sample of couples in Canada undergoing oocyte donation with known donors found that anonymity was a primary concern for recipients and donors: 80% of the sample had not confided in anyone at the time of the study and 70% did not intend to disclose any information at any time; 80% did not plan to inform the child.[1092] [Evidence level 3]

In a follow-up study of the first 30 Finnish volunteer oocyte donors, most donors were very satisfied with the experience at 12–18 months after donation. The adverse effects of the treatment had been slight and tolerable. A majority of the respondents reported that they had thought about the possibility

* This recommendation has been updated to reflect a new guideline issued by the joint working party of Association of Biomedical Andrologists (ABA), Association of Clinical Embryologists (ACE), British Andrology Society (BAS), British Fertility Society (BFS) and Royal College of Obstetricians and Gynaecologists (RCOG).

of a child from their donation (89%) and would have liked to have known whether pregnancy had been achieved in the recipient (67%). A majority thought the offspring should be told about their origin (59%). However, some 42% of the respondents preferred to receive no information concerning either the child or the recipient couple and 33% thought the child should be given identifying information about the donor. About 50% of the others would agree to the release of nonidentifying information. All donations had been carried out anonymously and without payment and no one regretted their donation.[1093] [Evidence level 3]

The attitudes of anonymous couples undergoing IVF toward sperm and oocyte donation were explored in a UK survey (n = 234). A high proportion of couples found the use of donor sperm acceptable for therapeutic, diagnostic and treatment purposes and 72%, 84% and 90%, respectively, were willing to donate oocytes for these purposes. Of potential oocyte donors, 41% would agree to non-anonymous donation, 12% would wish to meet the recipient couple and although only 4% wanted to choose the recipient, 25% of the couples would prefer a relative or friend as the recipient. Provision of nonidentifying information about the donor to the recipient couple was acceptable to almost 70%, whereas 40% found giving the same information to the child acceptable.[1094] Another UK survey (n = 399) compared the attitudes towards egg and sperm donation in four groups of subjects: women receiving egg donation, women receiving sperm donation, potential egg donors and a general population control group. Egg donation appeared to be as acceptable as sperm donation but subjects overall were more in favour of donor anonymity for sperm donation than for egg donation and the sperm recipients were more in favour of donor anonymity than egg recipients. Subjects demonstrated uncertainty on the issue of giving information to children conceived by gamete donation but held positive attitudes towards the counselling of both donors and recipients.[1095] [Evidence level 3]

A follow-up study (n = 23) of donor satisfaction in the USA found a high satisfaction rate with the experience (91%) and 74% would donate for another cycle given the chance. The transient adverse psychological symptoms reported by two donors were resolved with medical or psychological treatment.[1096] [Evidence level 3] A survey in the USA (n = 25) assessed the psychological characteristics and post-donation satisfaction of anonymous oocyte donors. Following oocyte donation, 80% of women stated that they would be willing to donate again. Post-donation satisfaction was high. Although monetary compensation for donation was provided, altruism was reported as the most salient motivating factor. A significant negative correlation was found between predonation financial motivation and post-donation satisfaction and between pre-donation ambivalence and post-donation satisfaction, suggesting that careful screening and counselling of donors with high levels of pre-donation financial motivation or ambivalence might be prudent.[1097] The increasing demand for young and healthy donors and the recent escalation of payment to oocyte donors in the USA have raised concerns in the attitudes of young donors who may not be able to adequately weigh the risks of ovarian hyperstimulation and oocyte retrieval against the benefit of large monetary reward.[1098] [Evidence level 3]

A review of the methodological adequacy of the psychosocial literature on information access when donated gametes and embryos are used to identified ten major flaws which may preclude any conclusion either way about the wisdom of promoting information disclosure and access to all parties concerned.[1099] [Evidence level 3]

Generally, oocyte donation is acceptable with oocyte donors having a high satisfaction rate. Counselling from someone who is independent of the treatment unit could contribute to this, as well as to the understanding of the potential risks and complications associated with this process.

Some 2000 children are born each year in the UK as a result of the use of donated gametes. Recent debates have focused on the issues surrounding privacy and disclosure among donor gamete recipients.[1100] In 2002, the Department of Health held a public consultation on the amount of information that should be given to donor offspring and parents of those who donated gametes. The HFEA recommended that there should be a move toward the removal of donor anonymity and that stronger guidelines should be developed on the counselling needs of those considering treatment with donor gametes and donor offspring seeking information on donors. A two-track system that allows some donors to be identified and others to preserve their anonymity should be rejected.[743] [Evidence level 4]

‘Egg sharing’

A possible solution to the imbalance between the large number of potential recipients and the currently small number of donors is the practice of egg sharing. ‘Egg sharing’ enables two or more infertile couples to benefit from a single IVF cycle.

A pilot study (n = 55, 25 donors and 30 recipients, 73 fresh and frozen cycles) to establish the place of ‘egg sharing’ in an assisted reproduction programme was undertaken. This study followed HFEA guidelines on medical screening of patients, counselling, age and rigid anonymity between the donor and recipient. Although the recipients were older than the donors (41.4 ± 0.9 years versus 31.6 ± 0.5 years), there were no differences in the number of eggs allocated, fertilisation rates or the mean number of embryos transferred. There were more births per woman among recipients than among donors (30% versus 20%), although the groups were too small to determine if this was statistically significant or not. This suggested that providing the donors are selected carefully, the ‘egg-sharing’ scheme whereby a subfertile donor helps a subfertile recipient is a constructive way of solving the problem of shortage of eggs for donation.[1101] A cohort study which compared the use of fresh embryos in donor cycles (n = 135) and standard IVF cycles (n = 474) confirmed similar pregnancy rates (17.5% and 18.7%) and implantation rates (7.5% and 7.2%) in the two groups.[1102] Careful patient selection and counselling from someone who is independent of the treatment unit for both the donors and recipients and their partners is clearly essential. [Evidence level 3]

A survey of attitudes of egg donors and recipients in the UK (n = 217) found that: donating or ‘sharing’ eggs is a social issue, with 94% of respondents having discussed it with partners, family or friends; 86% of ‘egg share’ donors and 79% of ‘egg share’ donor enquirers felt that helping the childless was as important as having a chance of IVF themselves. The treatment procedure caused the most anxiety for egg donors. However, 65% of respondents with prior experience of ‘egg sharing’ would do it again (63% of donors, 72% of recipients). Counselling was highly valued, with 84% of respondents agreeing that patients, donors and recipients should have time to talk over egg donation issues with a counsellor.[1103] [Evidence level 3]

‘Egg sharing’ is a new area of practice that has developed in response to a shortage of donor gametes. As yet, there has been little research to evaluate the effectiveness of counselling in relation to oocyte donation and egg sharing, and research to evaluate the effectiveness of counselling in terms of long-term psychological and social implications of these practices is needed.

Recommendations

Number	Recommendation
191	Oocyte donors should be offered information regarding the potential risks of ovarian stimulation and oocyte collection. **[2004]**
192	Oocyte recipients and donors should be offered counselling from someone who is independent of the treatment unit regarding the physical and psychological implications of treatment for themselves and their genetic children, including any potential children resulting from donated oocytes. **[2004]**
193	All people considering participation in an ‘egg-sharing’ scheme should be counselled about its particular implications. **[2004]**

Number	Research recommendation
RR 38	Research is needed to evaluate the effectiveness of counselling in relation to oocyte donation and ‘egg sharing’ in terms of the long-term psychological and social implications of these practices.

19 People with cancer who wish to preserve fertility

19.1 Introduction

The treatment of cancer frequently involves the use of radiotherapy and/or chemotherapy. Both of these treatments can have serious adverse effects, both immediate and delayed.

One of the side-effects of such cancer treatment is its impact on fertility, either by direct injury to the ovaries or testes from radiotherapy or via systemically administered chemotherapeutic agents.The marked success in the treatment of certain cancers affecting younger people and the associated improved survival for an increasing number of affected people means that consideration of the potential impact of the cancer treatment on fertility is one of the issues that should be discussed before that treatment is started. In some cases the individual's fertility will return after the cancer treatment is completed but in other cases fertility never returns, or is severely impaired.

Since the publication of the 2004 version of this guideline, it has become increasingly common for commissioners of NHS-funded healthcare to procure services that offer an opportunity to affected individuals to preserve their fertility prior to the start of cancer treatment.

Preservation of fertility involves some form of freezing, technically called cryopreservation. The methods used in clinical practice at the time of this guideline update involve cryopreservation of semen, oocytes and embryos. Cryopreservation of ovarian and testicular tissue is largely undertaken in a research setting.

19.2 Cryopreservation of semen, oocytes, embryos and ovarian tissue

Semen cryopreservation

Semen cryopreservation should be considered in conditions that impair fertility or need treatment likely to impair fertility, such as malignancies of the genital tract (for example testicular cancer and prostate cancer) or systemic malignancies (for example non-Hodgkin's or Hodgkin's lymphoma, and leukaemia). Survival rates in men with these conditions (who are often young) are promising and likely to improve in the future. For those about to receive chemotherapy or radiotherapy and those about to undergo a surgical procedure, loss or impairment of fertility is an important issue and cryopreservation of semen in such people has become a realistic option to preserve fertility, regardless of diagnosis and treatment[1105] (Wallace et al.,. 2005; Pacey, 2007).

Semen quality is adversely affected by the presence of cancer[1106] and current techniques in cryopreservation of human semen substantially decrease sperm quality. The particular diagnosis of malignancy (for example Hodgkin's disease) is not an adequate predictor of the effect of cryopreservation on human semen.[1107,1108] For men, elective sperm cryopreservation and banking at cancer diagnosis before the initiation of specific medical treatment and regardless of semen quality should be encouraged[1109–1112] and offered[1105] (Wallace et al., 2005; Pacey, 2007) as an essential part of any comprehensive cancer care programme.[1113,1114] Some people may later decide that the specimens are not needed[1112] (Pacey and Eiser, 2011). Successful outcomes with intrauterine

insemination (IUI) and in vitro fertilisation (IVF) following successful treatment for malignancy have been reported in one retrospective review.[1115] Cryopreserved semen from cancer patients before chemotherapy, although generally of poor quality, are sufficient for success with IVF or ICSI, irrespective of the duration of storage.[1110,1115–1118,] (Feldschuh et al.,. 2005) [Evidence level 3] An abstinence period of 24 to 48 hours can be recommended for sperm banking in cancer patients,[1119] although in practice any samples available in the short period before cancer treatment begins are acceptable.

The joint working party of the Royal College of Physicians, Royal College of Obstetricians and Gynaecologists, and Royal College of Radiologists on the effect of cancer treatment on reproductive function recommended that "sperm banking must be considered for all males prior to treatment that carries a risk of long-term gonadal damage" (RCP joint working party, 2007).

The particular issues facing adolescent boys who may also be capable of producing mature sperm and therefore benefiting from semen storage should be known to those treating their cancer and specialist advice and counselling should be available. A strategy for fertility services for survivors of childhood cancer has been developed, which highlights the concerns relating to consent to treatment and the need to consider the extent to which children are able and/or wish to participate in decision making.[1120] [Evidence level 3–4] (British Fertility Society [BFS], 2003). Before this is undertaken staff must be aware of and take account of the child protection law for anyone under the age of 18 (Crawshaw et al., 2007; Wylie and Pacey, 2011).

Cryopreservation of oocytes, embryos and ovarian tissue

Cryopreservation of semen has been a well established practice for many decades. The first report of a pregnancy using a frozen embryo was in 1983 (Trounson, 1983) and the first using a frozen oocyte was in 1986 (Chen et al., 1986).

Use of ovarian tissue to preserve fertility is a more recent development with the first reported live birth being in 2004 (Donnez et al., 2004).

Counselling

Counselling and information giving are an integral part of the management which will require a multidisciplinary input[1105] (Wallace et al., 2005; Pacey, 2007; Eiser et al., 2011; Pacey and Esier, 2011). This counselling should cover the issues surrounding the choice of whether to have oocytes or embryos frozen, given the need to have partner consent to use frozen embryos in the future, and the benefits of having oocytes frozen if that consent is withdrawn.

Review question

What is the effectiveness of cryopreservation (including vitrification) in fertility preservation strategies?

Evidence profile

This review aimed to establish the effectiveness of cryopreservation for men and women at risk of fertility loss through treatment of cancer. It is split into two broad sections: one for the cryopreservation of semen; and the other for the cryopreservation of embryos, oocytes and ovarian tissue.

The section on cryopreservation of semen only examines the clinical outcomes achieved and does not compare different techniques of freezing or the viability of the sperm after thawing. As the studies were non-comparative, they were presented in a table showing the main outcomes (see Table 19.1).

Although the benefit of cryopreservation of embryos, oocytes and ovarian tissue is well established, there is a debate about whether controlled-rate freezing or vitification should be the preferred technique. This review was split into two parts. The first part examined the clinical outcomes based on the use of cryopreserved embryos, oocytes and ovarian tissue (see Table 19.2). The second part investigated the technical viability of material that has been cryopreserved (see Table 19.3).

The three profiles presented in this review are as follows:

- Outcome of cryopreservation of semen (Table 19.1).
- GRADE findings for cryopreservation of embryos, oocytes and ovarian tissue: clinical outcomes (Table 19.2).
- GRADE findings for cryopreservation of embryos, oocytes and ovarian tissue: procedural outcomes (Table 19.3).

Description of included studies

Semen cryopreservation in cancer patients

Included studies

In total, 14 studies were included in this review (Agarwal et al., 2004; Audrins et al., 1999; Crha et al., 2009; Fitoussi et al., 2000; Hourvitz et al., 2008; Kelleher et al., 2001; Khalifa et al., 1992; Lass et al., 1998; Magelssen et al., 2005; Menon et al., 2009; Meseguer et al., 2006; Ragni et al., 2002; Revel et al., 2005; van Casteren et al., 2008). All were non-comparative retrospective cohort studies. The sample sizes ranged from 21 to 629. Where reported, the mean age ranged from 17.81 SD ± 0.14 years to 38.5 SD ± 9.5 years. A total of 4352 men with cancer underwent semen cryopreservation (three studies only reported those who requested their sample be used). Where reported (N = 1,825) the types of cancer were: testicular cancer (38.8%), Hodgkin's disease (22.8%) and other (38.4%). The percentage of cryopreserved tissue discarded ranged from 5.2% to 36.0% (reported in Audrins et al., 1999; Meseguer et al., 2006; Ragni et al., 2002; van Casteren et al., 2008) and use of stored tissue ranged from 1.9 % to 16.3% (Agarwal et al., 2004; Audrins et al., 1999; Crha et al., 2009; Fitoussi et al., 2000; Kelleher et al., 2001; Lass et al., 1998; Magelssen et al., 2005; Menon et al., 2009; Meseguer et al., 2006; Ragni et al., 2002; van Casteren et al., 2008).

Embryos, oocytes and ovarian tissue cryopreservation

Included studies – clinical outcomes

As randomised controlled trial (RCT) data comparing vitrification with controlled slow-freezing in cancer patients was not identified the review was expanded to include non-cancer patients.

Two RCTs (Smith et al., 2010; Wilding et al., 2010) with a total of 366 participants contributed data to this review. The mean age ranged from 31.6 SD ± 1.1 years to 33.6 SD ± 3.2 years. Neither the duration nor cause of infertility was reported in either study.

Included studies – aboratory outcomes

Eight studies (Balaban et al., 2008; Cao et al., 2009; Fasano et al., 2010; Huang et al., 2005; Isachenko et al., 2009; Kim et al., 2000; Li et al., 2007; Zheng et al., 2005) were included in the review. All studies were RCTs and used oocyte or embryo samples as the unit of randomisation. No demographic details were provided.

Table 19.1 Cryopreservation of semen for cancer patients (observational, non-comparative studies)

Study	Number of patients	Tissue discarded (n)	Embryo or egg used (n)	Basis for ART Choice	ART (cycles)	Pregnancy (n)	Live birth (n)
Agarwal et al., 2004	318	Not reported	31	Not reported	IUI (42)	2	3
					ICSI (19)	7	4
					IVF (26)	6	5
Audrins et al., 1999	258	93	18	AIH was first choice in the absence of poor semen quality or coexisting female factors	AIH (53)	3	1
					IVF	7	5

Study	Number of patients	Tissue discarded (n)	Embryo or egg used (n)	Basis for ART Choice	ART (cycles)	Pregnancy (n)	Live birth (n)
Crha et al., 2009	619	Not reported	28	Not reported	IUI (9)	2	2
					ICSI (44)	13	9
Fitoussi et al., 2000	94	Not reported	13	Patient request for IUI. Use of IVF following failed attempts of IUI	IUI (80)	-	2
					IVF (8)	-	0
Hourvitz et al., 2008	Not reported	Not reported	118	Not reported	IVF (169)	96	85
Kelleher et al., 2001	833	Not reported	64	Not reported	ICSI (28)	12	39
					AIH (35)	11	-
					IVF (28)	6	-
Khalifa et al., 1992	Not reported	Not reported	10	Quality of pre- and/or post-thaw spermatozoa	IVF (NR)	4	5
Lass et al., 1998	225	Not reported	6	Quality of frozen spermatozoa and centre criteria	IUI (NR)	2	2
					IVF (NR)	2	2
					ICSI (NR)	2	-
Magelssen et al., 2005	422	Not reported	29	Not reported	Not reported	16	14
Menon et al., 2009	156	Not reported	3	Not reported	Not reported	0	0
Meseguer et al., 2006	184	16	30	Not reported	ICSI (30)	14	12
					FET (5)	1	-
					Ai (5)	1	-
Ragni et al., 2002	686	124	28	Not reported	IUI (40)	3	12
					IVF + ET (6)	0	-
					ICSI (42)	11	-
Revel et al., 2005	Not reported	Not reported	21	ICSI was performed in cases of azoospermia	ICSI (62)	26	23
Van Casteren et al., 2008	557	29	42	Amount and quality of semen/female fertility factors	IUI (7)	1	25
					IVF (32)	8	
					ICSI (53)	16	

AI artificial insemination, AIH artificial insemination with husband's sperm, ART assisted reproduction technology, ET embryo transfer, FET frozen embryo transfer, ICSI intracytoplasmic sperm injection, IUI intrauterine insemination, IVF in vitro fertilisation, NR not reported

Table 19.2 GRADE findings for cryopreservation of embryos, oocytes and ovarian tissue: clinical outcomes

Number of studies	Number of patients/women		Effect		Quality
	Vitrification	Slow-freezing	Relative (95% CI)	Absolute (95% CI)	
Live full-term singleton births					
Oocytes					
No evidence reported					
Embryos					
1 (Wilding et al., 2010)	19/147 (13%)	17/141 (12%)	OR 1.1 (0.5 to 2.2)	8 more per 1000 (from 52 fewer to 110 more)	Moderate
Ovarian tissue					
No evidence reported					
Clinical pregnancy					
Oocytes					
1 (Smith et al., 2010)	18/48 (38%)	4/30 (13%)	OR 3.9 (1.2 to 13.0)	242 more per 1000 (from 19 more to 533 more)	High
Embryos					
1 (Wilding et al., 2010)	21/147 (14%)	19/141 (14%)	OR 1.1 (0.6 to 2.1)	8 more per 1000 (from 56 fewer to 111 more)	Moderate
Ovarian tissue					
No evidence reported					
Clinical pregnancy					
Oocytes					
1 (Smith et al., 2010)	18/48 (38%)	4/30 (13%)	OR 3.9 (1.2 to 13.0)	242 more per 1000 (from 19 more to 533 more)	High
Embryos					
1 (Wilding et al., 2010)	21/147 (14%)	19/141 (14%)	OR 1.1 (0.6 to 2.1)	8 more per 1000 (from 56 fewer to 111 more)	Moderate
Ovarian tissue					
No evidence reported					
Adverse pregnancy outcomes					
Oocytes					
No evidence reported					
Embryos					
No evidence reported					

Number of studies	Number of patients/women		Effect		Quality
	Vitrification	Slow-freezing	Relative (95% CI)	Absolute (95% CI)	
Ovarian tissue					
No evidence reported					
Multiple pregnancies (the number of pregnancies with more than one fetus)					
Oocytes					
No evidence reported					
Embryos					
No evidence reported					
Ovarian tissue					
No evidence reported					
Multiple births (the number of babies born from a multiple pregnancy)					
Oocytes					
No evidence reported					
Embryos					
No evidence reported					
Ovarian tissue					
No evidence reported					
Ovarian hyperstimulation syndrome (OHSS)					
Oocytes					
No evidence reported					
Embryos					
No evidence reported					
Ovarian tissue					
No evidence reported					
Fetal abnormalities					
Oocytes					
No evidence reported					
Embryos					
No evidence reported					
Ovarian tissue					
No evidence reported					
Patient satisfaction					
Oocytes					
No evidence reported					

Number of studies	Number of patients/women		Effect		Quality
	Vitrification	Slow-freezing	Relative (95% CI)	Absolute (95% CI)	
Embryos					
No evidence reported					
Ovarian tissue					
No evidence reported					
Health related quality of life					
Oocytes					
No evidence reported					
Embryos					
No evidence reported					
Ovarian tissue					
No evidence reported					
Anxiety and/or depression					
Oocytes					
No evidence reported					
Embryos					
No evidence reported					
Ovarian tissue					
No evidence reported					

CI confidence interval, OR odds ratio

Table 19.3 GRADE findings for cryopreservation of embryos, oocytes and ovarian tissue: procedural outcomes

Number of studies	Number of patients/women		Effect		Quality
	Vitrification	Controlled rate freezing	Relative (95% CI)	Absolute (95% CI)	
Post-thaw survival [a]					
Oocytes					
2 (Cao et al., 2009; Fasano et al., 2010)	376/423 (89%)	150/230 (65%)	OR 3.9 (2.6 to 5.9)	228 more per 1000 (from 179 more to 265 more)	Moderate

Number of studies	Number of patients/women		Effect		Quality
	Vitrification	Controlled rate freezing	Relative (95% CI)	Absolute (95% CI)	
Embryos					
4 (Balaban et al., 2008; Huang et al., 2005; Kim et al., 2000; Zheng et al., 2005)	441/505 (87%)	829/1147 (72%)	OR 1.9 (1.4 to 2.6)	109 more per 1000 (from 60 more to 148 more)	Moderate
Ovarian tissue					
No evidence reported					
Number with abnormal morphology[b]					
Oocyte					
No evidence reported					
Embryos					
2 (Balaban et al., 2008; Zheng et al., 2005)	59/271 (22%)	135/259 (52%)	OR 0.3 (0.2 to 0.4)	301 fewer per 1000 (from 229 fewer to 357 fewer)	Moderate
Ovarian tissue					
2 (Isachenko et al., 2009; Li et al., 2007)	25/126 (20%)	34/140 (24%)	OR 0.8 (0.4 to 1.4)	43 fewer per 1000 (from 122 fewer to 67 more)	Moderate

CI confidence interval, OR odds ratio

[ab]Post thaw survival' was defined differently between studies: Balaban –>50% of the blastomeres were intact or at least 3 viable cells and at least blatomere dividing by 18hrs post thaw culture; Zheng – 2hrs incubation, embryos assessed for integrity and number of surviving blastomeres. Those with half or more were classified as survived; Cao – microscopic evaluation 2 to 3 hours after culture based on the morphology of the oocyte membrane intergrity; Fasano – absence of overt cell degeneration, elongated shape, thick or distorted zona, expended perivitelline space and dark pronounced cytoplasm; Huang – 16 to 24 hrs culture then presented an ICM, trophoectoderm and a re-expanding blastocoels cavity; Kim – main article in Korean.

[d] 'abnormal morphology' was defined differently between studies: Balaban- 100% intact blastomere; Zheng – intact embryos; Li – Eosinophilia of the ooplasm, contraction and clumping of the chromatin material, and wrinkling of the nuclear membrane of the oocyte signs of atresia; Isachenko – grading of morphology of follicles grade 3 = partly or fully disrupted granulose or cytoplasm and picnoticnucleua classified as abnormal.

Evidence statements

Cryopreservation of semen

The available evidence was non-comparative and presented results from different assisted reproduction technology (ART) techniques. The results reported that fewer than 20% of patients used their stored samples. It is unclear how many samples were discarded.

Fourteen low quality observational studies reported that clinical pregnancies and live births were achieved using cryopreserved semen after thawing.

Cryopreservation of embryos, oocytes and ovarian tissue

Live full-term singleton births

There was no significant difference in the number of live full-term singleton births after vitrification of embryos compared with controlled rate freezing of embryos. No evidence was reported for the cryopreservation of oocytes or ovarian tissue.

Clinical pregnancy

There were significantly more clinical pregnancies using oocytes that had been cryopreserved using vitrification rather than controlled rate freezing.

There was no significant difference in the number of clinical pregnancies when comparing vitrification of blastocyst embryos with controlled rate freezing of embryos. No evidence was reported regarding the cryopreservation of ovarian tissue.

Adverse pregnancy outcomes

No evidence was reported for the cryopreservation of oocytes, embryos or ovarian tissue.

Multiple pregnancies

No evidence was reported for the cryopreservation of oocytes, embryos or ovarian tissue.

Multiple births

No evidence was reported for the cryopreservation of oocytes, embryos or ovarian tissue.

Ovarian hyperstimulation syndrome (OHSS)

No evidence was reported for the cryopreservation of oocytes, embryos or ovarian tissue.

Fetal abnormalities

No evidence was reported for the cryopreservation of oocytes, embryos or ovarian tissue.

Patient satisfaction

No evidence was reported for the cryopreservation of oocytes, embryos or ovarian tissue.

Health related quality of life

No evidence was reported for the cryopreservation of oocytes, embryos or ovarian tissue.

Anxiety and/or depression

No evidence was reported for the cryopreservation of oocytes, embryos or ovarian tissue.

Post-thaw survival

There was a significantly higher rate of post-thaw survival after vitrification of oocytes compared with controlled rate freezing of oocytes, and after vitrification of embryos compared with controlled rate freezing of embryos. No evidence was reported regarding the post-thaw survival rates after cryopreservation of ovarian tissue.

Number with abnormal morphology

There were significantly more embryos with abnormal morphology after controlled rate freezing compared with after vitrification.

There was no significant difference in the number of ovarian tissue samples with abnormal morphology after controlled rate freezing compared with after vitrification. No evidence was reported regarding the number of oocytes with abnormal morphology after cryopreservation.

Health economics profile

No formal health economic investigation was undertaken.

Evidence to recommendations

Relative value placed on the outcomes considered

The guideline development group (GDG) considered live full-term singleton birth as the most important outcome. However, very few studies reported this outcome. Clinical pregnancy rate is the outcome reported more often in the studies and the GDG felt that this can be used as a reasonable

surrogate outcome for live birth. However, not all clinical pregnancies result in a live birth at term. Furthermore, depending on the assisted reproductive treatment used to achieve conception (using the stored material) after the cancer treatment is successfully completed, multiple pregnancy could be a significant risk.

Post-thaw survival and the number of samples with abnormal morphology are important for determining the usefulness of any management strategy involving cryopreservation and for comparing the different techniques of cryopreservation without the confounder of the ART method used after cryopreservation.

Consideration of clinical benefits and harms

The GDG agreed that the evidence identified was representative of the available literature, but there was insufficient evidence to assess the effectiveness of different cryopreservation techniques used for semen.

The GDG was in agreement that the preservation of embryos and oocytes showed vitrification was preferable to controlled rate freezing in terms of benefits and harms, especially in relation to survival of frozen material.

The GDG concluded that there is currently not enough evidence to recommend vitrification for testicular and ovarian tissues. The GDG acknowledged, however, that as the technology improves this may become a viable option for men and women.

The GDG considered the efficacy of open and closed system vitrification but was not able to recommend a specific technique using the evidence available.

Consideration of health benefits and resource uses

The GDG was aware of the current clinical legislation for the freezing and storage of fertility tissue. As part of the provision of a fertility service, the freezing of semen, oocytes and embryos is funded by many primary care trusts in the UK in keeping with the recommendations made in the 2004 guideline. However, offering a service for the storage of material to preserve fertility while patients undergo cancer treatment is more variable. Legally, the stored tissue cannot be disposed of without patient consent and can remain in storage for a maximum of 55 years if there is evidence of ‘significant or premature infertility’ (Human Fertilisation and Embryology Authority, 2009).

The GDG was aware that the cost of storing tissue can be considerable. The GDG also noted the high rates of ‘non-use’ of stored tissue. One explanation for this observation was probably the fact that fertility returned in some men following treatment. The GDG noted in particular that a significant proportion of male cancer patients achieved spermatogenesis in the years following successful treatment, making their stored samples redundant: however, banked sperm can serve an important psychological function against the possibility of relapse. The GDG concluded that patients should expect to have their cryopreserved fertility material stored for a reasonable amount time, allowing them to have the opportunity to use it following treatment, but that process should involve a review with the patient after an appropriate interval regarding the need for ongoing storage.

Vitrification is a relatively new method of cryopreservation and the GDG acknowledged the training and resource requirements associated with an immediate switch to vitrification and the potential impact this would have on service provision in short-term.

Quality of evidence

Only non-comparative evidence from single centres was available for cryopreservation of semen, and studies provided very limited information on any of the main outcomes. This made the evidence liable to bias.

Low quality RCT data was available on cryopreservation of embryos, oocytes and ovarian tissue. There was significant heterogeneity between studies. Very limited information was available on cryopreservation of ovarian tissue.

The evidence shows beneficial post-thaw survival results for oocytes and embryos using vitrification. The data also shows significantly more embryos with abnormal morphology after controlled rate freezing compared with vitrification. The GDG members’ clinical consensus was that, although vitrification is a new technique, the limited evidence and their own experience demonstrates that

vitrification should be the preferred technique for the cryopreservation of oocytes and embryos. However, in the light the of the quality of evidence for the use of vitrification over controlled rate freezing and the resource implications outlined above, the recommendation indicates that vitrification should be only offered where it is available already. The evidence was not strong enough to prohibit the use of controlled rate freezing and it remains a viable alternative in centres where vitrification has not been introduced.

In order to make a more comprehensive recommendation, future research will be required to build on early studies that demonstrate the viability of vitrification use, specifically the preferred technique (either open or closed systems) and the long term effect of vitrification.

Other considerations

The GDG was of the view that there is variation in success of cryopreservation across the UK and that the need for cryopreservation varies by the type of cancer and treatment being used.

Information for the patient

The GDG highlighted the importance of discussion with patients, especially young adults, and recommended a number of existing reports on this subject, such as the report of the joint working party of the Royal College of Obstetricians and Gynaecologists (RCOG), Royal College of Pathologists (RCP) and Royal College of Radiologists (RCR) on the effect cancer treatment on reproductive function (Joint Working Party, 2007).

The GDG wished to reemphasise the importance of discussions between the clinician and patient at diagnosis. The GDG felt that the communication about fertility preservation is not ingrained in the treatment pathway, which is often to the detriment to the patient, and the disparity between male and female fertility treatment offered at diagnosis is evident in current practice. The implementation of the recommendations should address this pathway of treatment for women and increase the routine provision of information for a woman regarding her fertility during oncology consultations. The recommendations should also allow for a multi-disciplined approach, where fertility clinics and oncology clinicians work in tandem to treat patients, the aim of which is to understand the short- and long-term options from both a fertility and oncology perspective. The decisions made for the patient should take into account the diagnosis, treatment plan, expected outcome of subsequent fertility treatment, prognosis of the cancer treatment and viability of thawed material.

In addition, the GDG was aware that fertility units need to be able to respond with the appropriate degree of urgency to respond effectively to the request for cryopreservation in advance of cancer treatment.

Equalities

The GDG was strongly in favour of separating the policy on access to cryopreservation and storage found in the general fertility pathway from that within the treatment of cancer patients. The potential loss of natural fertility is the consequence of a cancer treatment regime and so it did not seem appropriate to put in place a policy that would inhibit their access to cryopreservation and storage. The GDG concluded that, where there were no specific biological or safety considerations, there should not be any barriers to referral for cryopreservation for men and women with cancer. Specifically, the GDG stressed that there should be no referral criteria to be fulfilled for cryopreservation in contrast to the detailed referral criteria laid down for access to fertility services. Nevertheless, in practice, the likelihood of future use of the stored material and potential for successful conception would be important considerations and discussion points with the patient. One specific issue that was discussed in this context was the upper age limit of the woman considering cryopreservation prior to cancer treatment. The GDG did not wish to make any formal recommendations in this regard but were conscious of the chances of success with assisted reproduction treatments with respect to a woman's age discussed at length elsewhere in this guideline (see Chapter 14). The GDG was also conscious that, in current clinical practice, there is a lower age limit that would limit women's access to treatment. The GDG believed that a lower age limit often found in the fertility care pathway is governed by the viability of treatment, like IVF. To use a lower age limit for a patient with cancer is therefore unacceptable.

When extracting fertility material from adolescents, staff must be aware of and take account of the child protection law for anyone under the age of 18. Furthermore, specialist advice and counselling

should be available and information provided on strategies for fertility services for survivors of childhood cancer.

The GDG wanted to note that the remit of the recommendations should only extend to the cryopreservation and storage of their fertility material. Should the patient wish to use their frozen material, the funding of the subsequent fertility treatment is not guaranteed. Each person should be aware that the decision to fund treatment would depend on their current status, which is particularly pertinent if their fertility returns following successful treatment. The option to access fertility treatment should be considered alongside the expected outcome of the procedure, on an individual basis. The GDG wished to be clear, however, that if assisted reproduction treatment has a reasonable chance of success then it should be offered to people following successful cancer treatment.

The GDG was of the view that if a male who is HIV positive wishes to cryopreserve his sperm then the consideration to use sperm washing should follow the pathway outlined in Chapter 6. The GDG was unaware of any other inequalities that need to be considered other than those outlined above.

Considerations for cryopreservation in women with cancer

To cryopreserve oocytes or embryos is an extended process that will involve ovarian stimulation and invasive treatment. The GDG noted that cryopreservation should be available where a woman's treatment may remove her natural fertility (or have a risk of doing so): however, in some scenarios the safety and viability of the process should be considered, as should its impact on the woman's cancer treatment by, for example, delaying commencement of such treatment.

The GDG acknowledged that, as in the general population, the upper age limit for undertaking cryopreservation and using frozen material in cancer patients is likely to be governed by biological factors, particularly in women, and that embryos may not always be available for cryopreservation prior to cancer treatment. The GDG felt that ovarian stimulation in a woman with poor prognostic factors could be harmful, with little chance of retrieving viable oocytes. The GDG was also aware that cancer treatment can induce an early menopause in women and that this consideration should be discussed.

The severity of the cancer and the timeframe for cancer treatment should be taken into account in any cryopreservation strategy, and healthcare professionals should acknowledge the difficulties of properly informing people about cryopreservation while they are undergoing cancer treatment.

Considerations for cryopreservation in men with cancer

The GDG acknowledged that cryopreservation of semen is a quick procedure and could, theoretically, be offered to all men. In men, the type of treatment and type of cancer will affect the restoration of fertility function. Men should be advised that in some cases there will be no long-term effect on their fertility.

The GDG considered the implications of returning fertility in men following treatment, particularly because it is not lawful for sperm banks to discard samples without the consent of the patient. The GDG discussed at what point in the man's cancer journey fertility can be considered to have returned and whether that consideration take into account the likelihood of relapse. It was concluded that in men where normal fertility has not resumed following cancer treatment or where men remain within treatment there would be a need to continue to store the sample. This is coherent with the HFEA code of practice (incorporating the Human Fertilisation and Embryology [HFE] Act 1990) where the storage of the sample should be dependent on the man having serious infertility or being at risk of serious infertility.

In cases where fertility has returned to an adequate level following successful treatment after the 10 year initial storage period, the GDG recommended that stored samples should not be retained. The implications of keeping unnecessary samples will have logistical and financial impacts on the storage centre, the patient and the service.

Extension of cryopreservation techniques outside of cancer treatment

The GDG was aware that the recommendations made within this remit are also applicable to people within the general fertility pathway. The efficacy of vitrification in female cryopreservation and slow rate controlled freezing in men can feasibly be extended to general population. The cost effectiveness

of such implementation could alter this judgement, where the population is much larger in the general infertility treatment pathway and most are without the specific requirements within this chapter's remit.

The scope of this guideline states that recommendations are to be outlined for people undergoing cancer treatment who wish preserve their fertility. The interpretation of the evidence was based on this and recommendations have been written specifically for this population. No recommendations are made for other groups who may prematurely lose their fertility. However, the GDG highlighted that the fact recommendations were not made for other groups should not be used as a justification for not funding cryopreservation in these groups and that the recommendations made in the guideline could be extrapolated to other groups within the population who may be at risk of losing their fertility due to treatment.

HFEA Code of Practice

The GDG was aware of the HFEA Code of Practice (HFEA, 2008) which states that the statutory period of storage of gametes is 10 years and incorporated that into this guidance. The statutory 10 years should be considered as a minimum time for storage. If the patient is at significant risk or remains infertile then the material should be stored beyond 10 years. The decision to continue storage should also consider the expected outcome of subsequent fertility treatment, as storing a sample beyond the reproductive age or viability of a patient would be unrealistic.

The cryopreservation of any fertility material should follow the Human Fertilisation and Embryology (HFE) Act 1990 (as amended by the HFEA). This is particularly pertinent to the consent and use of stored gametes, embryos or human admixed embryos.

Recommendations

Number	Recommendation
194	When considering and using cryopreservation for people before starting chemotherapy or radiotherapy that is likely to affect their fertility, follow recommendations in 'The effects of cancer treatment on reproductive functions' (2007)*. **[2013]**
195	At diagnosis, the impact of the cancer and its treatment on future fertility should be discussed between the person diagnosed with cancer and their cancer team. **[new 2013]**
196	When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors: • diagnosis • treatment plan • expected outcome of subsequent fertility treatment • prognosis of the cancer treatment • viability of stored/post-thawed material. **[new 2013]**
197	For cancer-related fertility preservation, do not apply the eligibility criteria used for conventional infertility treatment. **[new 2013]**
198	Do not use a lower age limit for cryopreservation for fertility preservation in people diagnosed with cancer. **[new 2013]**
199	Inform people diagnosed with cancer that the eligibility criteria used in conventional infertility treatment do not apply in the case of fertility cryopreservation provided by the NHS. However, those criteria will apply when it comes to using stored material for assisted conception in an NHS setting. **[new 2013]**

* Royal College of Physicians, The Royal College of Radiologists, Royal College of Obstetricians and Gynaecologists. The effects of cancer treatment on reproductive functions: Guidance on management. Report of a Working Party. London: RCP, 2007.

200 When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos or oocyctes. **[new 2013]**

201 Offer sperm cryopreservation to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile. **[new 2013]**

202 Use freezing in liquid nitrogen vapour as the preferred cryopreservation technique for sperm. **[new 2013]**

203 Offer oocyte or embryo cryopreservation as appropriate to women of reproductive age (including adolescent girls) who are preparing for medical treatment for cancer that is likely to make them infertile if:

- they are well enough to undergo ovarian stimulation and egg collection **and**
- this will not worsen their condition **and**
- enough time is available before the start of their cancer treatment. **[new 2013]**

204 In cryopreservation of oocytes and embryos, use vitrification instead of controlled-rate freezing if the necessary equipment and expertise is available. **[new 2013]**

205 Store cryopreserved material for an initial period of 10 years. **[new 2013]**

206 Offer continued storage of cryopreserved sperm, beyond 10 years, to men who remain at risk of significant infertility. **[new 2013]**

Number	Research recommendation
RR 39	What is the efficacy of vitrification of sperm?
RR 40	What is the long term outcome of babies resulting from the use of vitrified embryos or eggs?
RR 41	Is there a difference in the effectiveness of open vitrification systems compared to closed vitrification systems?
RR 42	What is the efficacy of cryopreservation of ovarian and testicular tissue?

20 Long-term safety of assisted reproduction treatments in women with infertility and their children

20.1 Introduction

Assisted reproduction treatments (ART) often involve the use of potent drugs and the artificial development of embryos. It has been speculated that these techniques may be associated with increased levels of long-term problems, such as cancer, in both the mothers and children compared with people who have not used ART.

The long-term impact on children born as the result of assisted reproduction was considered in the original guideline. However, it did not address the issue of the long-term impact of such interventions on the woman. Thus, for this guideline update, it was agreed to review the evidence for long-term effects in both women with infertility and the children born as a result of:

- drugs used for ovulation induction and ovarian stimulation, where these agents were separately identified in the studies
- in vitro fertilisation (IVF), with or without intracytoplasmic sperm injection (ICSI) where the individual components of the treatment were not defined.

Although it is recognised that multiple births and ovarian hyperstimulation syndrome (OHSS) have long-term effects, they were not included here as they have been addressed as early complications in the relevant chapters (see Chapters 8 and 14). In addition, the long-term risks of multiple births are examined in the NICE Multiple Pregnancy guideline (NICE clinical guideline 129, 2011).

This chapter reviews the evidence of the long-term effects of these interventions.

20.2 Long-term safety of ovulation induction and ovarian stimulation

Prion disease

The theoretical risk of transmitting prion disease, however unlikely, must always be considered when medicinal products are derived from or contain materials of human or bovine origin. In the case of gonadotrophins, such theoretical risks could arise from the human source material used to manufacture urinary-derived products or from bovine reagents used in the manufacture of recombinant products. However, there is no evidence of transmission of prion disease by any gonadotrophin.

It has been reported that abnormal prion protein has been identified in urine from patients with Creutzfeldt–Jacob disease.[625] Although it was noted that infectivity had not been demonstrated in animal experiments, the Committee on Safety of Medicines recommended that, as a precautionary measure, no human urine used in production of medicines should be sourced from a country with one or more indigenous cases of variant Creutzfeldt–Jacob disease. This reflects the position in the UK regarding the source of plasma used in the production of blood products.

One urinary product (Metrodin® High Purity), which is manufactured using human urine sourced in Italy, was withdrawn by the Medicines Control Agency in February 2003 after a case of variant Creuzfeldt–Jacob disease was reported in Italy. Other urinary products available in the UK are not affected because the urine is sourced from countries with no reported cases of variant Creuzfeldt–Jacob disease.

Recombinant products, where bovine materials are used in their manufacture, are subject to strict controls to ensure freedom from prion agents. These controls, agreed across Europe, cover the source of starting materials and donor animals, the type of tissue involved, manufacturing processes, quality control and audit procedures and how the material is used in the production of the recombinant medicine.

All recombinant and urinary gonadotrophins available in the UK comply with European safety requirements for transmissible spongiform encephalopathies.

Review question

What is the long-term safety of ovulation induction and ovarian stimulation strategies in women with infertility and their children?

Evidence profile

The GRADE profiles presented show results of included studies for the two parts of the review question.

- Long-term safety of ovulation induction and ovarian stimulation agents in women (Table 20.1).
- Long-term safety of ovulation induction and ovarian stimulation agents in children (Table 20.2).

Description of included studies

Twenty studies that investigated the long-term safety of ovulation induction and/or ovarian stimulation agents in women and children born after fertility treatment were reviewed (17 observational studies, one meta-analysis of oberservational studies and two systematic reviews of observational studies). The majority of the studies reported the outcomes of drugs used for both ovulation induction and ovarian stimulation.

Assessment of the included papers showed heterogeneity in terms of included populations, interventions, analysis and outcomes. There was paucity of data and poor reporting in some of the included studies presented. For the smaller number of studies looking at the impact of ovulation induction and ovarian stimulation agents, where confidence intervals were not reported in most papers, it is unclear how the investigators have reached their conclusions.

Since the original guideline was published, a number of new studies have become available, and some of these are more methodologically rigorous (larger samples, use of appropriate risk-adjustment). The majority of studies linked routine datasets to ascertain if women who used ovarian stimulants or IVF (and their children) had a higher risk of cancer and other conditions compared to the general population. However, the overall quality of the studies remains low.

Long-term safety of ovulation induction and ovarian stimulation agents in women

Sixteen studies assessed the safety of ovulation induction and ovarian stimulation agents in women. There were 13 papers (Althius et al., 2005a; Althius et al., 2005b; Brinton et al., 2004a; Brinton et al., 2004b; Calderon-Margalit et al., 2009; Gauthier et al., 2004; Hannibal et al., 2008a; Hannibal et al., 2008b; Rossing et al., 1994; Jensen et al., 2007; Jensen et al., 2009a; Jensen et al., 2009b; Sanner

et al., 2009) reporting on eight observational studies; two systematic reviews of observational studies (Klip et al., 2000; et al., Salhab et al., 2005) and one meta-analysis of observational studies (Zreik et al., 2010) included in this section. Either the mean or median duration of follow-up was reported in all the studies except Calderon-Margalit 2009; this varied from 8.1 to 33 years.

Long-term safety of ovulation induction and ovarian stimulation agents in children

Four studies focused on safety in children. All four studies (Brinton et al., 2004; Forman et al., 2007; Hovidtjorn et al., 2011; Tulandi et al., 2006) were observational studies. Duration of follow-up was reported in only one study (Hovidtjorn 2011) and varied from 4 to 13 years.

Table 20.1 GRADE findings for long-term safety of ovulation induction and ovarian stimulation agents in women

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Breast cancer					
Proportion of cases and rate ratios – GnRH (treated vs. control)					
1 (Jensen et al., 2007)	18/98	313/1,128	1.3 (0.8 to 2.2)	-	Very low
Number of cases and rate ratios – Clomifene (treated vs. general population)					
1 (Brinton et al., 2004)	80	-	1.0 (0.7 to 1.3)	-	Very low
Number of cases and relative risk – Clomifene (treated vs. control)					
1 (Gauthier et al 2004)	66	2,388	1.0 (0.8 to 1.2)	-	Very low
Proportion of cases and rate ratios - Clomifene (treated vs.control)					
1 (Jensen et al., 2007)	102/405	229/82	1.1 (0.9 to 1.4)	-	Very low
Hazard ratio - Clomifene (treated vs. general population)					
1 (Calderon-Margalit et al., 2009)	Not reported	Not reported	1.3 (0.8 to 2.0)	-	Very low
Risk ratios - Clomifene					
1 (Zreik et al., 2010)	Not reported	Not reported	1.1 (1.0 to 1.2)	-	Very low
Number of cases and rate ratios - Clomifene + Gonadotrophin (treated vs. general population)					
1 (Brinton et al., 2004)	28	-	1.2 (0.8 to 1.7)	-	Very low
Risk ratio - Clomifene + hMG					
4 (Zreik et al., 2010)	Not reported	Not reported	1.2 (1.0 to 1.5)	-	Very low
Number of cases and rate ratios - Gonadotrophins (treated vs. general population)					
1 (Brinton et al., 2004)	3	-	0.6 (0.2 to 1.8)	-	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Number of cases and relative risk - Gonadotrophins (treated vs. control)					
1 (Gauthier et al., 2004)	23	2,388	1.0 (0.7 to 1.5)	-	Very low
Proportion of cases and rate ratios - Gonadotrophins (treated vs. control)					
1 (Jensen et al., 2007)	36/165	295/1,061	1.2 (0.8 to 1.8)	-	Very low
Number of cases and relative risk - hCG (treated vs. control)					
1 (Gauthier et al 2004)	56	2,388	1.0 (0.7 to 1.3)	-	Very low
Proportion of cases and rate ratio - hCG (treated vs. control)					
1 (Jensen et al., 2007)	94/395	237/831	0.9 (0.7 to 1.2)	-	Very low
Cases vs. control – HCG					
1 (Salhab et al., 2005)	45/744	65/744	0.8 (0.5 to 1.2)	-	Very low
Proportion of cases and rate ratio – Progesterone (treated vs. control)					
1 (Jensen et al., 2007)	8/13	323/1,213	3.4 (1.6 to 7.1)	-	Very low
Risk ratio - other specific drugs (hCG, hMG, hMG +GnRH, GnRH, Gonadotrophins)					
11 (Zreik et al., 2010)	Not reported	Not reported	1.0 (0.9 to 1.1)	-	Very low
Uterine Cancer					
Proportion of cases and rate ratio – GnRH (treated vs. control)					
1 (Jensen et al., 2009)	7/110	76/1,133	1.1 (0.5 to 2.5)	-	Very low
Number of cases and risk ratios – Clomifene (treated vs. control)					
1 (Althuis et al., 2005)	19	20	1.8 (0.9 to 3.4)	-	Very low
Proportion of cases and rate ratio – Clomifene (treated vs. control)					
1 (Jensen et al., 2009)	29/417	54/826	1.4 (0.8 to 2.2)	-	Very low
Hazard ratio – Clomifene (treated vs. general population)					
1 (Calderon-Margalit et al., 2009)	Not reported	Not reported	4.6 (1.6 to 13.3)	-	Very low
Proportion of cases and rate ratio – Gonadotrophin (treated vs. control)					
1 (Jensen et al., 2009)	17/184	66/1,059	2.2 (1.1 to 4.5)	-	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Proportion of cases and rate ratio – hCG (treated vs. control)					
1 (Jensen et al., 2009)	31/413	52/830	1.4 (0.8 to 2.2)	-	Very low
Cervical cancer					
Number of cases and risk ratios - Clomifene (treated vs. control)					
1 (Althuis et al., 2005)	7	7	1.6 (0.5 to 4.7)	-	Very low
Number of cases and risk ratios – Gonadotrophins					
1 (Althuis et al., 2005)	2	12	1.4 (0.3 to 6.4)	-	Very low
Melanoma					
Proportion of cases and rate ratio - GnRH (treated vs. control)					
1 (Hannibal et al., 2008)	14/98	98/1,128	1.6 (0.8 to 3.1)	-	Very low
Number of cases and risk ratios – Clomifene (treated vs. control)					
1 (Althuis et al., 2005)	21	21	1.7 (0.9 to 3.1)	-	Very low
Proportion of cases and rate ratio – Clomifene (treated vs. control)					
1 (Hannibal et al., 2008)	42/406	70/820	1.1 (0.7 to 1.7)	-	Very low
Hazard ratio – Clomifene (treated vs. general population)					
1 (Calderon-Margalit et al., 2009)	Not reported	Not reported	2.6 (1.1 to 6.0)	-	Very low
Number of cases and risk ratios – Gonadotrophins (treated vs. control)					
1 (Althuis et al., 2005)	4	38	0.9 (0.3 to 2.6)	-	Very low
Proportion of cases and rate ratio - Gonadotrophins (treated vs. control)					
1 (Hannibal et al., 2008)	25/165	87/1061	1.7 (0.9 to 2.9)	-	Very low
Proportion of cases and rate ratio – hCG (treated vs. control)					
1 (Hannibal et al., 2008)	40/396	72/830	1.1 (0.7 to 1.7)	-	Very low
Non-Hodgkin's lymphoma					
Hazard ratio – Clomifene (treated vs. general population)					
1 (Calderon-Margalit et al., 2009)	Not reported	Not reported	2.5 (0.7 to 8.1)	-	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Thyroid					
Proportion of cases and risk ratios – GnRH (treated vs. control)					
1 (Hannibal et al., 2008)	4/98	25/1,213	1.8 (0.5 to 7.0)	-	Very low
Number of cases and risk ratios - Clomifene					
1 (Althuis et al., 2005)	8	10	1.4 (0.5 to 3.7)	-	Very low
Proportion of cases and rate ratio – Clomifene					
1 (Hannibal et al., 2008)	16/406	13/820	2.3 (1.1 to 4.8)	-	Very low
Number of cases and risk ratios – Gonadotrophins					
1 (Althuis et al., 2005)	2	16	1.1 (0.2 to 4.9)	-	Very low
Proportion of cases and rate ratio – Gonadotrophins					
1 (Hannibal et al., 2008)	6/165	23/1,061	1.4 (0.5 to 3.8)	-	Very low
Proportion of cases and rate ratio – hCG					
1 (Hannibal et al., 2008)	13/396	16/830	1.7 (0.8 to 3.5)	-	Very low
Proportion of cases and rate ratio – Progesterone					
1 (Hannibal et al., 2008)	2/13	27/1,213	10.14 (1.9 to 53.3)	-	Very low
Colon					
Number of cases and risk ratios - Clomifene (treated vs. control)					
1 (Althuis et al., 2005)	8	20	0.8 (0.4 to 1.9)	-	Very low
Number of cases and risk ratios – Gonadotrophins					
1 (Althuis et al., 2005)	0	28	Not calculable	-	Very low
Ovarian cancer					
Proportion of cases and rate ratio - GnRH (treated vs. control)					
1 (Jensen et al., 2009)	15/110	141/1,133	0.8 (0.4 to 1.5)	-	Very low
Number of cases and rate ratios – Clomifene (treated vs. population)					
1 (Brinton et al., 2004)	11	-	0.8 (0.4 to 1.6)	-	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Proportion of cases and rate ratio – Clomifene (treated vs. control)					
1 (Jensen et al., 2009)	58/417	98/824	1.1 (0.8 to 1.6)	-	Very low
Odds ratio – Clomifene					
1 (Klip et al., 2000)	Not reported	Not reported	0.9 (0.3 to 2.3)	-	Very low
1 (Klip et al., 2000)	Not reported	Not repoted	0.7 (0.2 to 2.0)	-	Very low
Invasive ovarian cancer – Clomifene					
1 (Sanner et al., 2009)	Not reported	Not reported	1.5 (0.3 to 7.4)	-	Very low
Number of cases and rate ratios - Clomifene + Gonadotrophins (treated vs. population)					
1 (Brinton et al., 2004)	4	-	1.0 (0.3 to 2.8)	-	Very low
Invasive ovarian cancer					
Rate ratio - Clomifene + Gonadotrophins (treated vs. general population)					
1 (Sanner et al., 2009)	Not reported	Not reported	0.7 (0.1 to 6.0)	-	Very low
Number of cases and rate ratio – Gonadotrophins (treated vs. general population)					
1 (Brinton et al., 2004)	1	-	1.2 (0.1 to 8.2)	-	Very low
Proportion of cases and rate ratio – Gonadotrophins (treated vs. control)					
1 (Jensen et al., 2009)	26/184	130/1,057	0.8 (0.5 to 1.4)	-	Very low
Invasive ovarian cancer					
Rate ratio - Gonadotrophins (treated vs. general population)					
1 (Sanner et al., 2009)	Not reported	Not reported	5.2 (1.7 to 16.2)	-	Very low
Proportion of cases and rate ratio – hCG (treated vs. control)					
1 (Jensen et al., 2009)	49/413	107/828	0.9 (0.6 to 1.3)	-	Very low
Odds ratio – hMG					
1 (Klip et al., 2000)	Not reported	Not reported	3.2 (0.9 to 11.8)	-	Very low
Odds ratio - Clomifene/hMG					
1 (Klip et al., 2000)	Not reported	Not reported	1.4 (0.7 to 3.1)	-	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Odds ratio - Clomifene/hCG					
1 (Klip et al., 2000)	Not reported	Not reported	1.2 (0.3 to 4.0)	-	Very low
hMG/hCG					
1 (Klip et al., 2000)	Not reported	Not reported	0.8 (0.2 to 3.7)	-	Very low
Ovarian tumour					
Relative risk – Clomifene (treated vs. control)					
1 (Rossing et al.,1994)	Not reported	Not reported	2.3 (0.5 to 11.4)	-	Very low
Borderline ovarian tumour					
Rate ratio - Clomifene (treated vs. general population)					
1 (Sanner et al., 2009)	Not reported	Not reported	3.1 (0.7 to 13.7)	-	Very low
Odds ratio – Clomifene					
1 (Klip et al., 2000)	Not reported	Not reported	1.3 (0.3 to 6.9)	-	Very low
Borderline ovarian tumour					
Rate ratio - Clomifene + Gonadotrophins (treated vs. general population)					
1 (Sanner et al., 2009)	Not reported	Not reported	2.7 (0.6 to 12.7)	-	Very low
Rate ratio – Gonadotrophins (treated vs. general population)					
1 (Sanner et al., 2009)	Not reported	Not reported	1.1 (0.1 to 10.2)	-	Very low
Odds ratio – hMG					
1 (Klip et al., 2000)	Not reported	Not reported	9.4 (1.7 to 52.1)	-	Very low
Odds ratio - CC/hMG					
1 (Klip et al., 2000)	Not reported	Not reported	3.1 (1.0 to 9.7)	-	Very low
Relative risk - hCG (treated vs. control)					
1 (Rossing et al.,1994)	Not reported	Not reported	1.0 (0.2 to 4.3)	-	Very low

CC clomifene citrate, CI confidence interval, GnRH gonadotropin-releasing hormone, hCG human chorionic gonadotropin, hMG human menopausal gonadotrophin

Table 20.2 GRADE findings for long-term safety of ovulation induction and ovarian stimulation agents in children

Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
Malformation					
Proportion of cases – Clomifene vs. letrozole vs. natural conception					
1 (Forman et al., 2007)	7/271 (2.6%)	0/94 (0%)	3/112 (3.2%)	-	Very low
Major malformation (VSD, oesophageal atresia, cleft palate, trisomy 18, Down's syndrome, Potter's syndrome)					
Proportion of cases - Clomifene					
1 (Tulandi et al., 2006)	10/293 (3.4%)	-	Not reported	-	Very low
Letrozole					
1 (Tulandi et al., 2006)	1/252 (0.4%)	-	Not reported	-	Very low
Clomifene + FSH					
1 (Tulandi et al., 2006)	2/104 (2%)	-	Not reported	-	Very low
Clomifene + FSH + Progesterone					
1 (Tulandi et al., 2006)	0/104 (0%)	-	Not reported	-	Very low
Letrozole					
1 (Tulandi et al., 2006)	2/262 (0.8%)	-	Not reported	-	Very low
Letrozole + Progesterone					
1 (Tulandi et al., 2006)	1/262 (0.4%)	-	Not reported	-	Very low
Letrozole + Metformin					
1 (Tulandi et al., 2006)	2/262 (0.8%)	-	Not reported	-	Very low
Minor malformations (Preauricular skin tag, congenital ptosis, plagiocephaly, dydrocele, hypospadia, polydactyly, syndactyly, umblilical and inguinal hernias)					
Proportion of cases – Clomifene					
1 (Tulandi et al., 2006)	6/293 (2.0%)	-	Not reported	-	Very low
Letrozole					
1 (Tulandi et al., 2006)	4/252 (1.6%)	-	Not reported	-	Very low
Clomifene + FSH					
1 (Tulandi et al., 2006)	0/104 (0%)	-	Not reported	-	Very low

Number of studies	Number of patients/women		Effect		Quality
	Comparator	Control	Relative (95% CI)	Absolute (95% CI)	
Clomifene + FSH + Progesterone					
1 (Tulandi et al., 2006)	1/104 (1.0%)	-	Not reported	-	Very low
Letrozole					
1 (Tulandi et al., 2006)	2/262 (0.8%)	-	Not reported	-	Very low
Letrozole + Progesterone					
1 (Tulandi et al., 2006)	1/262 (0.4%)	-	Not reported	-	Very low
Letrozole + Metformin					
1 (Tulandi et al., 2006)	0/262 (0%)	-	Not reported	-	Very low
Autism spectrum disorder					
Hazard rate ratio – Down regulation (study group vs. general population)					
1 (Hovidtjorn et al., 2011)	Not reported	Not reported	1.1 (0.5 to 2.5)	-	Very low
FSH					
1 (Hovidtjorn et al., 2011)	Not reported	Not reported	1.3 (0.9 to 1.9)	-	Very low
hCG					
1 (Hovidtjorn et al., 2011)	Not reported	Not reported	1.2 (0.8 to 1.7)	-	Very low
Clomifene					
1 (Hovidtjorn et al., 2011)	Not reported	Not reported	0.8 (0.5 to 1.3)	-	Very low
Childhood tumours					
Proportion and rate ratio – Clomifene (study group vs. control)					
1 (Brinton et al., 2004)	11/265	34/594	0.8 (0.4 to 1.6)	-	Very low
hCG					
1 (Brinton et al., 2004)	10/260	35/600	0.7 (0.3 to 1.5)	-	Very low
hMG					
1 (Brinton et al., 2004)	2/83	44/779	0.6 (0.1 to 3.1)	-	Very low

CI confidence interval, FSH follicle-stimulating hormone, hCG human chorionic gonadotropin, hMG human menopausal gonadotrophin, VSD ventricular septal defect

Evidence statements

Long-term safety of ovulation induction and ovarian stimulation agents in women

Narrative summary

All 16 studies were graded as very low quality because of their methodological limitations. The majority of the studies reported no link between use of ovulation induction or ovarian stimulation agents and later developing cancer.

Individual studies

A meta-analysis of 23 studies found the risk of developing breast cancer was not associated with the prior use of clomifene citrate, clomifene citrate plus human menopausal gonadotrophin (hMG) or other specific drugs (human chorionic gonadotrophin [hCG], hMG, hMG plus gonadotrophin-releasing hormone [GnRH], GnRH, gonadotrophins) in fertility treatment.

One cohort study found no association between the use of clomifene citrate and risk of developing uterine cancer.

One prospective cohort study found no association between the use of clomifene citrate, hCG or gonadotrophin and the subsequent risk of developing breast cancer.

One non-comparative cohort study found no association between the use of clomifene citrate and the risk of developing breast cancer or non-Hodgkin's lymphoma. However, there was an association between the use of clomifene citrate and risk of uterine cancer and melanoma.

One cohort study found no association between the use of clomifene citrate in fertility treatment and subsequent incidence of invasive ovarian cancer or borderline ovarian tumour. For the same study, there was no association between the use of clomifene citrate plus gonadotrophins and incidence of invasive ovarian cancer or borderline ovarian tumour. However, there was an association between the use of gonadotrophins and the incidence of invasive ovarian cancer, but not borderline ovarian tumour.

One cohort study found no association between the use of clomifene citrate, gonadotrophins or a combination of clomifene and gonadotrophins and incidence of ovarian cancer. The same study found the incidence of breast cancer was not associated with the prior use of clomifene citrate, gonadotrophins or a combination of clomifene citrate and gonadotrophins.

One case–cohort study found no association between the use of clomifene citrate, gonadotrophins, hCG or GnRH and later incidence of malignant melanoma. The same study also found no association between gonadotrophins or hCG and incidence of thyroid cancer. However, it found an association between the use of clomifene citrate or progesterone and the subsequent risk of developing thyroid cancer.

One case–cohort study found no association between the use of clomifene citrate, gonadotrophins, hCG or GnRH and incidence of breast cancer. However, the same study found an association between the use of progesterone and subsequent incidence of breast cancer. The study found no association between the use of clomifene citrate, hCG or GnRHa and incidence of uterine cancer, but it found an association between the use of gonadotrophins and the incidence of uterine cancer. The study also found no association between the incidence of ovarian cancer and the use of clomifene citrate, gonadotrophins, hCG or GnRH.

One case–cohort study found no association between the use of clomifene citrate or hCG and subsequently developing an ovarian tumour.

One review with only one relevant study found no association between use of hCG and the risk of developing breast cancer.

One review included two relevant studies which showed no association between the use of clomifene citrate, hMG, clomifene citrate and hMG, clomifene citrate and hCG, or hMG and hCG, and risk developing of ovarian cancer. The same review also found no association between the use of clomifene citrate or clomifene citrate/hMG and risk of borderline tumour. However, the same study found an association between hMG and risk of borderline tumour.

Long-term outcomes in children born as a result of ovulation induction or ovarian stimulation

Narrative summary

Four very low quality studies were found examining the association between use of ovulation induction or ovarian stimulation by mothers and long-term health problems in children born as a result of this treatment. None of the studies found an association between the use of ovulation induction or ovarian stimulation by the mother and subsequent long-term problems amongst children born as a result of such treatment.

Individual studies

One retrospective cohort study found no statistically significant difference in rate of malformations in children born to women treated with clomifene citrate or letrozole compared with by natural conception.

One retrospective cohort study found no association between autism spectrum disorders in children born to women who had used fertility treatment (clomifene citrate, down-regulation, follicle-stimulating hormone (FSH) or hCG) in order to become pregnant.

One case–cohort study found no association between the use of clomifene, hCG or hMG by women and subsequent development of tumour in children born as a result of this treatment.

One cohort study found no difference in the overall rates of major and minor malformations or chromosomal abnormalities between children newly born to mothers who conceived after letrozole or clomifene citrate treatments.

Health economics profile

No health economic studies were identified on the long-term harm of ovulation induction and ovarian stimulation drugs for both women being treated and the children born as a consequence of that treatment. Given that no clear association was found between the treatments and increased long-term harm, no specific health economic analysis was undertaken.

Evidence to recommendations

Relative value placed on the outcomes considered

The studies reported in each chapter of this guideline address the short-term consequences of the various treatments for infertility, such as OHSS, whereas, this chapter focussed on the long-term outcomes.

For the women treated with ovulation induction or ovarian stimulation agents the main outcomes reported were various forms of cancer. These are very important outcomes, although the guideline development group (GDG) considered it would have been better if, in addition, mortality rates had been reported by the studies.

For the children born following treatment with ovulation induction or ovarian stimulation agents the three outcomes reported (congenital malformations, childhood tumours and autism spectrum disorder) were all considered to be important. The main problem with this review was the small number of studies identified.

The GDG did comment that it was unfortunate that none of the studies reported on the long-term consequences of multiple births on families and the children themselves.

Consideration of clinical benefits and harms

All the included studies were undertaken to identify potential harms caused by ovulation induction or ovarian stimulation. If clear relationships between such treatments and serious conditions were identified then a reassessment of the use of these drugs would have to be undertaken. At the very least, couples would have to be given clear information about possible adverse effects.

In the majority of the studies the reported absolute risk of harm was low.

Consideration of health benefits and resource uses

As no clear connection was identified between ovulation induction and ovarian stimulation drugs and increased rates of long-term harm in women and children there are no resource implications.

Quality of evidence

Evidence was from retrospective observational studies mainly based on routine clinic databases. This type of data is liable to bias, the main one being patient selection. This makes case-mix adjustment essential as certain groups of subfertile women may be more prone to adverse events than control groups, but in many studies the case-mix was limited. The large number of comparisons undertaken means that there were likely to be a number of associations that were statistically significant. As a result data was graded as very low quality.

Other considerations

Patient information

The GDG stated that information given to patients must take account of any new findings on long-term health outcomes which may have been published subsequent to the publication of these guidelines.

IVF research

The GDG was conscious that although there was no direct evidence relating the use of ovulation induction or ovarian stimulation treatments and cancer, especially ovarian, there was recent evidence of an association between IVF and borderline ovarian tumours which is discussed in more detail in the second half of this chapter. In theory, that association, if causative, would be likely to be due to the ovarian stimulation part of the IVF treatment package.

Volume of research

The GDG commented on the paucity of long-term research on the subject. The longest length of follow-up in the studies reviewed was 20 years in women and 10 years in children, with the larger studies having the shorter follow-up. The GDG commented that this was a disappointing feature of this review given that IVF was first undertaken over 30 years ago and ovulation induction has been an accepted treatment for much longer.

Study details

The GDG noted the following:

- It was not possible to look at the use of ovulation induction in relation to World Health Organization (WHO) groupings. Indeed, virtually all the cases receiving ovulation induction had polycystic ovary syndrome (PCOS).
- Similarly, it was not possible to distinguish ovarian stimulation according to setting (such as in women with unexplained infertility or IVF).
- The ‘control’ populations reported on in some of the studies were normally populations of infertile people rather than the general population.
- The outcomes were not reported according to whether or not the infertility treatment had been successful and resulted in a pregnancy.

Equalities

The people considered in this review were:

- People who have vaginal intercourse.
- Specific patient subgroups listed in the guideline Scope that may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to have vaginal intercourse because of a clinically diagnosed physical disability or psychological problem
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
- People who are preparing for cancer treatment who may wish to preserve their fertility.

There were no other specific issues that needed to be addressed with respect to any of these subgroups in the context of long-term safety of ovulation induction and/or ovarian stimulation.

Recommendations

Number	Recommendation
207	Give people who are considering ovulation induction or ovarian stimulation up-to-date information about the long-term health outcomes of these treatments. **[new 2013].**
208	Inform women who are offered ovulation induction or ovarian stimulation that: • no direct association has been found between these treatments and invasive cancer **and** • no association has been found in the short- to medium-term between these treatments and adverse outcomes (including cancer) in children born from ovulation induction **and** • information about long-term health outcomes in women and children is still awaited. **[new 2013]**
209	Limit the use of ovulation induction or ovarian stimulation agents to the lowest effective dose and duration of use. **[new 2013]**

Number	Research recommendation
RR 43	Is there an association between ovulation induction or ovarian stimulationand adverse long term (over 20 years) effects in children born as a result, in the UK population?
RR 44	Is there an association between ovulation induction or ovarian stimulation and adverse long-term (over 20 years) effects in women in the UK? Why this is important Women need to be reassured that it is safe to undergo ovulation induction and ovarian stimulation and that these interventions will not lead to significant long-term health issues, especially ovarian malignancy. Both treatments are common in the management of infertile women. The use of ovarian stimulation in IVF is particularly important as IVF is the final treatment option for most causes of infertility. During the course of the review for this guideline update the GDG commented on the paucity of long-term research on the subject, despite the fact that the treatments have been established practice for over 30 years. The longest length of follow-up in the studies reviewed was 20 years, and the larger studies had shorter follow-up periods.

2013 Update

20.3 Long-term safety of IVF

Genetic risks and congenital malformations

The ability of assisted reproduction to circumvent natural barriers to conception has led to concerns about the safety of IVF and ICSI, including their potential to transmit genetic aberrations to the next generation and the long-term consequences on later development of children born as a result of these procedures. Overall, more than 1 million children in the world have been conceived through IVF since 1978.[603] In England and Wales, about 23,000 women were treated and about 8000 babies were born

as a result of IVF and/or ICSI in 2000–2001 (about 2500 of these babies were born as a result of ICSI).[743] This accounts for about 1.3% of all live births.[1126] [Evidence level 3]

To date, there have been no adequate prospective randomized controlled trials (RCTs) of sufficient power to assess the efficacy and safety of the various forms of assisted reproduction. Long-term follow-up studies are needed to investigate the safety implications for children born as a result of assisted reproduction.[1127] Thus far, follow-up studies have been hampered by the type of surveillance protocol, attrition rate, sample size and lack of standardisation in defining major anomalies. It is also important to recognise that any increased risk may be due to parental factors associated with infertility, which may have led to the use of IVF or ICSI in the first place.[1128] [Evidence level 3]

A systematic review[1133] of available literature found 30 cohort and case series studies reporting the outcome of ICSI pregnancies on five clinical outcomes (congenital malformations, growth disturbances, neurological development disturbances, chromosomal abnormalities and transmission of subfertility to male offspring).[1133] Of the 30 studies included in the review, 13 were rated as acceptable quality cohort studies with well-defined control groups and 17 were cohort or case studies of weaker design. The outcome most reported was congenital malformations. Overall, no increased risk of major birth defects, including chromosomal abnormalities, was found in offspring resulting from treatment of severe male infertility with ICSI compared with offspring conceived by standard IVF treatment or naturally (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.00 to 1.29, *P* = 0.06; test for heterogeneity *P* = 0.35, based on seven cohort studies and two reports). The available data did not indicate an increased risk of any particular malformation, as separate meta-analyses on specific categories of malformations did not show any increased risk after ICSI.[1133] [Evidence level 2b–3]

In contrast, a prospective multicentred cohort study carried out in Germany (not included in the systematic review) compared ICSI infants (n = 3372) with normally conceived infants (n = 30,940) and found major malformation in 8.6% of ICSI children versus 6.9% of normally conceived children (crude relative risk [RR] 1.25, 95% CI 1.11 to 1.40).[1128] [Evidence level 3]

Whether ICSI treatment of infertile couples with normal karyotypes increases the occurrence of chromosomal abnormalities in offspring is unclear. Sons of infertile males with Y chromosome microdeletions will probably inherit the same abnormality and are therefore likely to be infertile. Males with no known genetic cause for severely compromised sperm quality may also father sons with Y chromosome microdeletions.

Review question

What is the long-term safety of IVF in women with infertility and their children?

Description of included studies

Twenty observational studies that investigated the long-term safety of IVF in women and children born after fertility treatment were reviewed.

Assessment of the included papers showed heterogeneity in terms of included populations, interventions, analysis and outcomes. Therefore, the results presented in the GRADE profiles are not meta-analysed results of outcomes in all the included studies; rather, they are individually reported results of outcomes in the studies.

Long-term safety of IVF in women

Four observational studies (Kristiansson, 2007; Lerna-Geva, 2003; Pappo, 2008; Venn, 2001) were included in this part of the question. Mean/median duration of follow-up was reported in two studies (Kristiansoon, 2007; Van Leeuwen, 2011) and varied from 6.5 to 16.4 years.

Long-term safety of IVF in children

Sixteen observational studies (Bowen et al., 1998; Brandes et al., 1992; Hansen et al., 2002; Kallen et al., 2005; Klemetti et al., 2006; Klip et al., 2001; Leslie et al., 2003; Pinborg et al., 2004; Place & Englert et al., 2003; Marees et al., 2009; Moll et al., 2003; Montgomery et al., 1999; Morin et al., 1989; Raoul-Duval et al., 1994; Silver et al., 1999; Stromberg et al., 2002) investigated the long-term safety of IVF in women. Ten studies (Brandes et al., 1992; Hansen et al., 2002; Kallen et al., 2005; Klemetti et al., 2006; Klip et al., 2001; Montgomery et al., 1999; Morin et al., 1989; Pinborg et al., 2004; Silver et al., 1999; Stromberg et al., 2002) compared the rates of outcome in children born after IVF with

rates in children conceived naturally. Three studies (Bowen et al., 1998; Leslie et al., 2003; Place & Englert et al., 2003) compared outcomes in children born after ICSI, IVF and natural conception. Two studies (Marees et al., 2009; Moll et al., 2003) compared incidence of an outcome in IVF children with incidence in the general population. One study (Raoul-Duval et al., 1994) compared outcomes in children born after IVF, children born after IVF, ovarian stimulation (without IVF) and natural conception. Mean/median duration of follow-up was reported in two studies (Kallen, 2005; Klip, 2001) and varied from 4.6 to 7.8 years.

Evidence profile

The GRADE profiles presented show results of included studies for the two parts of the review question:

- Long-term safety of IVF in women (Table 20.3)
- Long-term safety of IVF in children (Table 20.4).

Table 20.3 GRADE finding for long-term safety of IVF in women

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Breast cancer/tumour					
Number of cases and standardised incidence ratios (IVF vs general population)					
1 (Pappo et al., 2008)	35/24.8	-	1.4 (1.0 to 2.0)	-	Very low
Proportions and adjusted rate ratios (IVF/non-IVF)					
1 (Kristiansson et al., 2006)	13/617	-	0.7 (0.4 to 1.3)	-	Very low
Proportions and standardised incidence ratios in IVF women					
1 (Lerna-Geva et al., 2003)	4/4.9	-	0.8 (0.2 to 2.1)	-	Very low
Cervix					
Proportions and adjusted rate ratios (IVF/ non-IVF)					
1 (Kristiansson et al., 2006)	35/2,328	-	0.9 (0.6 to 1.2)	-	Very low
Proportions and standardised incidence ratios in IVF women					
1 (Lerna-Geva et al., 2003)	3/0.7	-	4.6 (0.9 to 13.5)	-	Very low
Non-invasive tumour					
Proportions and adjusted rate ratios (IVF/non-IVF)					
1 (Kristiansson et al., 2006)	48/2,890	-	0.9 (0.6 to 1.2)	-	Very low
Invasive tumour					
Proportions and adjusted rate ratios (IVF/non-IVF)					
1 (Kristiansson et al., 2006)	41/1,565	-	1.0 (0.7 to 1.4)	-	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
All malignancies IVF group					
IVF vs. general population – standardised incidence ratios					
1 (Van Leeuwen et al., 2011)	61/19146	-	1.6 (1.2 to 2.0)	-	Very low
Non IVF vs. general population – standardised incidence ratios					
1 (Van Leeuwen et al., 2011)	16/6006	-	1.0 (0.6 to 1.7)	-	Very low
IVF vs. non IVF subfertility group – hazard ratios					
1 (Van Leeuwen et al., 2011)	-	-	2.1 (1.1 to 3.8)	-	Very low
Invasive ovarian cancer					
IVF vs. general population – standardised incidence ratios					
1 (Van Leeuwen et al., 2011)	30/19146	-	1.4 (0.9 to 1.9)	-	Very low
Non IVF vs. general population – standardised incidence ratios					
1 (Van Leeuwen et al., 2011)	12/6006	-	1.2 (0.6 to 2.2)	-	Very low
IVF vs. non IVF subfertility group – hazard ratios					
1 (Van Leeuwen et al., 2011)	-	-	1.1 (0.5 to 2.4)	-	Very low
Borderline ovarian tumours					
IVF vs. general population – standardised incidence ratios					
1 (Van Leeuwen et al., 2011)	31/19146	-	1.9 (1.3 to 2.7)	-	Very low
Non IVF vs. general population – standardised incidence ratios					
1 (Van Leeuwen et al., 2011)	4/6006	-	0.7 (0.2 to 1.7)	-	Very low
IVF vs. non IVF subfertility group – hazard ratios					
1 (Van Leeuwen et al., 2011)	-	-	6.4 (2.1 to 19.8)	-	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Ovary					
Proportions and standardised incidence ratios in IVF women					
1(Lerna-Geva et al., 2003)	1/0.6	-	1.7 (0 to 9.3)	-	Very low
Other cancers – melanoma, hodgkin's lymphoma, multiple myeloma, angiosarcoma, brain and sarcoma					
Proportions and standardised incidence ratios IVF women					
1 Lerna-Geva et al., 2003)	8/4.9	-	1.6 (0.7 to 3.2)	-	Very low
All cancers					
Proportions and standardised incidence ratios IVF women					
1 Lerna-Geva et al., 2003)	16/11	-	1.5 (0.8 to 2.4)	-	Very low
Deaths by cause and IVF treatment status – standardised mortality ratios					
All causes of death					
IVF-treated women					
1 (Venn et al., 2001)	72/124.9	-	0.6 (0.5 to 0.7)	-	Low
Non-IVF women					
1 (Venn et al., 2001)	51/82.4	-	0.6 (0.5 to 0.8)	-	Very low
Diseases of the circulatory system					
IVF-treated women					
1 (Venn et al., 2001)	7/16	-	0.4 (0.3 to 0.7)	-	Very low
Non-IVF women					
1 (Venn et al., 2001)	7/10.5	-	0.7 (0.4 to 1.2)	-	Very low
Injury and poisoning					
IVF treated women					
1 (Venn et al., 2001)	14/27.1	-	0.5 (0.4 to 0.8)	-	Very low
Non-IVF women					
1 (Venn et al., 2001)	9/19.3	-	0.5 (0.3 to 0.7)	-	Very low
Suicide					
IVF treated women					
1 (Venn et al., 2001)	3/10.2	-	0.3 (0.2 to 0.6)	-	Very low

Number of studies	Number of patients/women		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Non-IVF women					
1 (Venn et al., 2001)	4/6.9	-	0.6 (0.3 to 1.2)	-	Very low
Death by all neoplasms					
IVF treated women					
1 (Venn et al., 2001)	51/68.6	-	0.7 (0.6 to 0.9)	-	Very low
Non-IVF women					
1 (Venn et al., 2001)	29/39.2	-	0.7 (0.5 to 1.0)	-	Very low
Death by breast cancer					
IVF treated women					
1 (Venn et al., 2001)	26/23.1	-	1.1 (0.8 to 1.7)	-	Very low
Non-IVF women					
1 (Venn et al., 2001)	9/12.9	-	0.7 (0.4 to 1.2)	-	Very low

CI confidence interval, IVF in vitro fertilisation

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Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Cerebral palsy					
Proportions and adjusted ORs (children in IVF vs. control group)					
1 (Klemetti et al., 2006)	3.8	1.4	2.9 (1.6 to 5.3)	-	Very low
Singletons					
1 (Klemetti et al., 2006)	1.4	1.3	1.2 (0.4 to 3.3)	-	Very low
Proportions and adjusted ORs (all children in IVF vs control group)					
1 (Stromberg et al., 2002)	31/5,680 (0.5%)	17/11,360 (0.1%)	3.7 (2.0 to 6.6)	-	Very low
Singletons					
1 (Stromberg et al., 2002)	12/3,228 (0.37%)	15/11,070 (0.14%)	2.8 (1.3 to 5.8)	-	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Number of cases and adjusted ORs (children in IVF vs. control group)					
1 (Kallen et al., 2005)	37	2,754	1.1 (0.7 to 1.8)	-	Very low
Proportions and adjusted ORs (IVF-ICSI twins vs. control twins)					
1 (Pinborg et al., 2004)	11/3,393 (0.3%)	41/10,239 (0.4%)	1.2 (0.6 to 2.3)	-	Very low
IVF-ICSI twins vs. IVF-ICSI singletons					
1 (Pinborg et al., 2004)	11/3,393 (0.3%)	13/5130 (0.3%)	0.8 (0.4 to 1.8)	-	Very low
Behavioural disorders					
Number of cases and adjusted ORs (children in IVF vs. control group)					
1 (Kallen et al., 2005)	37	3,657	1.6 (1.1 to 2.2)	-	Very low
Proportions and adjusted ORs (children in IVF vs. control group)					
1 (Klemetti et al., 2006)	6.6	4.1	1.7 (1.1 to 2.5)	-	Very low
Singletons					
1 (Klemetti et al., 2006)	4.1	4.1	1.1 (0.6 to 1.9)	-	Very low
Proportion of children in IVF vs control					
1 (Stromberg et al., 2002)	3/5,680 (0.05%)	10/11,360 (0.08%)	0.6 (0.2 to 2.2)	-	Very low
Singletons					
1 (Stromberg et al., 2002)	1/3,228	10/11,070	0.4 (0.1 to 3.0)	-	Very low
Mental retardation					
Number of cases and adjusted ORs (children in IVF vs. control group)					
1 (Kallen et al., 2005)	17	2,023	1.0 (0.5 to 2.0)	-	Very low
Proportions and adjusted ORs (all children in IVF vs. control)					
1 (Stromberg et al., 2002)	7/5,680 (0.1%)	18/11,360 (0.2%)	0.8 (0.3 to 1.9)	-	Very low
Singletons					
1 (Stromberg et al., 2002)	3/3228 (0.09)	17/11,070 (0.15%)	0.8 (0.2 to 2.6)	-	Very low
Proportions and adjusted ORs (IVF-ICSI twins vs. control twins)					
1 (Pinborg et al., 2004)	19/3,393 (0.6%)	57/10,239 (0.6%)	1.0 (0.6 to 1.7)	-	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
IVF-ICSI twins vs. IVF-ICSI singletons					
1 (Pinborg et al., 2004)	19/3,393 (0.6%)	29/5,130 (0.6%)	1.1 (0.6 to 1.9)	-	Very low
Pneumonia					
Number of cases and adjusted ORs (children in IVF vs. control group)					
1 (Kallen et al., 2005)	449	42,293	1.1 (0.9 to 1.3)	-	Very low
Proportions and adjusted ORs (children in IVF vs. control group)					
1 (Klemetti et al., 2006)	9.9	11.4	0.9 (0.6 to 1.2)	-	Very low
Singletons					
1 (Klemetti et al., 2006)	9.6	11.4	0.8 (0.5 to 1.2)	-	Very low
Rate of hospitalisation					
Number of cases and adjusted ORs (children in IVF vs. control group)					
1 (Kallen et al., 2005)	Not reported	Not reported	2.1 (2.0 to 2.2)	-	Very low
Proportions and adjusted ORs (children in IVF vs. control group)					
1 (Klemetti et al., 2006)	40/4,397 (0.91%)	33/136,782 (0.02%)	1.4 (1.3 to 1.5)	-	Very low
Singletons					
1 (Klemetti et al., 2006)	34/2911 (1.17%)	32/131,459 (0.02%)	1.1 (1.0 to 1.2)	-	Very low
Any accident					
Number of cases and adjusted OR (children in IVF vs. control group)					
1 (Kallen et al., 2005)	2,234	220,166	1.6 (1.5 to 1.7)	-	Very low
Proportions and p-values (children in IVF vs sterility vs. control group)					
	IVF	Sterility	Control		
1 (Raoul-Duval et al., 1994)	5/25 (20%)	1/11 (9%)	4/13 (31%)	NS	-	Very low
Asthma					
Number of cases and adjusted ORs (children in IVF vs. control group)					
1 (Kallen et al., 2005)	816	61,572	1.4 (1.3 to 1.6)	-	Very low

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Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Proportions and adjusted ORs (children in IVF vs. control group)					
1 (Klemetti et al., 2006)	30.3	38.1	1.1 (0.9 to 1.3)	-	Very low
Singletons					
1(Klemetti et al., 2006)	26.5	27.8	1.0 (0.7 to 1.2)	-	Very low
Epilepsy					
Number of cases and adjusted ORs (children in IVF vs. control group)					
1 (Kallen et al., 2005)	70	5,767	1.5 (1.3 to 1.9)	-	Very low
Proportions and adjusted ORs (children in IVF vs. control group)					
1 (Klemetti et al., 2006)	3.3	2.5	1.3 (0.8 to 2.3)	-	Very low
Singletons					
1 (Klemetti et al., 2006)	3.4	2.5	1.4 (0.7 to 2.7)	-	Very low
Psychomotor development Index					
Mean±SD and *P*-value (ICSI vs. IVF vs. control)					
	ICSI	IVF	Control		
1 (Bowen et al., 1998)	95.9±10.7	101.8±8.5	102.5±7.6	0.86	-	Very low
Mean±SD and *P*-value (IVF vs. control)					
1 (Morin et al., 1989)	114±14	108±15	0.04	-	Very low
Mental development index					
Mean±SD and *P*-value (ICSI vs. IVF vs. control)					
	ICSI	IVF	Control		
1 (Bowen et al., 1998)	89.8±16.6	89.2±15.1	88.3±15.7	P-value <0.001	-	Very low
Mean±SD and *P*-value (IVF vs. control)					
1 (Morin et al., 1989)	115±13	111±13	0.12	-	Very low
Mean±SD and *P*-value (all children in IVF vs. Control group)					
1 (Brandes et al., 1992)	106±19.3	110.6±19.3	NS	-	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Performance skills/IQ					
Mean±SD and *P*-values (ICSI vs. IVF vs. control)					
	ICSI	IVF	Control		
1 (Leslie et al., 2003)	112±16	112±13	114±13	0.66	-	Very low
1 (Place and Englert, 2003)	92.4±12.6	90.5±14.7	100.6±12.2	0.2 (91.7 to 97.9)	-	Very low
Verbal skills/IQ					
Mean±SD and *P*-values (ICSI vs. IVF vs. control)					
	ICSI	IVF	Control		
1 (Leslie et al., 2003)	107±15	107±12	111±14	0.10	-	Very low
1 (Place and Englert, 2003)	97.2±13.1	94.1±14.7	106.3±14.7	0.1 (96.2 to 103)	-	Very low
IQ/ Full scale IQ					
Mean±SD and *P*-values (ICSI vs. IVF vs. control)					
	ICSI	IVF	Control		
1 (Leslie et al., 2003)	110±18	111±13	114±13	0.20	-	Very low
1 (Place and Englert, 2003)	94.1±12.7	91.7±15.4	103.9±14.1	0.1 (93.7 to 100.3)	-	Very low
Retinoblastoma					
Number of cases in IVF vs. general population					
1 (Marees et al., 2009)	7/2.57	-	2.5 (1.0 to 5.2)	-	Very low
Number of cases and risk ratio in IVF vs. general population					
1 (Moll et al., 2003)	5/0.69	-	7.2 (2.4 to 17.0)	-	Very low
Allergy					
Proportions and adjusted ORs (children in IVF vs. control group)					
1 (Klemetti et al., 2006)	59.9	53.8	1.1 (0.9 to 1.2)	-	Very low
Singletons					
1 (Klemetti et al., 2006)	61.8	54.0	1.1 (0.9 to 1.3)	-	Very low

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Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Appendicitis					
Number of cases and adjusted OR (children in IVF vs. control group)					
1 (Kallen et al., 2005)	64	12,458	1.3 (0.9 to 1.9)	-	Very low
Attention problems					
Proportion with normal scores (<85th percentile) and *P*-value (IVF males vs. controls)					
1 (Montgomery et al., 1999)	94	85	0.99	-	Very low
Proportion with normal scores (>95th percentile) and *P*-value (IVF males vs. control group)					
1 (Montgomery et al., 1999)	1.1	5	0.99	-	Very low
Body length					
Percentile and p-value (all children in IVF vs. control group)					
1 (Brandes et al., 1992)	39.3±29.0	40.9±28.3	NS	-	Very low
Child disability allowance					
Proportions and adjusted ORs (all children in IVF vs. control group)					
	10.6	9.5	1.1 (1.0 to 1.2)	-	Very low
Singletons					
1 (Klemetti et al., 2006)	10.5	9.5	1.1 (1.0 to 1.3)	-	Very low
Childhood cancer					
Number of cases and adjusted RR (IVF vs. control group)					
1 (Klip et al., 2001)	5	9	0.8 (0.2 to 2.4)	-	Very low
Chromosomal aberration					
Proportions and adjusted ORs (IVF vs. control group)					
1 (Stromberg et al., 2002)	9/5,680 (0.16%)	15/11,360 (0.13%)	1.2 (0.5 to 2.7)	-	Very low
Singletons					
1 (Stromberg et al., 2002)	5/3,228 (0.15%)	15/11,070 (0.14%)	1.1 (0.4 to 3.0)	-	Very low
Composite index					
Mean±SD and *P*-values (all children in IVF vs. control group)					
1 (Brandes et al., 1992)	106.2±8.0	104.4±10.2	NS	-	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Convulsion					
Number of cases and adjusted OR (children in IVF vs. control group)					
1 (Kallen et al., 2005)	272	12,459	1.5 (1.2 to 1.8)	-	Very low
Diabetes mellitus					
Proportions and adjusted ORs (all children in IVF vs. control group)					
1 (Klemetti et al., 2006)	0.9	0.5	1.6 (0.5 to 4.8)	-	Very low
Singletons					
1 (Klemetti et al., 2006)	1.0	0.5	2.0 (0.6 to 7.1)	-	Very low
Diarrhoea					
Proportions and adjusted ORs (all children in IVF vs. control group)					
1 (Klemetti et al., 2006)	44.2	38.6	1.2 (1.0 to 1.4)	-	Very low
Singletons					
1 (Klemetti et al., 2006)	35.4	38.1	0.9 (0.8 to 1.2)	-	Very low
Externalising problems					
Proportion with normal scores (<85th percentile) and *P*-value (IVF males vs. controls)					
1 (Montgomery et al., 1999)	94.3	85	0.99	-	Very low
Proportion with normal scores (>95th percentile) and *P*-value (IVF males vs. control group)					
1 (Montgomery et al., 1999)	1.7	5	0.98	-	Very low
Feeding difficulties					
Proportions and *P*-value (children in IVF vs. sterility vs. control group)					
	IVF	Sterility	Control		
1 (Raoul-Duval et al., 1994)	6/25 (0.2%)	3/11 (0.3%)	2/13 (0.2%)	NS	-	Very low
Fracture					
Number of cases and adjusted OR (children in IVF vs. control group)					
1 (Kallen et al., 2005)	228	32,969	1.1 (0.9 to 1.4)	-	Very low

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Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Head circumference					
Percentile and *P*-value (all children in IVF vs. control group)					
1 (Brandes et al., 1992)	45.5±22.5	45.9±23.1	NS	-	Very low
Infant illnesses					
Proportions and *P*-value (children in IVF vs. sterility vs. control group)					
	IVF	Sterility	Control		
1 (Raoul-Duval et al., 1994)	23/25 (90%)	10/11 (91%)	13/13 (100%)	NS	-	Very low
Infant insomnia					
Proportions and *P*-values (children in IVF vs. sterility vs. control group)					
	IVF	Sterility	Control		
1 (Raoul-Duval et al., 1994)	4/25 (16%)	0/11 (0%)	3/13 (23%)	NS	-	Very low
Internalising problems					
Proportion with normal scores (<85th percentile) and *P*-value (IVF males vs. controls)					
1 (Montgomery et al., 1999)	87.3	85	0.8	-	Very low
Proportion with normal scores (>95th percentile) and *P*-value (IVF males vs. control group)					
1 (Montgomery et al., 1999)	2.1	5	0.98	-	Very low
Long-term medication use					
Proportions and adjusted ORs (all children in IVF vs. control group)					
1 (Klemetti et al., 2006)	3.3	2.8	1.2 (1.0 to 1.4)	-	Very low
Singletons					
1 (Klemetti et al., 2006)	2.9	2.8	1.0 (0.8 to 1.3)	-	Very low
Major birth defects					
Proportion and adjusted OR (all children in IVF vs. control group)					
1 (Hansen et al., 2002)	75/837 (9%)	168/4,000 (4.2%)	2.0 (1.3 to 3.2)	-	Very low

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Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Mother-child relationship problems					
Proportion and *P*-values (children in IVF vs. sterility vs. control group)					
	IVF	Sterility	Control		
1 (Raoul-Duval et al., 1994)	2/25 (8%)	0/11 (0%)	1/13 (8%)	NS	-	Very low
Neurological sequelae					
Proportions and adjusted ORs (IVF-ICSI twins vs. control twins)					
1 (Pinborg et al., 2004)	30/3,393 (0.9%)	98/10,239 (1.0%)	1.1 (0.7 to 1.6)	-	Very low
IVF-ICSI twins vs. IVF-ICSI singletons					
1 (Pinborg et al., 2004)	30/3,393 (0.9%)	42/5130 (0.8%)	1.0 (0.6 to 1.5)	-	Very low
Sepsis					
Number of cases and adjusted OR (children in IVF vs. control group)					
1 (Kallen et al., 2005)	43	3,388	1.1 (0.7 to 1.8)	-	Very low
Social problems					
Proportion with normal scores (<85th percentile) and *P*-value (IVF males vs. controls)					
1 (Montgomery et al., 1999)	93.8	85	0.99	-	Very low
Proportion with normal scores (>95th percentile) and *P*-value (IVF males vs. control group)					
1(Montgomery et al., 1999)	2.8	5	0.09	-	Very low
Suspected developmental delay					
Proportions and adjusted ORs (all children in IVF vs. control group)					
1 (Stromberg et al., 2002)	22/5,680 (0.4%)	11/11,360 (0.1%)	4.0 (1.9 to 8.3)	-	Very low
Singletons					
1 (Stromberg et al., 2002)	6/3228 (0.19%)	10 (.09%)	2.0 (0.7 to 5.4)	-	Very low
Thought problems					
Proportion with normal scores (<85th percentile) and *P*-value (IVF males vs. controls)					
1 (Montgomery et al., 1999)	94.7	85	0.99	-	Very low

Number of studies	Number of people		Effect		Quality
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	
Proportion with normal scores (>95th percentile) and *P*-value (IVF males vs. control group)					
1 (Montgomery et al., 1999)	1.1	5	0.99	-	Very low
URTI					
Number of cases and adjusted OR (children in IVF vs. control group)					
1 (Kallen et al., 2005)	891	95,112	1.2 (1.1 to 1.3)	-	Very low
Weight					
Percentiles and *P*-values (all children in IVF vs. control group)					
1 (Brandes et al., 1992)	32.6±28.7	36.1±38.5	NS	-	Very low

CI confidence interval, ICSI intracytoplasmic sperm injection, IVF in vitro fertilisation, OR odds ratio, SD standard deviation, URTI upper respiratory tract infections

Evidence statements

Long-term safety of IVF in women

Narrative summary

The five studies were graded as low or very low quality because of their methodological limitations. One of the studies reported significantly lower mortality rates in women undergoing IVF compared with the general population while three studies reported no association between undergoing IVF and long-term problems in women. One study found a significant increase in rates of borderline ovarian tumours associated with IVF.

Individual studies

One prospective cohort study found no association between IVF treatment and an increased incidence of breast tumour or carcinoma *in situ* of the cervix. The same study also found no association between IVF treatment and increased incidence of all invasive or all non-invasive tumours.

One cross-sectional study found no association between IVF treatment and an increased risk of cancer of the breast, cervix, ovary, other cancers (melanoma, Hodgkin's lymphoma, multiple myeloma, angiosarcoma, brain and sarcoma) or all cancers.

One prospective cohort study found no association between IVF treatment and death as a result of breast cancer in women. However, the same study found lower mortality rates due to diseases of the circulatory system, injury and poisoning, suicide, neoplasms and all causes in women who had undergone IVF treatment compared with women in the general population.

One retrospective cohort study found no association between IVF treatment and an increased risk of breast cancer.

One retrospective cohort study compared ovarian cancer rates of women who underwent IVF with women with subfertility who did not. The study found a significant increase in rates of borderline ovarian tumours associated with IVF.

Long-term outcomes in children born as a result of IVF

Narrative summary

Sixteen studies were found examining the association between IVF treatment of mothers and long-term health problems in children born as a result of this treatment. Studies reported on a range of

conditions, but with little commonality across studies. Therefore, where the same condition was examined there were often conflicting results. It is difficult to make conclusions based on the quality of evidence and conflicting results.

Individual studies

One retrospective cohort study found no significant difference in child disability allowance, long-term medication use, epilepsy, diabetes mellitus, asthma, allergy, pneumonia in IVF children compared with non-IVF children. There were significantly more cases of cerebral, behavioural disorders and total number of hospital episodes in IVF children compared with non-IVF children.

One retrospective cohort study found significantly more major birth defects in ICSI and IVF children compared with non-IVF children.

One retrospective cohort study found a significantly higher incidence of hypospadias in male IVF children compared with non-IVF male children.

One cross-sectional study no significant difference in cerebral palsy, mental retardation or neurological sequelae between IVF–ICSI twins and non IVF–ICSI twins.

Two retrospective cohort studies found an association between IVF treatment and the increased incidence of retinoblastoma in children.

One cross-sectional study found no difference in risk of childhood cancer between IVF and non-IVF. One retrospective cohort study found an increased risk of cerebral palsy and suspected developmental delay in IVF children compared with non-IVF children but found no difference in risk of mental retardation, chromosomal aberration or behavioural disorders between the two groups.

One prospective cohort study found no difference in performance skills, verbal skills or intelligence quotient between ICSI children, IVF children and children conceived spontaneously.

One cross-sectional study found no difference in performance IQ, verbal IQ or full scale IQ between ICSI children, IVF children and children conceived spontaneously.

One retrospective cohort study found an increased risk of epilepsy, behavioural problems, convulsions, upper respiratory tract infection, asthma/bronchitis, any accident and rate of hospitalisations in IVF children compared with non-IVF children. There was no difference in risk of mental retardation, cerebral palsy, sepsis, pneumonia, appendicitis or fracture between both groups.

One cross-sectional study found no difference in thought problems, internalising problems or externalising problems when male or female IVF children were compared with non-IVF children.

One cross-sectional study found that IVF children showed better performance in psychomotor development index compared with non-IVF children but there was no difference in mental development index between the two groups.

One prospective cohort study found that ICSI children showed significantly delayed mental development index compared with IVF or non-IVF children. There was no significant association between the type of conception and mean psychomotor development index in the three groups.

One prospective cohort study found no difference in infant accidents, illnesses, insomnia, feeding difficulties or mother–child relationship between children born after IVF, ovarian stimulation (without IVF) and natural conception.

One retrospective cohort study found no difference in mental development index scores, composite index scores, weight, head circumference and body length when IVF children were compared with non-IVF children.

Health economics profile

No health economic studies were identified on the long-term harms of IVF. Given that no definitive association was found between the treatment and increased long-term harm, no specific health economic analysis was undertaken.

Evidence to recommendations

Relative value placed on the outcomes considered

The studies reported in each chapter of this guideline address the short-term consequences of the various treatments for infertility, such as OHSS. This chapter confined itself to the long-term outcomes.

For the women receiving IVF the range of outcomes reported in these studies was greater than those reported in the ovulation induction and ovarian stimulation studies (see Section 20.2). Apart from reporting various forms of cancer, importantly they reported overall mortality rates and conditions such as circulatory disease and suicide. The GDG agreed that these are very important outcomes.

For the children born following IVF a large number of outcomes were reported. Those relating to childhood cancers and neuro-developmental disability were considered to be the most important.

The GDG did comment that although these studies did not directly report the long-term consequences of multiple births on families and the children, the results in respect of neuro-developmental disability in the children could be considered an appropriate surrogate.

Consideration of clinical benefits and harms

The included studies were undertaken to identify potential harms caused by IVF. Some studies did identify significant increases in long-term harms, but the limitations of the study designs means that the accuracy and generalisability of these findings is difficult to assess.

In the majority of the studies the reported absolute risk of harm was low.

Consideration of health benefits and resource uses

As no clear connection was identified between IVF and increased rates of serious long-term harm in women and children there are no resource implications.

Quality of evidence

Evidence was largely from retrospective observational studies mainly based on routine clinic databases. This type of data is liable to bias, the main one being that of context of patient selection. This makes case-mix adjustment essential as certain groups of subfertile women may be more prone to adverse events than control groups, but in many studies the case-mix was limited. The large number of comparisons undertaken means that there were likely to be a number of associations that were statistically significant. As a result data was graded as very low quality.

Other considerations

Volume of research

The GDG commented on the paucity of long-term research on the subject. The longest length of follow-up in the studies reviewed was 20 years with the larger studies having the shorter follow-up. The GDG commented that this was a disappointing feature of this review given that IVF was first undertaken over 30 years ago.

Study details

The GDG noted the following:

- It was not possible to distinguish the impact of the individual components of an IVF treatment strategy.
- The ‘control’ populations reported on in some studies were normally populations of infertile people rather than the general population.
- The outcomes were not reported according to whether or not the infertility treatment had been successful and resulted in a pregnancy.

Effect of age on outcome of pregnancy

The GDG highlighted that the greatest risk factor for short- or long-term harm associated with pregnancy was the age of the mother. The GDG stated there was a considerable evidence base showing that increasing maternal age is associated with an increased risk of adverse outcomes of pregnancy including (Schmidt et al., 2011; Montan, 2007):

- multiple pregnancy
- chromosomal abnormalities
- early pregnancy loss
- antepartum and postpartum haemorrhage
- pre-eclampsia
- gestational diabetes
- fetal growth restriction
- perinatal mortality
- preterm delivery
- caesarean section
- maternal death.

Older women considering IVF should be made aware of these risks (see Chapter 14).

Equalities

The people considered in this review were

- People who have vaginal intercourse.
- Specific patient subgroups listed in the guideline Scope that may need specific consideration:
    - people in same-sex relationships who have unexplained infertility after donor insemination
    - people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychological problem
    - people with conditions or disabilities that require specific consideration in relation to methods of conception.
- People who are preparing for cancer treatment who may wish to preserve their fertility.

There were no other specific issues that needed to be addressed with respect to any of these subgroups in the context of IVF treatment.

Recommendations

Number	Recommendation
210	Give people who are considering IVF treatment, with or without ICSI, up-to-date information about the long-term health outcomes (including the consequences of multiple pregnancy) of these treatments. **[new 2013]**
211	Inform women that while the absolute risks of long-term adverse outcomes of IVF treatment, with or without ICSI, are low, a small increased risk of borderline ovarian tumours cannot be excluded. **[new 2013]**
212	Inform people who are considering IVF treatment that the absolute risks of long-term adverse outcomes in children born as result of IVF are low. **[new 2013]**
213	Limit drugs used for controlled ovarian stimulation in IVF treatment to the lowest effective dose and duration of use. **[new 2013]**

Number	Research recommendation
RR 45	What are the long-term (over 20 years) effects of IVF with or without intracytoplasmic sperm injection in children in the UK? **Why this is important** This topic is important in informing patients, service providers and society at large about the potential long-term safety of assisted reproduction. Both IVF and intracytoplasmic sperm injection involve manipulation of egg and sperm in the laboratory, with theoretical impacts on the development of the subsequent embryo. However, while the first successful live birth following IVF was over 30 years ago, there is relatively little long-term research on the subject. In the review undertaken in this guideline update, the longest length of follow-up in the studies reviewed was 20 years, and the larger studies had shorter follow-up periods.

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22 Abbreviations and glossary

22.1 Abbreviations

AFC	antral follicle count
AI	artificial insemination
AIH	artificial insemination by husband's sperm
AMH	anti-Mullerian Hormone
ART	assisted reproduction technology
ARR	absolute risk reduction
AUC	area under curve
AUROC	area under the receiver operating characteristic curve
BMI	body mass index
BNF	British National Formulary
CBAVD	congenital bilateral absence of vas deferens
CC	clomifene citrate
CCCT	clomifene citrate challenge test
CI	confidence interval
COH	controlled ovarian hyperstimulation
DET	double embryo transfer
DH	Department of Health
DHEA	di-hydro-epi-androsterone
DI	donor insemination
DNA	deoxyribonucleic acid
E2	oestradiol
ELISA	enzyme-linked immunosorbent assay
EM	expectant management
ESHRE	European Society for Human Reproduction and Embryology
eSET	elective single embryo transfer
ET	embryo transfer
FSH	follicle-stimulating hormone
FSP	fallopian sperm perfusion
GH	growth hormone
GIFT	gamete intrafallopian transfer

GnRH	gonadotrophin-releasing hormone
GnRHa	gonadotrophin-releasing hormone agonist
GDG	guideline development group
GP	general practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRP	Guideline Review Panel
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
hCG	human chorionic gonadotrophin
HCHS	hospital and community health services
HCV	hepatitis C virus
HELLP	(a severe form of pre-eclampsia comprising) haemolysis, elevated liver enzymes and low platelets
HFEA	Human Fertilisation and Embryology Authority
hFSH	human follicle-stimulating hormone
HIV	human immunodeficiency virus
hMG	human chorionic gonadotrophin
hp-FSH	highly purified follicle-stimulating hormone
hp-hMG	highly purified human chorionic gonadotrophin
HR	hazard ratio
HSG	hysterosalpingography
HU12	Health State Utilities Index mark II
HyCoSy	hysterosalpingo-contrast-sonogaphy
ICER	incremental cost effectiveness ratio
ICI	intra cervical insemination
ICSI	intracytoplasmic sperm injection
IU	international units
IUI	intrauterine insemination
IVF	in vitro fertilisation
LCR	ligase chain reaction
LH	luteinising hormone
LOD	laparoscopic ovarian diathermy
LR	likelihood ratio
LSHTM	London School of Hygiene and Tropical Medicine
MESA	microsurgical epididymal sperm aspiration
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NICE	National Institute for Clinical Excellence
NHS	National Health Service

NPV	negative predictive value
OHSS	ovarian hyperstimulation syndrome
OR	odds ratio
OV	ovarian volume
pFSH	purified follicle-stimulating hormone
PCOS	polycystic ovary syndrome
PCR	polymerase chain reaction
PCT	primary care trust
PESA	percutaneous epididymal sperm aspiration
PPV	positive predictive value
PROST	pronucleate stage tubal transfer
QALY	quality adjusted life year
QUADAS	quality assessment of studies of diagnostic accuracy
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled (clinical) trial
RCP	Royal College of Pathologists
RCR	Royal College of Radiologists
rFSH	recombinant follicle-stimulating hormone
rhCG	recombinant human chorionic gonadotrophin
rhFSH	recombinant human follicle stimulating hormone
rhLH	recombinant human luteinising hormone
rLH	recombinant luteinising hormone
ROC-AUC	receiver operator characteristic for the area under the curve
RR	relative risk (or risk ratio)
SA	sensitivity analysis
SD	standard deviation
SET	single embryo transfer
TEFNA	testicular fine needle aspiration
TESA	testicular sperm aspiration
TESE	testicular sperm extraction
TVS/TVUS	trans-vaginal ultrasound
uhCG	urinary human chorionic gonadotrophin
uFSH	urinary follicle-stimulating hormone
uhMG	urinary human menopausal gonadotrophin
WHO	World Health Organization
WTP	willingness to pay
ZIFT	zygote intrafallopian transfer

22.2 Glossary

Absolute risk	Measures the probability of an event or outcome occurring (for example an adverse reaction to the drug being tested) in the group of people under study. Studies that compare two or more groups of patients may report results in terms of the Absolute risk reduction.
Absolute risk reduction (ARR)	The ARR is the difference in the risk of an event occurring between two groups of patients in a study: for example, if 6% of patients die after receiving a new experimental drug and 10% of patients die after having the old drug treatment then the ARR is 10% – 6% = 4%. Thus, by using the new drug instead of the old drug, there is a 4% reduction in the absolute risk of death. Here the ARR measures the risk reduction associated with a new treatment. See also Absolute risk.
Applicability	The extent to which the results of a study or review can be applied to the target population for a clinical guideline.
Appraisal of evidence	Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria.
Assisted hatching	An in vitro procedure in which the zona pellucida of an embryo is either thinned or perforated by chemical, mechanical or laser methods to assist separation of the blastocyst (Zegers-Hochschild et al., 2009)
Assisted reproduction	The collective name for treatments designed to lead to conception by means other than sexual intercourse. Assisted reproduction techniques include intrauterine insemination (IUI), in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI) and donor insemination (DI). The term 'assisted reproduction technology' (ART) is the term sometimes used to collectively describe these procedures and interventions.
Best available evidence	The strongest research evidence available to support a particular guideline recommendation.
Bias	Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually does not. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, for example in the collection, analysis, interpretation, publication or review of research data. For examples see Selection bias, Performance bias, Information bias, Confounding factors, Publication bias.
Biochemical pregnancy (preclinical spontaneous abortion/miscarriage)	A pregnancy diagnosed only by the detection of hCG in serum or urine and that does not develop into a clinical pregnancy (Zegers-Hochschild et al., 2009).
Blastocyst	An embryo, 5 or 6 days after fertilisation, with an inner cell mass, outer layer of trophectoderm and a fluid-filled blastocoele cavity (Zegers-Hochschild et al., 2009).
Blinding or masking	The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned; for example a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against bias. See also Double-blind study.

Cancelled cycle	An IVF cycle in which ovarian stimulation or monitoring has been carried out with the intention to treat but the woman does not proceed to follicular aspiration or, in the case of a thawed embryo, to embryo transfer (Zegers-Hochschild et al., 2009).
Case–control study	A study that starts with the identification of a group of individuals sharing the same characteristics (for example people with a particular disease) and a suitable comparison (control) group (in the same example this would be people without the disease). All subjects are then assessed with respect to things that happened to them in the past, such as things that might be related to getting the disease under investigation. Such studies are also called retrospective, as they look back in time from the outcome to the possible causes.
Case report (or case study)	Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.
Case series	Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical audit	Clinical audit is a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. Aspects of the structure, processes and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual, team or service level and further monitoring is used to confirm improvement in healthcare delivery.
Clinical effectiveness	The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical 'effectiveness' is not the same as efficacy.
Clinical governance	A framework through which NHS organisations are accountable for both continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.
Clinical impact	The effect that a guideline recommendation is likely to have on a treatment, or treatment outcomes, of the target population.
Clinical question	This term is sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way it is called a focused question.
Clinical pregnancy	A pregnancy diagnosed by ultrasonographic visualisation of one or more gestational sacs or definitive clinical signs of pregnancy. It includes ectopic pregnancy. Note: Multiple gestational sacs are counted as one clinical pregnancy. (Zegers-Hochschild et al., 2009)
Clinical pregnancy rate	The number of clinical pregnancies expressed per 100 initiated cycles, aspiration cycles or embryo transfer cycles. Note: When clinical pregnancy rates are given, the denominator (initiated, aspirated or embryo transfer cycles) must be specified. (Zegers-Hochschild et al., 2009)
Clinician	A healthcare professional providing patient care, for example a doctor, nurse/midwife or physiotherapist.

Clinical trial	A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses controlled clinical trials and randomised controlled trials.
Cochrane Collaboration	An international organisation in which people find, appraise and review specific types of studies called randomised controlled trials. The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of health issues and is available electronically as part of the Cochrane Library.
Cochrane Library	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration). The Cochrane Library is available on CD-ROM and the Internet.
Cohort	A group of people sharing some common characteristic (such as patients with the same disease), followed up in a research study for a specified period of time.
Cohort study	An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that these patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, for example comparing mortality between one group that received a specific treatment and one group that did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.
Co-morbidity	Co-existence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.
Confidence interval	A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that is consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.
Confounder or confounding factor	Something that influences a study and can contribute to misleading findings if it is not understood or appropriately dealt with. For example, if a group of people who are exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could well be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.
Congenital anomalies/abnormalities	All structural, functional, and genetic anomalies diagnosed in aborted fetuses, at birth or in the neonatal period. (Zegers-Hochschild et al., 2009)

Consensus methods	A variety of techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic.
Consensus statement	A statement of the advised course of action in relation to a particular clinical topic, based on the collective views of a body of experts.
Considered judgement	The application of the collective knowledge of a guideline development group to a body of evidence, to assess its applicability to the target population and the strength of any recommendation that it would support.
Consistency	The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment), in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A controlled clinical trial where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost effectiveness	A type of economic evaluation that assesses the additional costs and benefits of doing something different. In cost effectiveness analysis, the costs and benefits of different treatments are compared. When a new treatment is compared with current care, its additional costs divided by its additional benefits is called the cost effectiveness ratio. Benefits are measured in natural units, for example cost per additional heart attack prevented.
Cost utility analysis	A special form of cost effectiveness analysis where benefit is measured in quality adjusted life years. A treatment is assessed in terms of its ability to extend or improve the quality of life.
Couple	Two people in a partnership, irrespective of gender and sexual orientation, who wish to have a baby but are having difficulty conceiving and are having investigations and possible treatment for infertility.
Cross-sectional study	The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a longitudinal study, which follows a set of people over a period of time.)
Cryopreservation	The freezing and storage of embryos, sperm or eggs for future use in IVF treatment cycles. The technique of controlled rate slow freezing is well established; vitrification is a newer ultra-rapid freezing process.
Declaration of interest	A process by which members of a working group or committee 'declare' any personal or professional involvement with a company (or related to a technology) that might affect their objectivity; for example if their position or department is funded by a pharmaceutical company.
Donor insemination	The placement of donor sperm into the vagina, cervix or womb.

Double blind study	A study in which neither the subject (patient) nor the observer (investigator or clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.
Economic evaluation	Comparative analysis of alternative courses of action in terms of both their costs and consequences.
Efficacy	The extent to which a specific treatment or intervention, under ideally controlled conditions (for example in a laboratory), has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care.
Elective	Name for clinical procedures that are regarded as advantageous to the patient but not urgent.
Embryo	The product of the division of the zygote to the end of the embryonic stage, eight weeks after fertilization. (Zegers-Hochschild et al., 2009)
Embryo transfer	The procedure in which one or more embryos are placed in the uterus or Fallopian tube. (Zegers-Hochschild et al., 2009)
Epidemiology	Study of diseases within a population, covering the causes and means of prevention
Evidence based	The process of systematically finding, appraising and using research findings as the basis for clinical decisions.
Evidence-based clinical practice	Evidence-based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence-based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research.
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
External validity	The degree to which the results of a study hold true in non-study situations, for example in routine clinical practice. May also be referred to as the generalisability of study results to non-study patients or populations.
Extrapolation	The application of research evidence based on studies of a specific population to another population with similar characteristics.
Exclusion criteria	See Selection criteria.
Expectant management	This is a formal approach that encourages conception through unprotected vaginal intercourse. It involves supportively offering an individual and/or copule information and advice about the regularity and timing of intercourse and any lifestyle changes which might improve their chances of conceiving. This approach does not involve any active clinical or therapeutic interventions.
Experimental study	A research study designed to test whether a treatment or intervention has an effect on the course or outcome of a condition or disease, where the conditions of testing are to some extent under the control of the investigator. Controlled clinical trial and randomised controlled trial are examples of experimental studies.
Fertilization	The penetration of the ovum by the spermatozoon and combination of their genetic material resulting in the formation of a zygote. (Zegers-Hochschild et al., 2009)

Forest plot	A graphical display of results from individual studies on a common scale, allowing visual comparison of results and examination of the degree of heterogeneity between studies.
Full cycle	This term is used to define a full IVF treatment, which should include one episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s).
Gamete intrafallopian transfer	A procedure in which eggs are retieved from a woman, mixed with sperm and immediately replaced in one or other of the woman's fallopian tubes so that they fertilise inside the body.
Generalisability	The extent to which the results of a study hold true for a population of patients beyond those who participated in the research. See also External validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the the best available for treating or diagnosing a particular condition.
Good practice point	Recommended good practice based on the expert experience of the guideline development group (and possibly incorporating the expertise of a wider reference group). A guideline development group may produce a 'Good practice point' (rather than an evidence based recommendation) on an important topic when there is a lack of research evidence.
Gonadotrophins	Hormones that stimulate the ovaries.
Grade of recommendation	A code (for example A, B, C, D) linked to a guideline recommendation, indicating the strength of the evidence supporting that recommendation.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in bibliographic retrieval systems.
Guideline	A systematically developed document which describes aspects of a patient's condition and the care to be given. A good guideline makes recommendations about treatment and care, based on the best research available, rather than opinion. It is used to assist clinician and patient decision-making about appropriate health care for specific clinical conditions.
Health economics	A field of conventional economics that examines the benefits of healthcare interventions (such as medicines) compared with their financial costs.
Health technology	Health technologies include medicines, medical devices such as artificial hip joints, diagnostic techniques, surgical procedures, health promotion activities (for example the role of diet versus medicines in disease management) and other therapeutic interventions.
Health Technology Appraisal	A health technology appraisal, as undertaken by NICE, is the process of determining the clinical and cost effectiveness of a health technology. NICE health technology appraisals are designed to provide patients, health professionals and managers with an authoritative source of advice on new and existing health technologies.
Heterogeneity	Lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different, in terms of the size of treatment effects, or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow up. Heterogeneity is often reported as an I^2 value.
Hierarchy of evidence	An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions that can be drawn from a well conducted study. Well conducted randomised controlled trials (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs which are in agreement

	represent stronger evidence than, say, one small RCT.) Well conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence.
Homogeneity	Where the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Inclusion criteria	See Selection criteria.
Inferitilty	In practice infertility is defined as the period of time people have been trying to conceive without success after which formal investigation is justified and possible treatment implemented. This 'assessment and possible treatment' threshold is: • 1 year for a woman of reproductive age who has not conceived • 6 cycles of artificial insemination for a woman of reproductive age who is having artificial inseminationto conceive (using either partner or donor sperm) • Earlier in women when: o the woman is 36 years or more o there is a known clinical cause of infertility or a history of predisposing factors for infertility.
Information bias	Pertinent to all types of study and can be caused by inadequate questionnaires (for example containing difficult or biased questions), observer or interviewer errors (such as lack of blinding), response errors (such as lack of blinding if patients are aware of the treatment they receive) and measurement error (for example a faulty machine).
Implantation	The attachment and subsequent penetration by the zona-free blastocyst (usually in the endometrium) that starts five to seven days after fertilisation. (Zegers-Hochschild et al., 2009)
Intention to treat analysis	An analysis of a clinical trial where patients are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they had dropped out, fully complied with the treatment, or crossed over and received the alternative treatment. Intention-to-treat analyses are favoured in assessments of clinical effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the treatment is used in practice.
Internal validity	Refers to the integrity of the study design.
Intervention	Healthcare action intended to benefit the patient, for example drug treatment, surgical procedure or psychological therapy.
Intra-cervical insemination	Clinical delivery of sperm into the cervical os.
Intracytoplasmic sperm injection	A variation of in vitro fertilisation in which a single sperm is injected into the inner cellular structure of an egg.
Intrauterine insemination	Clinical delivery of sperm into the uterine cavity.
In vitro fertilisation	A technique whereby eggs are collected from a woman and fertilised with a man's sperm outside the body. Usually, one or two resulting embryos are then transferred to the womb with the aim of starting a pregnancy.
Level of evidence	A code (for example 1a, 1b) linked to an individual study, indicating where it fits into the hierarchy of evidence and how well it has adhered to recognised research principles.
Literature review	A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.

Live full-term singleton birth	The complete expulsion or extraction from its mother of a product of fertilisation, which, after such separation, breathes or shows any other evidence of life such as heart beat, umbilical cord pulsation, or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached. (Zegers-Hochschild et al., 2009)
Live birth delivery rate	The number of pregnancies that resulted in at least one live born baby expressed per 100 initiated cycles, aspiration cycles or embryo transfer cycles. When delivery rates are given, the denominator (initiated, aspirated, or embryo transfer cycles) must be specified. (Zegers-Hochschild et al., 2009)
Longitudinal study	A study of the same group of people at more than one point in time. (This type of study contrasts with a cross-sectional study, which observes a defined set of people at a single point in time.)
Masking	See Blinding.
Meta-analysis	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible, for example because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also Systematic review and Heterogeneity.
Mild male factor infertility	The term 'mild' male factor infertility is used extensively in practice and in the literature. However, no formally recognised definition of what this means is currently available. Therefore, where the term 'mild' male factor infertility is applied in this guideline, it is defined as meaning: two or more semen analyses that have one or more variables which fall below the 5th centile as defined by WHO, 2010, and where the effect on the chance of pregnancy occurring naturally through vaginal intercourse within a period of 24 months would then be similar to people with unexplained infertility or mild endometriosis.
Methodological quality	The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.
Multicentre study	A study where subjects were selected from different locations or populations, such as a co-operative study between different hospitals or an international collaboration involving patients from more than one country.
Natural cycle IVF	An IVF procedure in which one or more oocytes are collected from the ovaries during a spontaneous menstrual cycle without any drug use. (Zegers-Hochschild et al., 2009)
Non-experimental study	A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.
Nulliparous	Having never given birth to a viable infant.
Observational study	In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (such as whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (such as whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way of representing probability. In recent years odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a confidence interval) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks and not odds) will be very similar. See also Relative risk, Risk ratio.

Outcome	The end result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.
Oocyte donation	The process by which a fertile woman donates her eggs to be used in the treatment of others or for research.
Ovarian Hyper-Stimulation Syndrome (OHSS)	An exaggerated systemic response to ovarian stimulation characterised by a wide spectrum of clinical and laboratory manifestations. It is classified as mild, moderate or severe according to the degree of abdominal distention, ovarian enlargement and respiratory, haemodynamic and metabolic complications. (Zegers-Hochschild et al., 2009)
Ovulation induction	Stimulation of the ovary to achieve growth and development of immature ovarian follicles (ideally monofollicular development) to reverse anovulation or oligo-ovulation.
Parous	Having borne at least one viable offspring.
Peer review	Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional, patient and carer representatives.
Pilot study	A small-scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study in order to highlight any problems or areas of concern, which can then be addressed before the full-scale study begins.
Placebo	Placebos are fake or inactive treatments received by participants allocated to the control group in a clinical trial, which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any placebo effect due to receiving care or attention.
Placebo effect	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
Power	See Statistical power.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
P value	If a study is done to compare two treatments then the *P* value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there is no difference between treatments is called the 'null hypothesis'.) In an example where the *P* value was 0.03, if there really was no difference between treatments, there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low, the validity of the assumption that there really is no difference between treatments should be questionned, with the conclusion that there probably is a difference between treatments. By convention, where the value of *P* is below 0.05 (that is, less than 5%) the result is seen as statistically significant. Where the value of *P* is 0.001 or less, the result is seen as highly significant. Hence *P* values tell us whether an effect can be regarded as statistically significant or not but do not relate to how big the effect might be, which is indicated by the confidence interval.
Qualitative research	Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates nonnumerical

	data, such as a patient's description of their pain rather than a measure of pain. In health care, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organisations. Qualitative research techniques, such as focus groups and in-depth interviews, have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the National Census, which counts people and households.
Random allocation or randomisation	A method that uses the play of chance to assign participants to comparison groups in a research study, for example by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions.
Randomised controlled trial	A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)
Relative risk	A summary measure which represents the ratio of the risk of a given event or outcome (such as an adverse reaction to the drug being tested) in one group of subjects compared with another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for risk ratio.
Reliability	Reliability refers to a method of measurement that consistently gives the same results. For example, someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession and if their assessments tend to agree then the method of assessment is said to be reliable.
Reproductive age	This is the period of time when women can reproduce and have babies.The ages of the menarche and menopause vary but on average currently they are 12 years and 51 years respectively. For the first 2–3 years after the menarche and the last 2–3 years before the menopause, women are anovulatory and infertile.
Retrospective study	A retrospective study deals with the present and past and does not involve studying future events. This contrasts with studies that are prospective.
Risk ratio	Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group. The term relative risk is sometimes used as a synonym of risk ratio.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.

Sample	A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole. Sampling refers to the way participants are selected for inclusion in a study.
Selection bias	Selection bias has occurred if: • the characteristics of the sample differ from those of the wider population from which the sample has been drawn; OR • there are systematic differences between comparison groups of patients in a study in terms of prognosis or responsiveness to treatment.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Semi-structured interview	Structured interviews involve asking people pre-set questions. A semi-structured interview allows more flexibility than a structured interview. The interviewer asks a number of open-ended questions, following up areas of interest in response to the information given by the respondent.
Statistical power	The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a *P* value of less than 5% in a statistical test (that is, a statistically significant treatment effect) if there really was an important difference (for example 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also *P* value.
Structured interview	A research technique where the interviewer controls the interview by adhering strictly to a questionnaire or interview schedule with pre-set questions.
Study population	People who have been identified as the subjects of a study.
Survey	A study in which information is systematically collected from people (usually from a sample within a defined population).
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a meta-analysis.
Target population	The people to whom guideline recommendations are intended to apply. Recommendations may be less valid if applied to a population with different characteristics from the participants in the research study, for example in terms of age, disease state or social background.
Validity	Assessment of how well a tool or instrument measures what it is intended to measure.