Università degli Studi di Padova
Dipartimento di salute della donna e del bambino – SDB
U.O.C. Clinica Ginecologica ed Ostetrica
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Giovanni Battista Nardelli

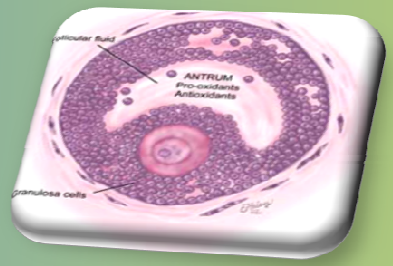
EFFECTS OF RECOMBINANT-LH SUPPLEMENTATION ON THE PROTEOMIC PROFILE OF FOLLICULAR FLUID FROM POOR RESPONDER PATIENTS: FOCUS ON FOLLICULAR GROWTH FACTORS AND OOCYTE MATURITY MARKERS

M. Noventa M.D.

UNIVERSITÀ DEGLI STUDI DI PADOVA

University of Padua
Woman and Child Health Department
Gynecologic and Obstetric Unit

BACKGROUND



Sped. abb. post. 70% DBC - PADOVA

REGIONE DEL VENETO - GIUNTA REGIONALE

REPUBBLICA ITALIANA

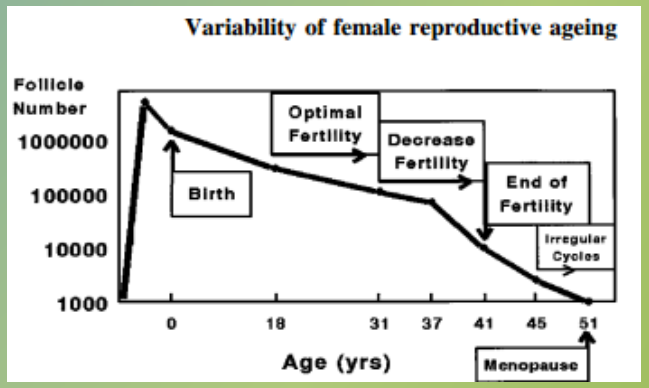
BOLLETTINO UFFICIALE

REGIONE DEL VENETO

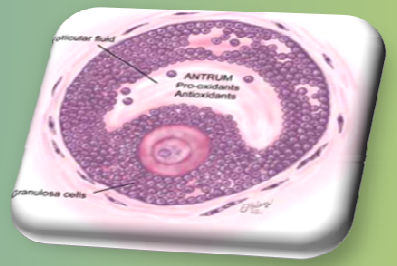
Venezia, venerdì 8 luglio 2011 — Anno XLII - N. 49

- l'età di accesso delle coppie sia così determinato:
  - età femminile fino al compimento di 50 anni
  - età maschile fino a compimento di 65 anni
- il numero dei cicli sia così determinato:
  - 4 cicli di trattamento di 1° livello nei limiti di dosaggio previsti dalla nota AIFA 74
  - 3 cicli di trattamento di 2° livello (pazienti arrivate ad eseguire il Pick up) nei limiti di dosaggio previsti dalla nota AIFA 74.

Circa l'età di accesso per le donne, essa viene determinata come sopra riportato in quanto si ritiene opportuno tener conto dell'aspettativa di vita in crescita, degli sviluppi della ricerca scientifica e quindi dare una maggiore opportunità alle donne.



BACKGROUND



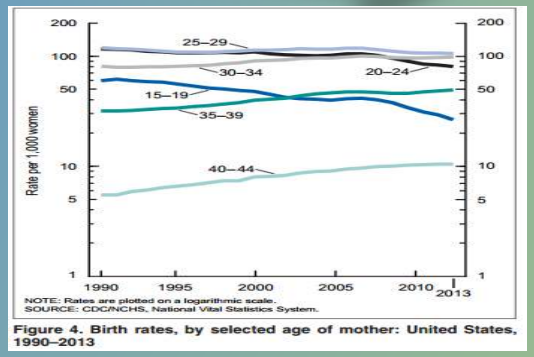
National Vital Statistics Reports

Volume 64, Number 1 — January 15, 2015

Births: Final Data for 2013

by Joyce A. Martin, M.P.H.; Brady E. Hamilton, Ph.D.; Michelle J.K. Osterman, M.H.S.; Sally C. Curtin, M.A.; and T.J. Mathews, M.S., Division of Vital Statistics

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for Health Statistics
National Vital Statistics System



NOTE: Rates are plotted on a logarithmic scale.
SOURCE: CDC/NCHS, National Vital Statistics System.

Figure 4. Birth rates, by selected age of mother: United States, 1990–2013

statistiche report

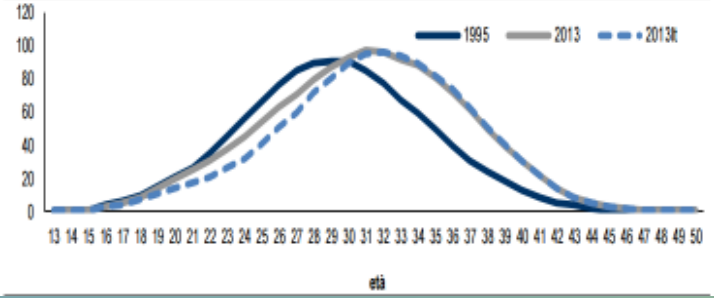
27 novembre 2014

Istat

Si diventa madri sempre più tardi

La distribuzione delle nascite per età della madre consente di mettere in evidenza lo spostamento della maternità verso età sempre più avanzate, caratteristica questa ancora più evidente per le madri di cittadinanza italiana (Prospetto 4). La posticipazione delle nascite ha contribuito al forte abbassamento della natalità osservato nel nostro Paese dalla seconda metà degli anni Settanta alla prima metà degli anni Novanta. Successivamente si è registrato un parziale recupero delle nascite precedentemente rinviate, in particolare da parte delle baby-boomers, che si è tradotto in un progressivo aumento delle nascite da madri con più di 35 anni, ravvisabile soprattutto al Nord e al Centro. Nel 2013 le donne hanno in media 31.5 anni alla nascita dei figli, oltre un anno e mezzo in più rispetto al 1995 (29,8), valore che sale a 32,1 anni per le madri di cittadinanza italiana.

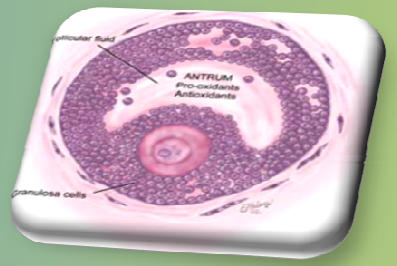
FIGURA 4. TASSI DI FECONDITÀ SPECIFICI PER ETÀ DELLE DONNE RESIDENTI IN ITALIA. Anni 1995 e 2013, valori per 1.000 donne



PROSPETTO 4. NATI PER CLASSI DI ETÀ DELLA MADRE E REGIONE. Anno 2013

REGIONI	Classi di età della madre								Totale	Totale madri		Madri italiane	
	<18	18-19	20-24	25-29	30-34	35-39	40-44	45 e +		< 25	>=40	< 25	>=40
	valori assoluti									valori percentuali			
TALIA	1.922	6.163	47.669	114.955	171.151	132.613	36.852	2.983	514.308	10,8	7,7	8,4	8,7

BACKGROUND



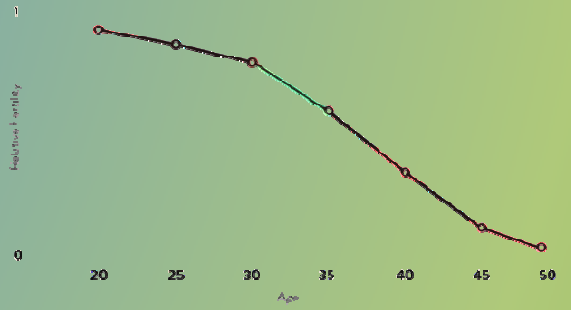
Human Reproduction, Vol.26, No.11 pp. 3063–3071, 2011
Advanced Access publication on September 9, 2011 doi:10.1093/humrep/der304

human reproduction ORIGINAL ARTICLE *Infertility*

The fertility myth: Israeli students' knowledge regarding age-related fertility decline and late pregnancies in an era of assisted reproduction technology

Yael Hashiloni-Dolev[1,*], Amit Kaplan[1], and Shiri Shkedi-Rafid[2,3]

DISINFORMATION



This epidemiological and social trend has not been compensated by biological changes of women reproductive life and so, **numerous couples, suffering from age-related infertility due to a *diminished ovarian reserve*** (OR), **turn to assisted reproductive technologies** (ART)

Tutte le tecniche (I, II, III livello e scongelamento embrioni e ovociti)							2005-2012	
N° di coppie trattate	46.519	52.206	55.437	59.174	63.840	69.797	73.570	72.543
N° di cicli iniziati	63.585	70.695	75.280	79.125	85.385	90.944	96.427	93.634
N° di gravidanze ottenute	9.499	10.608	11.685	12.767	14.033	15.274	15.467	15.670
N° di gravidanze monitorate	5.392	8.108	9.884	10.825	11.691	13.537	13.395	13.484
% di gravidanze perse al follow-up	43,2	23,6	15,4	15,2	16,7	11,4	13,4	14,0
N° parti	4.033	6.148	7.513	8.319	8.896	10.387	10.065	10.101
N° di nati vivi	4.940	7.507	9.137	10.212	10.819	12.506	11.933	11.974

BACKGROUND

8° REPORT

ATTIVITÀ DEL REGISTRO NAZIONALE ITALIANO DELLA PROCREAZIONE MEDICALMENTE ASSISTITA

2012

Figura 2.20: Distribuzione dei cicli a fresco (FIVET-ICSI) per classi di età delle pazienti. Anni 2005-2012.

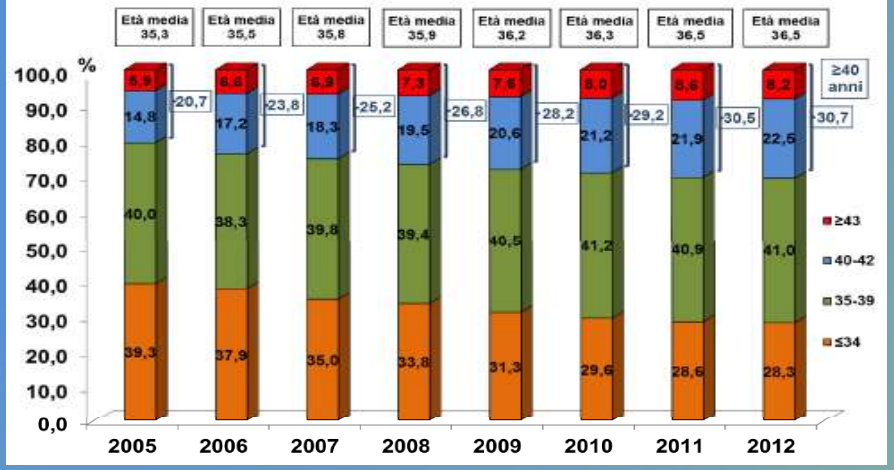
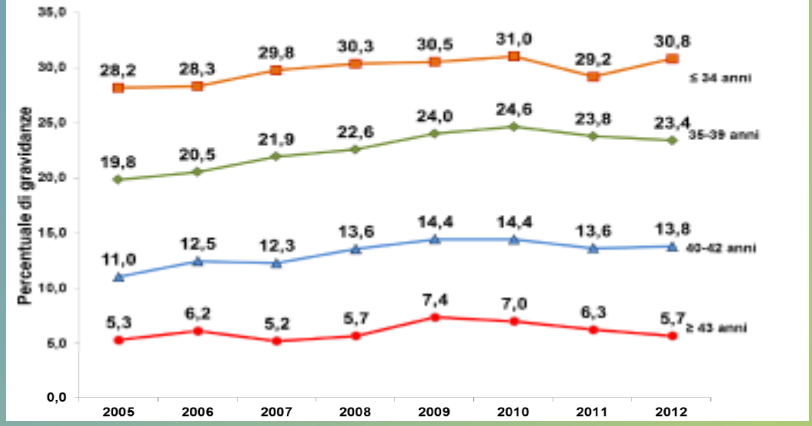
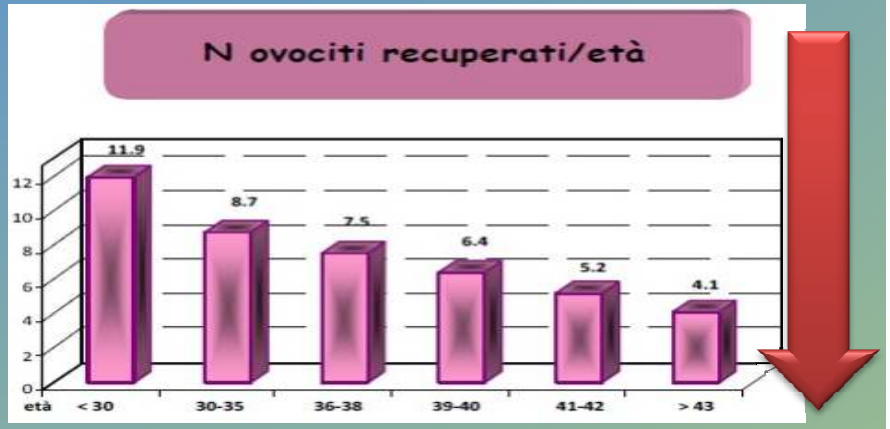
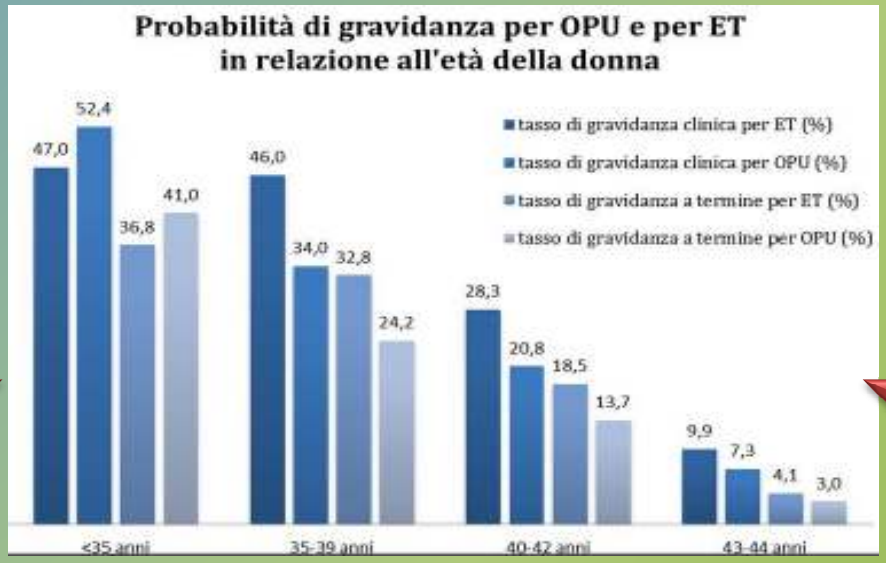


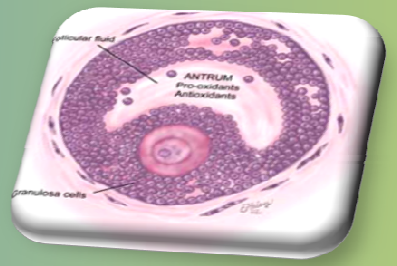
Figura 2.28: Percentuali di gravidanza sui prelievi da tecniche a fresco (FIVET e ICSI) per classi di età delle pazienti. Anni 2005-2012.







BACKGROUND



Original Article

Ovarian Reserve Test: An Impartial Means to Resolve the Mismatch Between Chronological and Biological Age in the Assessment of Female Reproductive Chances

Salvatore Gizzo, MD[1], Alessandra Andrisani, MD, PhD[1], Federica Esposito, MD[1], Alessandra Oliva, BS[1], Cecilia Zicchina, BS[1], Denise Capuzzo, MD[1], Michele Gangemi, MD[1], and Giovanni Battista Nardelli, MD[1]

Reproductive Sciences
2014, Vol. 21(5) 633-639
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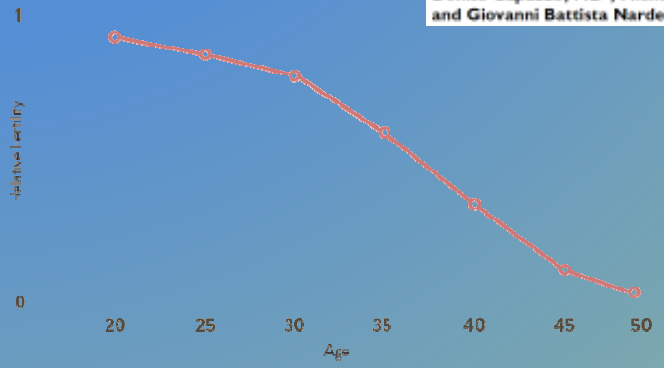


Human Reproduction, Vol.26, No.7 pp. 1616–1624, 2011
Advanced Access publication on April 19, 2011 doi:10.1093/humrep/der092
human reproduction
ESHRE PAGES

ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: the Bologna criteria†

A.P. Ferraretti[1,*], A. La Marca[2], B.C.J.M. Fauser[3], B. Tarlatzis[4], G. Nargund[5], and L. Gianaroli[1] on behalf of the ESHRE working group on Poor Ovarian Response Definition‡

Results: POR definition

Following the same logical approach utilized for polycystic ovarian syndrome (PCOS) diagnostic criteria (The Rotterdam ESHRE/American Society for Reproductive Medicine (ASRM) Sponsored PCOS Consensus Workshop Group, 2004), a consensus was reached on the minimal criteria needed to define POR.

At least two of the following three features must be present:

(i) Advanced maternal age (≥40 years) or any other risk factor for POR;

(ii) A previous POR (≤3 oocytes with a conventional stimulation protocol);

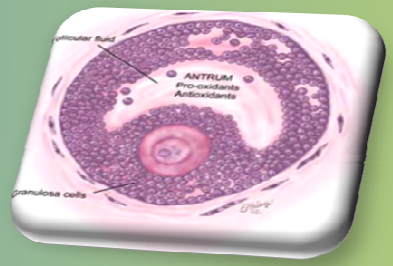
(iii) An abnormal ovarian reserve test (i.e. AFC <5–7 follicles or AMH <0.5–1.1 ng/ml).

Two episodes of POR after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT.

By definition, the term POR refers to the ovarian response and, therefore, one stimulated cycle is considered essential for the diagnosis of POR. However, patients over 40 years of age with an abnormal ORT may be dassified as poor responders since both advanced age and an abnormal ORT may indicate reduced ovarian reserve and act as a surrogate of ovarian stimulation cycle. In this case, the patients should be more properly defined as expected PORs.

.....Diagnosis

BACKGROUND



Research Article

Female Aging Alters Expression of Human Cumulus Cells Genes that Are Essential for Oocyte Quality

Tamadir Al-Edani,[1,2] Said Assou,[1,2] Alice Ferrières,[1,2] Sophie Bringer Deutsch,[1,3] Anna Gala,[1,3] Charles-Henri Lecellier,[4] Ounissa Aït-Ahmed,[1,2] and Samir Hamamah[1,2,3]

Apoptosis (2013) 18:201–211
DOI 10.1007/s10495-012-0783-5

ORIGINAL PAPER

The apoptotic transcriptome of the human MII oocyte: characterization and age-related changes

SPECIAL TOPIC
• REVIEW •
August 2012 Vol.55 No.8: 670–678
doi: 10.1007/s11427-012-4594-3

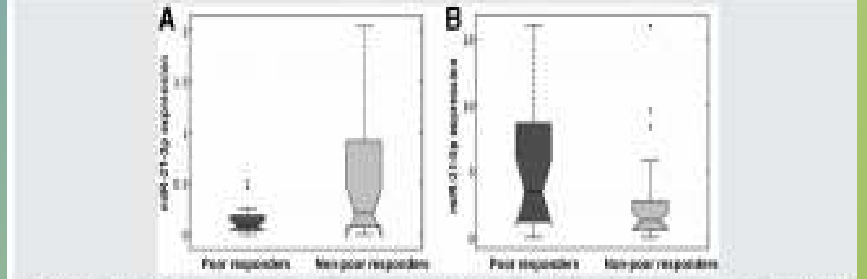
Epigenetic changes associated with oocyte aging

LIANG XingWei[1,2], MA JunYu[1], SCHATTEN Heide[3] & SUN QingYuan[1*]

Poor ovarian response in women undergoing in vitro fertilization is associated with altered microRNA expression in cumulus cells

Cengiz Karakaya, Ph.D.,[a,b] Ozlem Guzeloglu-Kayisli, Ph.D.,[a] Asli Uyar, Ph.D.,[a,c] Amanda N. Kallen, M.D.,[a] Elnur Babayev, M.D.,[a] Nuray Bozkurt, M.D.,[b] Evrim Unsal, Ph.D.,[d] Onur Karabacak, M.D.,[b] and Emre Seli, M.D.[a]

FIGURE 1

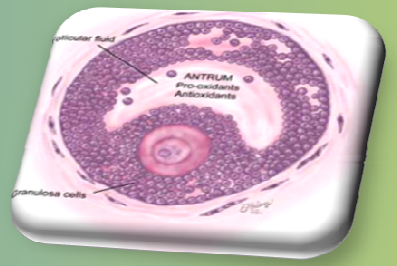


The distributions of miR-21 expression according to ovarian response are shown as box plots. (A) miR-21-5p expression is significantly lower in the poor-responder group ($P < .05$). (B) miR-21-3p expression is significantly higher in the poor-responder group ($P < .01$). The shaded area and the error bars represent 75% and 95%, respectively.

Fertility and Sterility Poor ovarian response and microRNA Vol. 99, No. 6, May 2013

..... Pathogenesis

BACKGROUND



Reproductive BioMedicine Online (2015) 30, 581–592

www.sciencedirect.com
www.rbmonline.com

ELSEVIER

ARTICLE

How to define, diagnose and treat poor responders? Responses from a worldwide survey of IVF clinics

Pasquale Patrizio [a,*], Alberto Vaiarelli [b], Paolo E Levi Setti [c], Kyle J Tobler [d], Gon Shoham [e], Milton Leong [f], Zeev Shoham [g,h]

A total of 272 IVF units from 45 countries responded to the survey. Of those, responses from 196 units met the quality-assurance parameters representing a total of 124,700 IVF cycles.

Table 7 Estimated proportion of poor ovarian response patients seen within respondent IVF clinics.

Estimated proportion of poor ovarian response patients treated at the IVF clinic (%)	*Number of respondent-cycles (%)*
<5	3000 (2)
6–10	51,700 (41)
11–15	28,000 (22)
16–20	23,900 (19)
21–25	7500 (6)
26–30%	10,100 (8)
>30	500 (0)

Table 9 The combinations of gonadotrophins used in IVF protocols designed specifically for patients with poor ovarian reserve.

Gonadotrophin combinations	*Number of respondent-cycles (%)*
rFSH and hMG	53,100 (43)
hMG alone	25,500 (20)
rFSH alone	25,100 (20)
rFSH and rLH	11,700 (9)
rFSH and low dose hCG	7200 (6)
None of the above	2100 (2)

HCG = human chorionic gonadotrophin; HMG = human menopausal gonadotropin; rFSH = recombinant follicle stimulating hormone; rLH = recombinant luteinizing hormone.

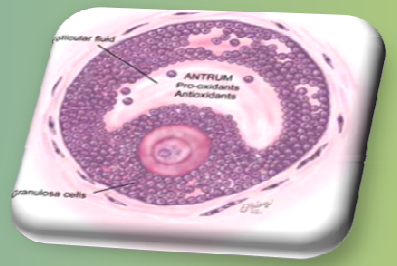
Table 8 The preferred IVF protocol for poor ovarian responders.

Protocol used	*Number of respondent-cycles (%)*
No GnRH analogues	1200 (1)
GnRH agonist using a flexible regimen	2500 (2)
GnRH agonist, long protocol	11,800 (9)
GnRH agonist microdose, short protocol	18,900 (15)
GnRH agonist, short protocol	25,400 (20)
GnRH antagonist protocol	64,900 (52)

GnRH = gonadotrophin-releasing hormone.

..... Treatment?????????????

BACKGROUND



GYNECOLOGICAL ENDOCRINOLOGY

http://informahealthcare.com/gye
ISSN: 0951-3590 (print), 1473-0766 (electronic)

Gynecol Endocrinol, Early Online: 1–5
© 2014 Informa UK Ltd. DOI: 10.3109/09513590.2014.997228

informa healthcare

REVIEW ARTICLE

Poor responders in IVF: an update in therapy

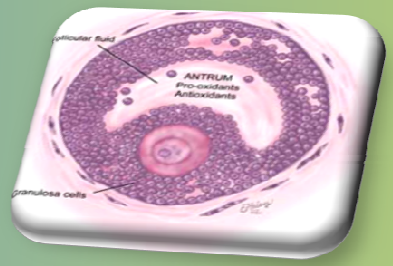
V. Giovanale, F. M. Pulcinelli, E. Ralli, F. M. Primiero, and D. Caserta

..... Treatment??????????????

Table 1. Different studies and therapeutic approaches on pharmacological treatment for poor responders patients.

Therapy	Author	Year	Positive results for POR in IVF
Modified flare protocol versus modified long protocol	Weissman et al.	2003	A modified long "mini-dose" protocol
Standard long protocol (group A) versus GnRH antagonist (group B)	Marci et al.	2005	Group B
GnRH antagonist (GnRH-ant) versus GnRH agonist (GnRH-a)	Pu et al.	2011	GnRH-ant.
Flare-up versus GnRH-antagonist	Malmusi et al.	2005	Flare-up treatment
GnRH antagonist multidose protocol versus standard long agonist protocol	Tazegul et al.	2008	Non-significant results
Microdose GnRH agonist (GnRH-a) flare-up versus multiple dose GnRH antagonist protocols	Kahraman et al.	2009	Non-significant results
GnRH agonist versus GnRH antagonist	Xiao et al.	2013	GnRH antagonist
GnRH antagonist and recombinant LH (rLH) versus GnRH agonist	De Placido et al.	2006	GnRH antagonist and recombinant LH (rLH)
Natural-cycle IVF versus microdose GnRH analog flare.	Morgia et al.	2004	Non-significant results
Dehydroepiandrosterone (DHEA) supplementation before the first cycle of IVF	Wiser	2010	DHEA supplementation
GH administration in therapeutic protocols with GnRH-a and gonadotropins	Kolibianakis	2009	GH administration in therapeutic protocols with GnRH-a and gonadotropins
Low-dose hCG alone to replace FSH-containing gonadotropins	Filicori et al.	2009	Low-dose hCG
Effects of addition or modulation of androgens	Sunkara	2011	Non-significant results
rLH or low-dose rhCG supplementation administered in the midfollicular phase in microdose GnRH-a flare-up cycles	Berkkanoglu	2007	Non-significant results
Combination rFSH or rLH in ovarian stimulation	Barrenetxea	2008	rLH
Combination of clomiphene citrate (CC) with rFSH	D'Amato G.	2004	Combination of CC with rFSH
Transdermal testosterone	Massin	2006	Non-significant results
Transdermal testosterone	Fábregues	2009	Transdermal testosterone
Transdermal testosterone	Chung-Hoon	2011	Transdermal testosterone
Incorporation of letrozole	Goswami	2004	Incorporation of letrozole
GnRH antagonist protocol, using ganirelix acetatate, versus a microdose GnRH agonist	Schmidt	2005	Non-significant results
Incorporation of adjuvant low-dose aspirin	Lok	2004	Non-significant results

BACKGROUND



Recombinant-LH supplementation

Bühler et al. Reproductive Biology and Endocrinology 2014, 12:6
http://www.rbej.com/content/12/1/6

RBE REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

RESEARCH Open Access

A large, multicentre, observational, post-marketing surveillance study of the 2:1 formulation of follitropin alfa and lutropin alfa in routine clinical practice for assisted reproductive technology

Klaus Bühler[1*], Olaf GJ Naether[2] and Wilma Bilger[2]

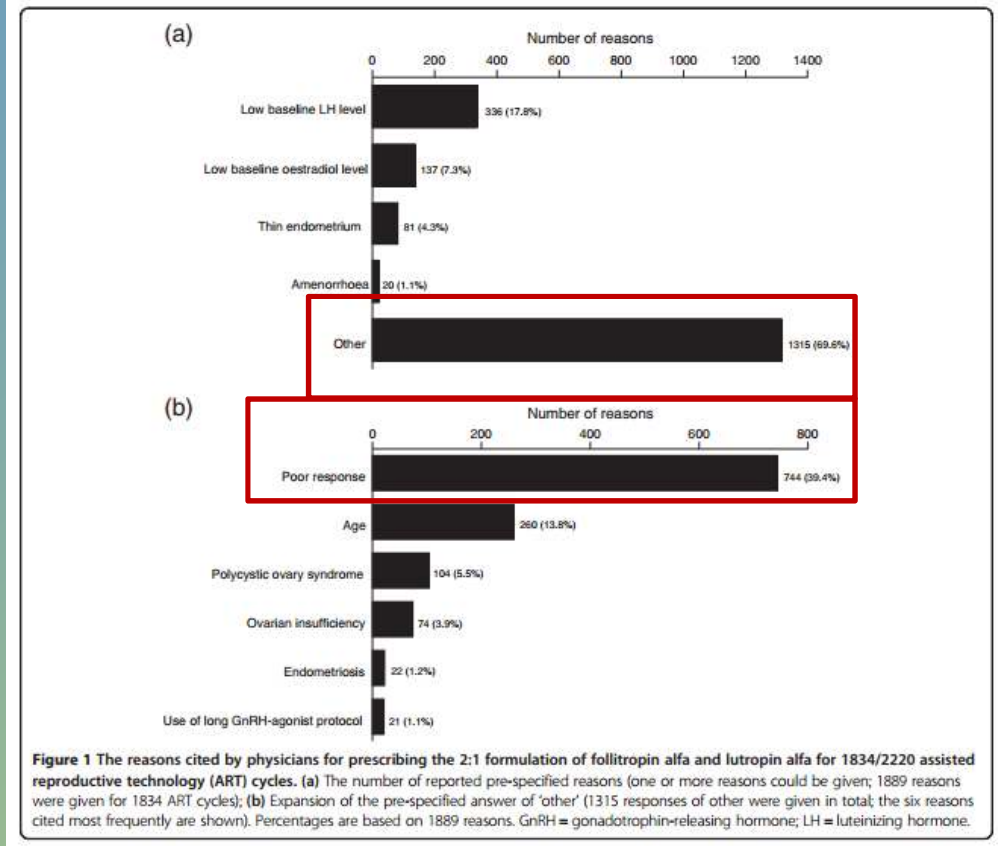
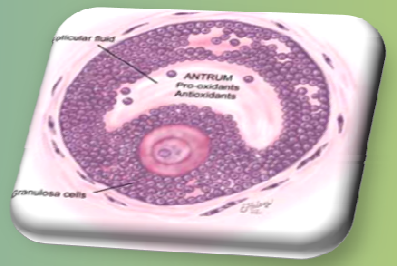


Figure 1 The reasons cited by physicians for prescribing the 2:1 formulation of follitropin alfa and lutropin alfa for 1834/2220 assisted reproductive technology (ART) cycles. (a) The number of reported pre-specified reasons (one or more reasons could be given; 1889 reasons were given for 1834 ART cycles); **(b)** Expansion of the pre-specified answer of 'other' (1315 responses of other were given in total; the six reasons cited most frequently are shown). Percentages are based on 1889 reasons. GnRH = gonadotrophin-releasing hormone; LH = luteinizing hormone.

BACKGROUND



Xiong et al. Reproductive Biology and Endocrinology 2014, 12:109
http://www.rbej.com/content/12/1/109

RB&E REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

REVIEW Open Access

Recombinant luteinizing hormone supplementation in women undergoing in vitro fertilization/ intracytoplasmic sperm injection with gonadotropin releasing hormone antagonist protocol: a systematic review and meta-analysis

Yujing Xiong†, Zhigin Bu†, Wei Dai, Meixiang Zhang, Xiao Bao and Yingpu Sun*

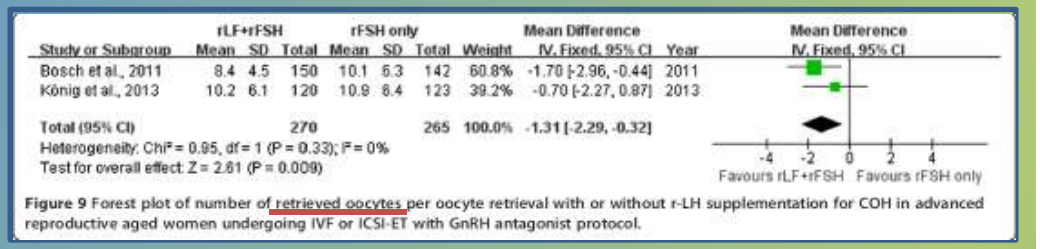


Figure 9 Forest plot of number of retrieved oocytes per oocyte retrieval with or without r-LH supplementation for COH in advanced reproductive aged women undergoing IVF or ICSI-ET with GnRH antagonist protocol.

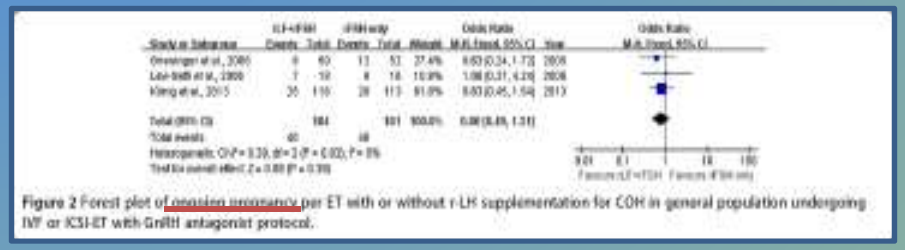


Figure 2 Forest plot of [illegible] pregnancy per ET with or without r-LH supplementation for COH in general population undergoing IVF or ICSI-ET with GnRH antagonist protocol.

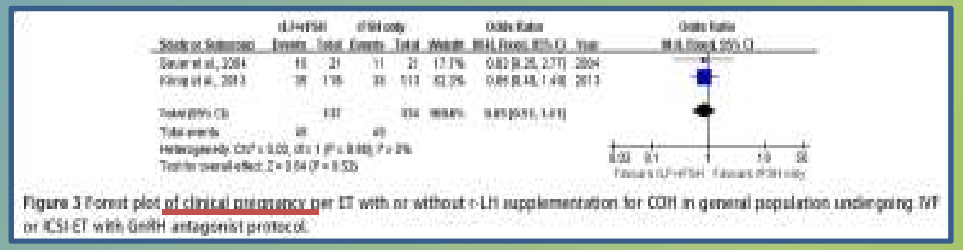
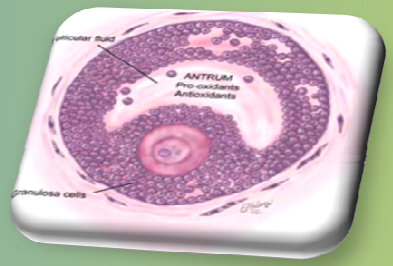


Figure 3 Forest plot of clinical pregnancy per ET with or without r-LH supplementation for COH in general population undergoing IVF or ICSI-ET with GnRH antagonist protocol.

The objective of this meta-analysis is to assess the impact of LH supplementation in women undergoing in vitro fertilization/ intracytoplasmic sperm injection (IVF/ICSI) with gonadotropin releasing hormone (GnRH) antagonist protocol. No significant difference in outcomes between LH supplementation and r-FSH alone in women undergoing IVF/ICSI with GnRH antagonist protocol is currently present; and further studies are necessary for more solid conclusions on pregnancy likelihood to be drawn.

BACKGROUND



The use of recombinant luteinizing hormone in patients undergoing assisted reproductive techniques with advanced reproductive age: a systematic review and meta-analysis

Micah J. Hill, D.O.,[a] Eric D. Levens, M.D.,[a,b] Gary Levy, M.D.,[a] Mary E. Ryan, M.L.S.,[c] John M. Cookman, M.D.,[a] Alan H. DeCherney, M.D.,[a] and Brian W. Whitcomb, Ph.D.[a]

TABLE 2

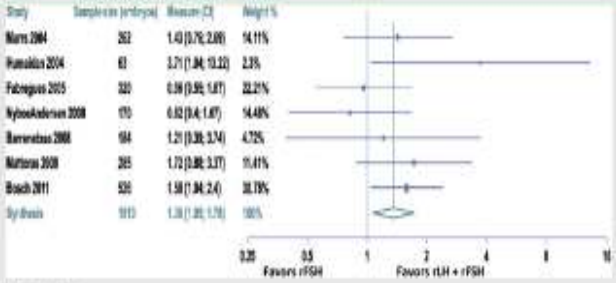
Secondary outcomes of studies included in the systematic review and meta-analysis.

	E_2 day of hCG (pg/mL)			Oocytes			Metaphase II oocytes			Fertilization (% or no.)		
Study	rLH + rFSH	rFSH	*P* value	rLH + rFSH	rFSH	*P* value	rLH + rFSH	rFSH	*P* value	rLH + rFSH	rFSH	*P* value
Marrs et al. 2003 (18)		NR			NR		9.3	8.3	NS		NR	
Humaidan et al. 2004 (19)	1,514	1,116	NS	10.3	9.4	NS		NR		61.9	47.6	NS
Fabregues et al. 2006 (20)	1,658	2,186	NS	6.3	7.9	<.001	5.5	6.9	<.001		NR	
Barmeotoea et al. 2008 (22)	3,304	2,914	NS	5.4	5.6	NS	4.6	5.1	NS		NR	
HybouAndersen et al. 2008 (21)		NR		8.5	9.3	NS		NR			NR	
Mattorras et al. 2009 (23)		NR		8.3	8.9	NS	6.7	7.0	NS	48	49	NS
Bosch et al. 2011 (24)	1,560	1,386	NS	8.4	10.1	.008	6.6	7.0	NS	68	61	027

Note: NR = not reported; NS = not statistically significant.

Hill. Recombinant LH in patients of advanced reproductive age. Fertil Steril 2012.

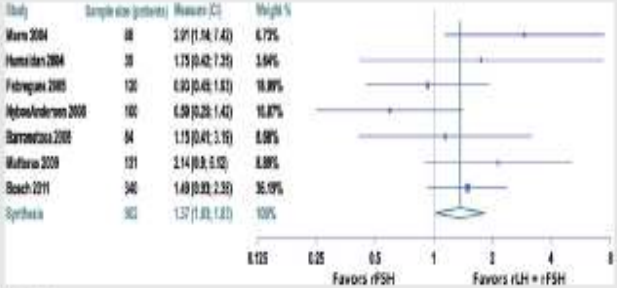
FIGURE 1



Forest plot of embryo implantation.

Hill. Recombinant LH in patients of advanced reproductive age. Fertil Steril 2012.

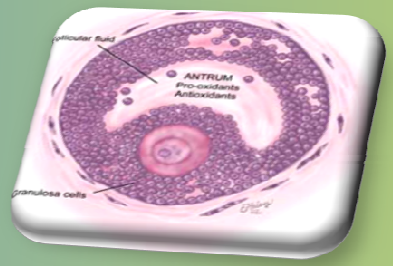
FIGURE 2



Forest plot of clinical pregnancy.

Hill. Recombinant LH in patients of advanced reproductive age. Fertil Steril 2012.

BACKGROUND



Xiong et al. Reproductive Biology and Endocrinology 2014, 12:109
http://www.rbej.com/content/12/1/109

RB&E REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

REVIEW Open Access

Recombinant luteinizing hormone supplementation in women undergoing in vitro fertilization/ intracytoplasmic sperm injection with gonadotropin releasing hormone antagonist protocol: a systematic review and meta-analysis

Yujing Xiong†, Zhiqin Bu†, Wei Dai, Meixiang Zhang, Xiao Bao and Yingpu Sun*

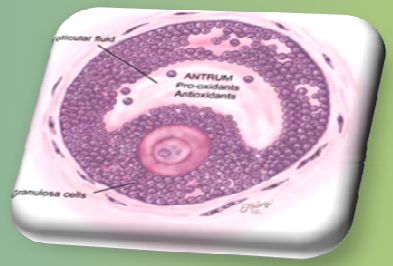
The use of recombinant luteinizing hormone in patients undergoing assisted reproductive techniques with advanced reproductive age: a systematic review and meta-analysis

Micah J. Hill, D.O.,[a] Eric D. Levens, M.D.,[a,b] Gary Levy, M.D.,[a] Mary E. Ryan, M.L.S.,[c] John M. Cookman, M.D.,[a] Alan H. DeCherney, M.D.,[a] and Brian W. Whitcomb, Ph.D.[d]

Low sample size of all available studies
Not standardized dose and timing of LH supplementation
Lack of adequate patients selection (POR???)

Did not permit to obtain strong results in favour of LH supplementation (if not in case of hypogonadotrophic hypogonadism), in particular when a GnRH-antagonist protocol is applied

BACKGROUND



Recombinant LH supplementation during IVF cycles with a GnRH-antagonist in estimated poor responders: A cross-matched pilot investigation of the optimal daily dose and timing

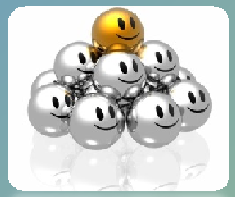
SALVATORE GIZZO, ALESSANDRA ANDRISANI, MARCO NOVENTA, SERENA MANFÈ, ALESSANDRA OLIVA, MICHELE GANGEMI, GIOVANNI BATTISTA NARDELLI and GUIDO AMBROSINI

Department of Women's and Children's Health, Assisted Reproductive Unit of the Gynecological and Obstetrics Clinic, University of Padua, 35128-Padua, Italy


ESHRE PAGES

ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: the Bologna criteria

Patients treated with
150 UI of rLH beginning with GnRH-ant
showed significantly better outcomes in terms of



Total number of follicles >10mm,

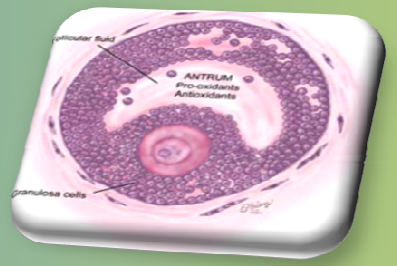
Follicles >16mm and 17-Estradiol at ovulation-induction

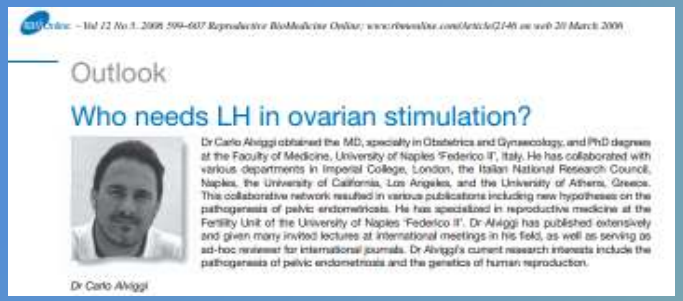
Total number of oocytes and MII-oocytes

Total number of embryos, number of grade-1 embryos

Pregnancy rate.

BACKGROUND





Outlook

Who needs LH in ovarian stimulation?

Dr Carlo Alviggi obtained the MD, specialty in Obstetrics and Gynaecology, and PhD degrees at the Faculty of Medicine, University of Naples 'Federico II', Italy. He has collaborated with various departments in Imperial College, London, the Italian National Research Council, Naples, the University of California, Los Angeles, and the University of Athens, Greece. This collaborative network resulted in various publications including new hypotheses on the pathogenesis of pelvic endometriosis. He has specialized in reproductive medicine at the Fertility Unit of the University of Naples 'Federico II'. Dr Alviggi has published extensively and given many invited lectures at international meetings in his field, as well as serving as ad-hoc reviewer for international journals. Dr Alviggi's current research interests include the pathogenesis of pelvic endometriosis and the genetics of human reproduction.

Dr Carlo Alviggi

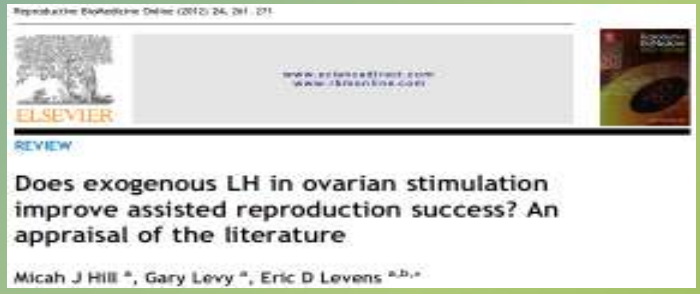
- Women of advanced reproductive age
- Women with an abnormal response to r-hFSH
- Patients treated with GnRH antagonists

if in one hand the **GnRH-antagonist** induces a fast and profound pituitary suppression, with a clear advantage in term of premature LH surge avoidance, in the other hand **LH activity is dramatically reduced and the follicles which have been recruited in a physiological FSH and LH environment are dramatically deprived of their LH sustenance** which result in a significant reduction of oestrogens concentration via aromatase activity reduction

The data from numerous assisted reproduction studies confirm that most patients will respond to gonadotrophin preparations containing only FSH. However, 10–12% of patients may fail to respond adequately to this type of ovarian stimulation. Presumably these patients lack adequate concentrations of endogenous LH after pituitary down-regulation and would benefit from the addition of LH to ovarian stimulation. Clearly, patients with hypogonadotrophic hypogonadism require exogenous LH to achieve optimal assisted reproduction outcomes. A growing body of evidence also suggests that patients >35 years may have improved assisted reproduction outcomes with the addition of exogenous LH. Beyond that, clinicians have few tools available to

ARTICLE

GnRH agonist and GnRH antagonist protocols in ovarian stimulation: differential regulation pathway of aromatase expression in human granulosa cells

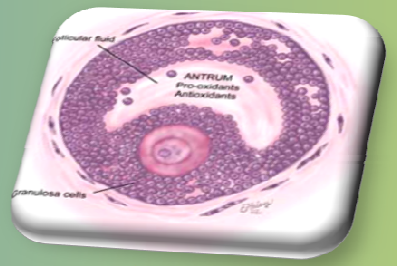


REVIEW

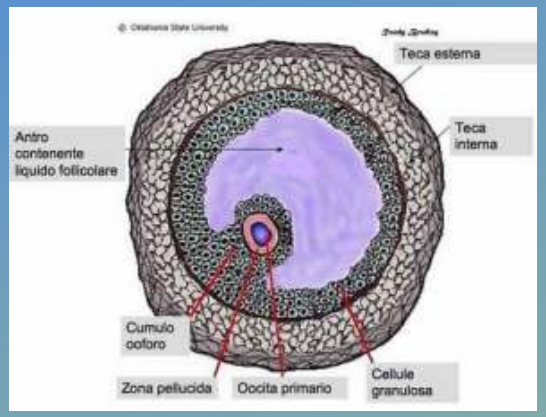
Does exogenous LH in ovarian stimulation improve assisted reproduction success? An appraisal of the literature

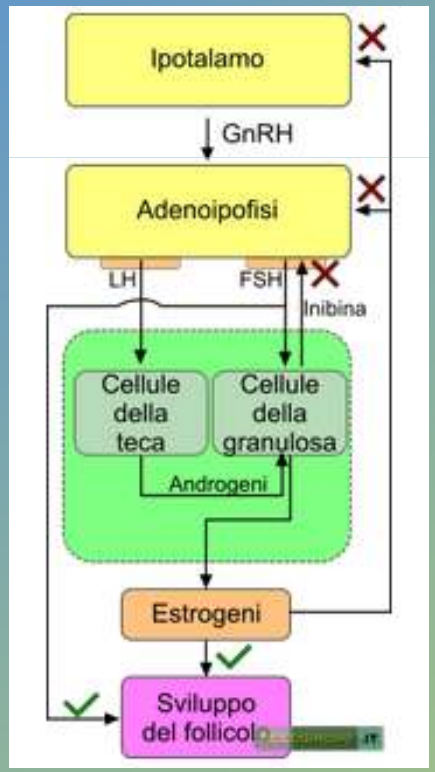
Micah J Hill [a], Gary Levy [a], Eric D Levens [a,b,*]

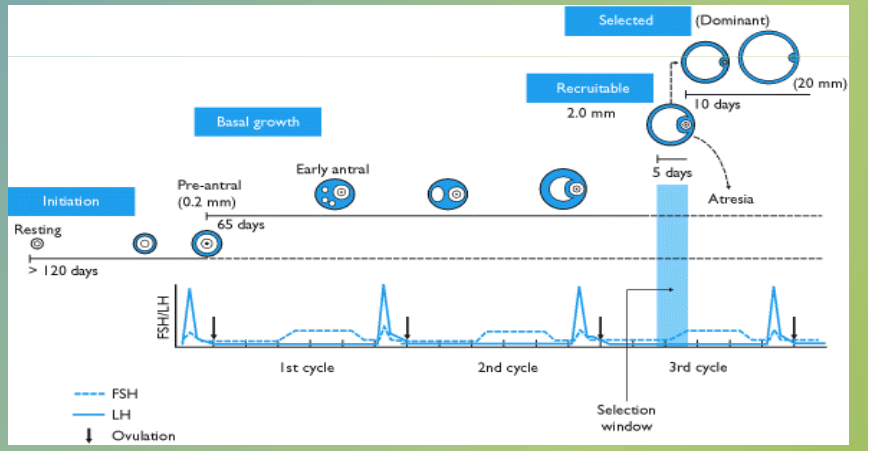
BACKGROUND

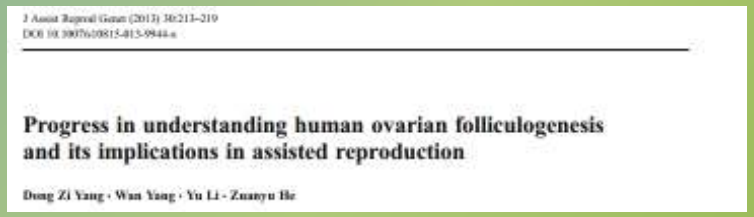


To understand the possible clinical advantages of LH supplementation we must remember that this gonadotropin exert a **fundamental physiological action in both the somatic and germ cell compartment of the ovarian follicle**





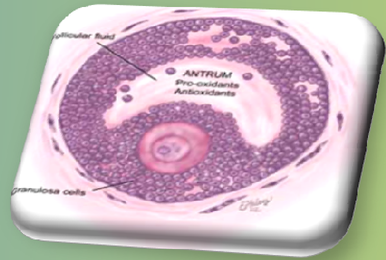


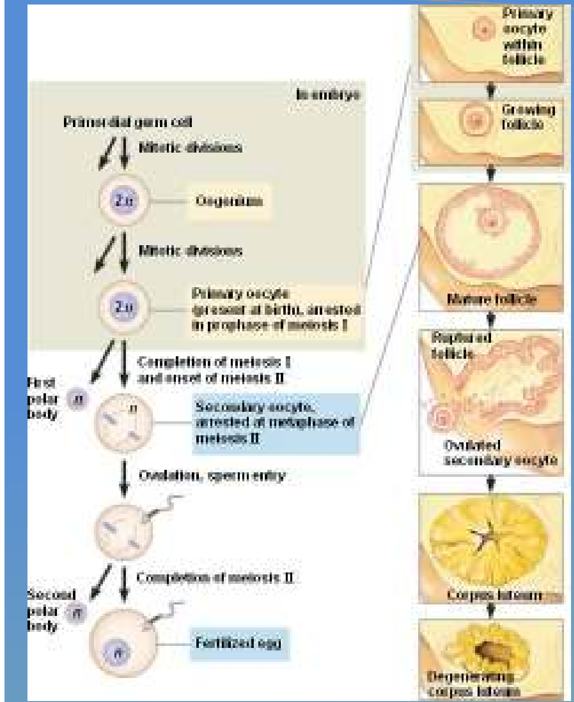

J Assist Reprod Genet (2013) 30:213–219
DOI 10.1007/s10815-013-9944-x

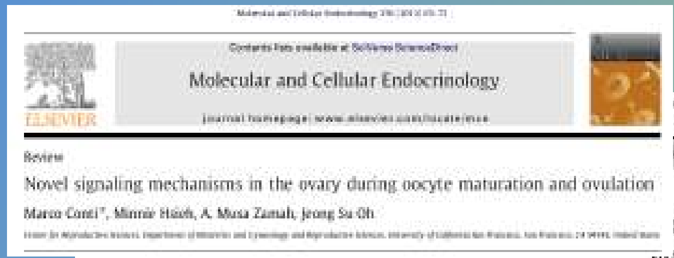
Progress in understanding human ovarian folliculogenesis and its implications in assisted reproduction

Dong Zi Yang · Wan Yang · Yu Li · Zuanyu He

BACKGROUND





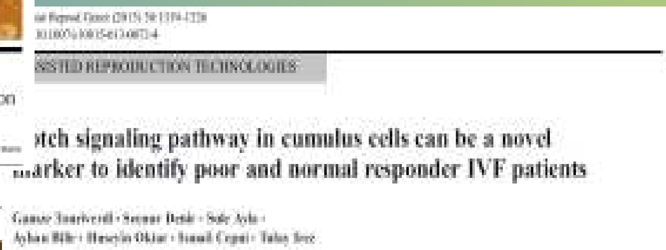


Molecular and Cellular Endocrinology

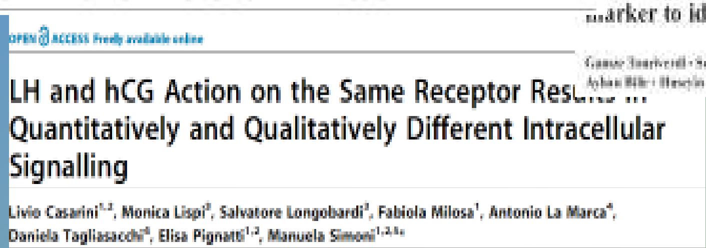
Review

Novel signaling mechanisms in the ovary during oocyte maturation and ovulation

Marco Conti, Minnie Hsieh, A. Musa Zamah, Jeong Su Oh



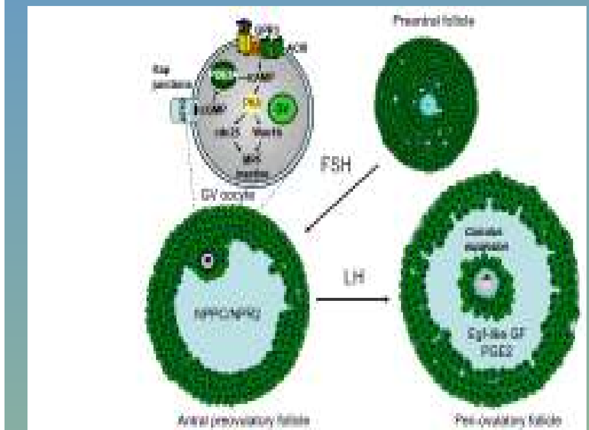
Notch signaling pathway in cumulus cells can be a novel marker to identify poor and normal responder IVF patients

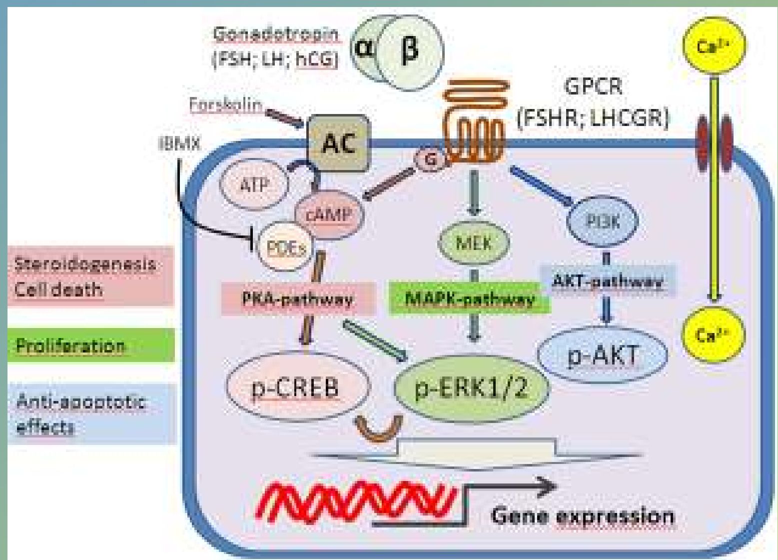


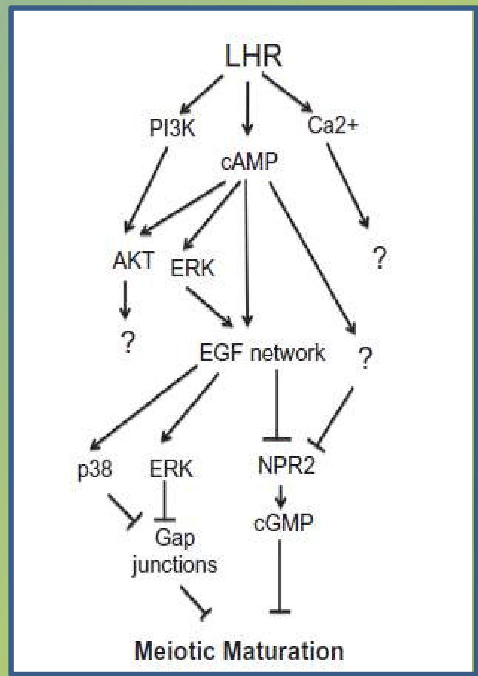
OPEN ACCESS Freely available online

LH and hCG Action on the Same Receptor Results in Quantitatively and Qualitatively Different Intracellular Signalling

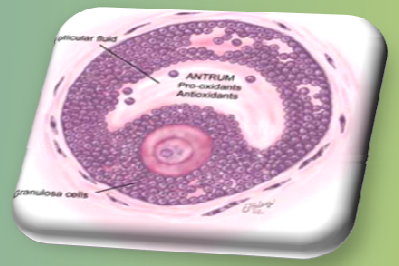
Livio Casarini[1,2], Monica Lispi[3], Salvatore Longobardi[3], Fabiola Milosa[1], Antonio La Marca[4], Daniela Tagliasacchi[4], Elisa Pignatti[1,2], Manuela Simoni[1,2,5]







STUDY QUESTION

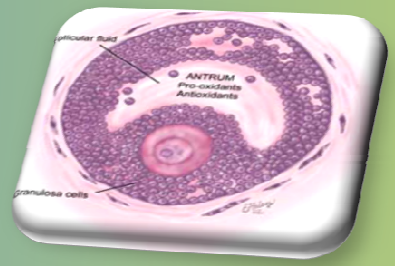


May recombinant-LH supplementation during IVF cycles in poor responder patients influence the pathways involved in follicular growth and oocyte maturity?

Which pathways of follicular signaling are influenced by recombinant-LH supplementation?

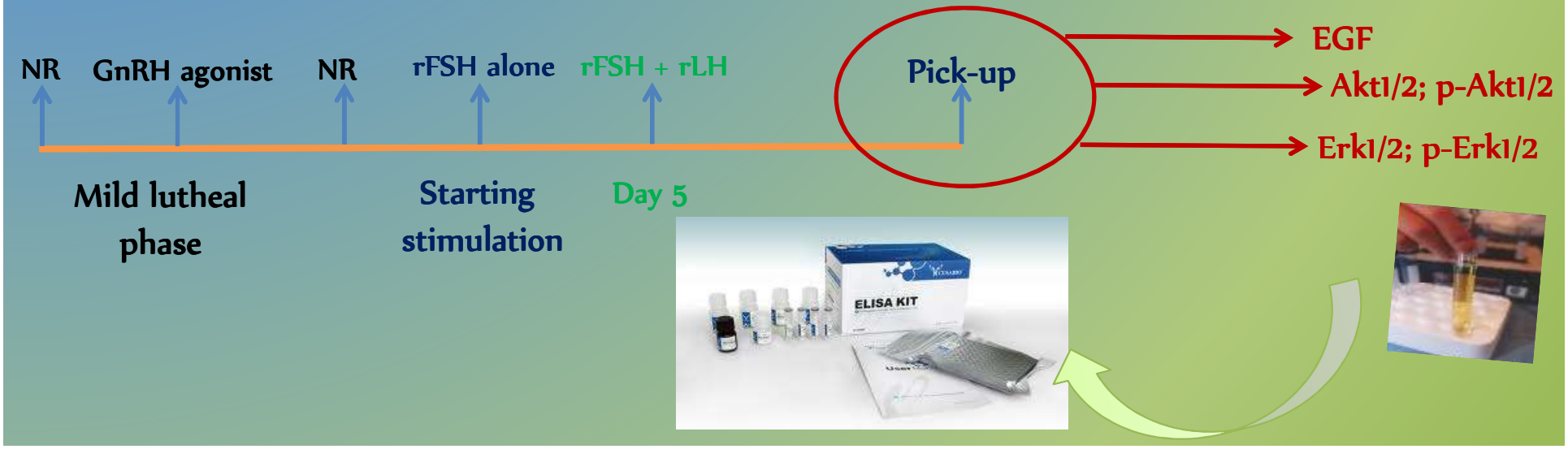
Can these factors explain the clinical advantages observed in poor responder patients after recombinant-LH supplementation?

STUDY DESIGN

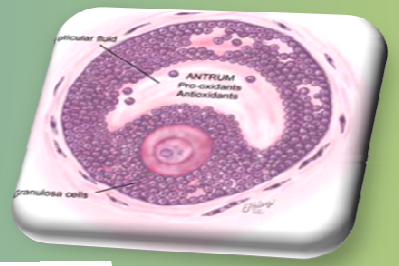


Observational longitudinal crossover study on 28 poor responder patients >42 years older

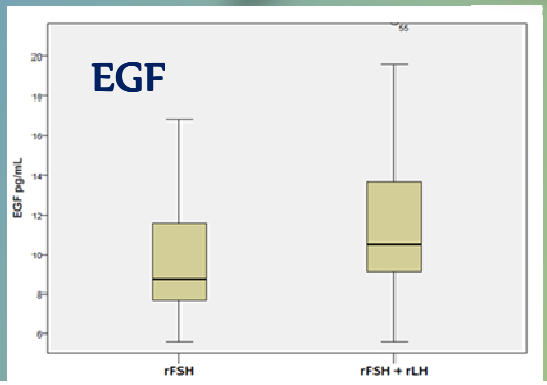
S-COS: standard-long-agonist-protocol using r-FSH (starting dose: 300 IU)
(in case of FAILURE of treatment)
LH-COS: S-COS +rLH (150IU day) from day 5 of stimulation
(treatment done within 6 months after previous cycle)

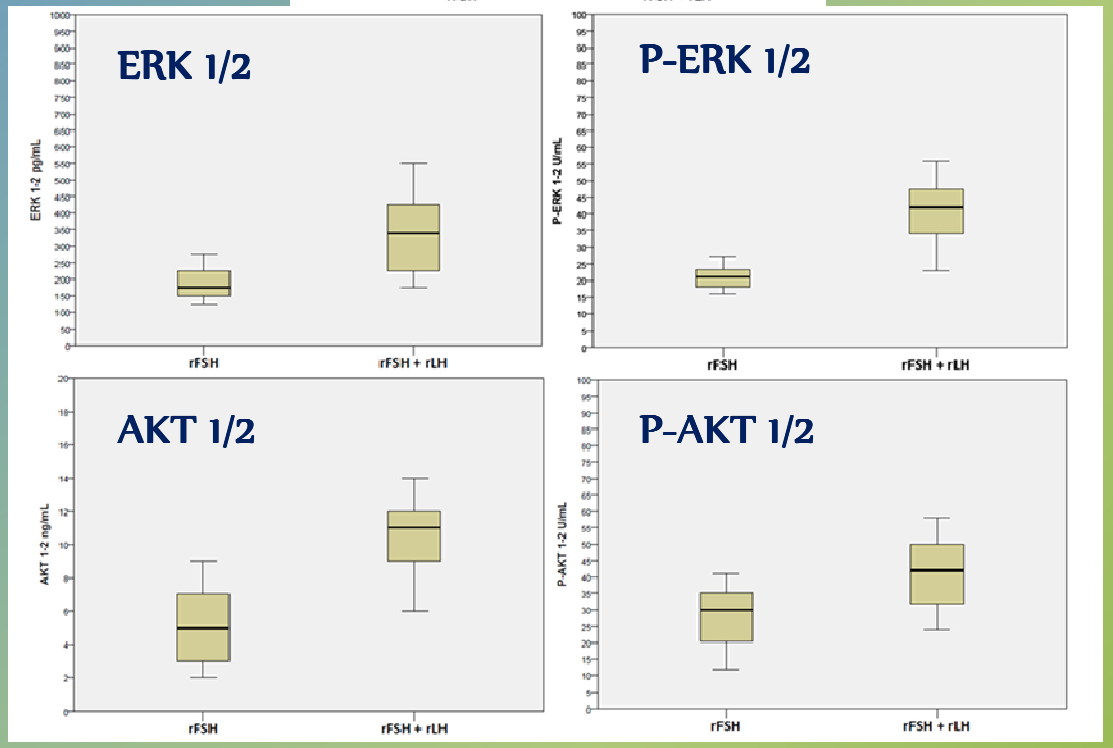


RESULTS



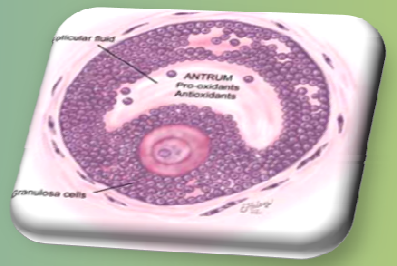
	GROUPS	Number	Mean values	Std. Deviation	p Value
EGF pg/mL	S-COS	28	9,40	2,92	
	LH-COS	28	11,75	3,95	<0.05
ERK 1-2 pg/mL	S-COS	28	184,82	50,15	
	LH-COS	28	332,14	111,35	<0.001
p-ERK 1-2 U/mL	S-COS	28	20,89	3,41	
	LH-COS	28	40,18	10,37	<0.001
AKT 1-2 ng/mL	S-COS	28	5,35	2,45	
	LH-COS	28	10,42	2,08	<0.001
p-AKT 1-2 U/mL	S-COS	28	28,07	8,98	
	LH-COS	28	42,36	10,06	<0.001



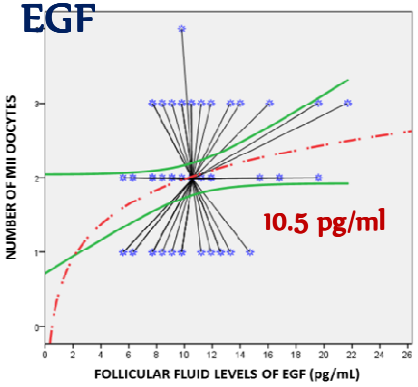


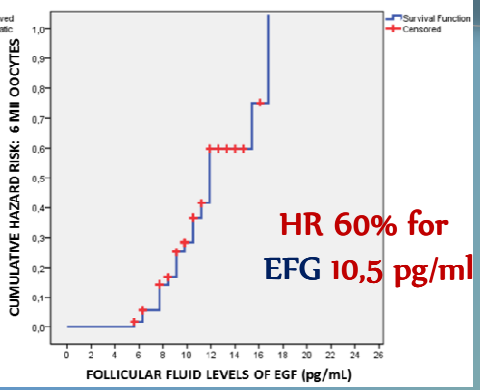
ALL GROWTH FACTORS
RESULTED SIGNIFICANTLY
INCREASED
IN FOLLICULAR FLUID
AFTER SUPPLEMENTATION
WITH r-LH

RESULTS

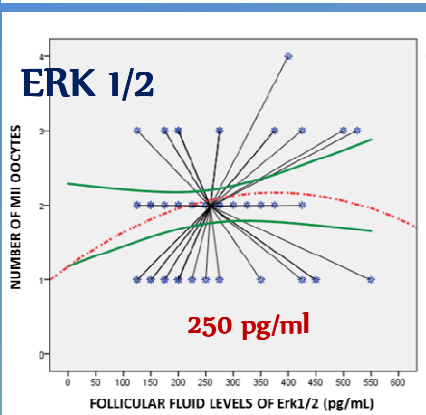


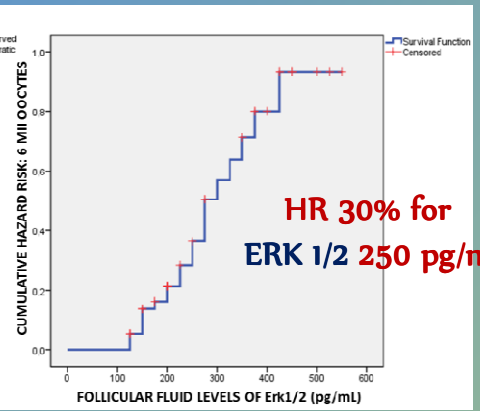
EGF



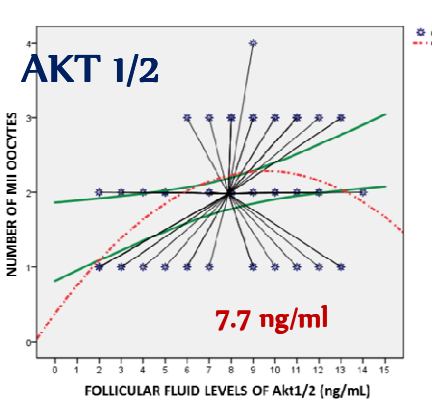


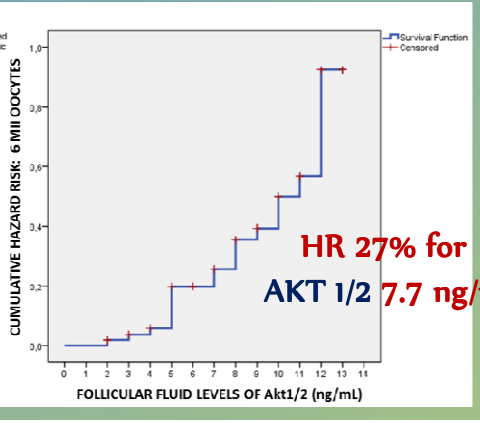
ERK 1/2





AKT 1/2





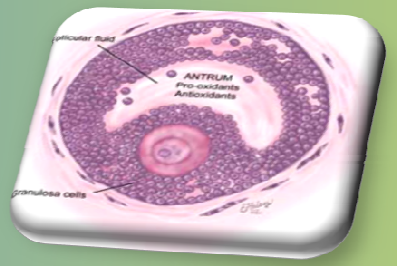
The FF concentration of all the mentioned biomarkers were correlated with both **number of MII oocytes** retrieved and **Grade 1 embryos**

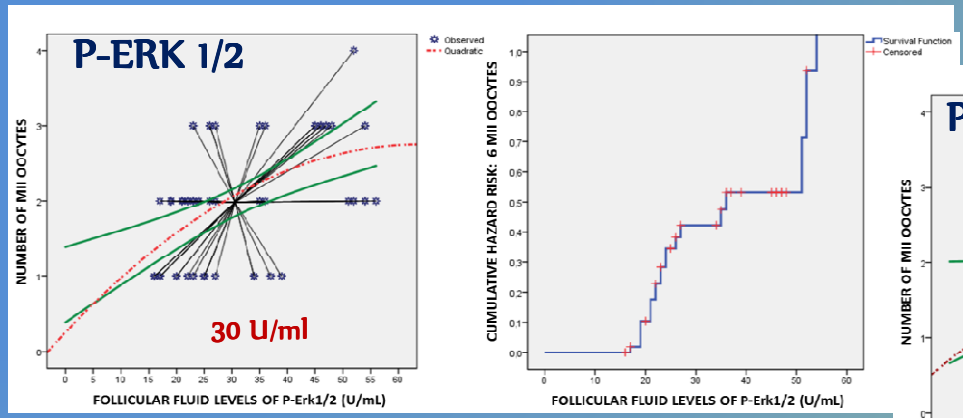
Kaplan-Meier estimator: 6 MII oocytes the event
(6 represented the max number of MII oocytes retrieved)

Both **Erk 1/2** and **Akt 1/2** the regression model clearly showed a **deflection in case of increasing dose more than 500 pg/ml and 13 ng/ml**, respectively

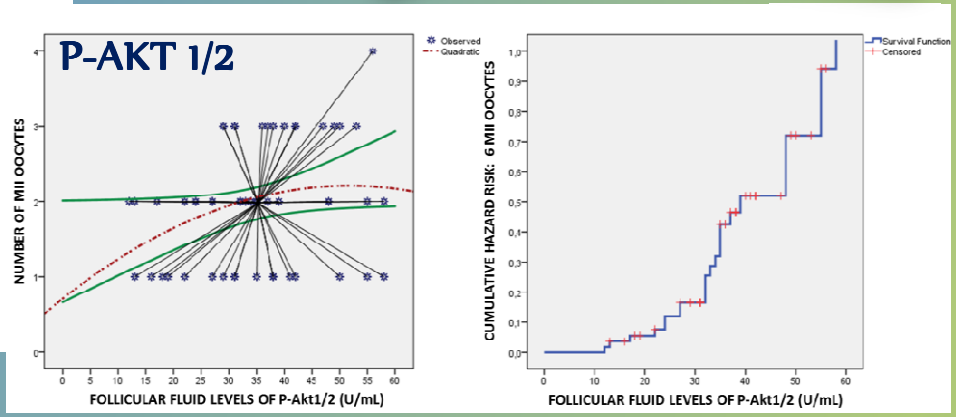
	TREATMENT	MEAN VALUE ± D.S.	RANGE	*P*
RETRIEVED OOCYTES (total number)	S-COS	3.60 ± 1.08	2-8	0.26
	LH-COS	4.00 ± 2.58		
	TOTAL	3.80 ± 1.94		
MII RETRIEVED OOCYTES (total number)	S-COS	2.30 ± 0.95	1 - 6	< 0.001
	LH-COS	2.90 ± 1.66		
	TOTAL	2.60 ± 1.35		
OBTAINED EMBRYOS	A	1.90 ± 0.74	0 -5	N.S.
	B	2.10 ± 1.45		
	TOTAL	2.00 ± 1.12		
I DEGREE EMBRYOS	A	0.40 ± 0.52	0 - 3	0.004
	B	1.50 ± 0.85		
	TOTAL	0.95 ± 0.89		

RESULTS

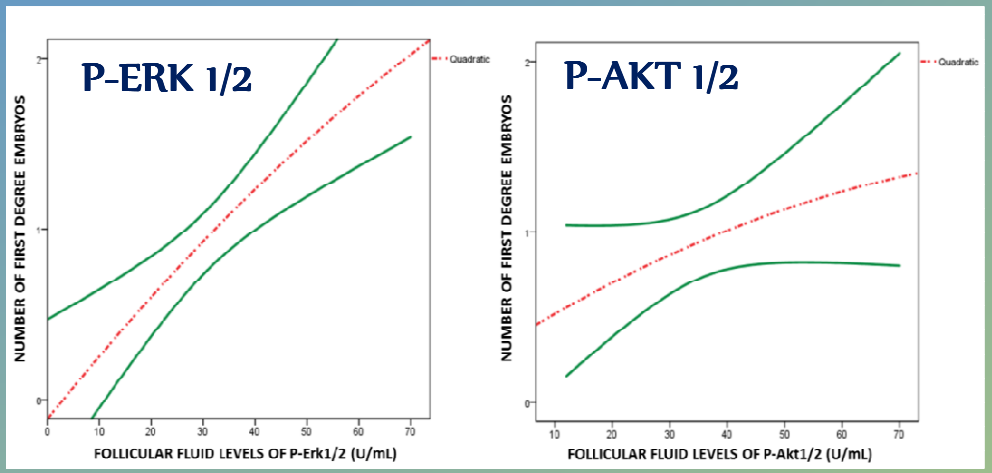




HR 45% for
P-ERK 1/2 30 U/ml



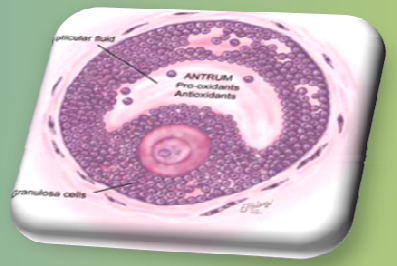
HR 48% for
P-ERK 1/2 35 U/ml



Association with highest rate of **1st degree embryos**: only FF fluid levels of P-ERK 1/2 and P-AKT 1/2 showed significant association.

- **P-ERK 1/2** showed a very high correlation [r^2:0.973; $p<0.0001$]
- **P-AKT 1/2** showed an acceptable correlation [r^2:0.624; $p<0.05$]

CONCLUSIONS



In poor-responder patients, recombinant-LH supplementation during IVF influences the pathways involved in follicular growth and oocyte maturity.

The treatment significantly increases follicular levels of
EGF, ERK-1/2 and AKT-1
[particularly the availability of the phosphorylated forms]

These evidences explain the improvements in qualitative and quantitative ovarian response.

The strong correlation between p-ERK-1/2 and p-AKT-1 and first degree embryos seems to suggest a potential role of r-LH in influencing also the embryo quality