Università degli Studi di Padova
Dipartimento di Scienze Ginecologiche e della Riproduzione Umana
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Giovanni Battista Nardelli

STATIN USE:

CONSERVATIVE TARGETED THERAPY FOR PATIENTS AFFECTED BY ENDOMETRIOSIS

ENSTABLISHED EVIDENCES AND NEW INSIGHT

Dott. A. Vitagliano

Endometriosis

Linda C Giudice, Lee C Kao

Lancet 2004; 364: 1789–99

Division of Reproductive Endocrinology and Infertility, Center for Research on Women's Health and Reproduction, Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA 94305-5317, USA
(L C Giudice MD, L C Kao MD)

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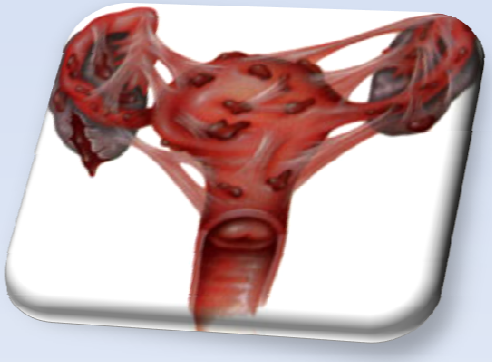
Endometriosis is an oestrogen-dependent disorder that can result in substantial morbidity, including pelvic pain, multiple operations, and infertility. New findings on the genetics, the possible roles of the environment and the immune system, and intrinsic abnormalities in the endometrium of affected women and secreted products of endometriotic lesions have given insight into the pathogenesis of this disorder and serve as the background for new treatments for disease-associated pain and infertility. Affected women are at higher risk than the general female population of developing ovarian cancer, and they also may be at increased risk of breast and other cancers as well as autoimmune and atopic disorders. Clinicians should assess and follow up affected women for these and other associated disorders. There will probably be a new repertoire of approaches for treatment and perhaps cure of this enigmatic disorder in the near future.

Panel 1: Theories on the pathogenesis of endometriosis

Retrograde menstruation/transplantation
Coelomic metaplasia
Altered cellular immunity
Metastasis
Genetic basis
Environmental basis
Multifactorial mode of inheritance with interactions between specific genes and the environment



Panel 3: **Genes and gene products aberrantly expressed in endometrium from women with endometriosis**

Aromatase
Endometrial bleeding factor
Hepatocyte growth factor
17-β-hydroxysteroid dehydrogenase
HOXA10
HOXA11
Leukaemia inhibitory factor
Matrix metalloproteinases 3, 7, and 11
Tissue inhibitors of metalloproteinases
Progesterone-receptor isoforms
Complement 3
Glutathione peroxidase
Catalase
Thrombospondin 1
Vascular endothelial growth factor
Integrin $\alpha_v\beta_3$
Glycodelin

Panel 4: **Agents used to treat endometriosis (from Rice[147])**

Androgens
Danazol: 400–800 mg daily orally for 4–6 months

GnRH agonists
Leuprolide: 1 mg daily subcutaneously
Leuprolide depot: 3·75 mg intramuscularly every 28 days
Buserelin: 300–400 µg three times daily intranasally
Goserelin: 3·6 mg subcutaneously every 28 days
Nafarelin: 400–800 µg daily intranasally

Progestagens
Gestrinone: 2·5–5·0 mg daily
Medroxyprogesterone acetate: 20–30 mg daily orally for 6 months, then 100 mg intramuscularly every 2 weeks for 2 months, then 200 mg intramuscularly each month for 4 months

Oral contraceptives
Combination oestrogen/progestagen: ethinyl oestradiol 30–35 µg plus a progestagen, 1 tablet daily for 4–6 months

Published in final edited form as:
Fertil Steril. 2010 May 1; 93(7): 2424–2428. doi:10.1016/j.fertnstert.2009.09.017.

Patients' report on how endometriosis affects health, work, and daily life

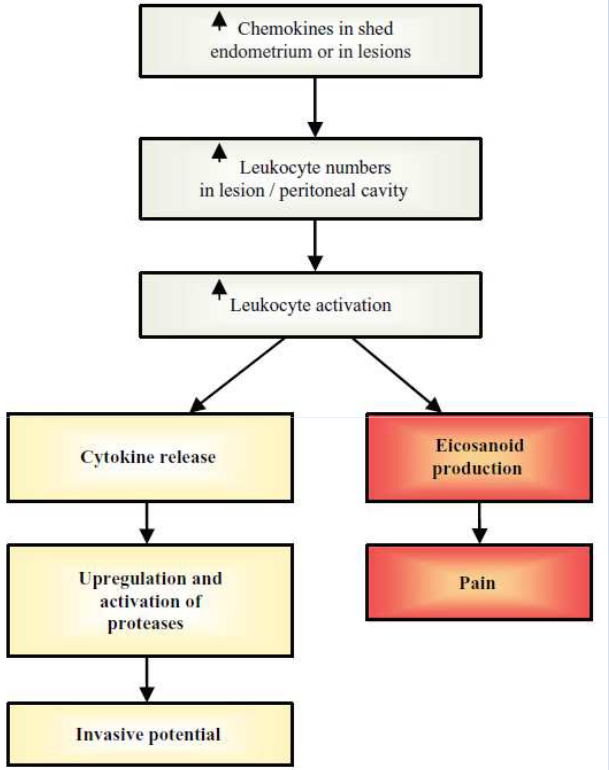
Human Reproduction Update, Vol.19, No.6 pp. 625–639, 2013
Advanced Access publication on July 24, 2013 doi:10.1093/humupd/dmt027

human reproduction update

The social and psychological impact of endometriosis on women's lives: a critical narrative review

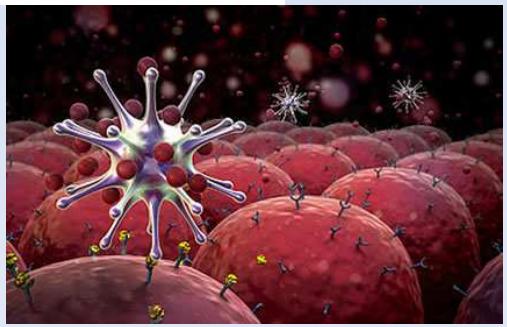
Lorraine Culley[1,*], Caroline Law[1], Nicky Hudson[1], Elaine Denny[2], Helene Mitchell[1], Miriam Baumgarten[3], and Nick Raine-Fenning[3]

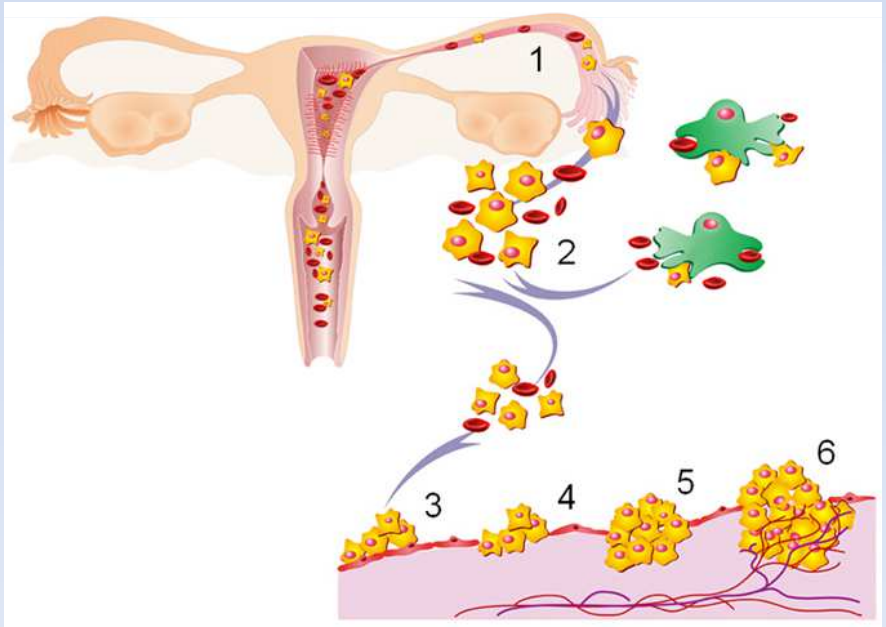
Reproductive Sciences Vol. 16, No. 4, April 2009 341



Priorities for Endometriosis Research: Recommendations From an International Consensus Workshop

Peter A. W. Rogers, BSc, PhD, Thomas M. D'Hooghe, MD, PhD, Asgerally Fazleabas, PhD, Caroline E. Gargett, PhD, Linda C. Giudice, MD, PhD, MSc, Grant W. Montgomery, PhD, Luk Rombauts, MD, PhD, Lois A. Salamonsen, PhD, and Krina T. Zondervan, DPhil





Università degli Studi di Padova - Dipartimento di salute della Donna e del Bambino
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof GB Nardelli

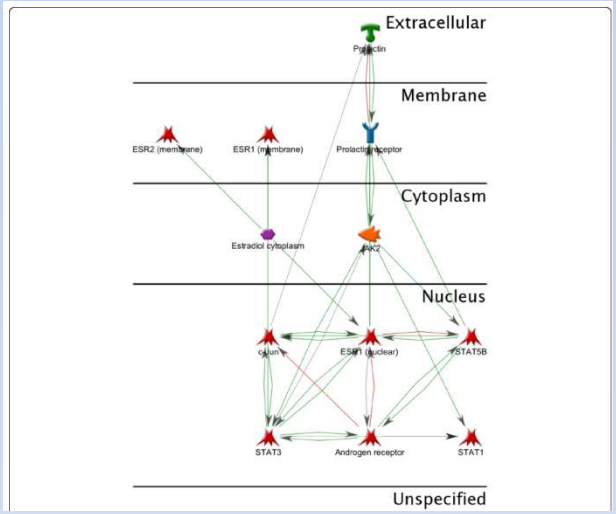
Aznaurova *et al. Reproductive Biology and Endocrinology* 2014, **12**:50
http://www.rbej.com/content/12/1/50

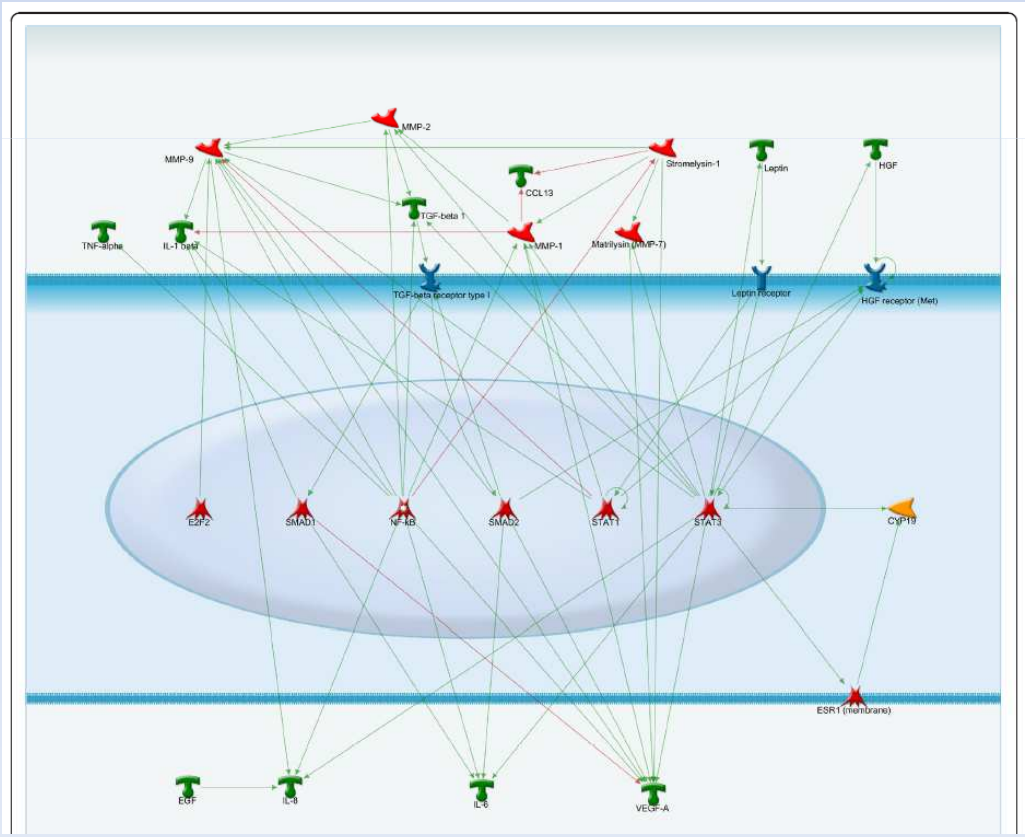
RB&E REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

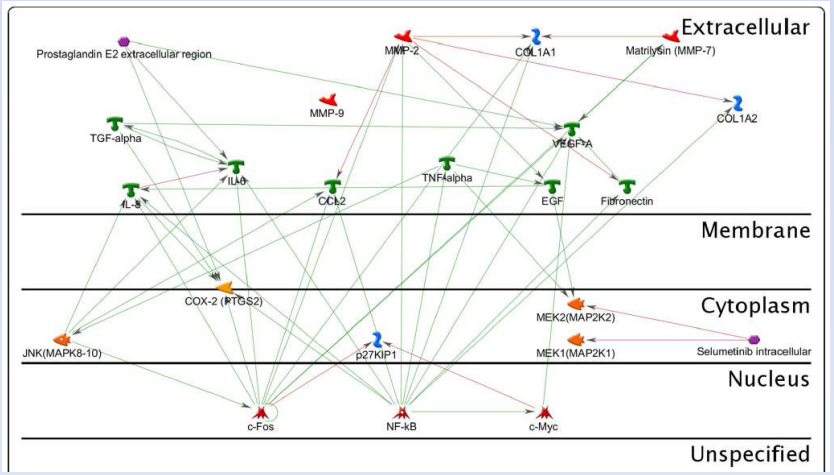
REVIEW Open Access

Molecular aspects of development and regulation of endometriosis

Yana B Aznaurova[1,3,5*], Marat B Zhumataev[1,3,5], Tiffany K Roberts[2], Alexander M Aliper[3,5,6] and Alex A Zhavoronkov[1,3,4]





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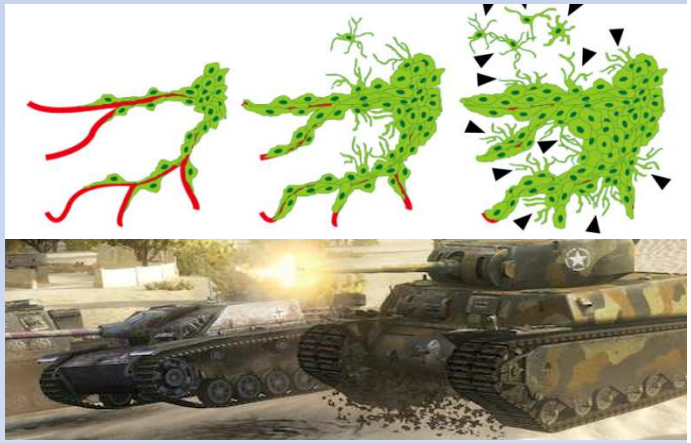
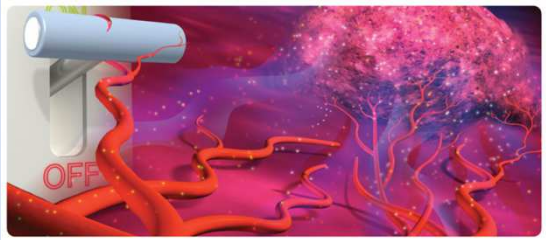


TISSUE IMPLANTATION
INHIBITION OF METALLOPROTEINASE MATRIX
NEO-VASCULARIZATION
ANTI-ANGIOGENIC ACTIVITY
ENDOMETRIAL PROLIFERATION
INHIBITION OF ENDOMETRIAL PROLIFERATION
OXIDATIVE STRESS / INFLAMMATION
ANTI-INFLAMMATORY AND ANTIOXIDANT ACTIVITY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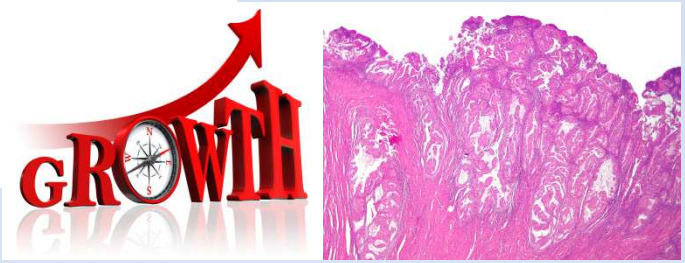
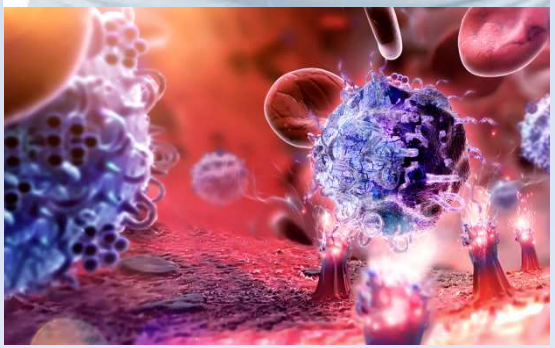
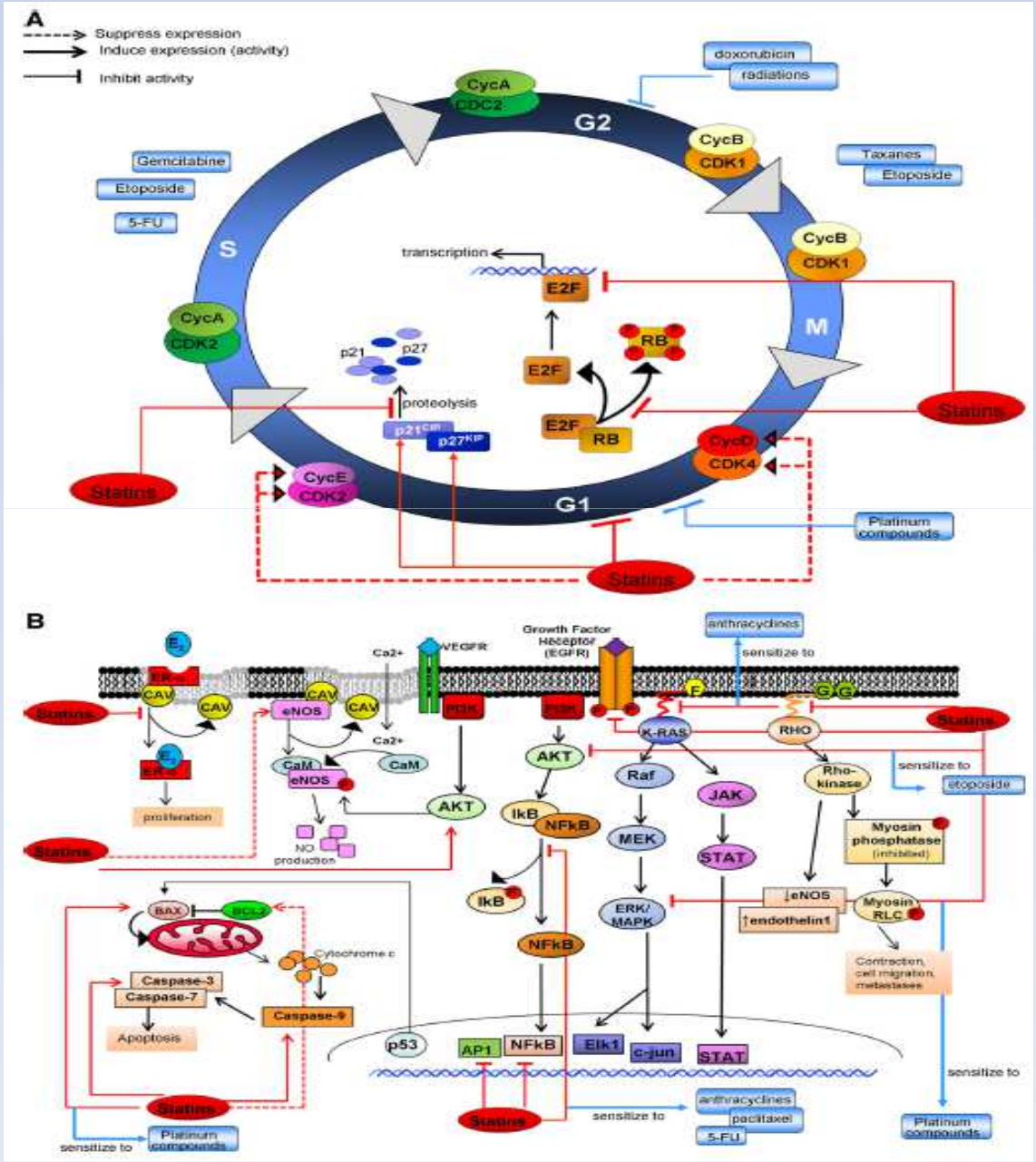

GROWTH




Angiogenesis


MIRACLES
HAPPEN


STATIN??


A
Suppress expression
Induce expression (activity)
Inhibit activity
doxorubicin
radiations
CycA
CDC2
G2
CycB
CDK1
Taxanes
Etoposide
Gemcitabine
Etoposide
5-FU
S
transcription
E2F
CycB
CDK1
M
CycA
CDK2
p21
p27
RB
E2F
proteolysis
E2F
RB
Statins
Statins
CycD
CDK4
CycE
CDK2
G1
Platinum compounds
Statins
B
anthracyclines
sensitize to
Growth Factor Receptor (EGFR)
VEGFR
Ca2+
Statins
eNOS
CAV
Ca2+
PI3K
P
G
X-RAS
RHO
Statins
CaM
eNOS
CaM
AKT
Raf
JAK
Rho-kinase
sensitize to
etoposide
proliferation
AKT
IkB
NFkB
MEK
STAT
Myosin phosphatase
(inhibited)
NO production
Statins
BAX
BCL2
Cytochrome c
IkB
ERK/MAPK
↓eNOS
↑endothelin1
Myosin RLC
NFkB
Contraction, cell migration, metastases
Caspase-3
Caspase-7
Caspase-9
Apoptosis
p53
AP1
NFkB
Elk1
c-jun
STAT
sensitize to
Statins
sensitize to
anthracyclines
paclitaxel
5-FU
Platinum compounds
sensitize to

European Journal of Obstetrics & Gynecology and Reproductive Biology 179 (2014) 153–158

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European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review

Could statins constitute a novel treatment for endometriosis? Systematic review of the literature

Year	First author	Experimental model	Main subject
2006	Piotrowski et al. [8]	*In vitro*	Mevastatin and simvastatin induce inhibition of DNA synthesis in human endometrial stromal cells.
2007	Oktem et al. [20]	*In vivo*	Reduction of the volume of endometrial implants induced in animal models (rats) and reduction of VEGF levels.
2007	Esfandiari et al. [21]	*In vitro*	Inhibition of cell proliferation and angiogenesis in an experimental model for the development of endometriosis-type tissue.
2009	Bruner-Tran et al. [12]	*In vitro*	How simvastatin acts on MMP-3, evaluated in cultures of endometrial stromal cells.
2009	Nasu et al. [11]	*In vitro*	Effects of simvastatin on the proliferation and contraction of endometriotic stromal cells in a three-dimensional collagen gel culture system.
2010	Yilmaz et al. [24]	*In vivo*	Effects of atorvastatin on VEGF, TIMP-2 and MMP-9concentrations in a model of endometriosis in rats.
2010	Sharma et al. [31]	*In vitro*	Atorvastatin increases the expression of anti-inflammatory genes, such as PPAR and LXR, and possible anti-inflammatory, anti-oxidant, and anti-angiogenic properties.
2010	Sokalska et al. [13]	*In vitro*	Inhibitory effects of simvastatin on the growth of human endometrial stromal cells associated with disruption of isoprenylation, increased apoptosis, and disruption of the cytoskeleton.
2012	Cakmak et al. [37]	*In vivo*	Effect of statins on the expression of monocyte chemotactic protein 1 (MCP-1) in endometrial implants in an animal model (rats) and in cultured endometriosis cells.
2012	Sokalska et al. [25]	*In vitro*	Effects of simvastatin on the invasion of endometrial stromal cells and the expression of selected genes relevant to this invasion: MMP-2, MMP-3, TIMP-2 and CD44.
2013	Sokalska et al. [16]	*In vivo*	Simvastatin interacts with retinoic acid on the proliferation and apoptosis of endometrial stromal cells.
2013	Villanueva et al. [42]	*In vitro*	Mechanism of action of resveratrol and its interactions with simvastatin in primary cultures of human endometrial stromal cells.
2013	Almassinokiani et al. [45]	*In vivo*	Comparison of the efficacy of simvastatin *versus* GnRH-a on endometriosis in reducing endometriosis pain following laparoscopic surgery for endometriosis.

BIOLOGY OF REPRODUCTION (2012) 87(1):2, 1–6
Published online before print 4 April 2012.
DOI 10.1095/biolreprod.111.098806

Simvastatin Decreases Invasiveness of Human Endometrial Stromal Cells[1]

Anna Sokalska,[3,4] Amanda Cress,[3] Kaylon L. Bruner-Tran,[5] Kevin G. Osteen,[5] Hugh S. Taylor,[6] Israel Ortega,[3,7] and Antoni J. Duleba[2,3]

Human Reproduction Vol.22, No.5 pp. 1474–1480, 2007
Advance Access publication January 18, 2007
doi:10.1093/humrep/del505

High-dose atorvastatin causes regression of endometriotic implants: a rat model

Mesut Oktem[1,4], Ibrahim Esinler[1], Derya Eroglu[1], Nihan Haberal[2], Nilufer Bayraktar[3] and Hulusi B.Zeyneloglu[1]

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM
THE ENDOCRINE SOCIETY
http://jcem.endojournals.org/

Simvastatin Induces Apoptosis and Alters Cytoskeleton in Endometrial Stromal Cells

Anna Sokalska, Donna H. Wong, [...], and Antoni J. Duleba

Main Outcome Measures: The effect of simvastatin (10 and 30 μM) and/or geranylgeranyl pyrophosphate (GGPP, 30 μM) on caspase 3 and 7 activity, DNA fragmentation, and HES cell morphology was evaluated.

Results: Simvastatin induced significant time- and concentration-dependent apoptotic effects on HES cells as determined by increased activity of executioner caspases and DNA fragmentation. Simvastatin also caused profound alterations in HES cell morphology and F-actin cytoskeleton.

Original Articles

Statins Inhibit Monocyte Chemotactic Protein 1 Expression in Endometriosis

Reproductive Sciences
19(6) 572-579

DOI: 10.1177/1933719111430998
http://rs.sagepub.com
SAGE

Hakan Cakmak, MD[1], Murat Basar, PhD[1,2], Yasemin Seval-Celik, PhD[1], Kevin G. Osteen, PhD[3], Antoni J. Duleba, MD[4], Hugh S. Taylor, MD[1], Charles J. Lockwood, MD[1], and Aydin Arici, MD[1]

MEDICAL SCIENCE MONITOR

PRODUCT INVESTIGATIONS

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DOI: 10.12659/MSM.883967

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Published: 2013.07.05

Effects of simvastatin in prevention of pain recurrences after surgery for endometriosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEFG 1 Fariba Almassinokiani
BDF 1 Abolfazl Mehdizadeh
BDF 1 Elaheh Sariri
CDE 2 Mansour Rezaei
ABDEFG 3 Alireza Almasi
ABDEFG 3 Hossein Akbari
ABDEFG 1 Abdolreza Pazouki
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BDF 4 Jila Amirkhani
BDF 1 Shahla Chaichian
BDF 1 Mansoureh Vahdat
BDF 1 Ashrafsadat Moosavi
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BDF 1 Zeinab Tamannaei

1 Minimally Invasive Surgery Research Center, Tehran University of Medical Sciences, Tehran, Iran
2 Community Development and Health Research Center of Kermanshah University of Medical Sciences, Kermanshah, Iran
3 Tehran University of Medical Sciences, Tehran, Iran
4 Azad University of Medical Sciences, Tehran, Iran

Background: To compare efficacy of simvastatin with GnRHa (Decapeptyl 3.75 mg) on endometriosis-related pains following surgery for endometriosis.

Material/Methods: Sixty women with pelvic endometriosis, after laparoscopic diagnosis and conservative laparoscopic surgery, were treated with either simvastatin (n=30) for 16 weeks or Decapeptyl (n=30) every 4 weeks for 4 doses.

Results: Using VAS, the score of dyspareunia, dysmenorrhea, and pelvic pain 6 months after laparoscopic surgery declined significantly in both groups (p=0.001), but the difference between results of the 2 groups was not significant (p>0.05).

Conclusions: Both treatment modalities showed comparable effectiveness in the treatment of pains related to endometriosis.

Original Paper

European Surgical Research

Eur Surg Res 2007;39:98–102
DOI: 10.1159/000099156

Received: September 14, 2006
Accepted after revision: November 29, 2006
Published online: February 1, 2007

The Role of Simvastatin on Postoperative Peritoneal Adhesion Formation in an Animal Model

EDITORIAL

The Use of Statins in Postoperative Adhesion Prevention

J. B. C. van der Wal, MD, and J. Jeekel MD, PhD

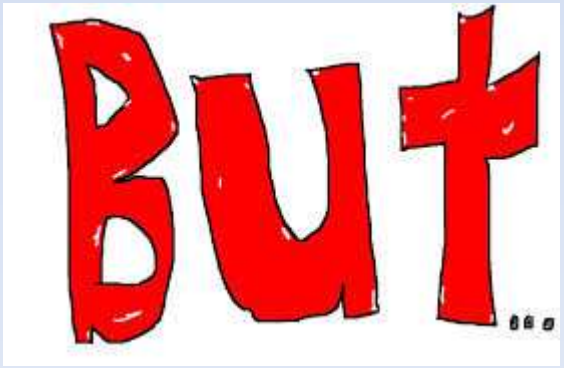
FEATURE

Statins (HMG-CoA Reductase Inhibitors) Decrease Postoperative Adhesions by Increasing Peritoneal Fibrinolytic Activity

Cary B. Aarons, MD, Philip A. Cohen, MD,* Adam Gower, MS,* Karen L. Reed, PhD,* Susan E. Leeman, PhD,† Arthur F. Stucchi, PhD,* and James M. Becker, MD, FACS**


Magic Pill


You -are-
the
Perfect Drug
&
I'm addicted to
-you-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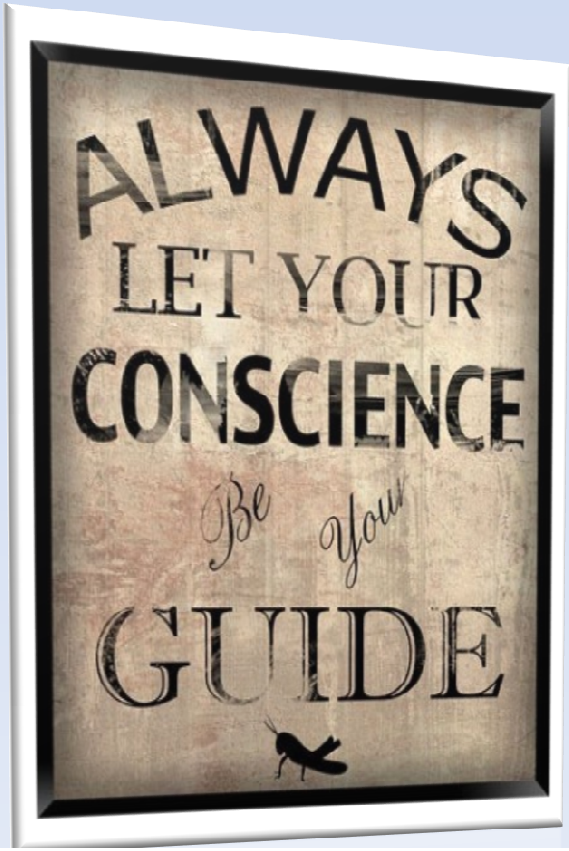
ALWAYS
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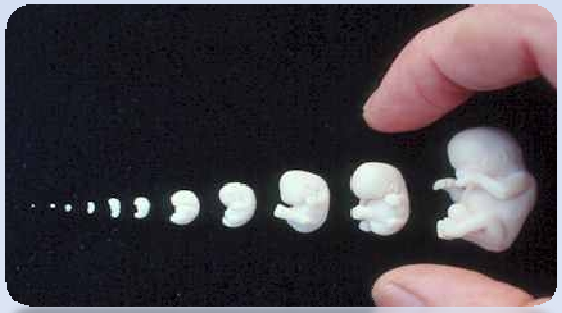
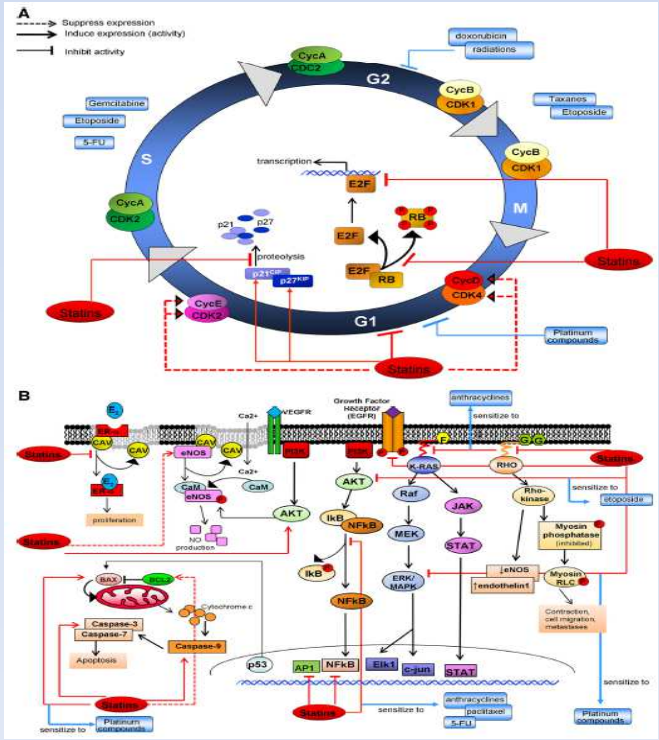
CONSCIENCE
Be your
GUIDE


Reflect

Although the patient selection was random, in patients who wanted to become pregnant immediately, we had the obligation to prescribe simvastatin rather than GnRHa. None of the patients had a history of previous surgery or GnRHa treatment. We followed the patients for continuation of drugs and adverse effects of simvastatin.





Human Reproduction Vol.20, No.10 pp. 2866–2872, 2005 doi:10.1093/humrep/dei120
Advance Access publication June 15, 2005.

Simvastatin has deleterious effects on human first trimester placental explants

I.Kenis[1], S.Tartakover-Matalon[1,5], N.Cherepnin[2], L.Drucker[1], A.Fishman[3], M.Pomeranz[3] and M.Lishner[1,4]

[1]Oncogenetic Laboratory, Department of Internal Medicine 'A', [2]Department of Internal Medicine 'F' and [3]Department of Obstetrics & Gynecology, Sapir Medical Center, Kfar-Saba and [4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[5]To whom correspondence should be addressed at: Oncogenetic Laboratory, Sapir Medical Center, 45 Tshernehovski Str., Kfar-Saba 44281, Israel. E-mail: matalon.shelly@clalit.org.il

BACKGROUND: Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMG-CoA reductase), the rate-limiting enzyme of the mevalonate pathway, and have been used successfully in the treatment of hypercholesterolaemia. Animal models have provided evidence for the teratogenic effects of statins on pregnancy outcome. Thus statins are contraindicated during pregnancy. However, conflicting data are available from inadvertent use of statins in human pregnancy. Therefore we decided to explore the effects of simvastatin on the placenta in an *in vitro* human placental model. METHODS: Human first trimester placental explants that were grown on matrigel were exposed to medium supplemented with simvastatin. Migration of extravillous trophoblast cells was assessed by visual observation. Proliferative and apoptotic events of the trophoblast cells were assesed by immunohistochemical examination using anti-Ki67 and anti-activated caspase-3 antibodies respectively. Hormone levels were measured. RESULTS: Simvastatin sharply inhibited migration of extravillous trophoblast cells from the villi to the matrigel ($P < 0.05$). Moreover, simvastatin inhibited half of the proliferative events in the villi ($P < 0.05$) and increased apoptosis of cytotrophoblast cells compared to control. Moreover, simvastatin significantly decreased secretion of progesterone from the placental explants ($P < 0.01$). CONCLUSION: Simvastatin adversely affects human first trimester trophoblast.

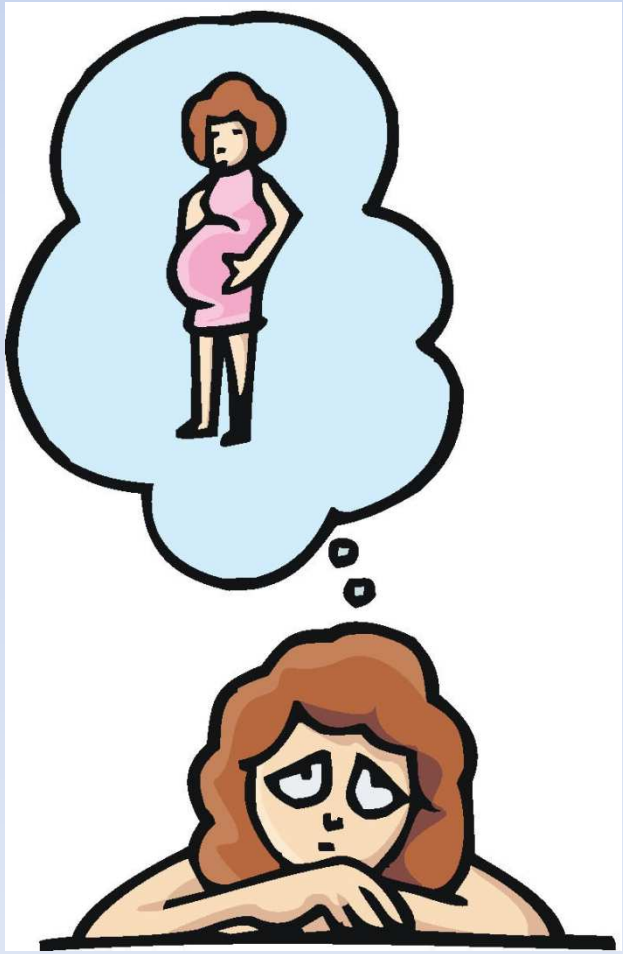
REVIEW ARTICLE
Drugs 2012; 72 (6): 773-788
0012-6667/12/0006-0773/$55.55/0

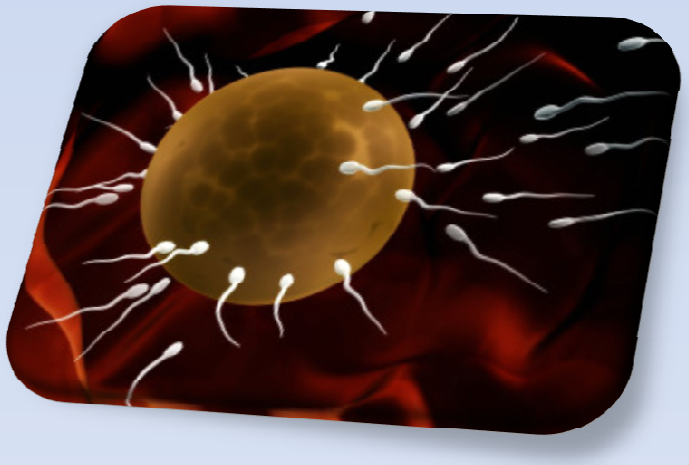
Statins and Pregnancy

Between Supposed Risks and Theoretical Benefits

Edouard Lecarpentier,[1] *Olivier Morel,*[2] *Thierry Fournier,*[3] *Elisabeth Elefant,*[4] *Pascale Chavatte-Palmer*[5,6] and *Vassilis Tsatsaris*[1,3,6]

In this review we evaluate the theoretical benefits and supposed risks of statins in pregnant women. After a brief overview of the pharmacodynamic properties of statins, we address the question of the teratogenic risk of statins, and then detail the rationale for the therapeutic potential of statins in preeclampsia. The teratogenic risk attendant upon use of statins is unclear because the available data are contradictory, but statins remain contraindicated in pregnant women.





MOLECULAR REPRODUCTION AND DEVELOPMENT 73:1277–1283 (2006)

Depletion of Substrates for Protein Prenylation Increases Apoptosis in Human Periovulatory Granulosa Cells

EMILIA RUNG,[1] P. ANDERS FRIBERG,[1] CHRISTINA BERGH,[2] AND HÅKAN BILLIG[1]*

BIOLOGY OF REPRODUCTION 72, 538–545 (2005)
Published online before print 22 September 2004.
DOI 10.1095/biolreprod.104.033878

Progesterone-Receptor Antagonists and Statins Decrease De Novo Cholesterol Synthesis and Increase Apoptosis in Rat and Human Periovulatory Granulosa Cells In Vitro[1]

Emilia Rung,[3] P. Anders Friberg,[3] Ruijin Shao,[3] D.G. Joakim Larsson,[3] Eva Ch. Nielsen,[3] Per-Arne Svensson,[4] Björn Carlsson,[4] Lena M.S. Carlsson,[4] and Håkan Billig[2,3]

Department of Physiology and Pharmacology[3] and Research Centre for Endocrinology and Metabolism, Department of Internal Medicine,[4] Göteborg University, SE-40530 Göteborg, Sweden

ORIGINAL ARTICLE

Endocrine Research

Statins Inhibit Growth of Human Theca-Interstitial Cells in PCOS and Non-PCOS Tissues Independently of Cholesterol Availability

Anna Sokalska, Piotr C. Piotrowski, Izabela J. Rzepczynska, Amanda Cress, and Antoni J. Duleba

The NEW ENGLAND JOURNAL of MEDICINE

TITLE PAGE

May long term statin use for endometriosis treatment reduce the fertility of young women who have not completed their reproductive program?

Amerigo Vitagliano[1]M.D, Salvatore Gizzo[1]M.D, Marco Noventa[1]M.D. & Giovanni Battista Nardelli

1 - Department of Woman and Child Health – University of Padua, Padua, Italy

Running Title: evidence on statin use and fertility impairment.

Keywords: statin use; endometriosis; infertility; ovarian reserve; periconceptional exposure.

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