Endometrium and ART: Any contradiction?

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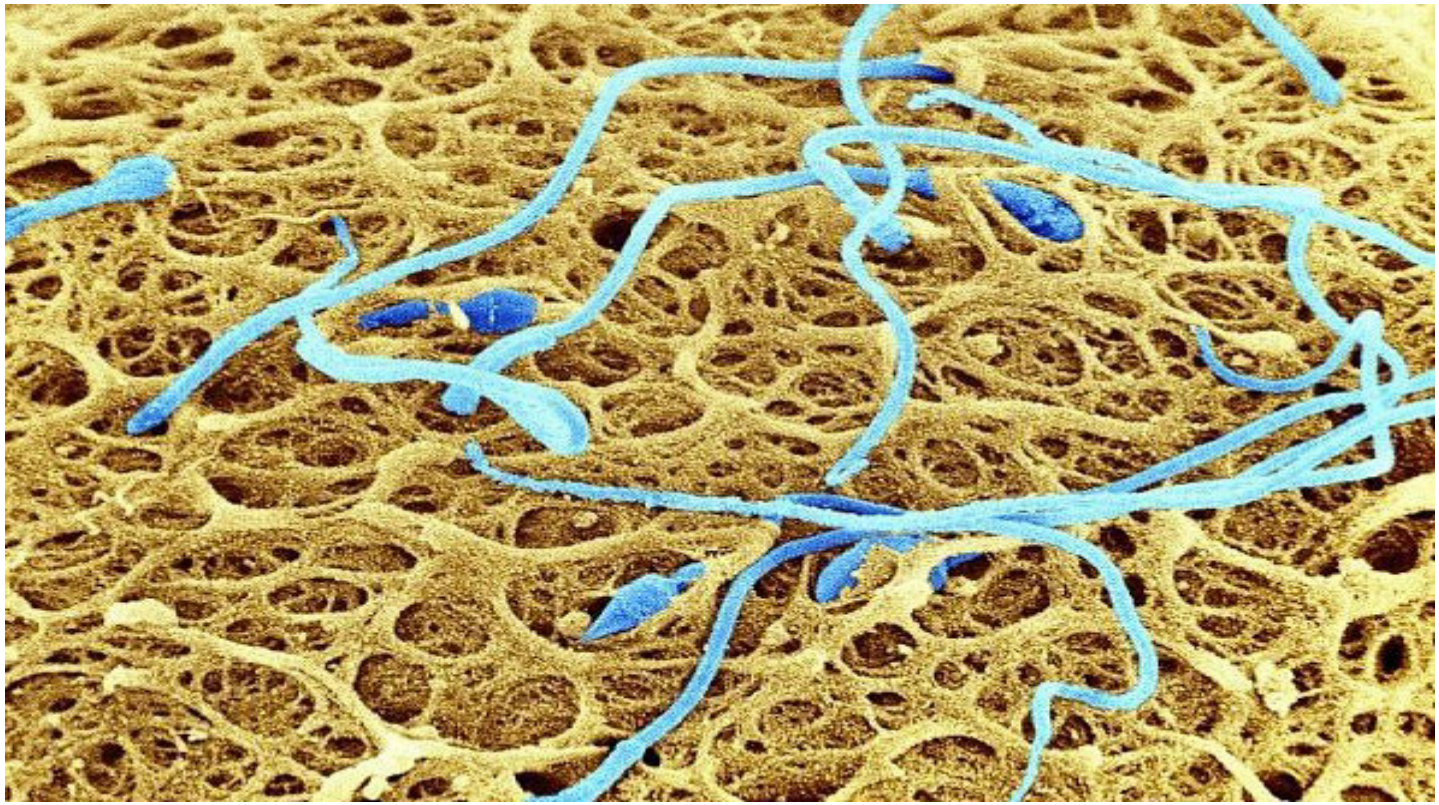
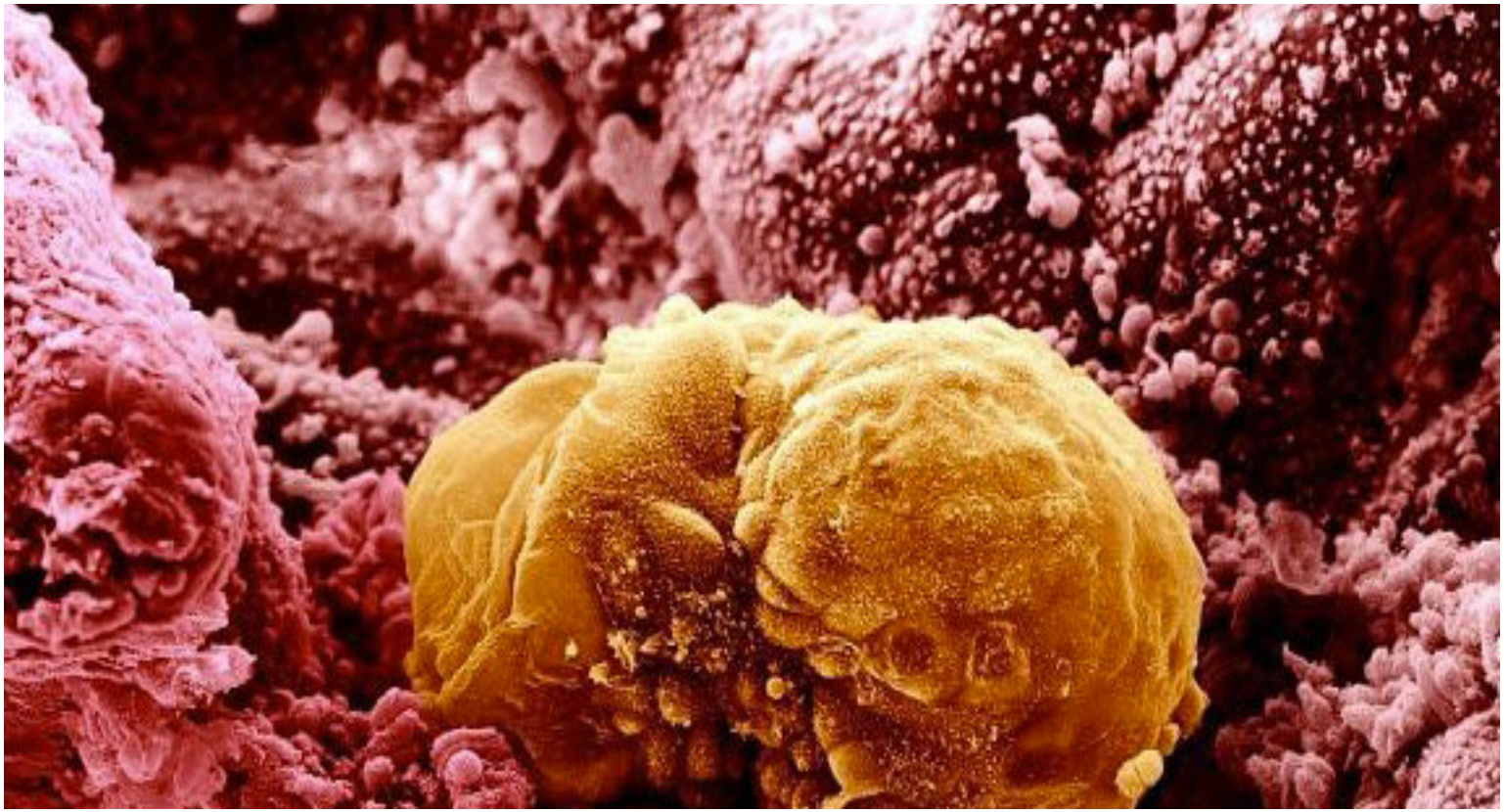
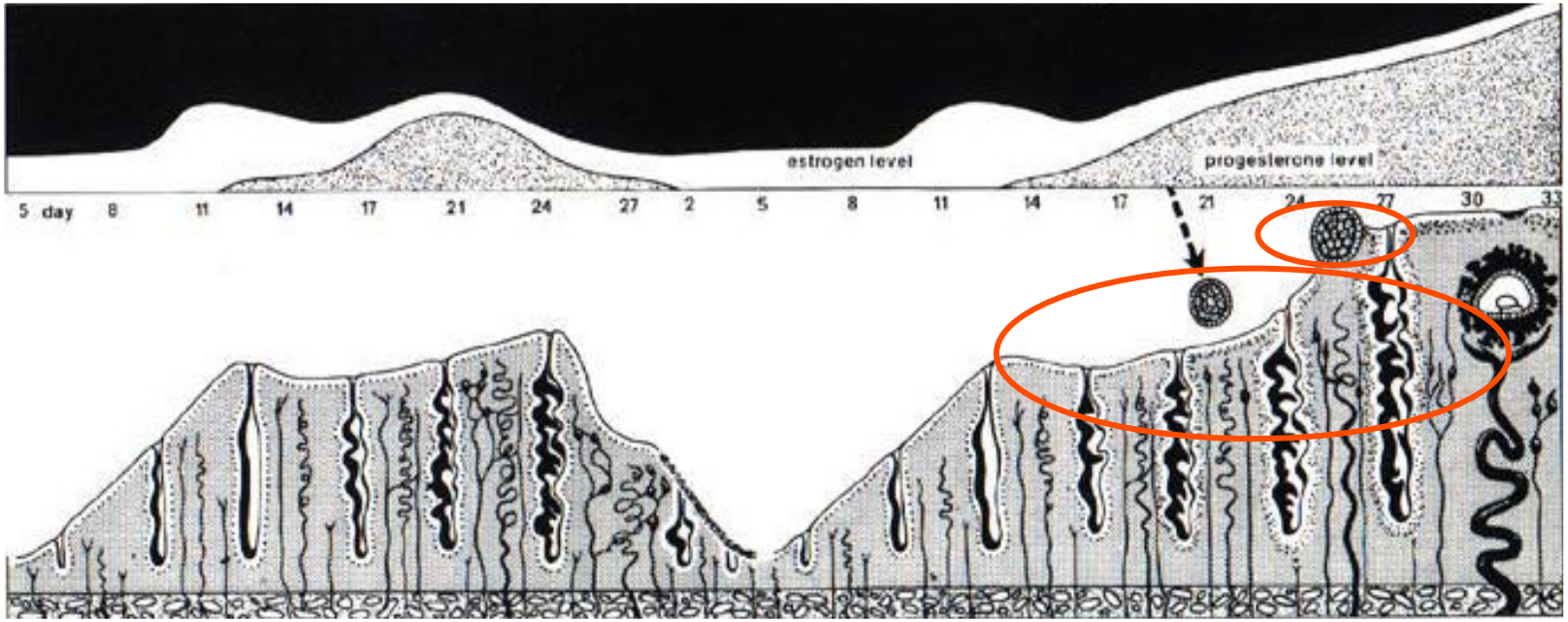
Importance of Oocyte and sperm



Embryo implantation



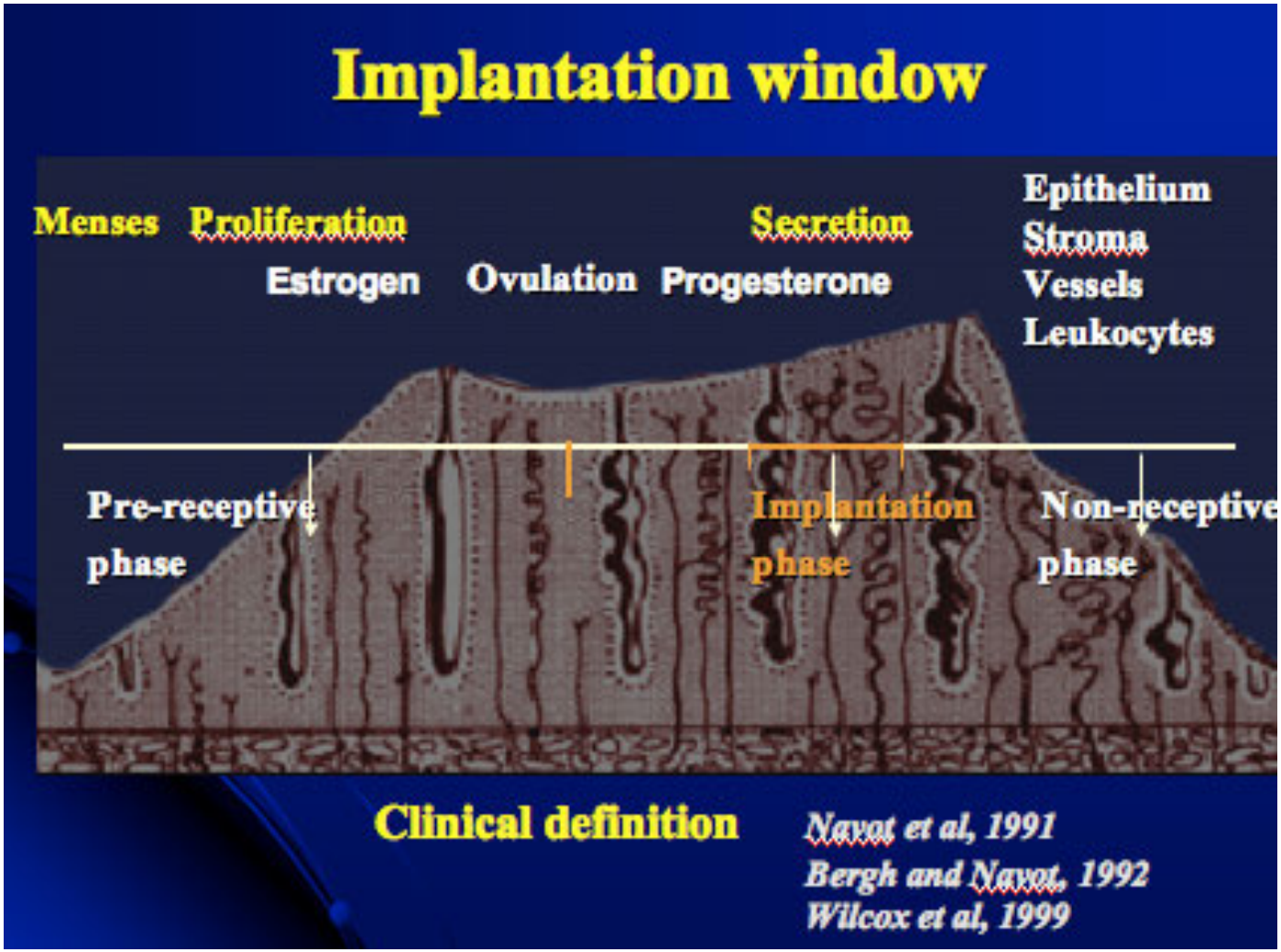


E **embryo quality**

U **endometrial receptivity**

IVF pregnancy $1-[(1-U)+U(1-E)^n]$

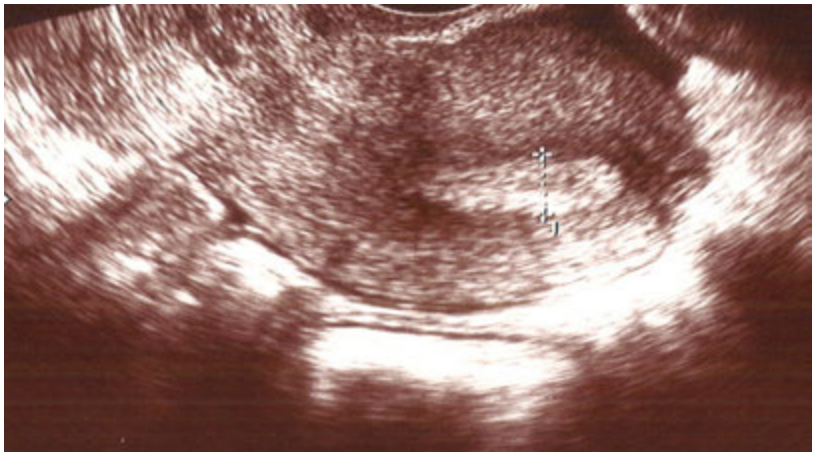
Rogers et al, 1986

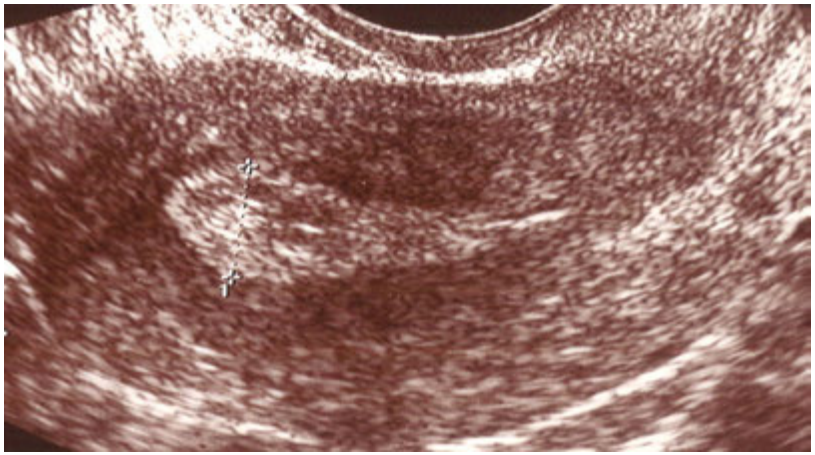

Implantation window
Menses
Proliferation
Estrogen
Ovulation
Secretion
Progesterone
Epithelium
Stroma
Vessels
Leukocytes
Pre-receptive phase
Implantation phase
Non-receptive phase
Clinical definition
Navot et al, 1991
Bergh and Navot, 1992
Wilcox et al, 1999

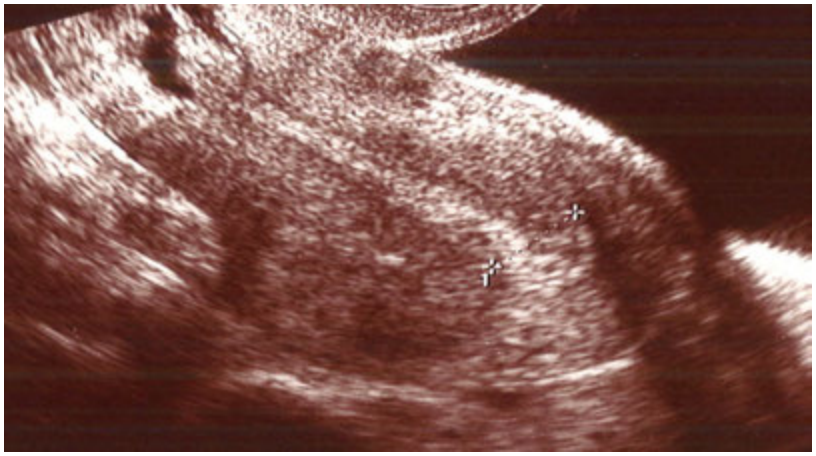
- Even though the blastocyst can implant in different human tissues, surprisingly in the endometrium, this phenomenon can only occur during a self-limited period spanning between days 20 and 24 of a regular menstrual cycle (day LH+7 to LH+11)

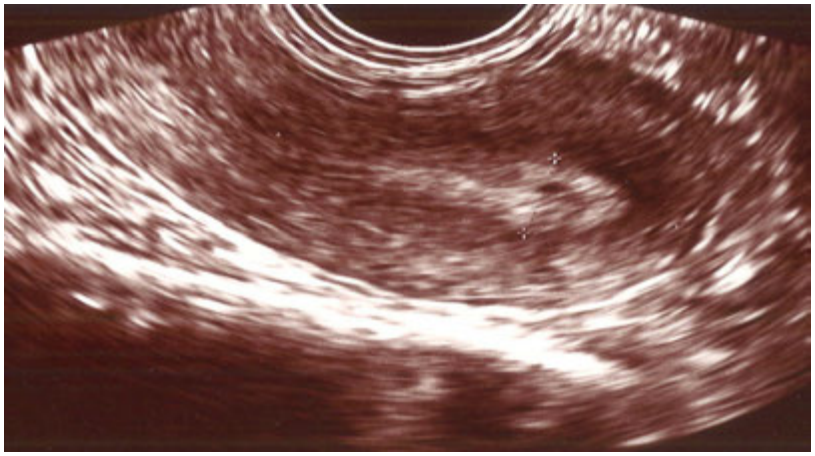
Psychoyos et al.,1973

Human endometrium: US









Zondek et al. 1930

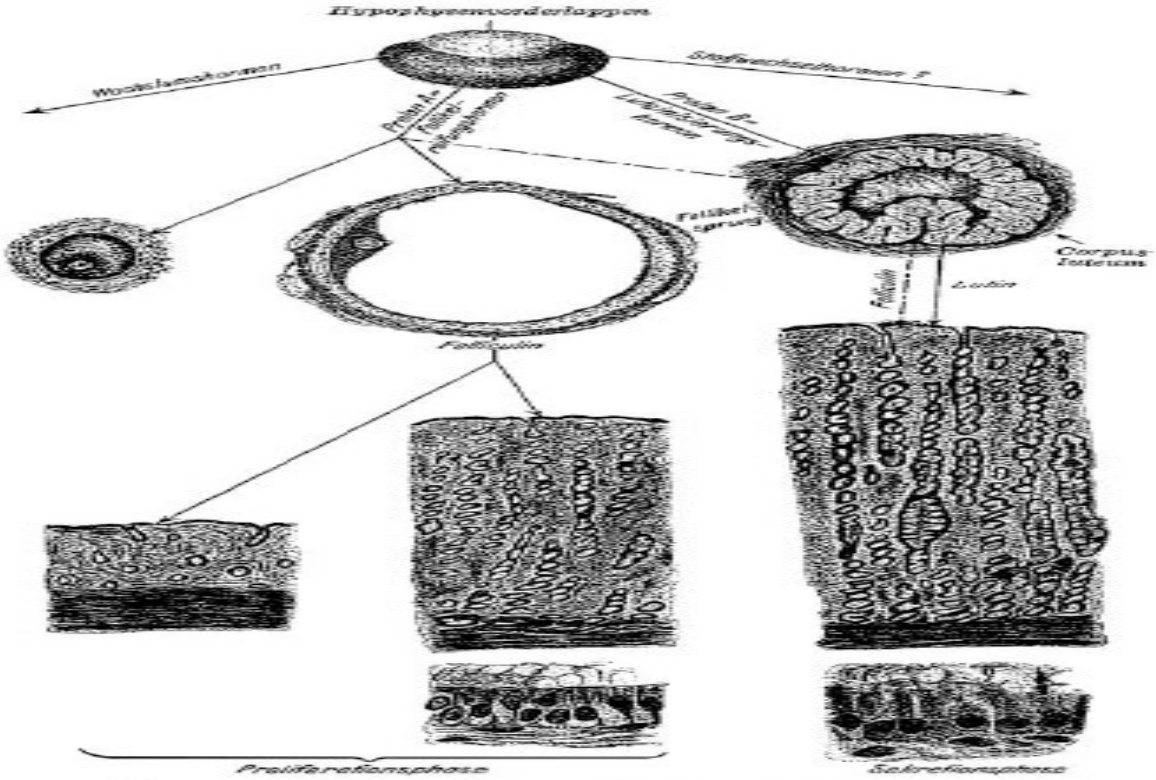
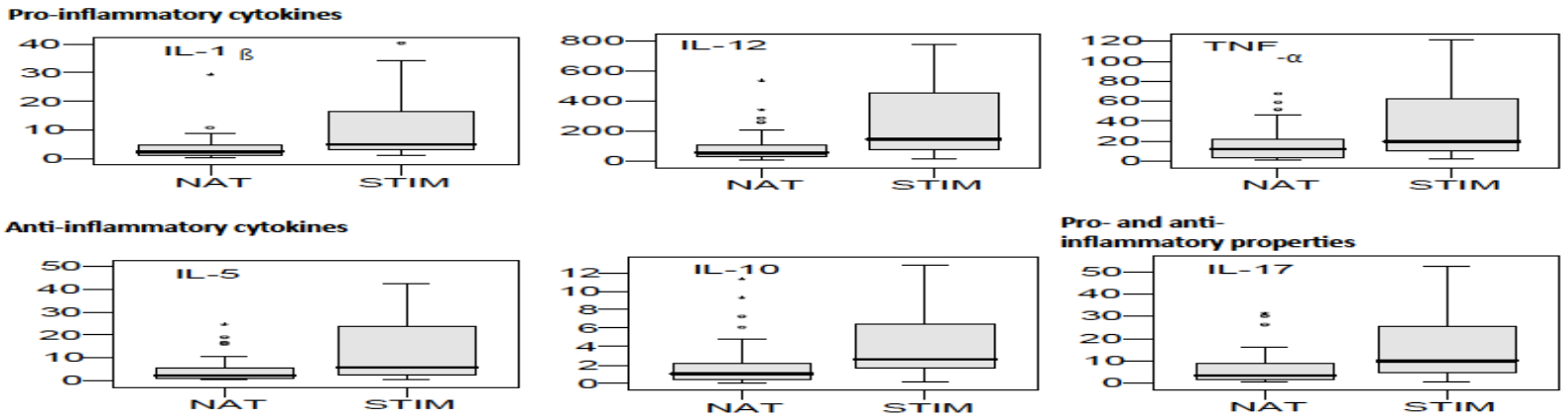


Abb. 1. Hypophysenvorderlappen und Genitalfunktion des Weibes.

Figure 1. Zondek's illustration of the relationship between the hypothalamus, pituitary, ovaries, and endometrium (Zondek, 1930). Reprinted by permission from Zondek (1930), Ueber die Hormones des Hypophysenvorderlappens. Klin Wochenschrift 9,245–248, Copyright Springer Verlag.

Ovarian stimulation: intrauterine cytokine profile

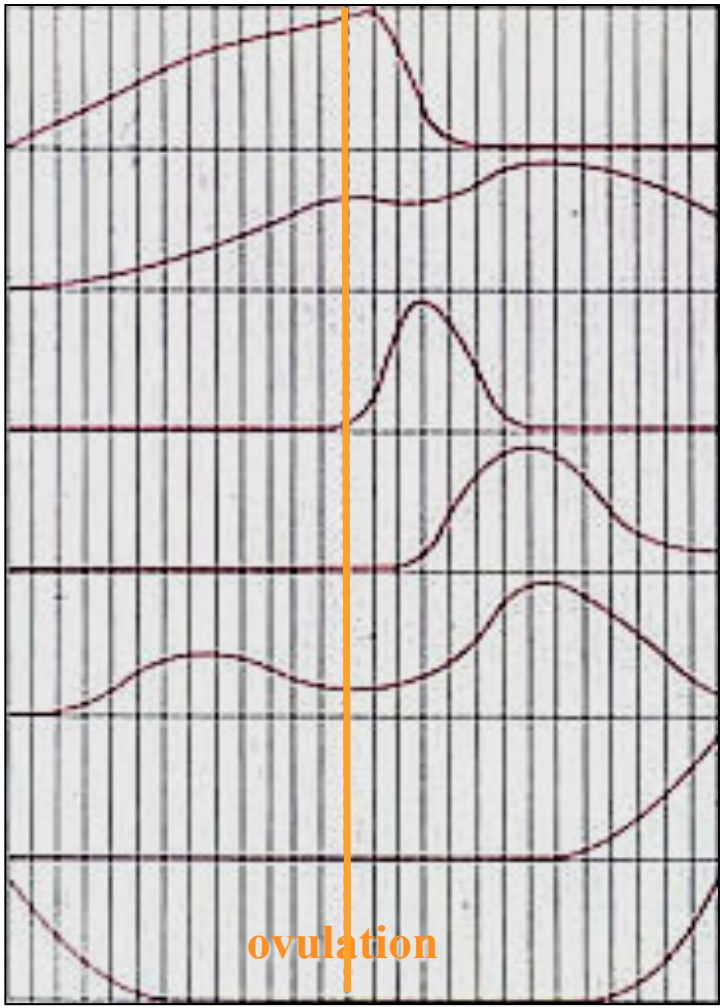


Multivariable analysis in 203 patients showed significant relations between the number of oocytes retrieved and secretion concentrations of IL-12, Dkk-1 (positive) and VEGF, IL-15 (negative).

Boomsma et al. Fertil Steril 2010

Endometrial dating

1 14 28



GLAND MITOSES

TORTUOSITY OF GLANDS

BASAL VACUOLATION

SECRETION

STROMAL EDEMA

PSEUDODECIDUAL REACTION

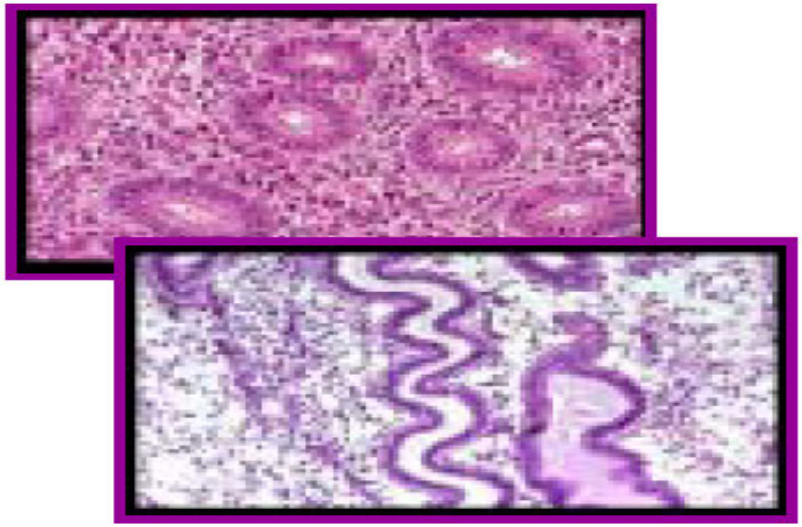
LEUKOCYTIC INFILTRATE

Noyes et al. Fertil Steril, 1950

Noyes criteria=dating

1. Gland mitosis
2. Pseudo-stratification of nuclei
3. Basal vacuolation
4. Secretion
5. Stromal edema
6. Pseudo-decidual reaction
7. Stromal mitosis
8. Leukocytic infiltration

"Out of phase": >2 days delay



Noyes et al. Fertility and sterility 1950

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Histological findings

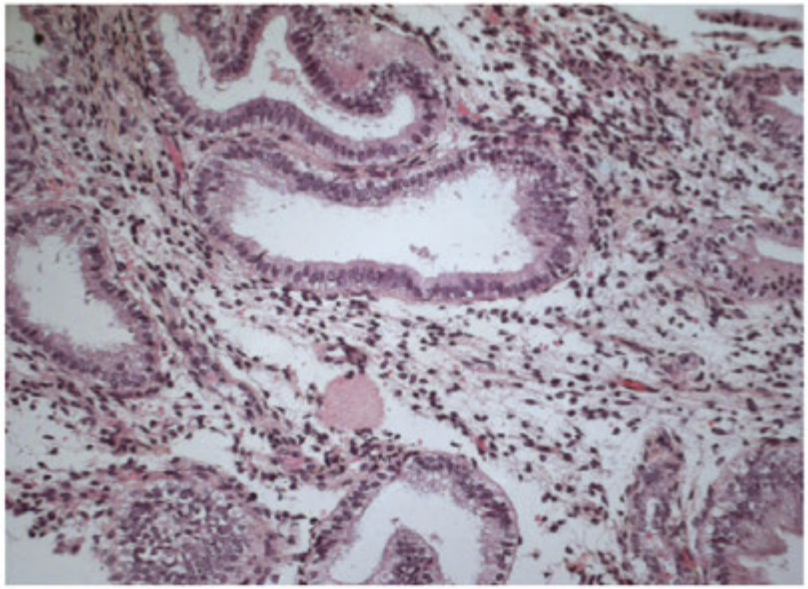


Figure 1. Representative endometrial biopsy on day 21 of an artificial cycle after micronized progesterone. Patients with premature ovarian failure received estrogen from days 1 to 21 and vaginal progesterone from days 15 to 21. (Coiled glands with active secretion and minimal residual vacuoles. Stromal oedema.) Absence of mitotic activity. The maturation corresponds to day 6 of the luteal phase (haematoxylin and eosin staining, x 200).

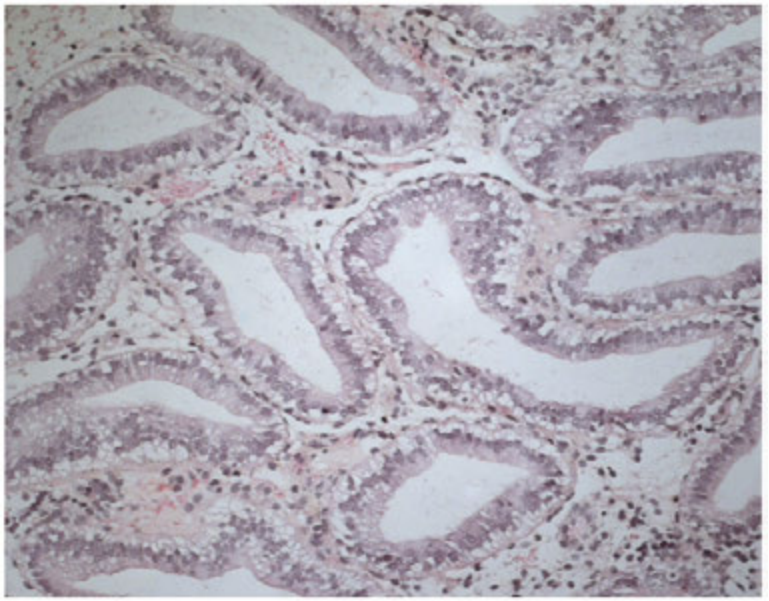
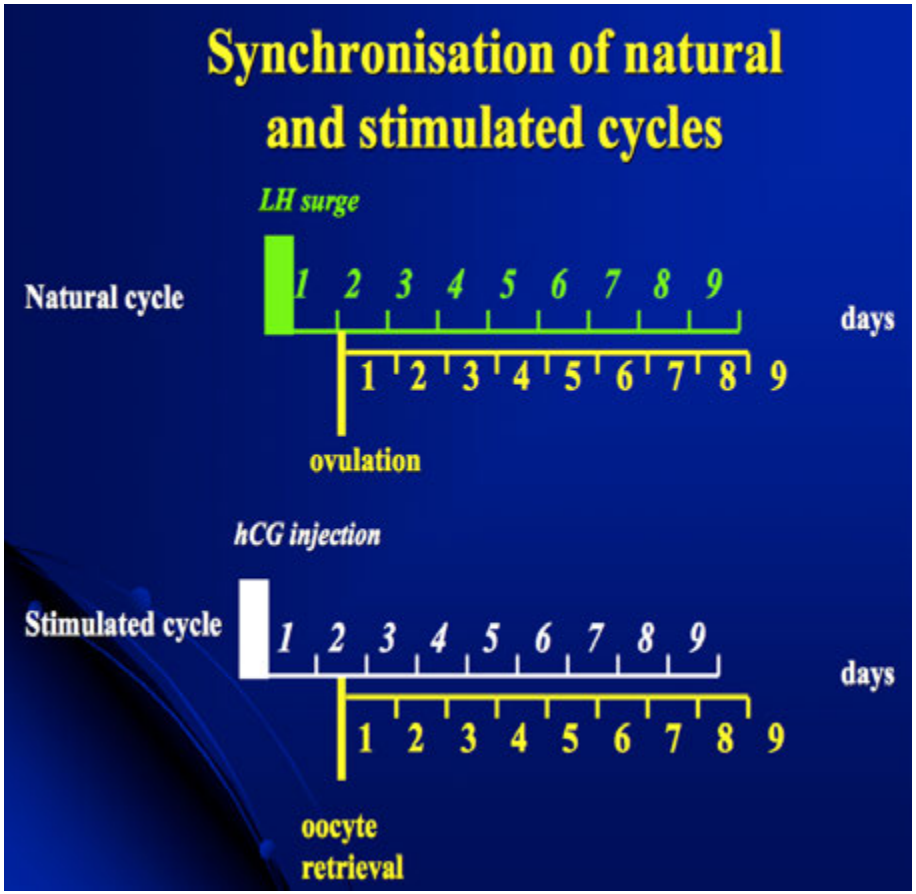
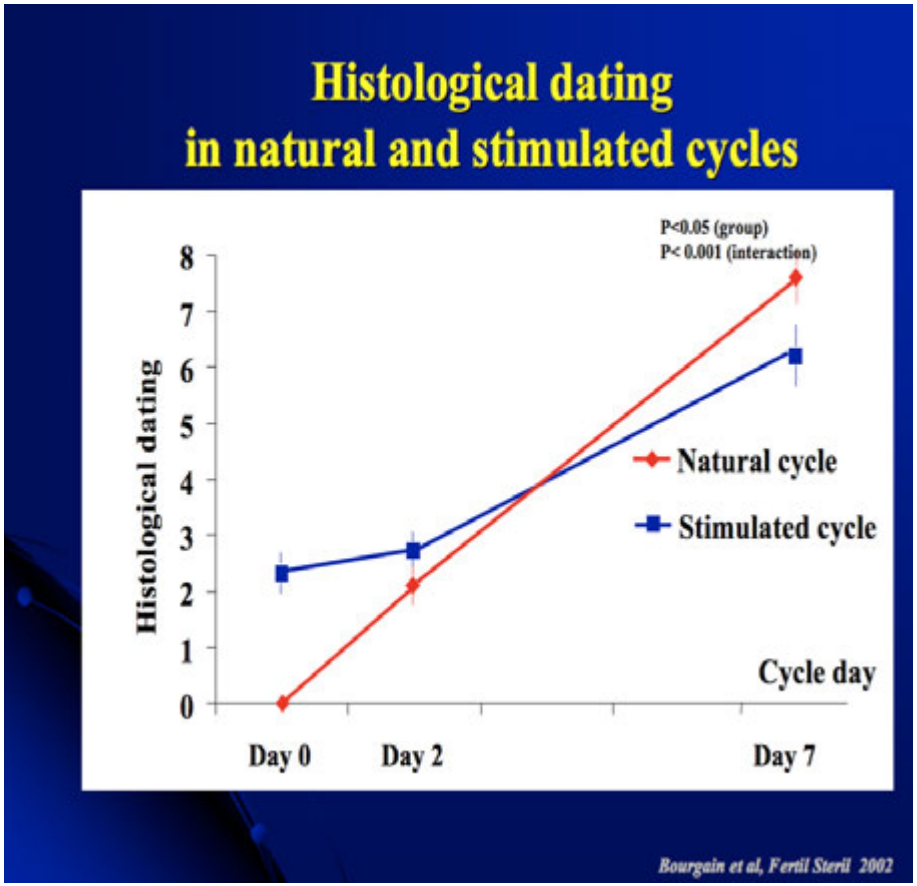


Figure 2. Representative endometrial biopsy on day 21 of an artificial cycle after oral dydrogesterone. Small glands with minimal coiling and persistant homogeneous subnuclear vacuoles and pseudostratified nuclei. (No stromal edema. Focal mitotic activity.) The maturation corresponds to days 2–3 of the luteal phase (haematoxylin and eosin staining, x 200)

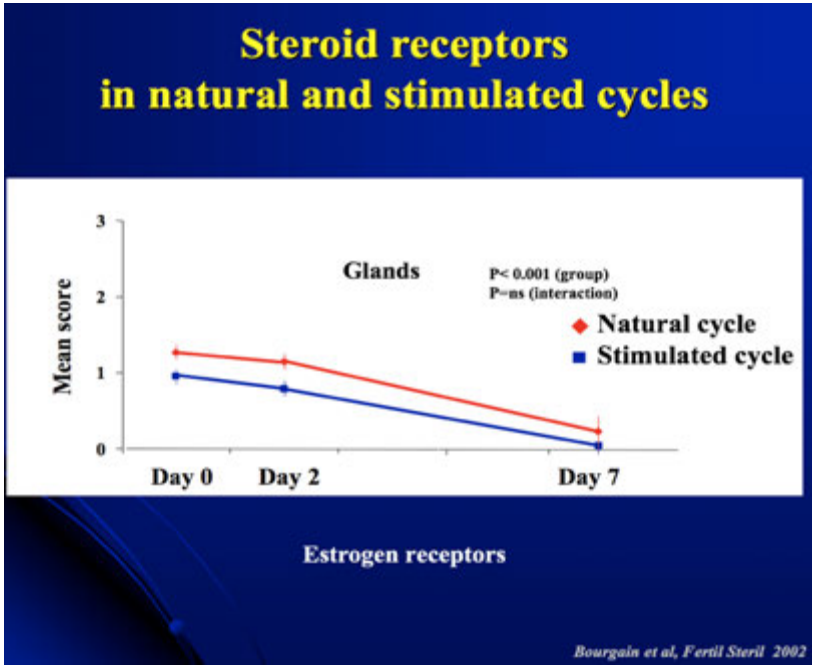
Fatemi et al., Human Reproduction, 2007

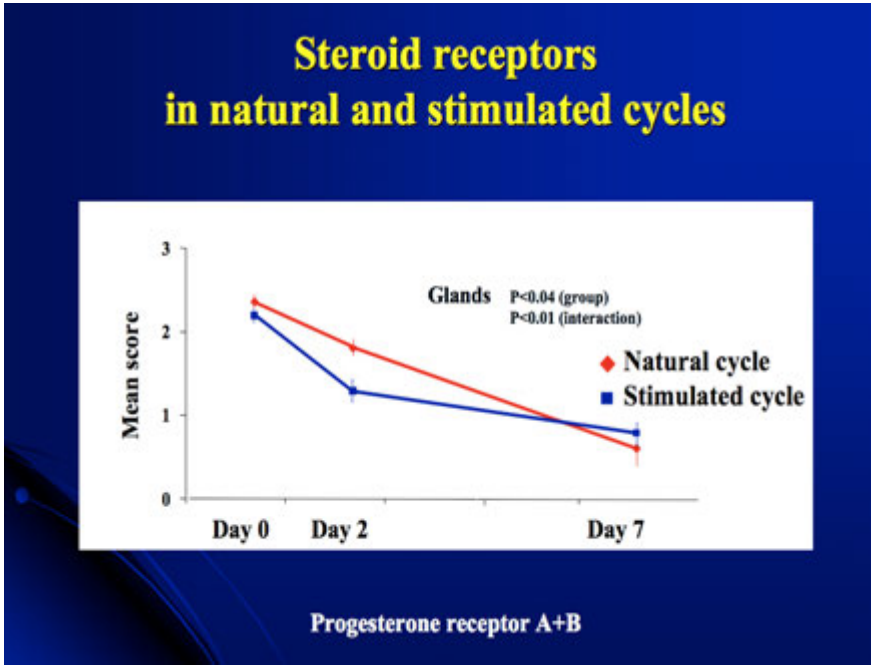
ART and endometrial advancement





ART and endometrial advancement an outcome



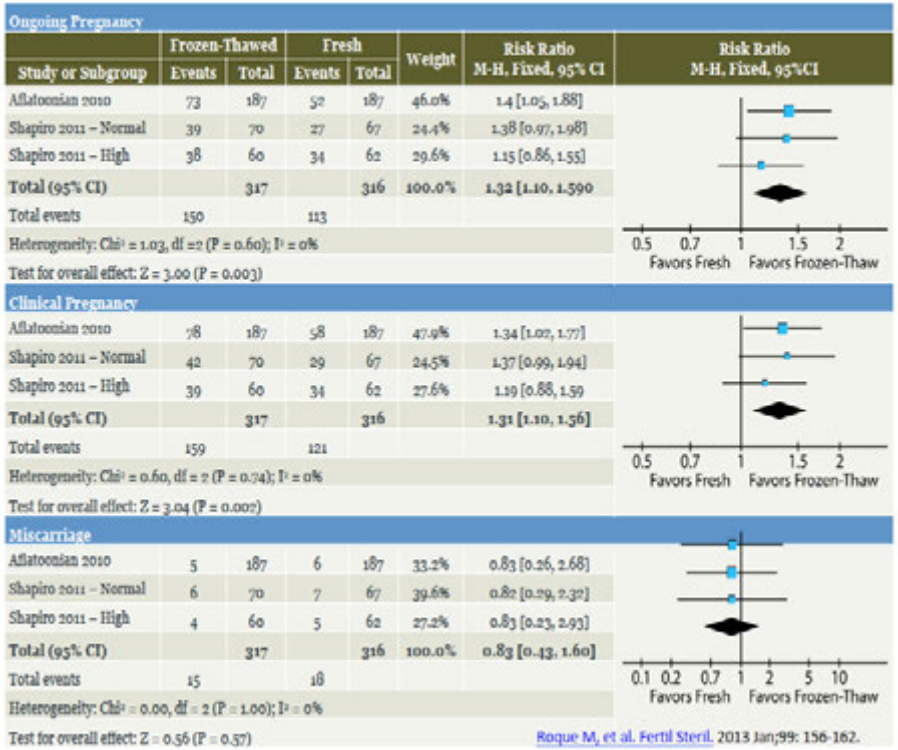


Endometrial morphology and pregnancy

	Cell type	Pregnant	Not pregnant	p-value
Histological dating		2.18 (0.22)	2.86 (0.15)	P<0.039

Fresh vs Fret: Quid?

Meta-analysis results



Study or Subgroup	Frozen-Thawed Events	Frozen-Thawed Total	Fresh Events	Fresh Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ongoing Pregnancy						
Aflatoonian 2010	73	187	52	187	46.0%	1.4 [1.05, 1.88]
Shapiro 2011 – Normal	39	70	27	67	24.4%	1.38 [0.97, 1.98]
Shapiro 2011 – High	38	60	34	62	29.6%	1.15 [0.86, 1.55]
Total (95% CI)		317		316	100.0%	1.32 [1.10, 1.590
Total events	150		113			
Heterogeneity: Chi² = 1.03, df =2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 3.00 (P = 0.003)						
Clinical Pregnancy						
Aflatoonian 2010	78	187	58	187	47.9%	1.34 [1.02, 1.77]
Shapiro 2011 – Normal	42	70	29	67	24.5%	1.37 [0.99, 1.94]
Shapiro 2011 – High	39	60	34	62	27.6%	1.19 [0.88, 1.59
Total (95% CI)		317		316		1.31 [1.10, 1.56]
Total events	159		121			
Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 3.04 (P = 0.002)						
Miscarriage						
Aflatoonian 2010	5	187	6	187	33.2%	0.83 [0.26, 2.68]
Shapiro 2011 – Normal	6	70	7	67	39.6%	0.82 [0.29, 2.32]
Shapiro 2011 – High	4	60	5	62	27.2%	0.83 [0.23, 2.93]
Total (95% CI)		317		316	100.0%	0.83 [0.43, 1.60]
Total events	15		18			
Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.56 (P = 0.57)						

Roque M, et al. Fertil Steril. 2013 Jan;99: 156-162.

Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis

Eleven studies met the inclusion criteria

- Singleton pregnancies after transfer of frozen thawed embryos were associated with better perinatal outcomes compared with those after fresh IVF embryo transfer

Lower relative risks (RR) and 95% confidence intervals (CI) after FET for:

	RR	95% CI
Antepartum haemorrhage	0.67	0.55–0.81
Preterm birth	0.84	0.78–0.90
Small for gestational age	0.45	0.30–0.66
Low birth weight	0.69	0.62–0.76
Perinatal mortality	0.68	0.48–0.96

Maheshwari A et al. Fertil Steril. 2013;100:1615-1621.

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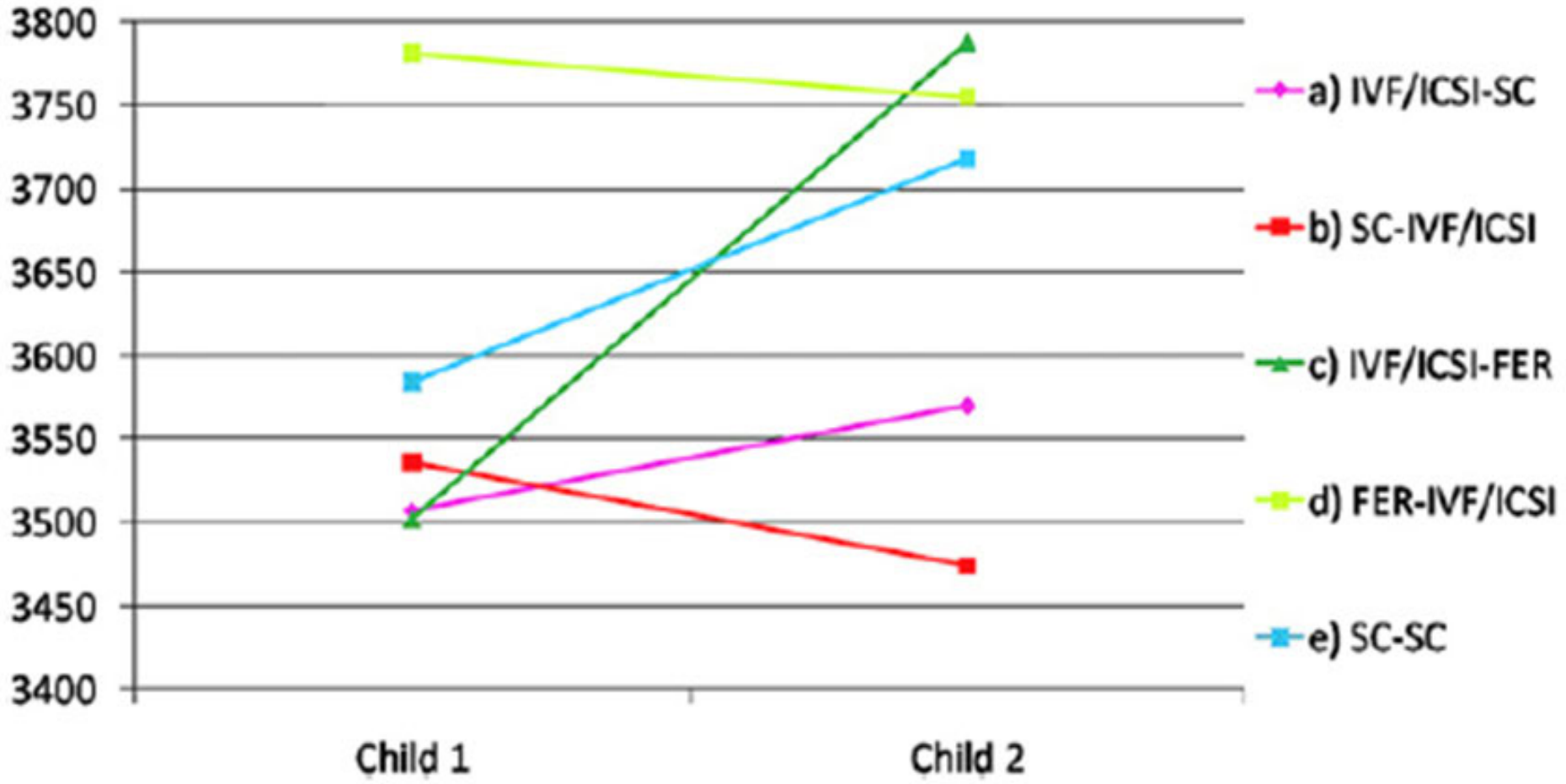
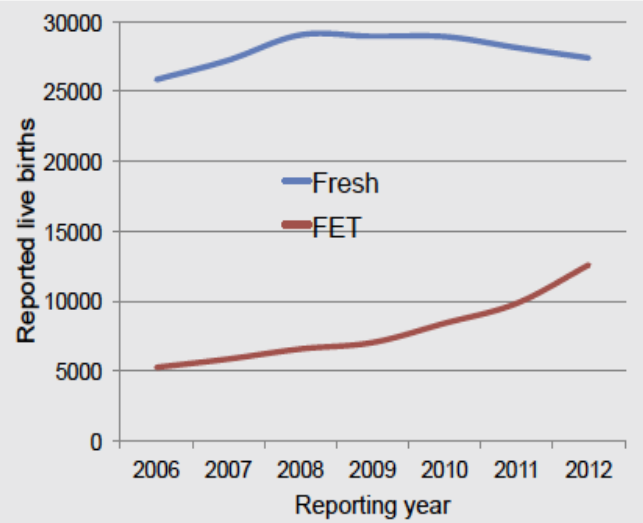
Danish sibling study



Henningsen AK, et al. Fertil Steril 2011;95:959–63.

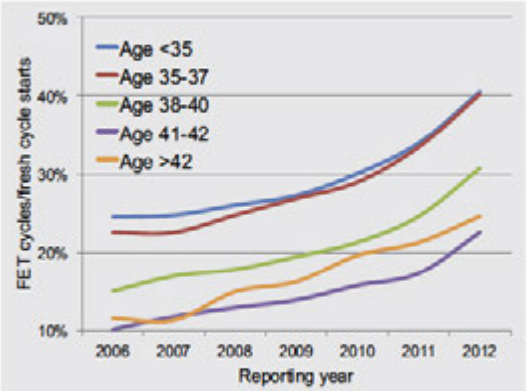
FET vs Fresh, anno 2014



Trends in estimated numbers of live births with fresh transfer and FET. These estimates were calculated by multiplying the reported numbers of cycles and the respective birth rates on SART's national report, and summing across age groups.

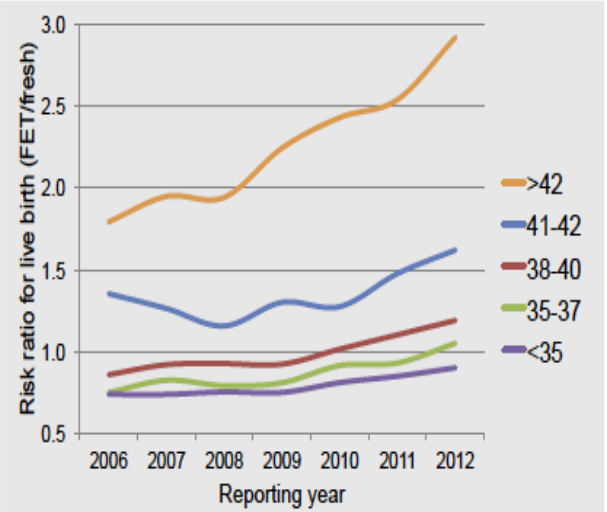
Shapiro. Cryopreservation of embryo cohorts. Fertil Steril 2014.

FIGURE 1



Trends in the ratio of the numbers of reported frozen–thawed embryo transfers to reported fresh cycle starts in each SART age group.

Shapiro. Cryopreservation of embryo cohorts. Fertil Steril 2014.



Trends in RR for live birth per transfer in FET vs. fresh transfer by SART age group. An RR exceeding 1.0 indicates greater birth rate with FET. By 2012 the birth rate per transfer with FET exceeded that for fresh transfer in the four oldest age groups.

Shapiro. Cryopreservation of embryo cohorts. Fertil Steril 2014.

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FET cycle regimen

Table I Overview of studies included in a meta-analysis to determine the optimal means of preparing the endometrium in FET cycles in patients undergoing IVF.

Study and year	Design	Population	Allocation	Outcome
True NC versus modified NC				
Chang et al. (2011)	Retrospective cohort	644 cycles (tNC 310, mNC 130, AC 204), ovulatory patients	Preference, costs	CP/OP
Fatemi et al. (2010)	RCT	124 cycles (tNC 61, mNC 63), ovulatory patients	Concealed allocation, non-blinded	OP
Tomax et al. (2012)	Retrospective cohort	4470 cycles (tNC 1019, mNC 444, AC 2858), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/LB
Weissman et al. (2009)	Retrospective cohort	132 cycles (tNC 71, mNC 61), ovulatory patients	Preference	CP/LB
Weissman et al. (2011)	RCT	55 cycles (tNC 30, mNC 25), ovulatory patients	Concealed allocation non-blinded	CP/OP/LB
NC versus AC				
Cattoli (1994)	RCT	100 cycles (AC 56, NC 44), ovulatory patients	Not stated	CP
Chang et al. (2011)	Retrospective cohort	644 cycles (tNC 310, mNC 130, AC 204), ovulatory patients	Preference, costs	CP/OP
Givens et al. (2009)	Retrospective cohort	807 cycles (NC 602, AC 205), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/LB
Handke et al. (2012)	Retrospective cohort	203 cycles (NC 148, AC 55), ovulatory and anovulatory patients	Not stated	CP
Kawamura (2007)	Retrospective cohort	856 cycles (NC 720, AC 136), ovulatory patients	Preference	ChP/CP/LB
Loh and Leong (1999)	Retrospective cohort	212 cycles (NC 51, AC 161), ovulatory patients	Preference	CP/LB
Morozov et al. (2007)	Retrospective cohort	242 cycles (AC 174, NC 68), ovulatory patients	Not stated	CP
Tomax et al. (2012)	Retrospective cohort	4470 cycles (tNC 1019, mNC 444, AC 2858), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/LB
Xiao et al. (2011)	Retrospective cohort	1020 cycles (NC 380, AC 640), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/OP
NC versus AC with GnRH				
al Shawaf et al. (1993)	Retrospective cohort	149 cycles (AC 72, NC 77), ovulatory and anovulatory patients	Age, cycle characteristics	CP
Gelbaya et al. (2006)	Retrospective cohort	417 cycles (NC 212, AC + GnRH 205), ovulatory patients	Changed protocol	CP/LB
Hill et al. (2010)	Retrospective cohort	1391 cycles (NC 240, AC + GnRH 1151), ovulatory and anovulatory patients	Preference, cycle characteristics	ChP/CP/LB
Queenan et al. (1994)	Retrospective cohort	528 cycles (NC 398, AC + GnRH 230), ovulatory and anovulatory patients	Cycle characteristics	CP/OP
Tanos et al. (1996)	Quasi-randomized	304 cycles (NC 219, AC + GnRH 85), ovulatory and anovulatory patients	Preference, cycle characteristics	CP
AC versus AC with GnRH				
Dal Prato et al. (2002)	RCT	296 cycles (AC 150, AC + GnRH 145), ovulatory patients	Concealed allocation, non-blinded	CP
El Toukhy et al. (2004)	RCT	234 cycles (AC 117, AC + GnRH 117), ovulatory patients	Concealed allocation, non-blinded	CP/LB
Simon et al. (1998)	RCT	106 cycles (AC 53, AC + GnRH 53), ovulatory and anovulatory patients	Not stated	CP/OP

AC, artificial FET cycle; mNC, modified natural cycle FET; AC with GnRH, artificial with GnRH cycle; NC, natural cycle; CP, clinical pregnancy; OP, ongoing pregnancy; LB, life birth; tNC, true natural cycle FET.

Groenwoud et al, 2013

IVI GCC

Cryopreserved-thawed human embryo transfer: spontaneous natural cycle is superior to human chorionic gonadotropin–induced natural cycle

Human Mousavi Fatemi, M.D., Ph.D.,[a] *Dimitra Kyrou, M.D.,*[a] *Claire Bourgain, M.D., Ph.D.,*[b] *Etienne Van den Abbeel, Ph.D.,*[c] *Georg Griesinger, M.D., Ph.D.,*[d] *and Paul Devroey, M.D., Ph.D.*[a]

[a] Center for Reproductive Medicine, [b] Department of Pathology, and [c] Department of Embryology, Dutch-Speaking Free University Brussels, Brussels, Belgium; and [d] Department of Obstetrics and Gynecology, Campus Luebeck, University Clinic of Schleswig-Holstein, Luebeck, Germany

Objective: To assess whether there is a difference in the ongoing pregnancy rate after transferring frozen-thawed embryos in natural cycles with spontaneous LH-P rise compared with natural cycles controlled by hCG for final oocyte maturation and ovulation.
Design: Randomized controlled trial.
Setting: Tertiary referral center.
Patient(s): A total of 168 patients were assigned randomly to undergo frozen ET on day 3 from October 2007 until November 2008. Finally, analysis was performed in 124 patients; 61 belonged to the spontaneous LH group and 63 to the hCG group.
Intervention(s): In the spontaneous LH group the transfer was planned 5 days after the LH surge. In the hCG group, the cryopreserve ET was planned 5 days after the administration of 5000 IU of hCG, when an endometrial thickness of $\geq$7 mm and a follicle of $\geq$17 mm were present on ultrasound examination.
Main Outcome Measure(s): Ongoing pregnancy rate.
Result(s): The study was terminated early, when a prespecified interim analysis found a significantly higher ongoing pregnancy rate in the spontaneous LH group as compared with the hCG group (31.1% vs. 14.3%; difference 16.9%, 95% confidence interval 4.4%–28.8%).
Conclusion(s): The results suggest the superiority of the natural cycle as compared with the natural cycle controlled by hCG administration in cryothawed ET cycles. (Fertil Steril® 2010;94:2054–8. ©2010 by American Society for Reproductive Medicine.)

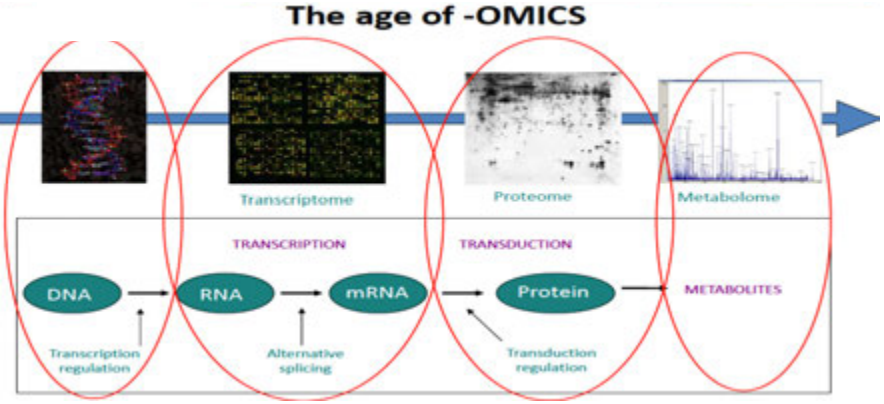
Key Words: Cryopreserved-thawed embryo transfer, FET, human chorionic gonadotropin, LH spontaneous

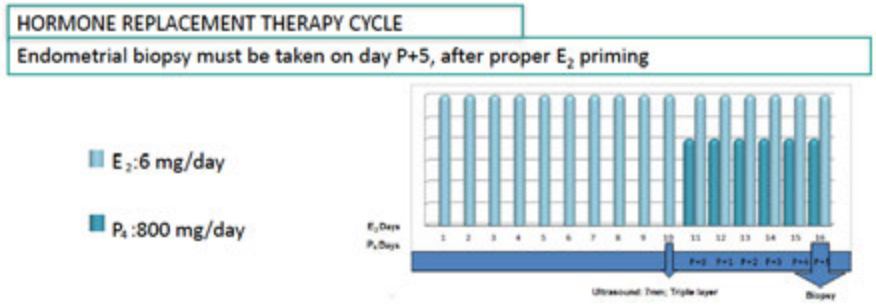
ERA

The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure

Maria Ruiz-Alonso, M.Sc.,[b] David Blesa, Ph.D.,[a,b] Patricia Díaz-Gimeno, Ph.D.,[a,c] Eva Gómez, M.Sc.,[a] Manuel Fernández-Sánchez, M.D.,[d] Francisco Carranza, M.D.,[d] Joan Carrera, M.D.,[e] Felip Vilella, Ph.D.,[a] Antonio Pellicer, M.D., Ph.D.,[a,b] and Carlos Simón, M.D., Ph.D.[a,b]

[a] Fundación Instituto Valenciano de Infertilidad, and Instituto Universitario IVIVincliva, Valencia University, Valencia; [b] Iviomics, Paterna; [c] Computational Medicine Institute, Centro de Investigación Principe Felipe, Valencia; [d] Instituto Valenciano de Infertilidad Sevilla, Seville; and [e] Clínica Girona Unidad de Reproducción Humana, Girona, Spain





Hum Reprod. 2014 Sep;29(9):1957-67. doi: 10.1093/humrep/deu171. Epub 2014 Aug 8.

Deciphering the proteomic signature of human endometrial receptivity.

Garrido-Gómez T[1], Quiñonero A[2], Antúnez O[3], Díaz-Gimeno P[2], Bellver J[2], Simón C[4], Domínguez F[5].

Fertil Ste

GENETICS

A genomic diagnostic tool fo
receptivity based on the tran

Patricia Díaz-Gimeno, Ph.D.,[a,b] José A. Horcajadas, Ph.D.,[c] Francisco J. Esteban, Ph.D.,[d] Pilar Alamá, M.D.,[a,b] Antonio

[a] Fundación IVI-Instituto Universitario IVI, University of Valencia, [b] Clínico de Valencia, Valencia University, Valencia; [c] iGenomix, Vale Jaén, Jaén; and [d] Centro de Investigación Príncipe Felipe, Valencia,

Objective: To create a genomic tool composed of a customi
domestrial dating and to detect pathologies of endometrial ori
endometrial receptivity.

Fertil Steril. 20

The accuracy and reprod
the endometrial receptiv
superior to histology as a
method for endometrial r

Patricia Díaz-Gimeno, Ph.D.,[a,b] María Ruiz-Alonso, Ph.D.,[c] David Blesa, Ph.D.,[c] José A. Martínez-Conejero, Ph.D.,[c] Pilar Alamá, M.D.,[d] Nicolás Garrido, Ph.D.,[b] and Carlos Simón, M.D.[a,b,c,d,e]

[a] Fundación IVI, Instituto Universitario Instituto Valenciano de Infertilidad, Univer Investigación Sanitaria, Hospital Clínico Universitario de Valencia; [c] INCLIVA; and [d] Valencia, Valencia, Spain

Objective: To compare the accuracy and reproducibility of the endometrial receptivity a

Fertil Steril.

The endometrial rece
diagnosis and person
transfer as a treatmer
with repeated implant

María Ruiz-Alonso, M.Sc.,[a] David Blesa, Ph.D.,[a,b] Patricia Díaz-Gimer Manuel Fernández-Sánchez, M.D.,[a] Francisco Carranza, M.D.,[a] Joan Antonio Pellicer, M.D., Ph.D.,[a,b] and Carlos Simón, M.D., Ph.D.[a,b]

[a] Fundación Instituto Valenciano de Infertilidad, and Instituto Universitar [b] Islámica, Paterna; [c] Computational Medicine Institute, Centro de Investi Valenciano de Infertilidad Sevilla, Seville; and [d] Clínica Gimna Unidad de Rep

Hum Reprod. 2014

human reproduction CASE REPORT *Infertility*

What a difference two days make:
"personalized" embryo transfer (pET)
paradigm: A case report and pilot study

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Fertil Steril. 2014

Impact of final oocyte maturation
using gonadotropin-releasing
hormone agonist triggering and
different luteal support protocols
endometrial gene expression

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Objective: To use microarray technology to analyze endometrial gene expression after gonadotropin-releasing h (GnRH-a) triggering with four different protocols of luteal support in comparison with results obtained after a h gonadotropin (hCG) trigger.
Design: Prospective, randomized, controlled trial.
Setting: University-affiliated private assisted-reproduction center.
Patient(s): 25 healthy oocyte donors undergoing controlled ovarian stimulation.
Intervention(s): On day of final oocyte maturation, randomization to [1] GnRH-agonist triggering and luteal su estradiol (2 mg/8 hours) and vaginal progesterone (200 mg/12 hours), [2] GnRH-a and a daily dose of 150 IU of r from oocyte pickup, [3] GnRH-a and a single bolus of 60 μg of recombinant hCG on oocyte pickup, [4] GnRH-a an 20 μg of recombinant hCG separated by 48 hours, or [5] 250 μg of recombinant hCG for trigger and standard lutei endometrial biopsy samples collected 7 days after triggering.
Main Outcome Measure(s): Gene expression using the Endometrial Receptivity Array (ERA) and pathway and netv study groups 1–4 compared with controls (group 5).
Result(s): The 56 genes in group 1 (25 up-regulated and 31 down-regulated) exhibited altered expression compared w from group 2 (13 up-regulated and 23 down-regulated), 44 from group 3 (28 up-regulated and 16 down-regulated), regulated and 10 down-regulated) from group 4.
Conclusion(s): Differences were seen in endometrial gene expression related to the type of ovulation trigger and lutei ever, gene expression after the GnRH-a trigger and modified luteal support adding LH/hCG activity more closely resembles the pattern seen in the hCG group.
Clinical Trial Registration Number: EudraCT 2011-003250-34. (Fertil Steril® 2014;101: 138–46. ©2014 by American Society for Reproductive Medicine.)
Key Words: Endometrial receptivity, gene expression, GnRH agonist, ovarian stimulation

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/bermejoa-gnrh-agonist-endometrial-gene-expression/

Hum Reprod. 2014

human reproduction ORIGINAL ARTICLE *Infertility*

Deciphering the proteomic signature
of human endometrial receptivity

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STUDY QUESTION: Are there any proteomic differences between receptive (R) and non-receptive (NR) endometrial receptivity array (ERA)-diagnosed endometria obtained on the same day of a hormonal replacement therapy (HRT) treatment cycle?

SUMMARY ANSWER: There is a different proteomic signature between R and NR ERA-diagnosed endometrium obtained on the same day of HRT cycles.

WHAT IS KNOWN ALREADY: The human endometrial transcriptome has been extensively investigated in the last decade resulting in the development of a new diagnostic test based on the transcriptomic signature of the window of implantation (WOI). Much less is known about the proteomics derived from the transcripts present during the WOI.

STUDY DESIGN, SIZE, AND DURATION: This study was a basic proteomic analysis of human endometrial biopsies taken from twelve IVF patients.

PARTICIPANTS/MATERIALS, SETTING, AND METHODS: Human endometrial biopsies were collected during HRT cycles after 5 days of progesterone (P) administration, and diagnosed as receptive (R; $n = 6$) or non-receptive (NR; $n = 6$) by the ERA test. Endometrial proteins were extracted, labelled and separated using differential in-gel electrophoresis (DIGE). Proteins were identified using mass spectrometry, followed up by *in silico* analysis. Validation studies using western blots and immunolocalization were performed for the progesterone receptor membrane component 1 (PGRMC1) and annexin A6 (ANXA6) proteins.

MAIN RESULTS AND THE ROLE OF CHANCE: DIGE analysis followed by protein identification by MALDI-MS and database searches revealed 24 differentially expressed proteins in R versus NR samples. *In silico* analysis showed two pathways which were significantly different between R and NR samples. Expression of PGRMC1 and ANXA6 was validated and localized by western blots and immunohistochemistry. These results highlight these proteins as key targets likely to be important in the comprehension of human endometrial receptivity.

LIMITATIONS, REASONS FOR CAUTION: This was mainly a descriptive study with no functional studies on the proteins found. We also used a low number of human endometrial samples for the DIGE analysis.

Hum Reprod. 2014

human reproduction ORIGINAL ARTICLE *Reproductive biology*

The impact of using the combined oral
contraceptive pill for cycle scheduling on
gene expression related to endometrial
receptivity

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STUDY QUESTION: Does the combined oral contraceptive pill (COCP) change endometrial gene expression when used for cycle programming?

SUMMARY ANSWER: COCP used for scheduling purposes does not have a significant impact on endometrial gene expression related to endometrial receptivity.

WHAT IS KNOWN ALREADY? Controversy exists around COCP pretreatment for IVF cycle programming, as some authors claim that it might be detrimental to the live birth rate. Microarray technology applied to the study of tissue gene expression has previously revealed the behavior of genes related to endometrial receptivity under different conditions.

STUDY DESIGN, SIZE, AND DURATION: Proof-of-concept study of 10 young healthy oocyte donors undergoing controlled ovarian stimulation (COS) recruited between June 2012 and February 2013.

PARTICIPANTS/MATERIALS, SETTING, AND METHODS: Microarray data were obtained from endometrial biopsies from 10 young healthy oocyte donors undergoing COS with GnRH antagonists and recombinant FSH. In group A ($n = 5$), COCP pretreatment was used for 12–16 days, and stimulation began after a 5-day pill-free interval. Stimulation in group B ($n = 5$) was initiated on cycle day 3 after a spontaneous menses. Endometrial biopsies were collected 7 days after triggering with hCG.

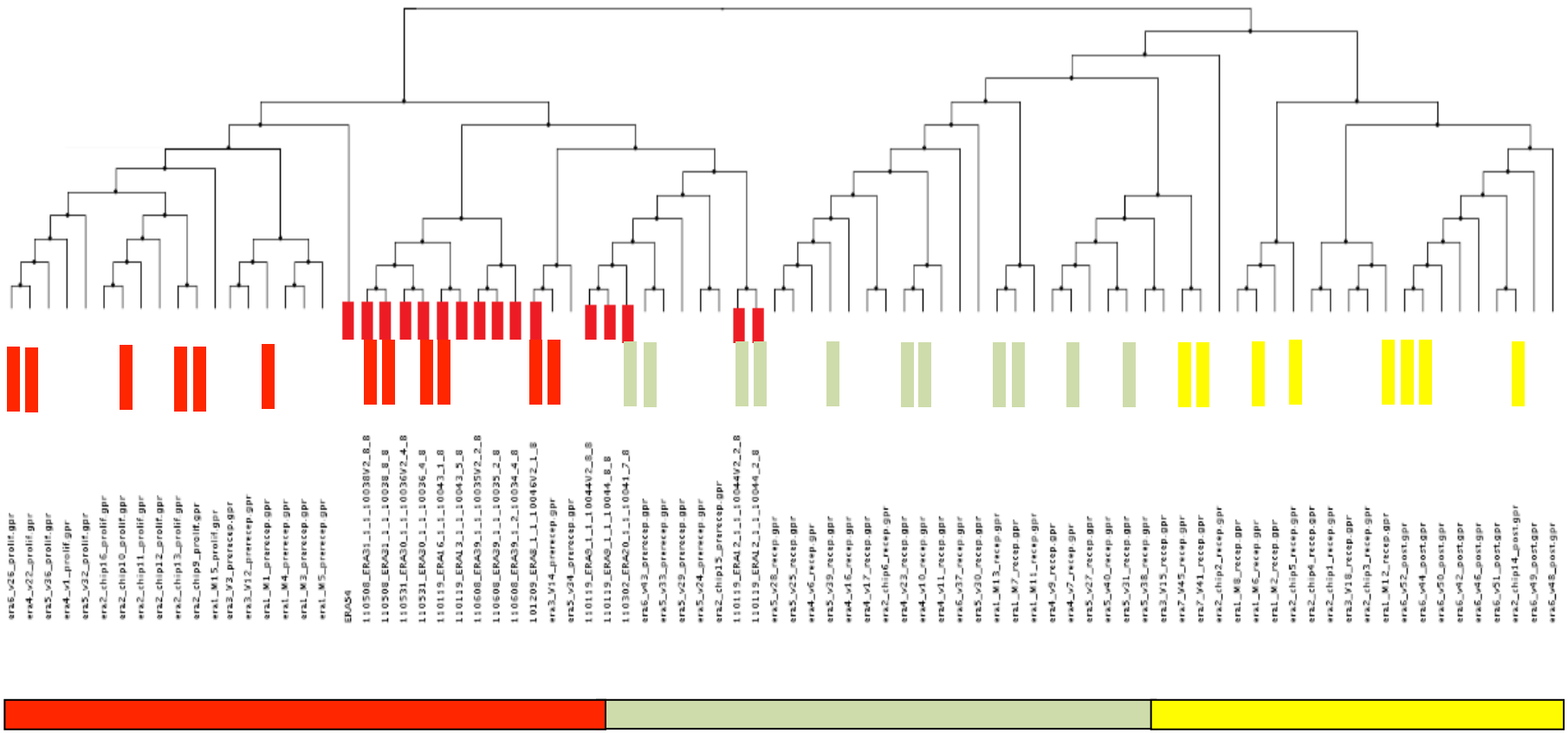
MAIN RESULTS AND THE ROLE OF CHANCE: No individual genes exhibited increased or decreased expression (fold change (FC) >2) in patients with prior COCP treatment (group A) compared with controls (group B). However, the results of the functional analysis showed a total of 11 biological processes that were significantly enriched in group A compared with group B (non-COCP).

LIMITATIONS, REASONS FOR CAUTION: The Endometrial Receptivity Array (ERA) has only been validated on endometrial samples obtained in natural cycles and after hormonal replacement treatment (HRT). Therefore, it was not possible in this study to classify the endometrial samples as receptive or non-receptive. We used the ERA to focus on 238 genes that are intimately related to endometrial receptivity, thus simplifying the analysis and understanding of the data.

WIDER IMPLICATIONS OF THE FINDINGS: Cycle scheduling is common in IVF units and is used to avoid weekend retrievals and/or to distribute evenly the workload for better efficiency. Our failure to detect any relevant changes in the genes related to the window of implantation when cycles were programmed with COCP pretreatment suggests that, despite controversial clinical results in previous studies, the use of COCPs

GCC

Predictor classifies the molecular receptivity status of the endometrium

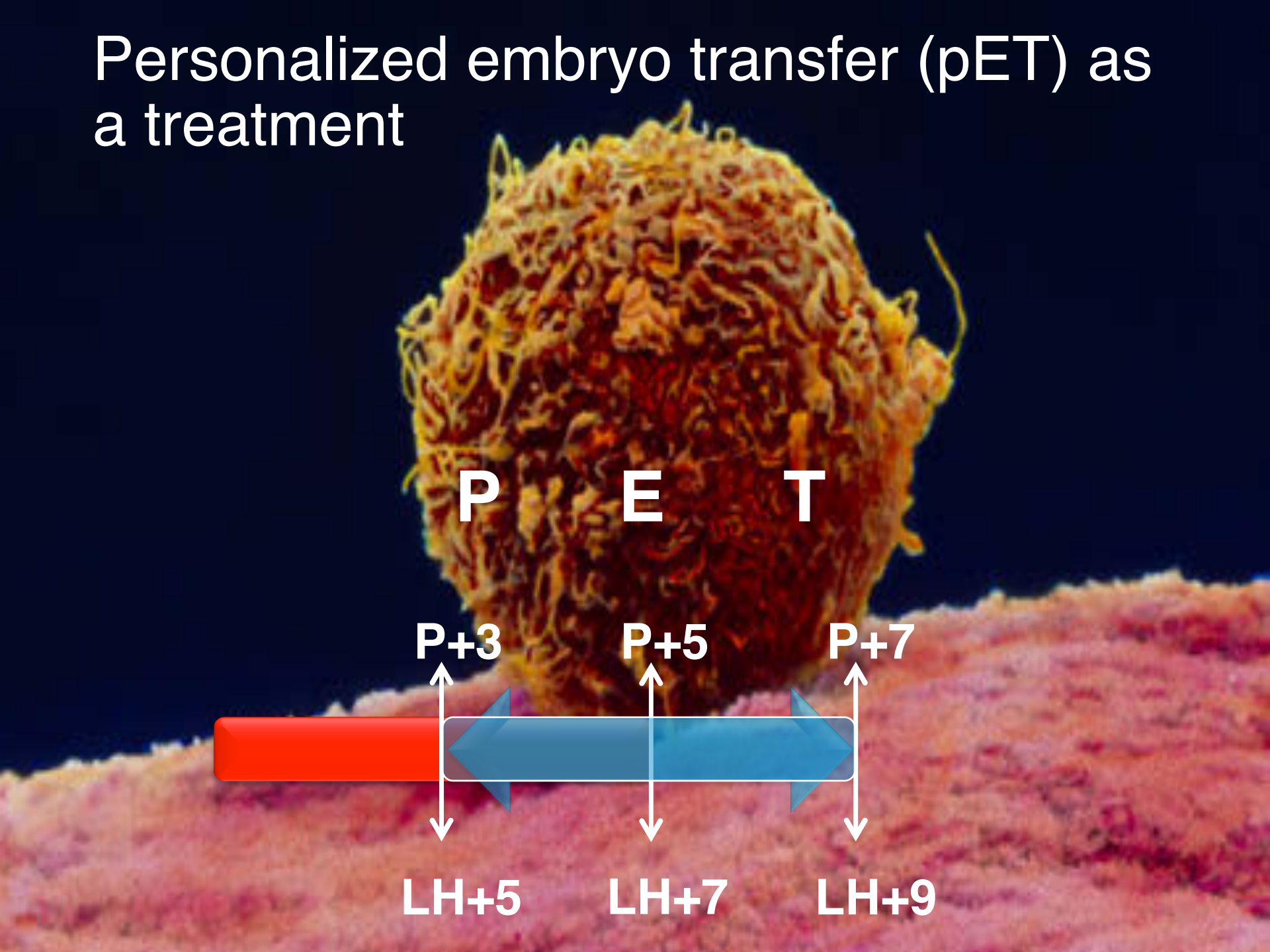


Pre-Receptive

Receptive

Post-Receptive

Personalized embryo transfer (pET) as a treatment



OMICS and ERA

- 'Omics' high-throughput analyses have started to revolutionize our understanding of human endometrial physiology and pathophysiology
- Nevertheless, the knowledge remains incomplete, inconsistent and without strong clinical application
- Technical limitations, including data analysis remain
  - These need further development

- The ERA need further validation in natural and stimulated cycles

How to improve the endometrial receptivity?

Injuries to epithelial tissue surfaces are generally associated with:

- Platelet deposition and clot formation
- A tissue-specific inflammatory infiltrate
- Epithelial repair (epiboly)
- Influx of myofibroblasts
- Matrix deposition
- Wound closure
- Local remodelling
- Generally there is minimal fibrosis and no scarring in mucosal tissues

How to improve the endometrial receptivity?

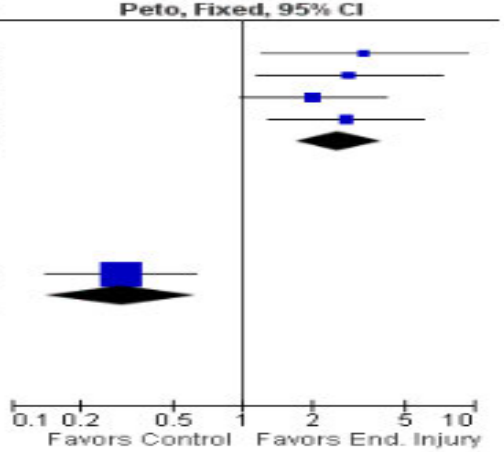
Endometrial injury in women undergoing assisted reproductive techniques (Review)

Nastri CO, Gibreel A, Raine-Fenning N, Maheshwari A, Ferriani RA, Bhattacharya S, Martins WP

THE COCHRANE COLLABORATION®

Figure 5. Forest plot of comparison: 1 Effectiveness, outcome: 1.3 Clinical pregnancy per allocated woman grouped by timing of injury.

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.3.1 Injury in the previous cycle						
Karimzadeh 2009	13	58	4	57	16.9%	3.36 [1.20, 9.37]
Narvekar 2010	16	49	7	51	20.7%	2.88 [1.14, 7.28]
Nastri 2011	28	60	18	60	33.2%	2.01 [0.97, 4.19]
Selcuk University 2011	30	50	17	50	29.2%	2.81 [1.29, 6.14]
Subtotal (95% CI)		**217**		**218**	**100.0%**	**2.61 [1.71, 3.97]**
Total events	87		46			
Heterogeneity: Chi² = 0.79, df = 3 (P = 0.85); I² = 0%						
Test for overall effect: Z = 4.45 (P < 0.00001)						
1.3.2 Injury on the day of oocyte retrieval						
Karimzade 2010	9	77	26	79	100.0%	0.30 [0.14, 0.63]
Subtotal (95% CI)		**77**		**79**	**100.0%**	**0.30 [0.14, 0.63]**
Total events	9		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.17 (P = 0.002)						



IVI GCC

How to improve the endometrial receptivity?

Offer Endometrial scratch

Endometrial injury performed prior to the embryo transfer cycle improves clinical pregnancy and live birth rates in women undergoing ART.

Nastri et al, 2012

Full Text (HTML)

The effect of endometrial injury on ongoing pregnancy rate in unselected subfertile women undergoing *in vitro* fertilization: a randomized controlled trial

Hum. Reprod. (2014) 29 (11): 2474-2481 first published online September 8, 2014

Hum Reprod. 2014 Nov;29(11):2474-81. doi: 10.1093/humrep/deu213. Epub 2014 Sep 8.

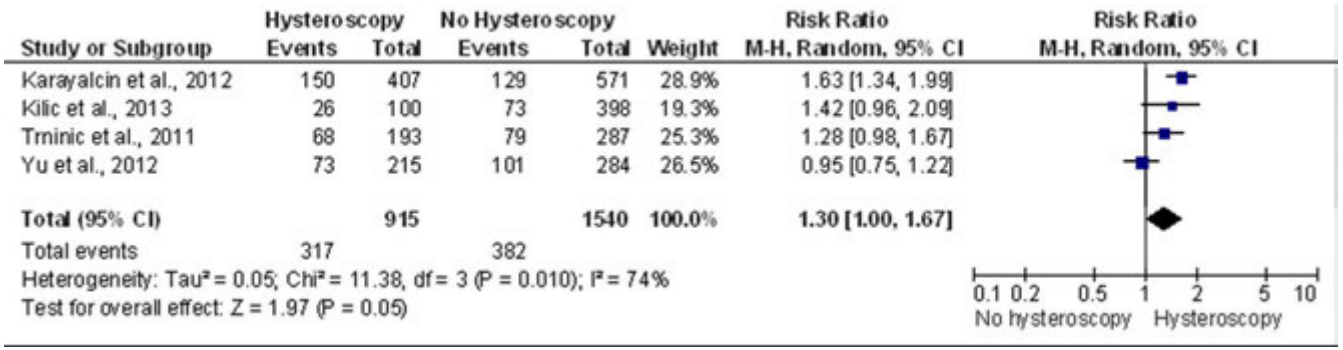
The effect of endometrial injury on ongoing pregnancy rate in unselected subfertile women undergoing in vitro fertilization: a randomized controlled trial.

Yeung TW[1], Chai J[2], Li RH[2], Lee VC[2], Ho PC[2], Ng EH[2].

Hysteroscopy prior to the first IVF cycle: A systematic review and meta-analysis

Jyotsna Pundir, Vishal Pundir, Kireki Omanwa, Yacoub Khalaf, Tarek El-Toukhy

Reproductive BioMedicine Online
Volume 28, Issue 2, Pages 151-161 (February 2014)
DOI: 10.1016/j.rbmo.2013.09.025



Study or Subgroup	Hysteroscopy Events	Hysteroscopy Total	No Hysteroscopy Events	No Hysteroscopy Total	Weight	Risk Ratio M-H, Random, 95% CI
Karayalcin et al., 2012	150	407	129	571	28.9%	1.63 [1.34, 1.99]
Kilic et al., 2013	26	100	73	398	19.3%	1.42 [0.96, 2.09]
Trninic et al., 2011	68	193	79	287	25.3%	1.28 [0.98, 1.67]
Yu et al., 2012	73	215	101	284	26.5%	0.95 [0.75, 1.22]
Total (95% CI)		**915**		**1540**	**100.0%**	**1.30 [1.00, 1.67]**
Total events	317		382			

Heterogeneity: Tau² = 0.05; Chi² = 11.38, df = 3 (P = 0.010); I² = 74%
Test for overall effect: Z = 1.97 (P = 0.05)

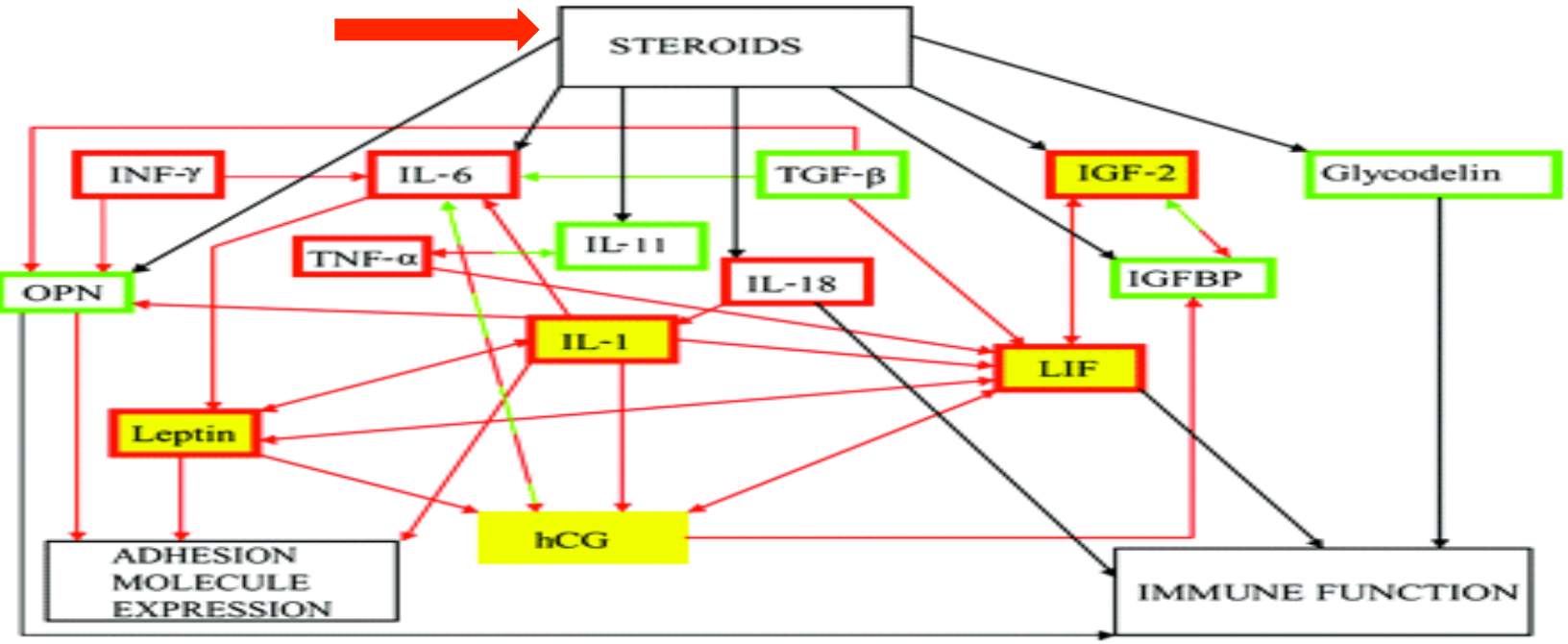
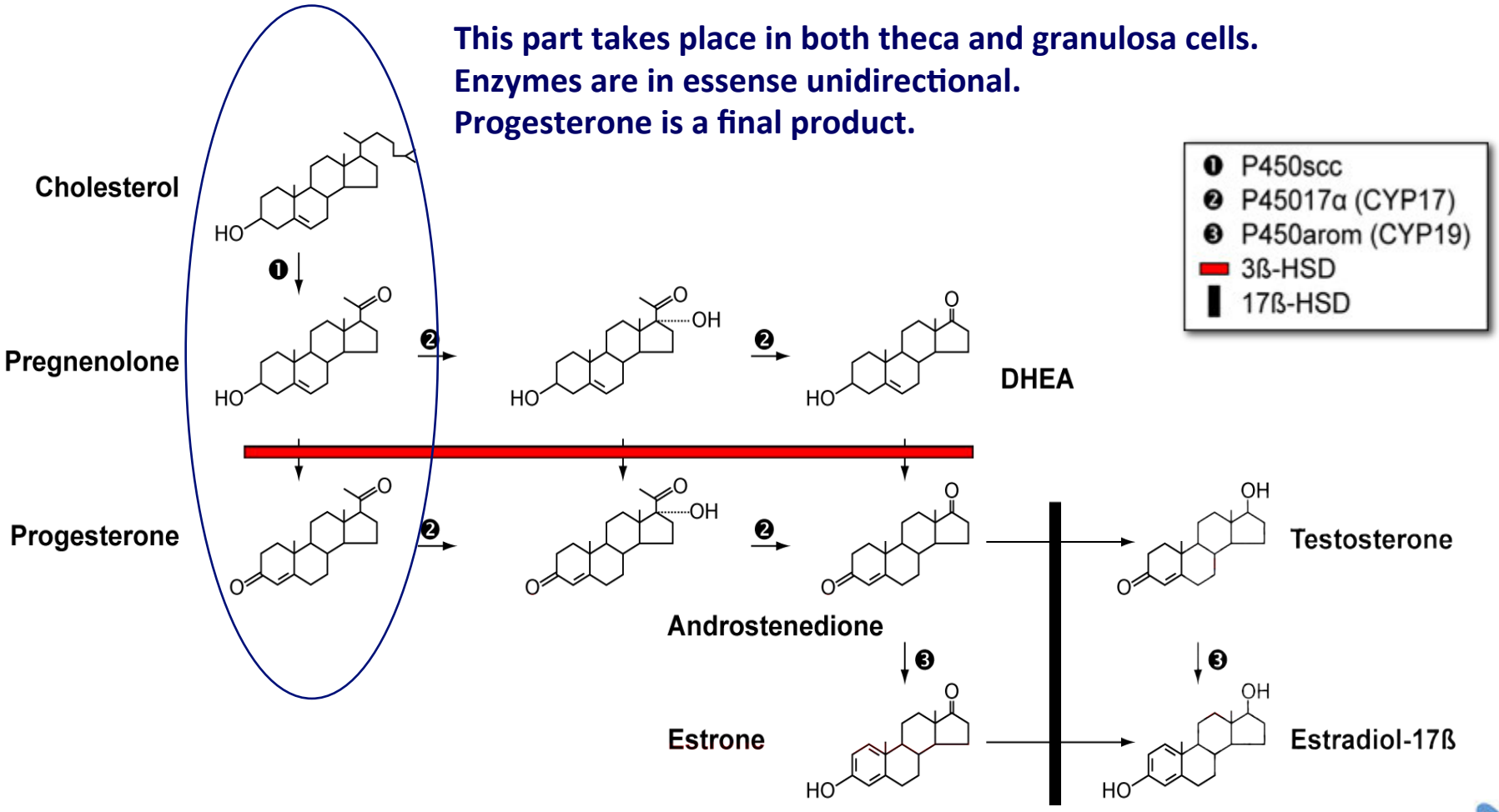


Figure 1.

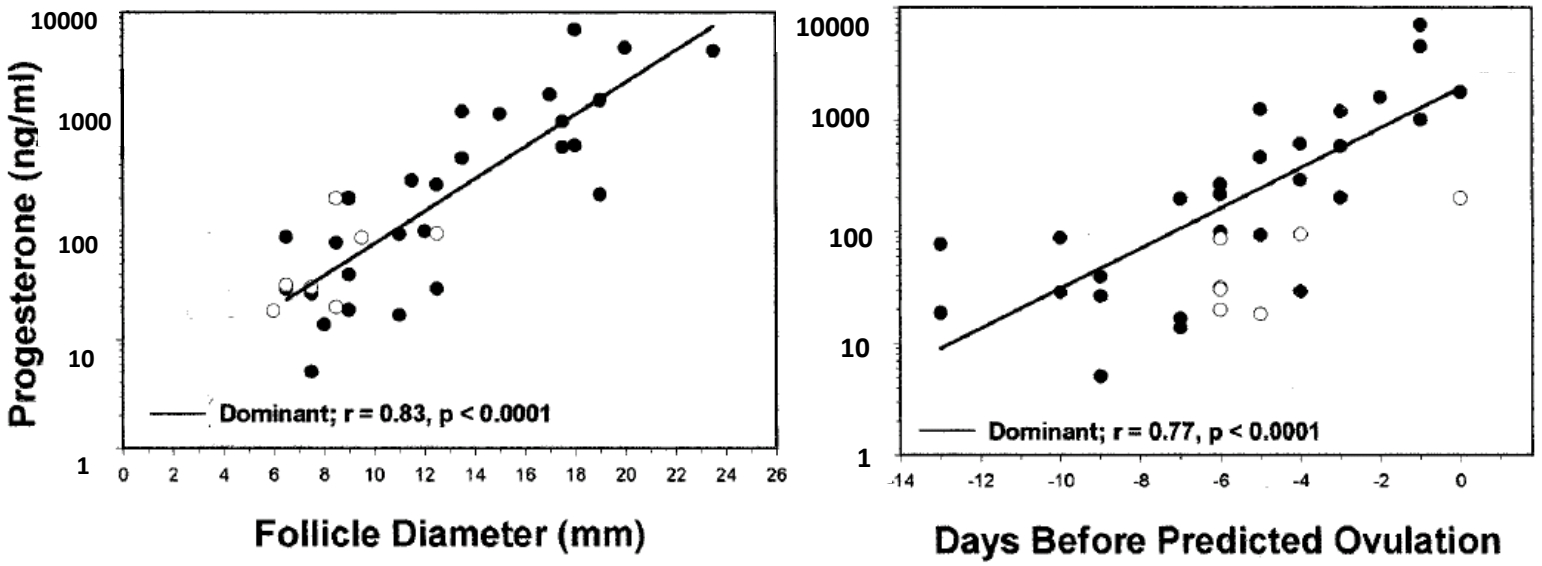
Schematic representation of the most important cytokine interactions surrounding the time of implantation. Boxes: red, proinflammatory; green, anti-inflammatory; black, not applicable; yellow, produced by blastocyst. Arrows: red, stimulatory; green, inhibitory; black, modulating in general. hCG, Human chorionic gonadotropin.

Van Mourik et al, 2009

Human ovarian steroidogenesis



Intrafollicular concentrations of progesterone in relation to follicular development



1ng/ml progesterone = 3,18 nmol/l

Schneyer AL *et al.. JCEM*, 2000,**83,**3319

Van Vaerenbergh et al 2011

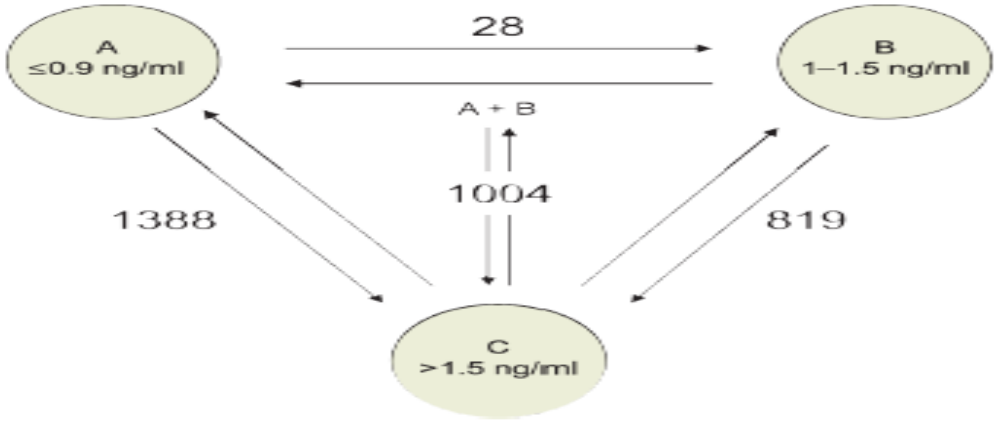
- Patients were divided into three groups:
  - (A) P <= 0.9 ng/mL
  - (B) 1 <= P <= 1.5 ng/mL
  - (C) P > 1.5 ng/mL

- Gene expression analysis:
  - a small number of significantly differentially expressed probe sets between groups A and B (5 up/23 down in B) and a large difference between groups B and C (607 up/212 down) (P<=0.05,FC>=1.4)

This is the first study to demonstrate a distinct difference in endometrial gene expression profile between patients with a P serum level above and

- below the threshold of 1.5 ng/mL on the day of hCG administration

Advancement of gene expression



Differential gene expression between groups of progesterone concentration
(A = ≤0.9 ng/ml; B = 1–1.5 ng/ml; C = >1.5 ng/ml)

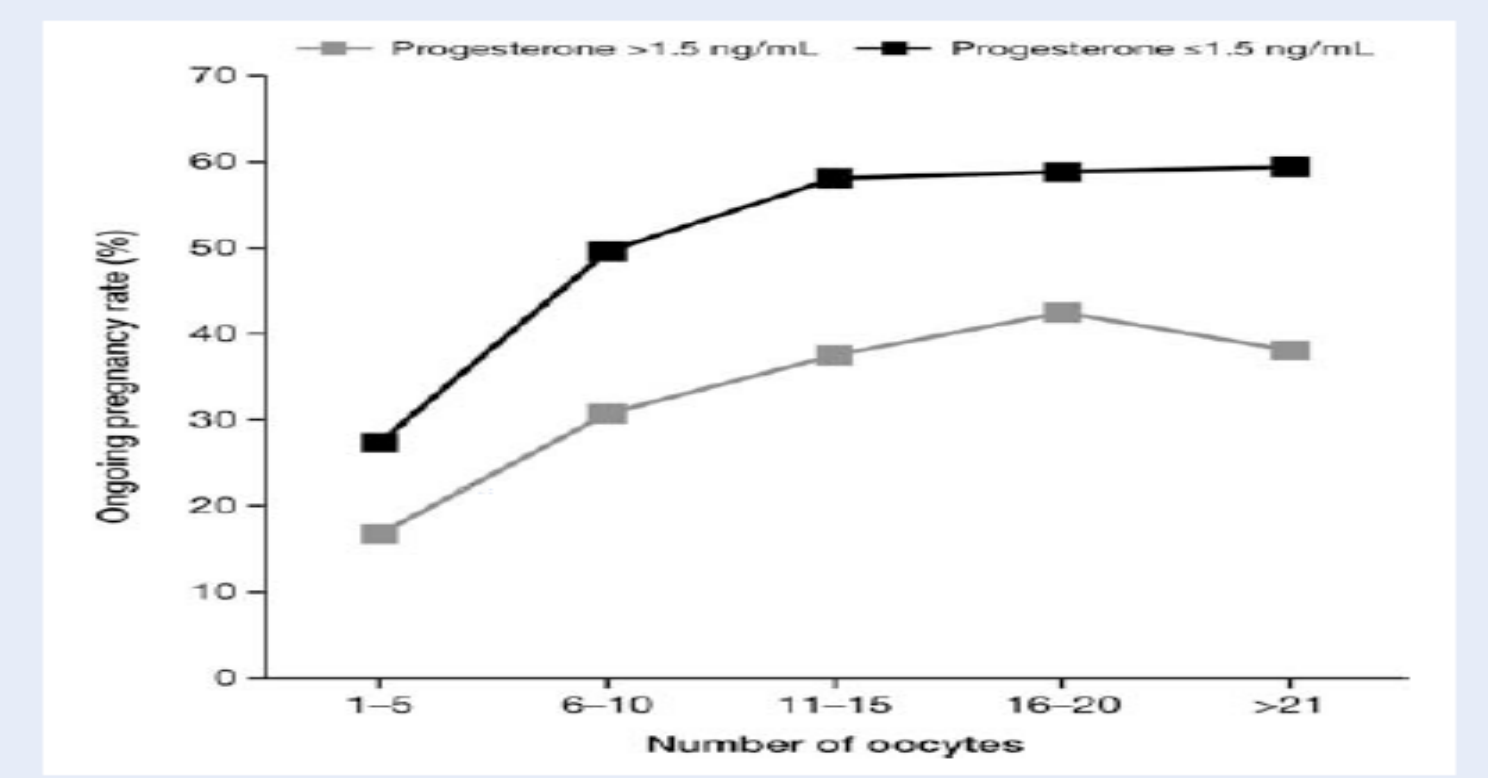
Van Vaerenbergh et al. Reproductive BioMedicine Online 2011: 22: 263-271.

High Progesterone and gene-expression

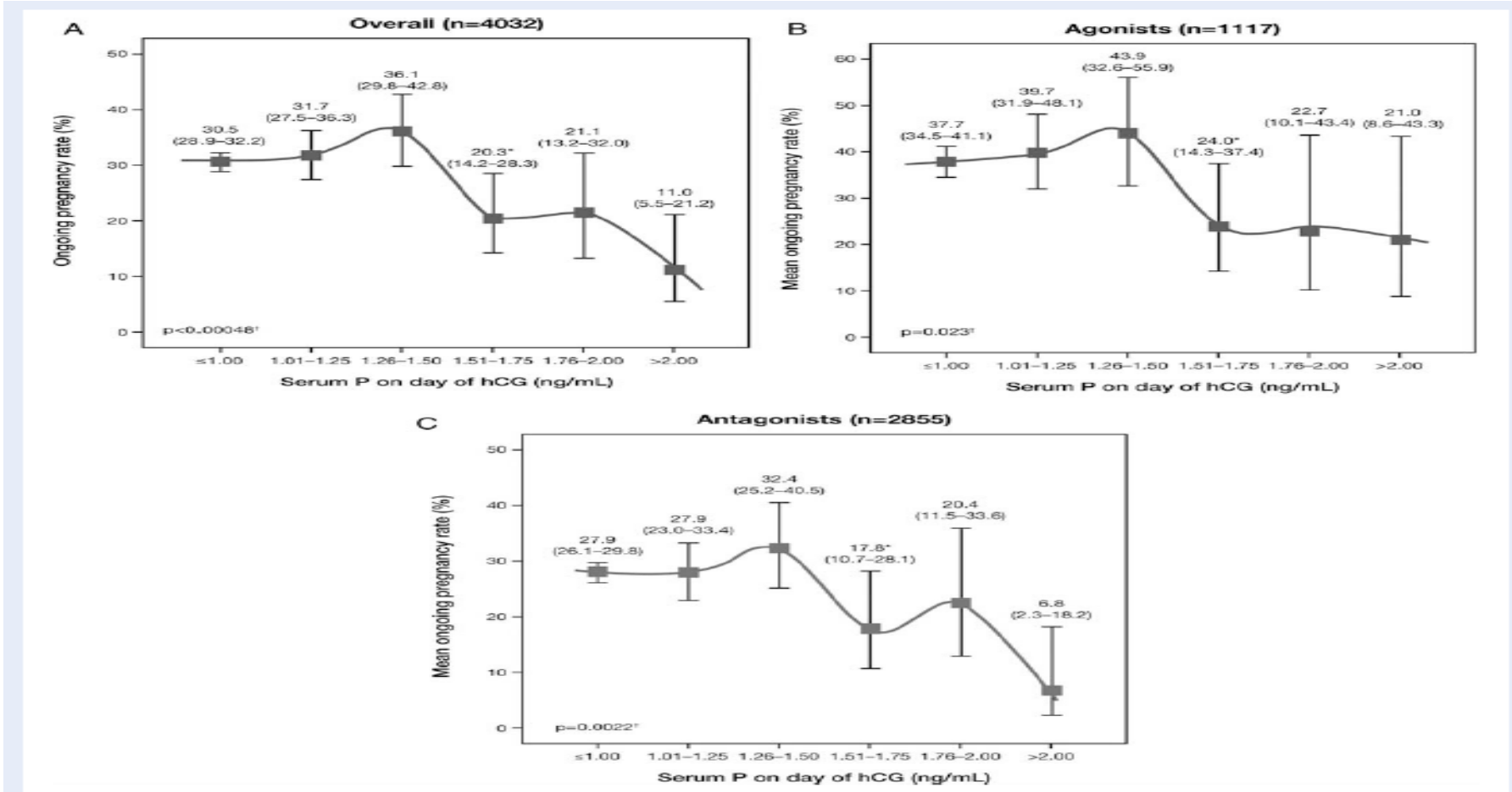
- **Progesterone rise on HCG day in GnRH antagonist/rFSH stimulated cycles affects endometrial gene expression.**

Van vaerenbergh et al, 2011

Bosch et al., 2010



Bosch et al., 2010



Geva et al., 1998

Table III. Serum hormone concentrations and the main indication for IVF in group I patients

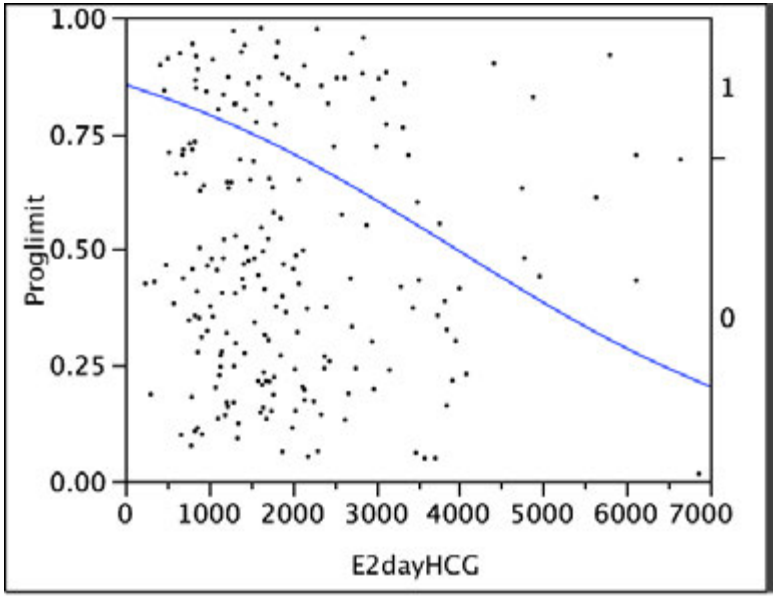
	P >3 nmol/l	P <3 nmol/l
DHEA-S (μmol/l)[a]	5.34 ± 3.18	4.96 ± 3.70
Free testosterone (pmol/l)[a]	6.85 ± 6.50	6.30 ± 2.30
LH/FSH ratio[a]	1.05 ± 1.00	0.97 ± 0.32
Androstenedione (nmol/l)[a]	6.24 ± 3.73	6.18 ± 2.50
Oestradiol (pmol/l)[b]	7578 ± 2650[c]	4418 ± 4842
Egg number	15.50 ± 6.70[c]	7.81 ± 3.73
Main indication for IVF (%):		
Mechanical	36.2 (21)[d]	48.6 (174)
Male factor	32.8 % (19)	21.5 (77)
PCOS	17.2 (10)	12.8 (46)
Unexplained	13.9 (8)	17.0 (61)

Probability of high P levels versus E2 levels and number of follicles on day hCG

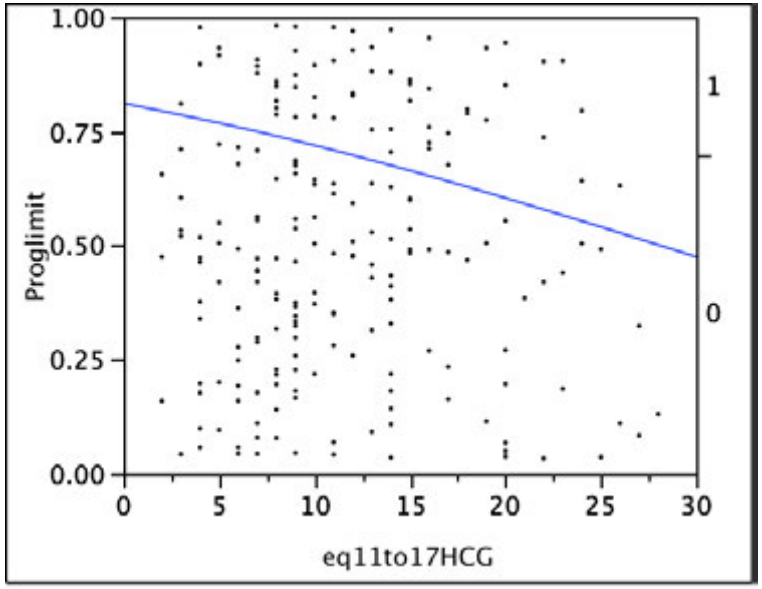
- A logistic regression model was performed to assess the relationship between E2 and number of follicles on hCG day with progesterone rise >1.5 ng/mL

  A significant effect on progesterone rise was observed for both E2 (p <0.001) and number of follicles (p=0.041)

E2



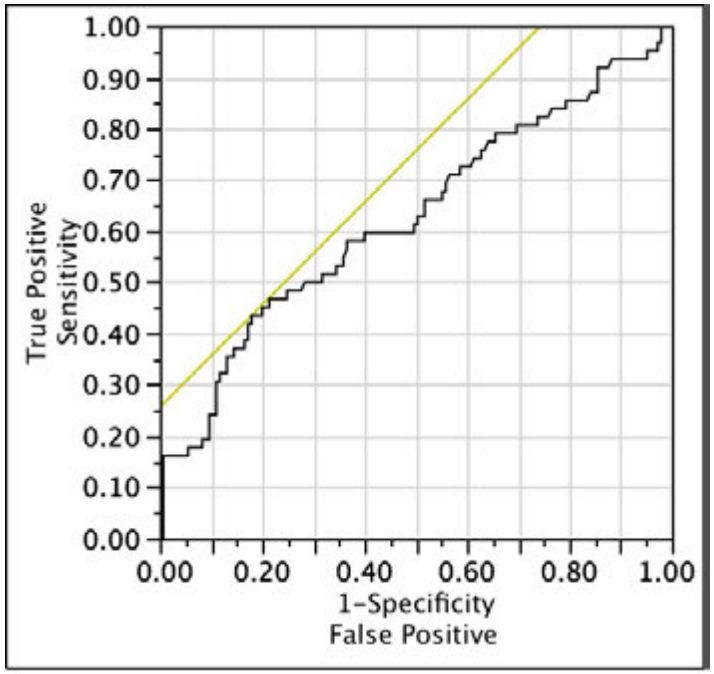
Number of follicles



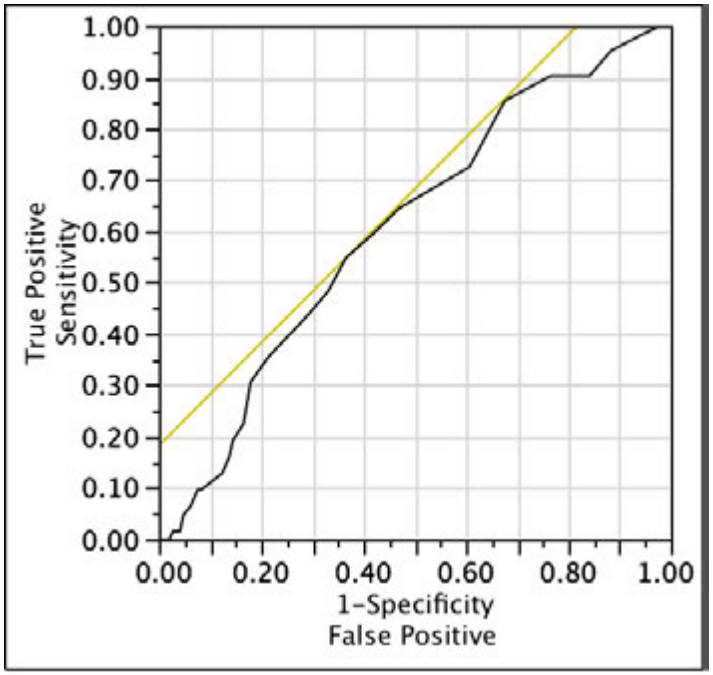
Kyrou et al. 2012

Area under the ROC curve for serum E2 and number of follicles on day of hCG

- Cut-off for serum E2 on day hCG = 2428 pg/ml.
  - Specificity = 0.821; sensitivity = 0.436 (AUC=0.625, PPV=51%, NPV=77%)
- Cut-off for the number of follicles (≥ 11mm) = 12 follicles
  - Specificity =0.635; sensitivity = 0.548 (AUC=0.608, PPV=39%, NPV=77%)



E2

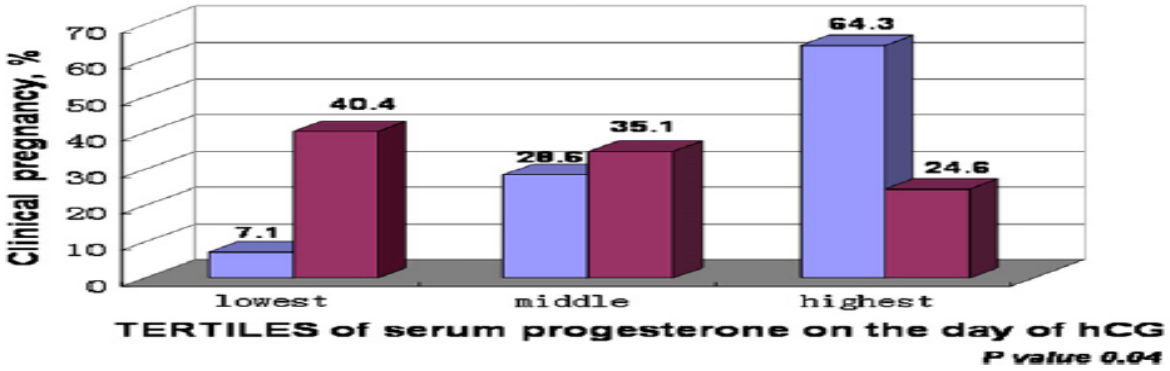


Number of follicles

Kyrou et al. 2012

FIGURE 1

Outcome of frozen-thawed embryo transfer (FET) by serum progesterone on the day of hCG administration. Blue bars: clinical pregnancy after FET. Purple bars: unsuccessful FET.



Polotsky. Serum progesterone and FET outcome. Fertil Steril 2009.

"It is clear that high serum progesterone during the follicular phase jeopardizes the endometrial receptivity"

Fatemi and Van Varenbergh, 2015

Conclusion1:

- Ovarian stimulation changes the endometrial environment
- Implantation requires a reciprocal interaction between blastocyst and endometrium, culminating in a small window of implantation
  - Genetic information of the embryo is a contributing factor to implantation
- Implantation itself is governed by an array of endocrine, paracrine and autocrine modulators of embryonic and maternal origin.

Conclusion2:

- Need for further research on endometrial "inflammation" prior IVF
- Importance of Progesterone!
  - High serum progesterone levels prior hCG administration is a frequent event
    - Independently from the GnRH analogue used
    - Related to the total FSH dose and number and size the of oocytes

Conclusion3:

- High serum progesterone levels prior hCG administration is associated with a decreased pregnancy rate
- Most probably due to a negative impact on the endometrium
- IVF treatment: Optimisation and individualisation of ovarian stimulation and final oocyte maturation
- Possible solution: Segmentation of IVF?
  "Natural Endometrium"

Thank you

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