Recent Developments in the Transmission of Human Life

19-21 January 2023

Berlin, Germany

Welcome to all Participants

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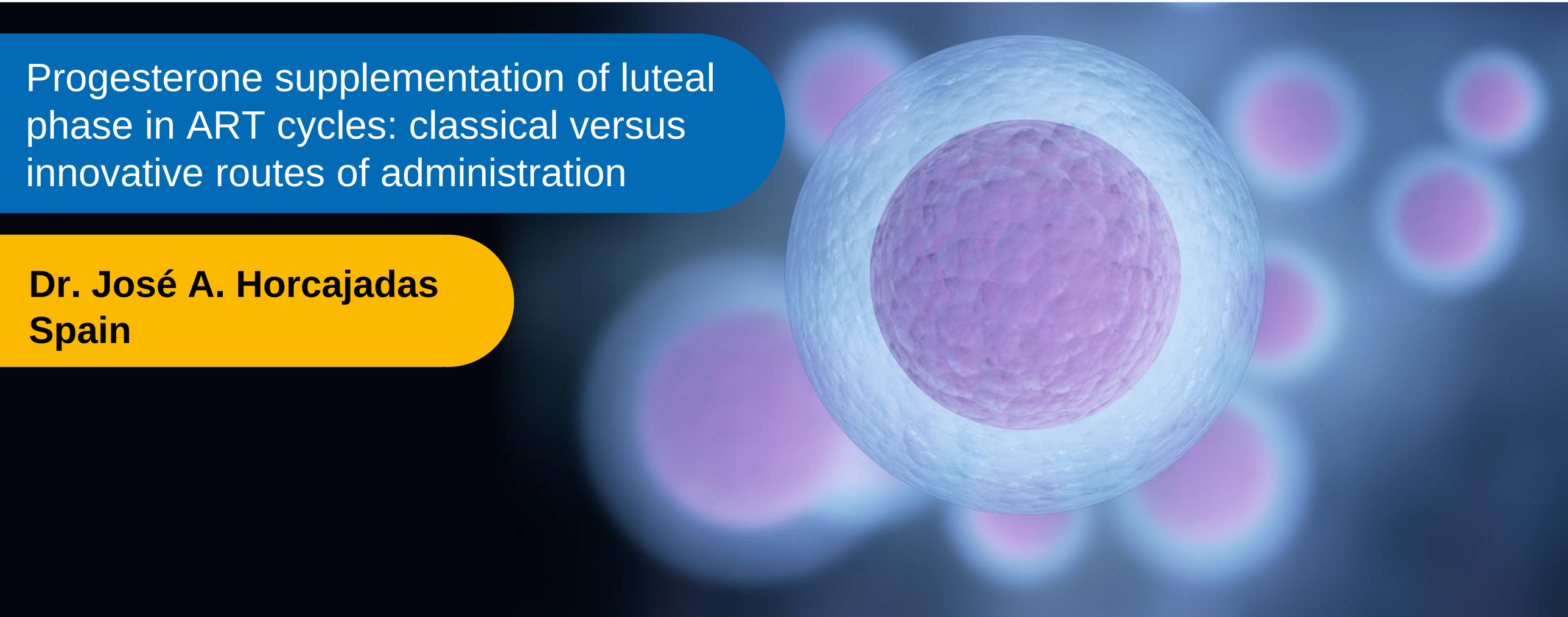
Recent Developments in the Transmission of Human Life

Progesterone supplementation of luteal phase in ART cycles: classical versus innovative routes of administration

Dr. José A. Horcajadas
Spain



Progesterone supplementation of luteal phase in ART cycles: classical versus innovative routes of administration

Dr. José A. Horcajadas

Full Assistant Professor, University Pablo de Olavide, Seville, Spain

Faculty Disclosure

I received grants, contracts, honoraria or consultation fees from:

- **Overture Life**, fees and partern, Madrid, Spain
- **SINAE**, fees and partern, Seville, Spain
- **Fullgenomics**, fees and partern, Barcelona, Spain
- **HoMu Health Ventures**, fees and partern, Barcelona, Spain
- **Clínica Tambre**, fees, Madrid, Spain
- **Pronacera Therapeutics**, fees and partern, Seville, Spain

EMBRYONIC IMPLANTATION

Health embryo at blastocyst stage

-

To select the best embryo/s

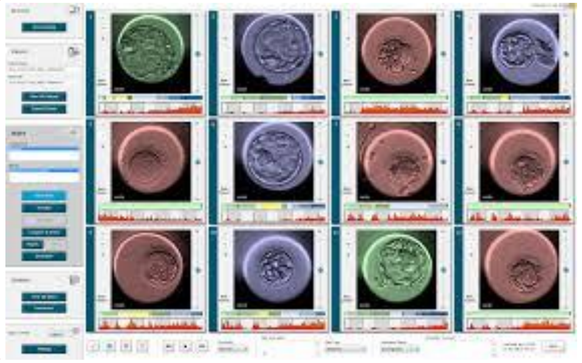
MOLECULAR DIALOGUE

Endometrial Receptivity

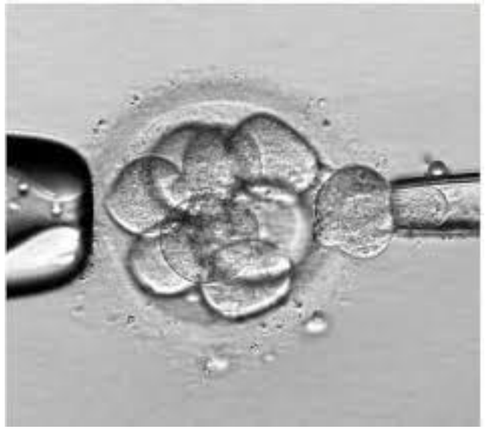
To improve the receptivity in the endometria under stimulated cycles

To know the bases of Infertility of endometrial origin

Embryonic Evaluation



Morphology
Morphokinetics

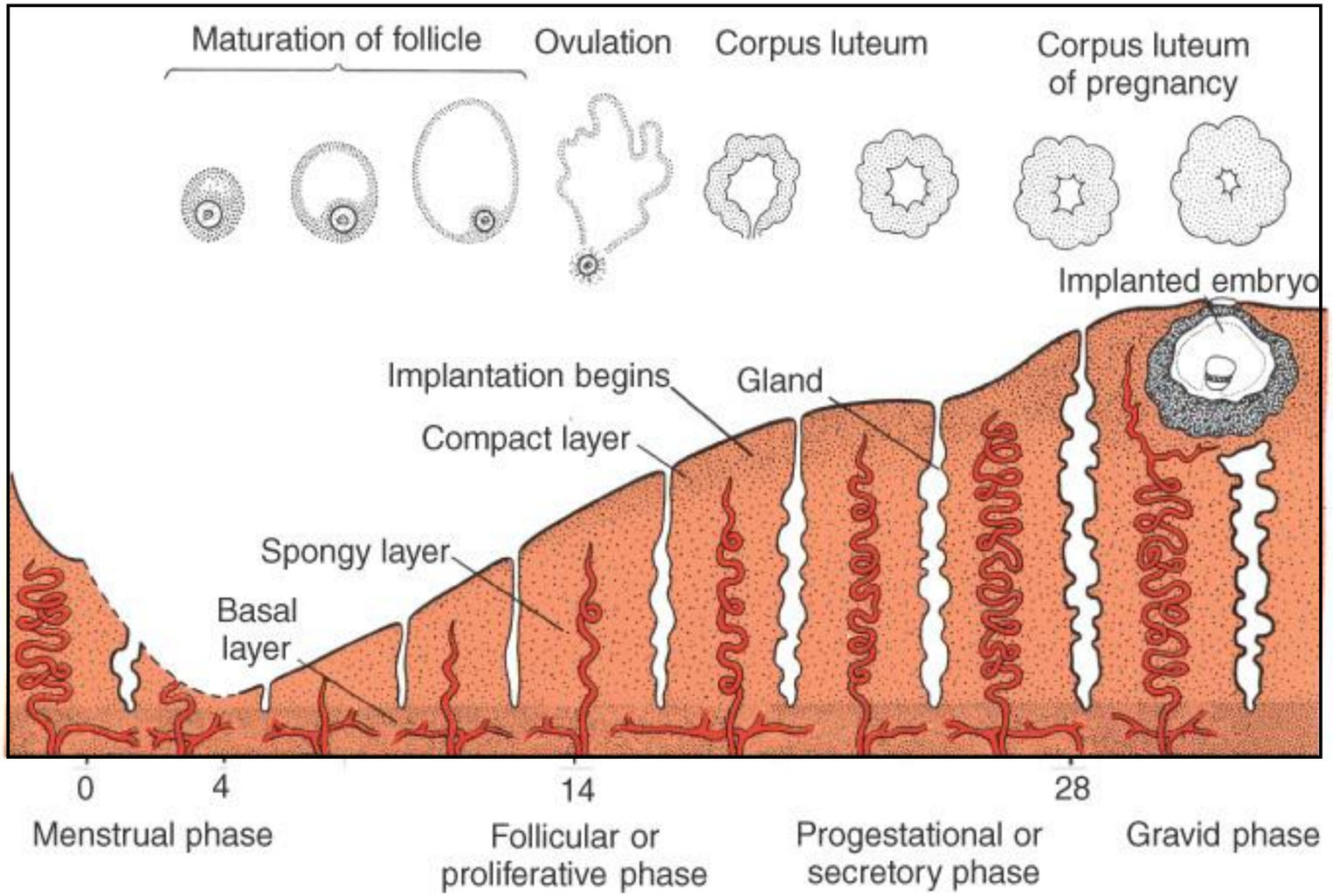


PGT
NI-PGT

Metabolomics

<70% **REACHING THE TOP**

INTRODUCTION TO THE HUMAN ENDOMETRIUM



(a)

When the proliferation of the epithelial cells of the endometrial glands of the inner surface of the lumen cavity is stimulated by estrogen, the progesterone produced by granulosa cells induces **gland glycogen accumulation.**

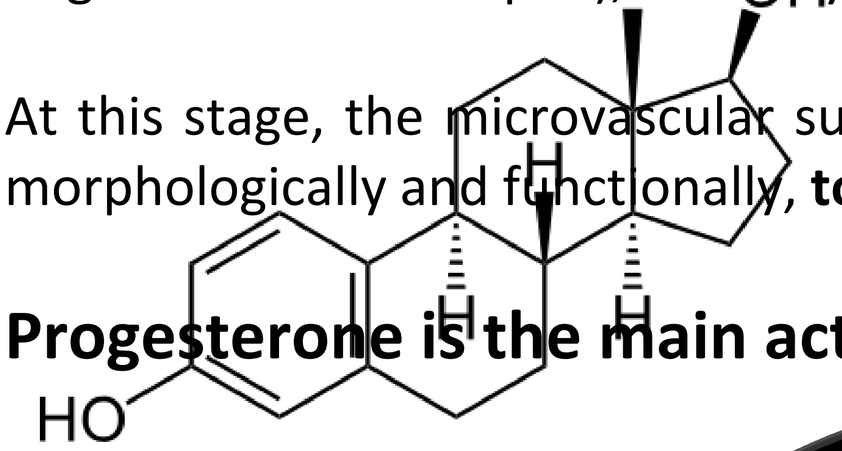
ESTRADIOL

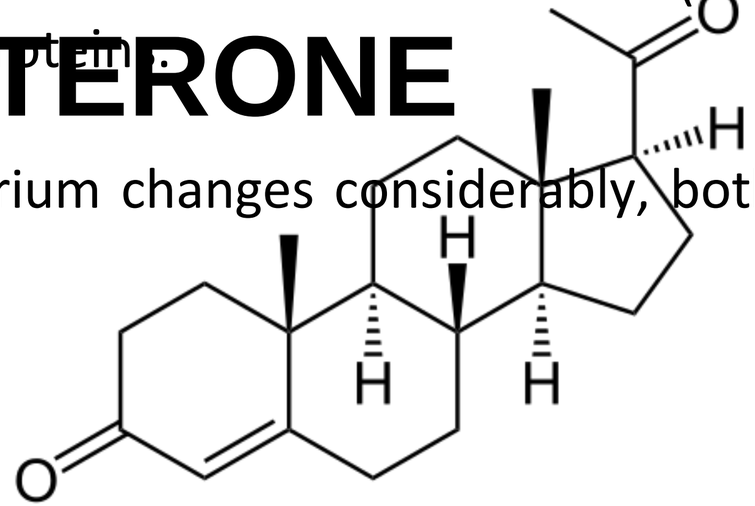
Consequently, the epithelial cells become pluri-stratified and stromal cells become **decidual** (i.e., larger and round-shaped), and they acquire the ability to produce prolactin.

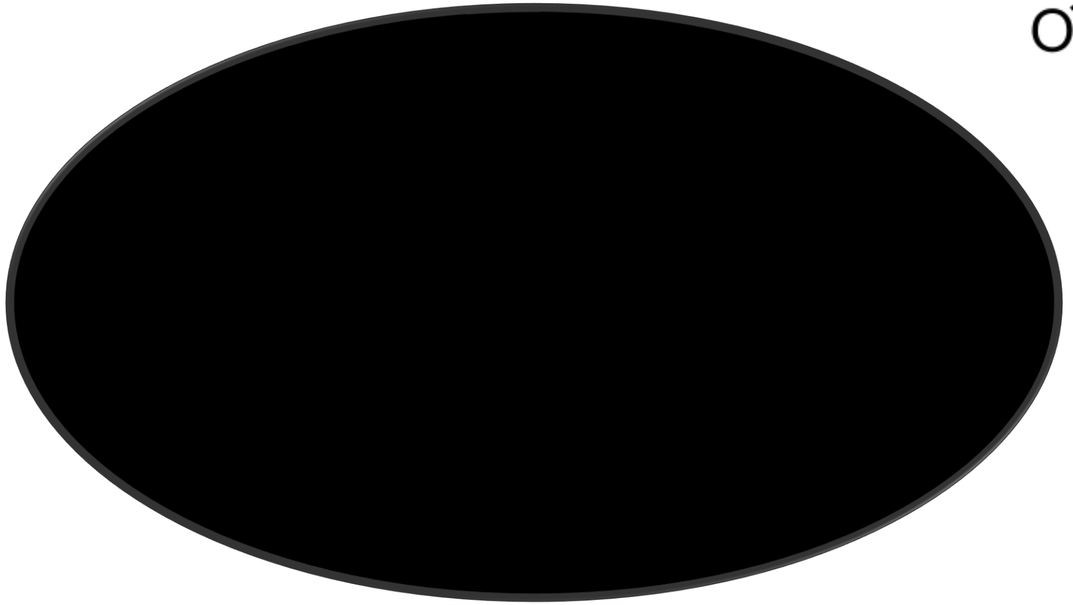
PROGESTERONE

At this stage, the microvascular supply in the functional endometrium changes considerably, both morphologically and functionally, **to enable embryo implantation.**

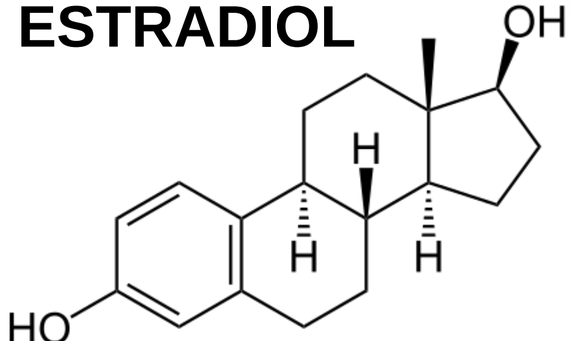
Progesterone is the main actor in all these phases



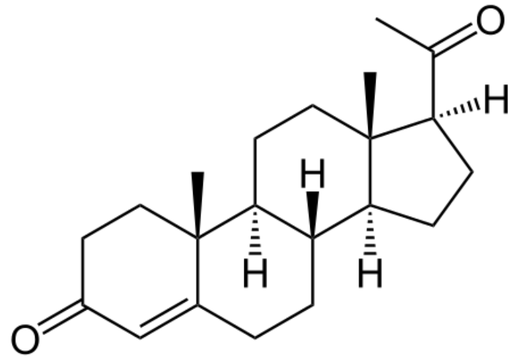


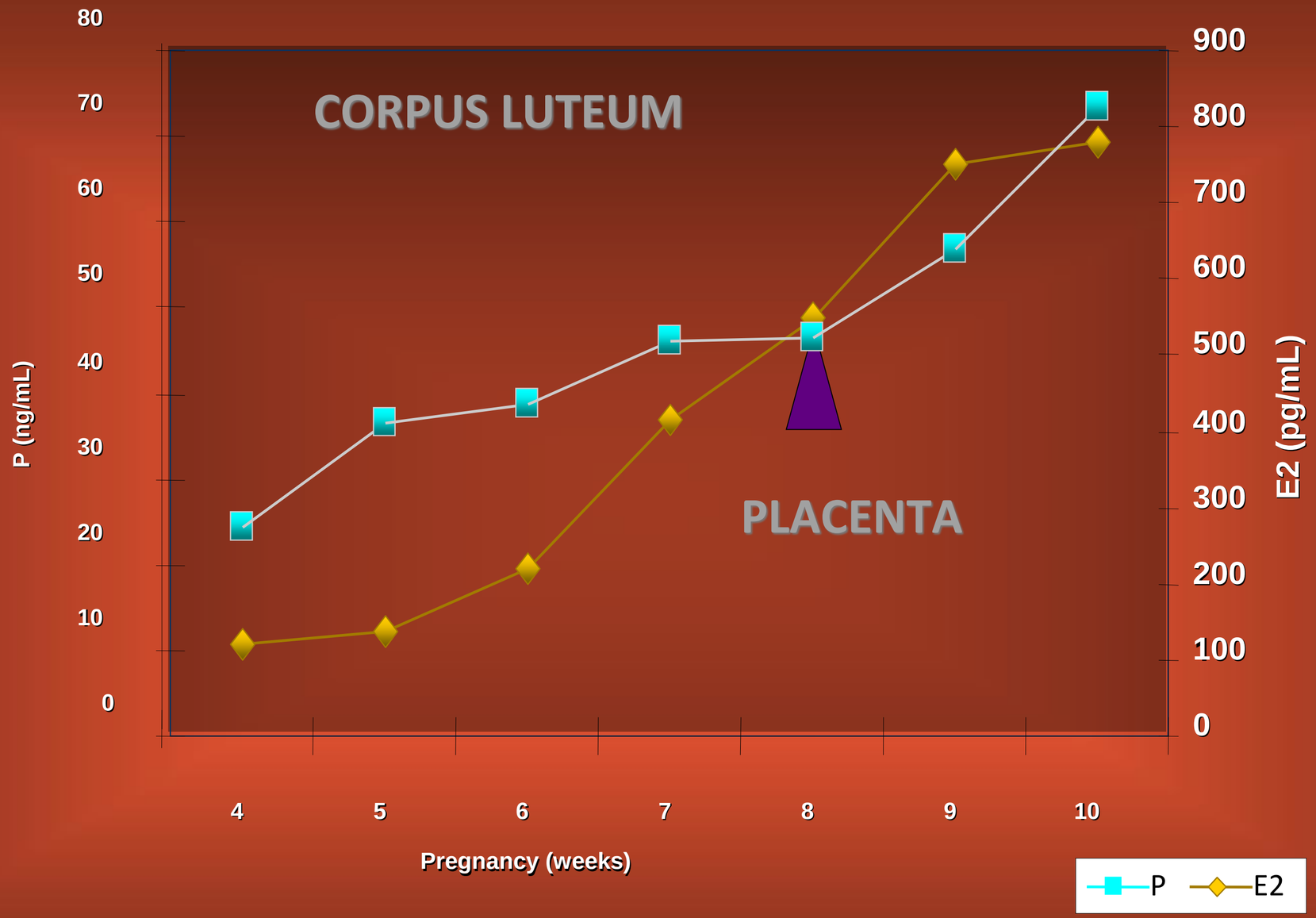


ESTRADIOL



PROGESTERONE





Csapo et al., *Am J Obstet Gynecol*. 1972

Csapo et al., Am J Obstet Gynecol. 1973

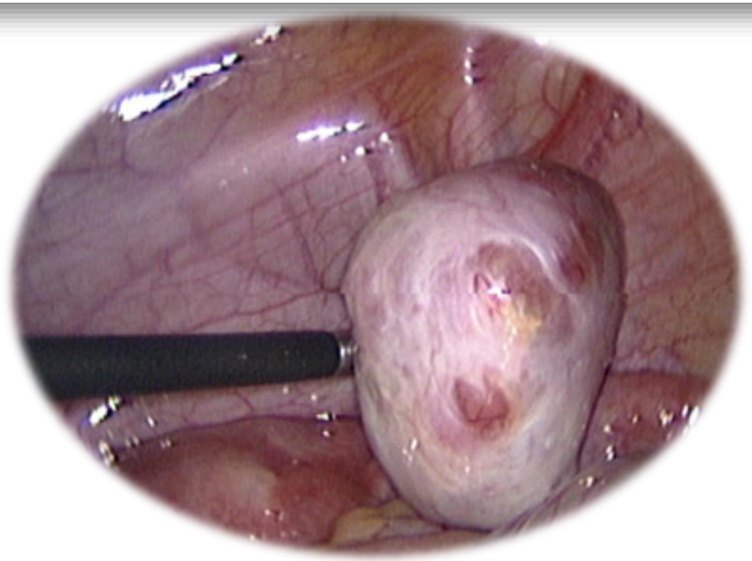
Scott et al., Fertil Steril. 1991

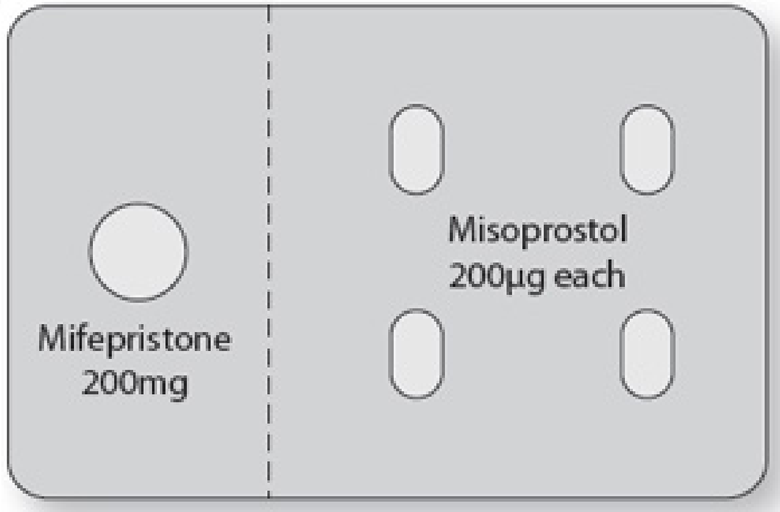
LUTEECTOMIA

Obstet Gynecol Surv. 1978 Feb;33(2):69-81.

Indispensability of the human corpus luteum in the maintenance of early pregnancy. Luteectomy evidence.

Csapo AI, Pulkkinen M.



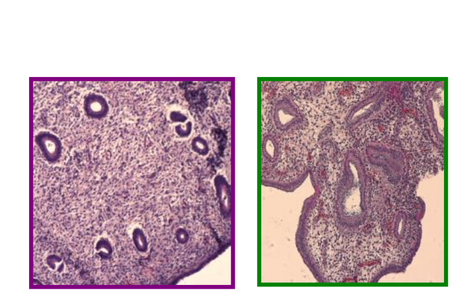


N Engl J Med. 1993 May 27;328(21):1509-13.

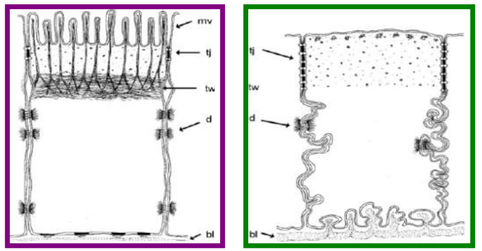
Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol.

Peyron R[1], Aubény E, Targosz V, Silvestre L, Renault M, Elkik F, Leclerc P, Ulmann A, Baulieu EE.

THE RECEPTIVE ENDOMETRIUM

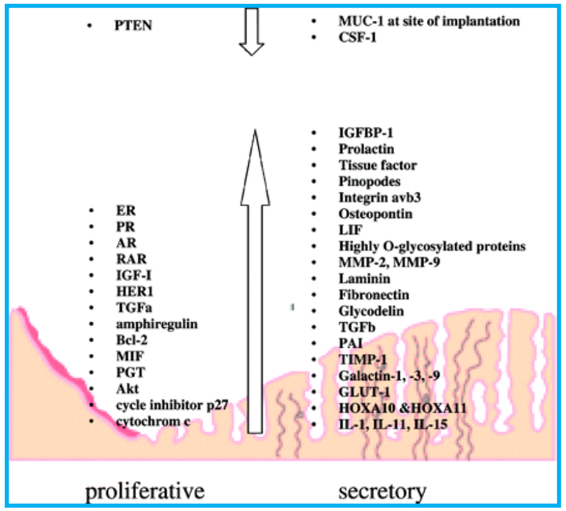


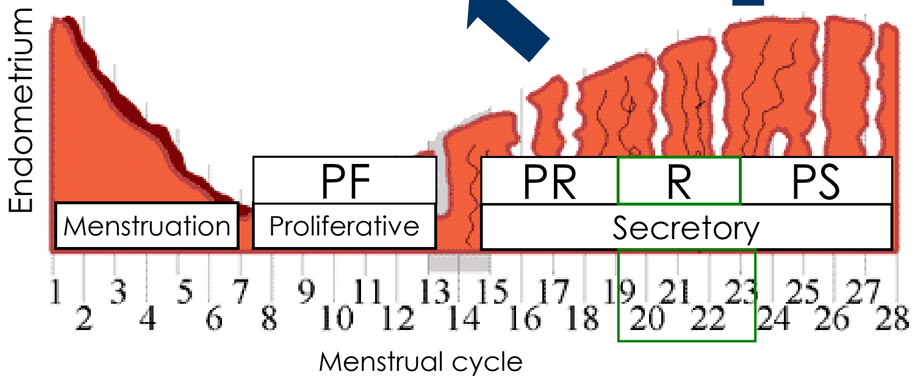
Tissue



Cells

Molecules





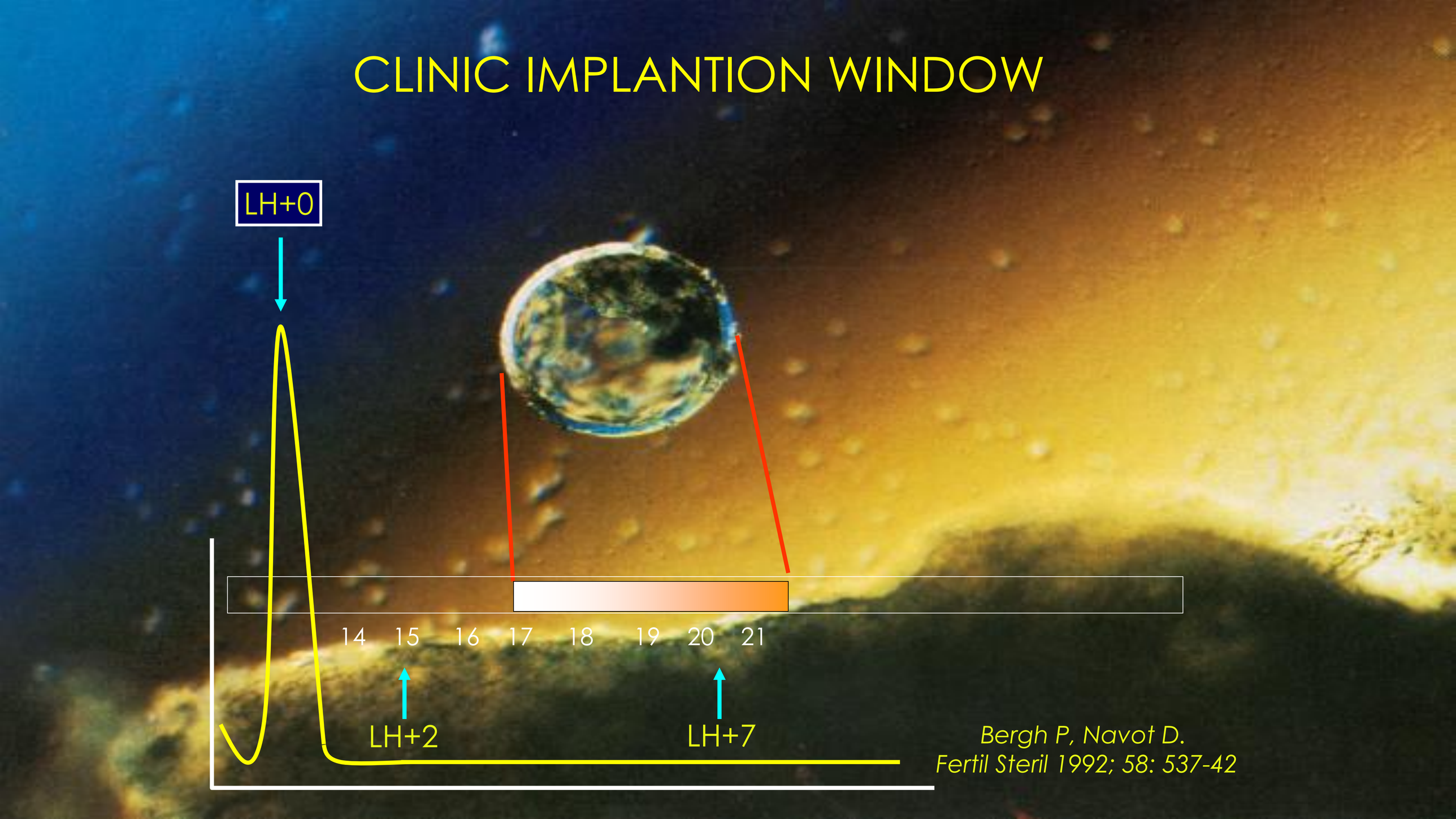
Endometrial Receptivity

Window of Implantation: WOI

PF: proliferative
PR: pre-receptive
R: receptive
PS:post-receptive

Clinical Interest

CLINIC IMPLANTION WINDOW



Bergh P, Navot D.
Fertil Steril 1992; 58: 537-42

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Why to support with P?

- To prepare the endometrium for embryo implantation

- To maintain pregnancy

- Uterine relaxation (miscarriage?)

- Embryo immunetolerance

Cochrane Database Syst Rev. 2015 Jul 7;7:CD009154. doi: 10.1002/14651858.CD009154.pub3.

Luteal phase support for assisted reproduction cycles.

van der Linden M[1], Buckingham K, Farquhar C, Kremer JA, Metwally M.

While the efficacy of progesterone in fresh embryo transfer (ET) is now well established, the optimal LPS in frozen embryo transfer (FET) **has yet to be established,** particularly in terms of indication to treatment, route of administration, and treatment duration.
Bulleti et al., 2022

Progesterone vs placebo/no treatment (eight RCTs, 875 women)
Evidence suggests a higher rate of live birth or ongoing pregnancy in the progesterone group (OR 1.77, 95% CI 1.09 to 2.86, five RCTs, 642 women, I2 = 35%, very low-quality evidence).

Progesterone in the luteal phase

It doesn’t exist a consensus in the minimal P concentration to define the right luteal function[1]

P concentration can vary widely in different scenarios:

- Normal or abnormal cycles[2]
- Fertile and infertile women[3]

P secretion is pulsatile[4]

- It can vary from 2 to 40 ng/mL in a short period of time

1. The Practice Committee of the American Society for Reproductive Medicine. *Fertil Steril*. 2008;90(Suppl 3):S150-S153.
2. Shepard MK, Senturila YD. *Fertil Steril*. 1977;28(5):541-548.
3. Dodson KS, et al. *Br J Obstet Gynaecol*. 1975;82:615-624.
4. Filicori M et al. *J Clin Invest*. 1984;73(6):1638-1647.

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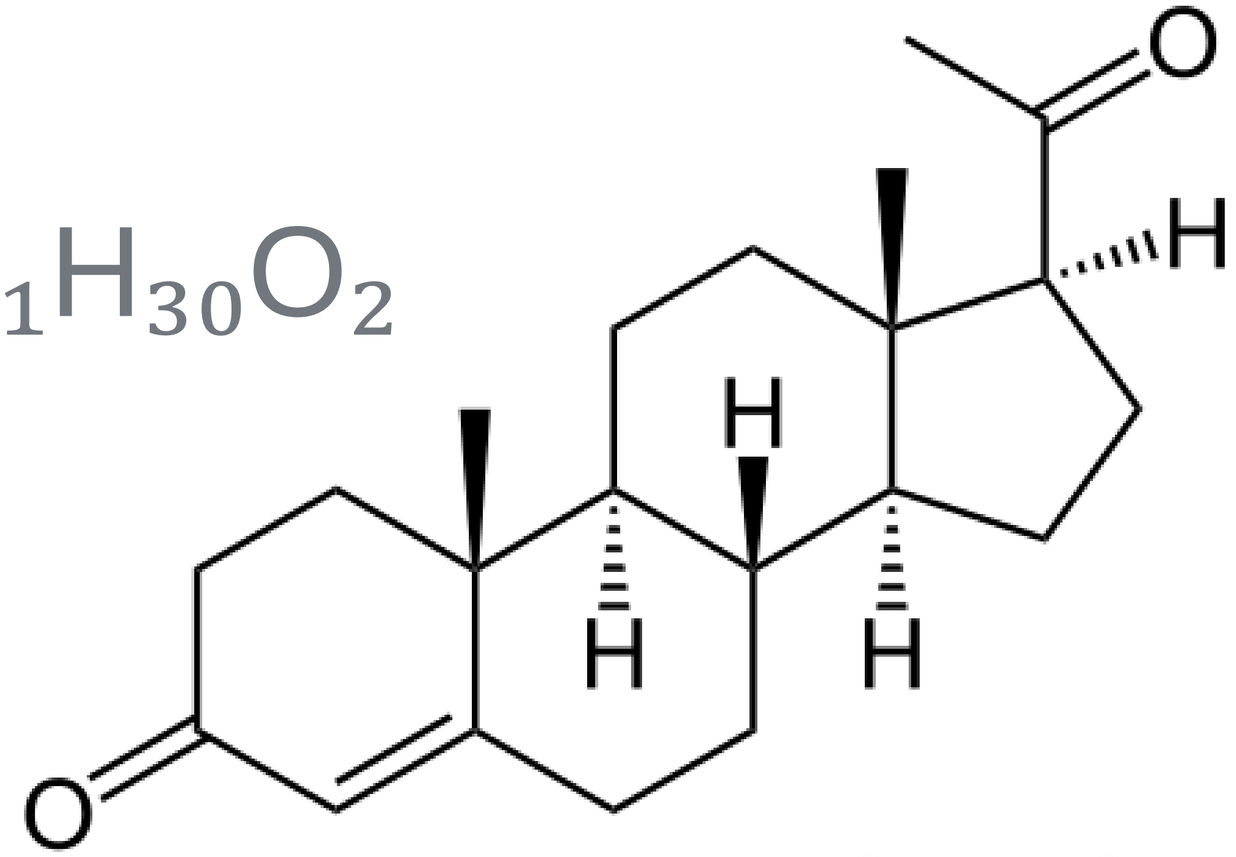
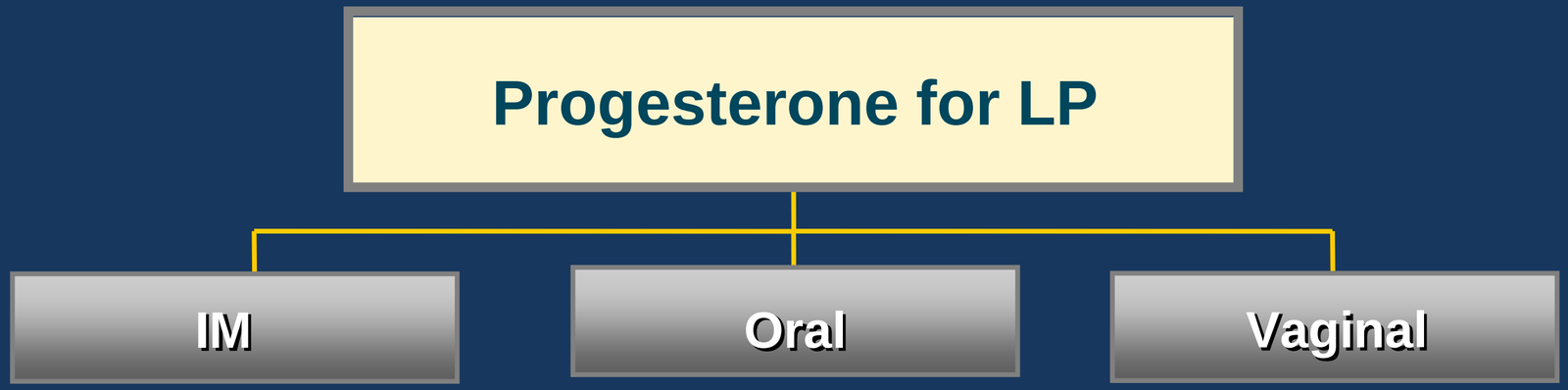
PROGESTERONE

$C_{21}H_{30}O_2$



George W. Corner and Allen M. Willard, 1929

Progesterone



Others:

- transdermic
- sublingual
- rectal
- nasal

Oral Progesterona

Advantages

- Easy administration[1]
- Lower rate of multiple pregnancy[2]

Disadvantages

- Efficacy questioned [1]
- Low bioavailability and hig variability[1]
- High metabolites rate (lower endometrial impact) [1]
- Delayed endometrial development[1]
- Erratic absorption
- High incidence of secondary effects such as sedation[1]

1. Khan N, et al. *Fertil Steril.* 2009;91(6):2445-2450.
2. van der Linden M, et al. *Cochrane Database Syst Rev.* 2012;(10):CD009154.

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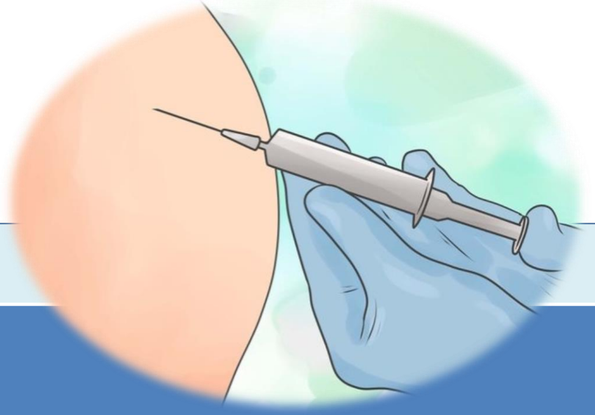

IM Progesterone

Advantages[1,2]

- Effective
- One dose per day
- Phisiological levels in serum (high)

Disadvantages[1,2]

- Painful
- Absesses (sometimes)
- Alergic reaction due to the oil (sometimes)
- It is not possible autoadministration
- Anxiety
- Acute eosinophilic pneumonia after IVF
- High levels of P4 are not always an indication of endometrial effects

1. Khan N, et al. *Fertil Steril.* 2009;91(6):2445-2450.
2. Miles RA, et al. *Fertil Steril.* 1994;62(3):485-490

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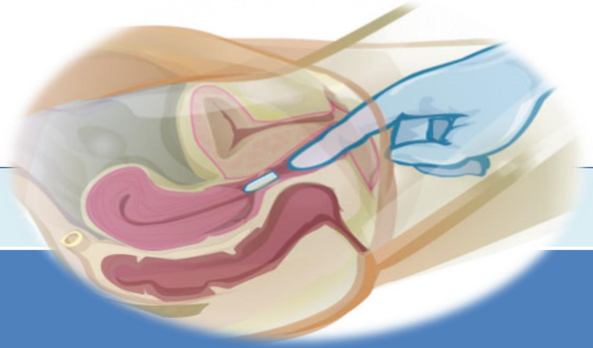


Vaginal Progesterone

Advantages[1,3]

- High availability
- Rapid absorption
- No hepatic pass
- Effective
- Autoadministration
- High levels for 48h
- Less advers effects

Disadvantages[1]

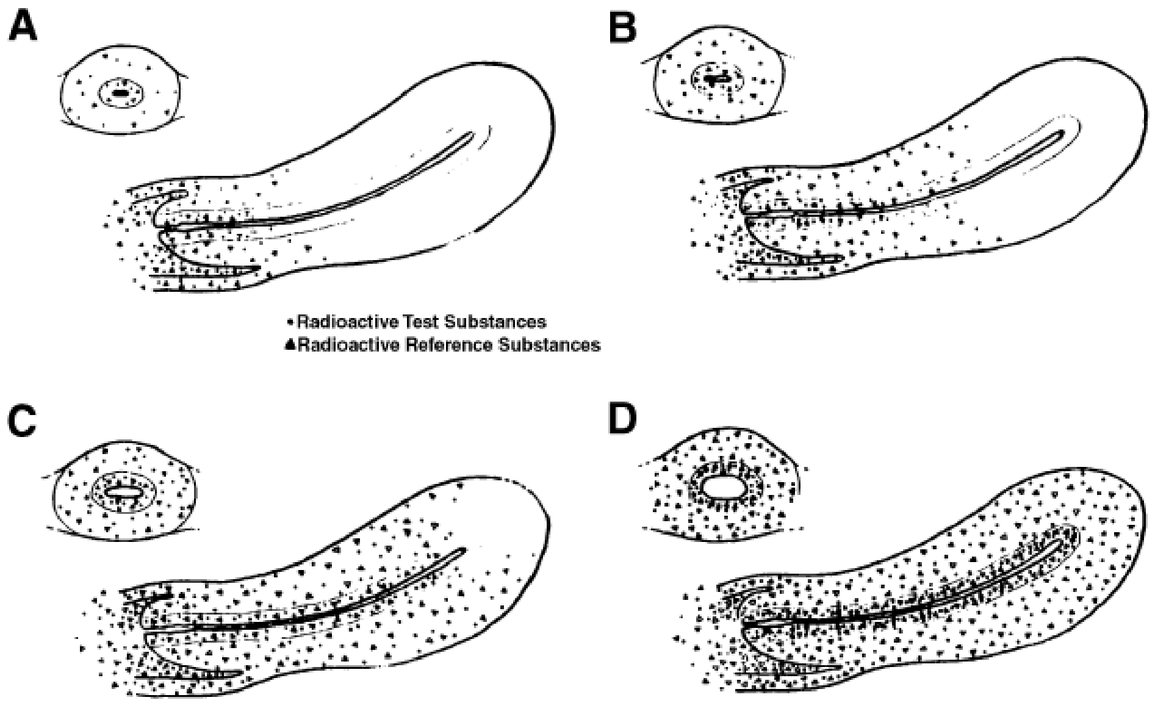
- Capsules (pearls)
  - Multiple doses per day
  - Residue
  - Infections and irritation
- Gel
  - Aplication could be disgusting
  - Vaginal acumulation and irritation

1. Khan N, et al. *Fertil Steril.* 2009;91(6):2445-2450.
2. Bulletti C, et al. *Hum Reprod.* 1997;12(5):1073-1079.
3. Hubayter ZR, et al. *Fertil Steril.* 2008;89(4):749-758.

Hum Reprod. 1997 May;12(5):1073-9.

Targeted drug delivery in gynaecology: the first uterine pass effect.

Bulletti C[1], de Ziegler D, Flamigni C, Giacomucci E, Polli V, Bolelli G, Franceschetti F.



VAGINAL Progesterone

1. Progesterone diffusion

"Phenomenon of first uterine pass"

Bulletti et al., Hum Reprod 1997

2. Good correlation between serum and endometrial P levels

Cicinelli et al., Obstet Gynecol 2000

Oral versu…for in vitro fertiliza…l study.

Intramuscular versus oral progesterone for IVF: differences in pregnancy results.

Variable	Route of administration	
	IM (n = 19)	PO (n = 24)
No. of clinical pregnancies/no. of oocyte retrievals (%)	11/19 (57.9)	11/24 (45.8)
No. of patients with multiple implantation/total no. of pregnant patients (%)	9/11 (81.8)	4/11 (36.3)
No. of higher-order multiple implantations	4*	0
Implantation rate per embryo (%)	40.9	18.1†

Note: PO = oral.

* Three sets of quadruplets and one set of triplets.

† $P = .004$ (versus IM).

Oral progesterone and IM progesterone result in comparable levels of circulating progesterone.

However, oral progesterone results in a reduced implantation rate per embryo

Fertil Steril. 2014 Mar;101(3):627-8. doi: 10.1016/j.fertnstert.2014.01.018. Epub 2014 Feb 1.

Luteal phase support for frozen embryo transfer cycles: intramuscular or vaginal progesterone?

Casper RF[1].

- In conclusion, for **FET or donor oocyte cycles**, we propose that the use of progesterone in oil injections may reduce uterine contractility and endometrial wave activity **better** than vaginal progesterone suppositories.

- Intramuscular progesterone may be beneficial for luteal support, at least until blastocyst attachment or implantation has occurred, when a switch back to vaginal progesterone could be considered.

Hum Reprod. 2014 Aug;29(8):1706-11. doi: 10.1093/humrep/deu121. Epub 2014 May 20.

Progesterone replacement with vaginal gel versus i.m. injection: cycle and pregnancy outcomes in IVF patients receiving vitrified blastocysts.

Shapiro DB[1], Pappadakis JA[2], Ellsworth NM[3], Hait HI[4], Nagy ZP[3].

	IMP ($n = 682$)	Crinone 8% ($n = 238$)
Implantation rate	46.4 ± 42.0	45.6 ± 42.5
Positive serum hCG	496 (72.7)	168 (70.6)
Clinical pregnancy	421 (61.7)	144 (60.5)
Spontaneous abortion	91 (13.3)	28 (11.8)
Live birth[b]	332 (49.1)	116 (48.9)

Hum Reprod. 2014 Oct 10;29(10):2212-20. doi: 10.1093/humrep/deu194. Epub 2014 Aug 6.

A randomized, controlled trial comparing the efficacy and safety of aqueous subcutaneous progesterone with vaginal progesterone for luteal phase support of in vitro fertilization.

Baker VL[1], Jones CA[2], Doody K[3], Foulk R[4], Yee B[5], Adamson GD[6], Cometti B[7], DeVane G[8], Hubert G[9], Trevisan S[7], Hoehler F[10], Jones C[2], Soules M[11].

	Prolutex	Endometrin
Initial serum β-hCG positive		
PP	56.4 (221/392)	59.0 (230/390)
ITT	55.3 (221/400)	57.5 (230/400)
Clinical pregnancy (6–7 weeks of gestation)		
PP	42.6 (167/392)	46.4 (181/390)
ITT	41.8 (167/400)	45.3 (181/400)
Ongoing pregnancy (12 weeks of gestation—primary efficacy variable)		
PP	41.6 (163/392)	44.4 (173/390)
ITT	40.8 (163/400)	43.3 (173/400)
Live birth		
PP	41.1 (161/392)	43.1 (168/390)
ITT	40.3 (161/400)	42.0 (168/400)

Fertil Steril. 2012 Dec;98(6):1464-9. doi: 10.1016/j.fertnstert.2012.08.007. Epub 2012 Sep 6.

Intramuscular progesterone versus 8% Crinone vaginal gel for luteal phase support for day 3 cryopreserved embryo transfer.

Kaser DJ[1], Ginsburg ES, Missmer SA, Correia KF, Racowsky C.

Clinical outcome	IMP (n = 440)	8% Crinone (n = 298)	*P* value[a]
Implantation rate[b]	30.4 ± 36.8	19.6 ± 32.2	.39
Biochemical pregnancy	51 (11.6)	39 (13.1)	.73
Clinical pregnancy	225 (51.1)	110 (36.9)	<.001
Spontaneous abortion	44 (10.2)	34 (11.5)	.61
Live birth[c]	169 (39.1)	72 (24.4)	<.0001

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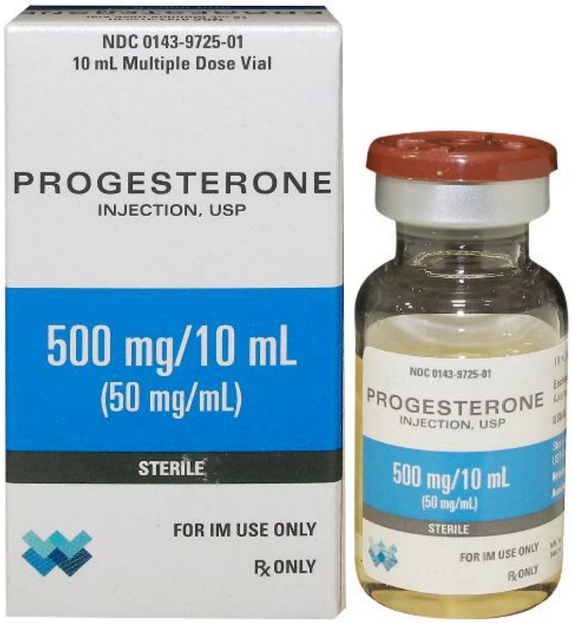
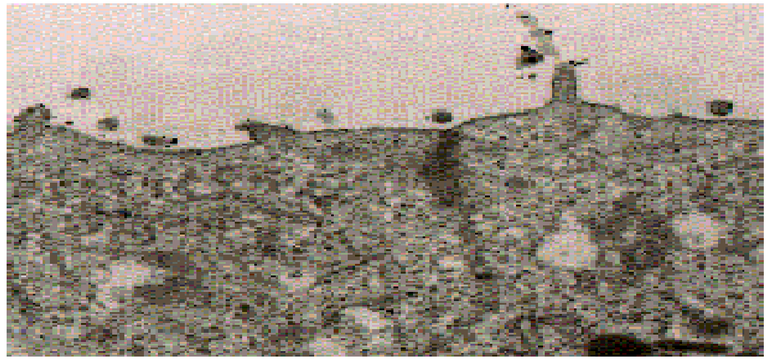
OLEIC SOLUTION



MICRONIZED

Receptive endometrium features

Morphological markers
Biochemical markers
Gene expression pattern



PITFALLS OF HISTOLOGICAL DATING FOR ENDOMETRIAL EVALUATION

- **Li TC, Dockery P, Rogers AW, Cooke ID (1989)** How precise is histologic dating of Endometrium using the standard dating criteria. Fertil Steril 51:759-63.

- **Balasch J, Fabregues F, Creus M, Vanrell JA. (1992)** The usefulness of endometrial biopsy for luteal phase evaluation in infertility Hum Reprod 7:973-7.

- **American Society for Reproductive Medicine (2000)** A practice committee report: optimal evaluation of the infertile female ASRM, 2000:1-6.

- **Murray MJ, Meyer WR, Zaino RJ, Lessey BA, et al., (2004)** A critical analysis of the accuracy, reproducibility, and clinical utility of histology endometrial dating in fertile women. Fertil Steril 81:1333-43.

- **Coutifaris C, Myers ER, et al., (2004)** Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertil Steril 82:456-61.

PITFALLS OF HISTOLOGICAL DATING FOR ENDOMETRIAL EVALUATION

Randomized Studies

Interobserver and cycle to cycle (60%) variations

Murray et al., 2004 Fertil. & Steril. 81:1333-1343

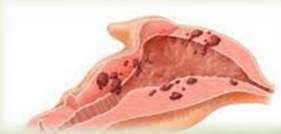
Endometrial dating is not related to the fertility status

Coutifaris et al., 2004 Fertil. & Steril. 82:1264-1272

Histological dating is not the definitive method for the diagnosis of luteal phase deficiency or to guide clinical management in infertility

Gene Expression Analysis in…

4,821 **Cancer**



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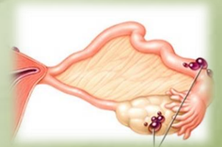
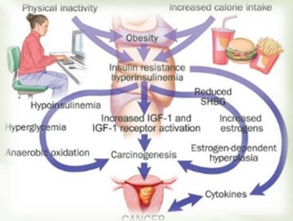
Adenomyosis



1,019

Endometriosis

122



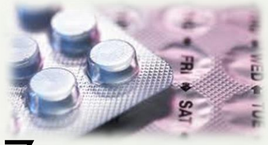
Obese

Endometrium

Myomas

28

Contraception



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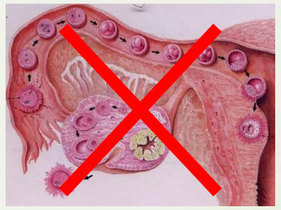
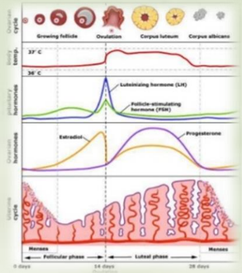
Implantation failure

35



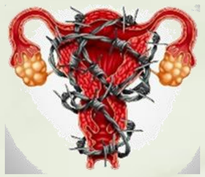
Stimulated cycles

335



Endometritis

32



Total: >7,000 (2022)

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FIRST GLOBAL STUDY

0013-7227/02/$15.00/0
Printed in U.S.A.

Endocrinology 143(6):2119–2138

Global Gene Profiling in Human Endometrium during the Window of Implantation

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SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

IMPLANTATION FAILURE

SCIENTIFIC REPORTS

OPEN

Received: 04 August 2015
Accepted: 11 December 2015
Published: 22 January 2016

An endometrial gene expression signature accurately predicts recurrent implantation failure after IVF

Yvonne E. M. Koot[1,*], Sander R. van Hooff[2,*], Carolien M. Boomsma[1], Dik van Leenen[2], Marian J. A. Groot Koerkamp[2], Mariëtte Goddijn[3], Marinus J. C. Eijkemans[1,4], Bart C. J. M. Fauser[1], Frank C. P. Holstege[2,*] & Nick S. Macklon[1,5,*]

ENDOMETRIAL DISORDERS: 126 GENE MODEL

2010

Genome-based expression profiling as a single standardized microarray platform for the diagnosis of endometrial disorder: an array of 126-gene model

Ling-Hong Tseng, M.D.,[a] *Ilen Chen M.S.,*[b] *Ming-Yang Chen M.S.,*[c] *Hong Yan, Ph.D.,*[b] *Chao-Nin Wang, M.D.,*[a] *and Chyi-Long Lee, M.D.*[a]

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Objective: To assess the molecular signatures underlying endometrial disorder using cDNA microarray.
Design: Gene expression-based oligonucleotide array of the normal endometrium.
Setting: University hospital.
Patient(s): Humans.
Intervention(s): Endometrial tissues were obtained from 28 normal cycling women undergoing endometrial biopsy. RNA was extracted from each tissue and all labeled samples were hybridized to Affymetrix Human U133 plus 2.0 array.
Main Outcome Measure(s): Transcriptional response.
Result(s): Hierarchical cluster analysis with the Mahalanobis distance revealed a "126-gene" model, which are up-regulated at mid-secretory phase, moderately expressed at late-secretary phase, and down-regulated at late-secretory phase. Furthermore, the mechanisms underlying the receptivity of human endometrium at mid-secretary phase can be summarized: first, complex metabolic reactions are involved. Second, the activation of complement and coagulation cascades promotes muscle contraction, chemotaxis, phagocyte recruitment, and peritoneal inflammation. Third, Ephrin A-mediated axon guidance promotes retrograde menstruation. Fourth, autophagic degradation is suggested to be responsible for the new blood vessel formation. In addition, DKK1 is up-regulated, indicating that WNT signaling pathway may contribute to the development of endometrial disorders.
Conclusion(s): The success of this innovation has supported the use of microarray-based genome expression profiling as a single standardized platform for diagnosis of endometrial disorders. (Fertil Steril® 2010;94:114–9. ©2010 by American Society for Reproductive Medicine.)

Key Words: Human endometrium, menstrual cycle, endometrial disorder, cDNA microarray

SCIENTIFIC SEMINARS
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ENDOMETRIAL RECEPTIVITY TESTS 2011

A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature

Patricia Díaz-Gimeno,[a,b] *José A. Horcajadas, Ph.D.,*[c] *José A. Martínez-Conejero, Ph.D.,*[c] *Francisco J. Esteban, Ph.D.,*[d] *Pilar Alamá, M.D.,*[a,b] *Antonio Pellicer, M.D.,*[a,b] *and Carlos Simón, M.D.*[a,b,e]

[a] Fundación IVI-Instituto Universitario IVI, University of Valencia, Valencia; [b] Instituto de Investigación, Sanitaria del Hospital Clinico de Valencia, Valencia University, Valencia; [c] iGenomix, Valencia; [d] Department of Experimental Biology, University of Jaén, Jaén; and [e] Centro de Investigación Principe Felipe, Valencia, Spain

Objective: To create a genomic tool composed of a customized microarray and a bioinformatic predictor for endometrial dating and to detect pathologies of an endometrial origin. To define the transcriptomic signature of human endometrial receptivity.
Design: Two cohorts of endometrial samples along the menstrual cycle were used: one to select the genes to be included in the customized microarray (endometrial receptivity array [ERA]), the other to be analyzed by ERA to train the predictor for endometrial dating and to define the transcriptomic signature. A third cohort including pathological endometrial samples was used to train the predictor for pathological classification.
Setting: Healthy oocyte donors and patients.
Patient(s): Healthy fertile women (88) and women with implantation failure (5) or hydrosalpinx (2).
Intervention(s): Human endometrial biopsies.
Main Outcome Measure(s): The gene expression of endometrial biopsies.
Result(s): The ERA included 238 selected genes. The transcriptomic signature was defined by 134 genes. The predictor showed a specificity of 0.8857 and sensitivity of 0.99758 for endometrial dating, and a specificity of 0.1571 and a sensitivity of 0.995 for the pathological classification.
Conclusion(s): This diagnostic tool can be used clinically in reproductive medicine and gynecology. The transcriptomic signature is a potential endometrial receptivity biomarkers cluster. (Fertil Steril® 2010;■:■–■. ©2010 by American Society for Reproductive Medicine.)

Key Words: Endometrial receptivity, endometrial dating, microarray, transcriptomic signature, predictor, diagnostic tool

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

ENDOMETRIAL RECEPTIVITY TESTS 2018

Human Reproduction, pp. 1–9, 2018
doi:10.1093/humrep/dex370

human reproduction

ORIGINAL ARTICLE *Infertility*

Development of a new comprehensive and reliable endometrial receptivity map (ER Map/ER Grade) based on RT-qPCR gene expression analysis

M. Enciso[1,*,†], J.P. Carrascosa[2,†], J. Sarasa[1], P.A. Martínez-Ortiz[3], S. Munné[4], J.A. Horcajadas[2,*], and J. Aizpurua[3]

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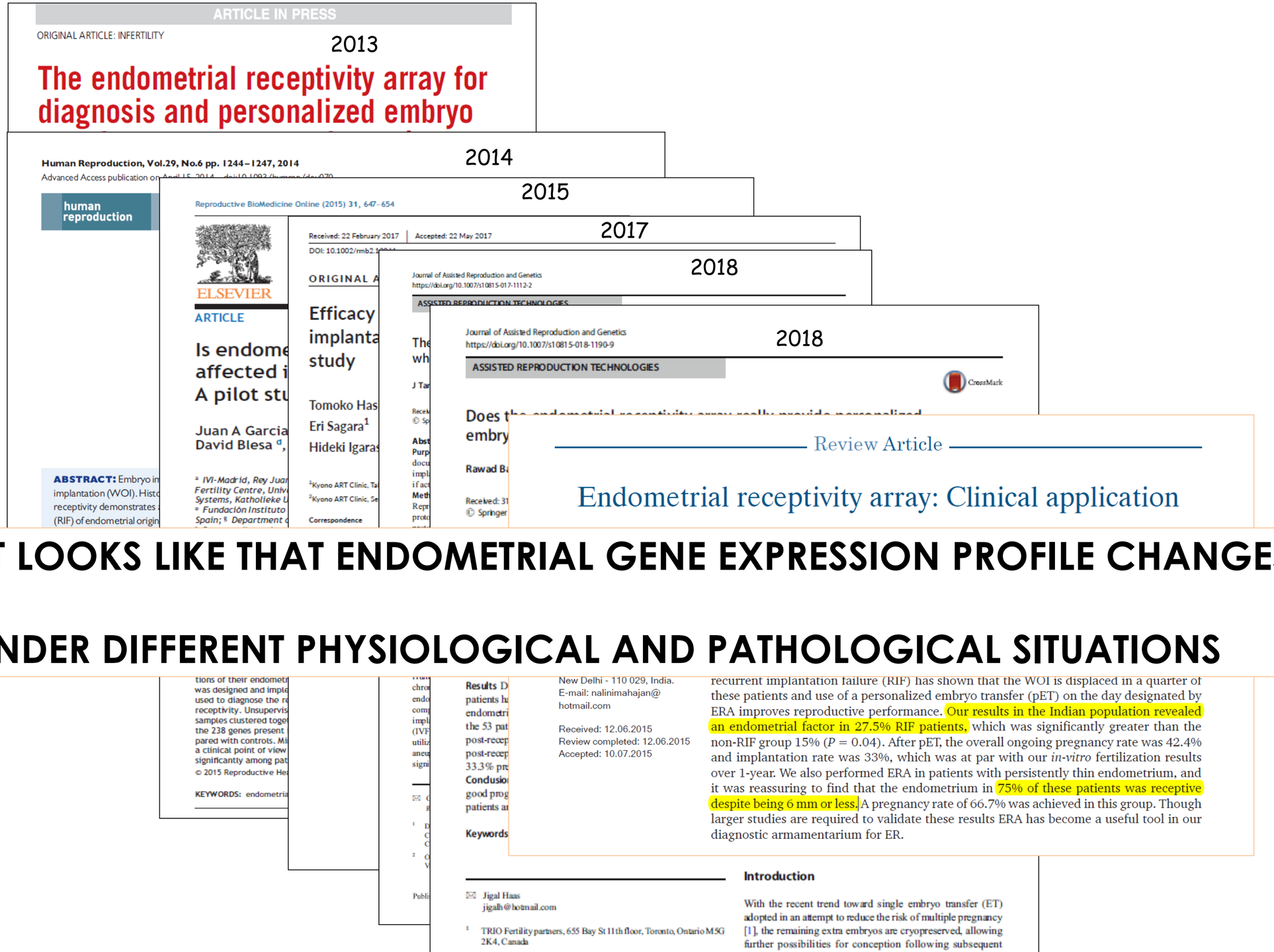
ARTICLE IN PRESS
ORIGINAL ARTICLE: INFERTILITY
2013
The endometrial receptivity array for diagnosis and personalized embryo
Human Reproduction, Vol.29, No.6 pp. 1244–1247, 2014
2014
human reproduction
Reproductive BioMedicine Online (2015) 31, 647–654
2015
ELSEVIER
ARTICLE
Received: 22 February 2017 | Accepted: 22 May 2017
2017
Journal of Assisted Reproduction and Genetics
https://doi.org/10.1007/s10815-017-1112-2
2018
Journal of Assisted Reproduction and Genetics
https://doi.org/10.1007/s10815-018-1190-9
ASSISTED REPRODUCTION TECHNOLOGIES
2018
CrossMark
Review Article
Endometrial receptivity array: Clinical application
IT LOOKS LIKE THAT ENDOMETRIAL GENE EXPRESSION PROFILE CHANGES
UNDER DIFFERENT PHYSIOLOGICAL AND PATHOLOGICAL SITUATIONS
New Delhi - 110 029, India.
E-mail: nalinimahajan@hotmail.com
Received: 12.06.2015
Review completed: 12.06.2015
Accepted: 10.07.2015
recurrent implantation failure (RIF) has shown that the WOI is displaced in a quarter of these patients and use of a personalized embryo transfer (pET) on the day designated by ERA improves reproductive performance. Our results in the Indian population revealed an endometrial factor in 27.5% RIF patients, which was significantly greater than the non-RIF group 15% (P = 0.04). After pET, the overall ongoing pregnancy rate was 42.4% and implantation rate was 33%, which was at par with our in-vitro fertilization results over 1-year. We also performed ERA in patients with persistently thin endometrium, and it was reassuring to find that the endometrium in 75% of these patients was receptive despite being 6 mm or less. A pregnancy rate of 66.7% was achieved in this group. Though larger studies are required to validate these results ERA has become a useful tool in our diagnostic armamentarium for ER.
Introduction
With the recent trend toward single embryo transfer (ET) adopted in an attempt to reduce the risk of multiple pregnancy [1], the remaining extra embryos are cryopreserved, allowing further possibilities for conception following subsequent
Jigal Haas
jigalh@hotmail.com
TRIO Fertility partners, 655 Bay St 11th floor, Toronto, Ontario M5G 2K4, Canada

RBMO

ELSEVIER

2020

ARTICLE

A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF

KEY MESSAGE

This study demonstrates the clinical potential of personalized embryo transfer guided by the endometrial receptivity analysis test at the first appointment, which should be confirmed in larger randomized controlled trials.

ABSTRACT

Research question: Does clinical performance of personalized embryo transfer (PET) guided by endometrial receptivity analysis (ERA) differ from frozen embryo transfer (FET) or fresh embryo transfer in infertile patients undergoing IVF?

Design: Multicentre, open-label randomized controlled trial; 458 patients aged 37 years or younger undergoing IVF with blastocyst transfer at first appointment were randomized to PET guided by ERA, FET or fresh embryo transfer in 16 reproductive clinics.

Results: Clinical outcomes by intention-to-treat analysis were comparable, but cumulative pregnancy rate was significantly higher in the PET (93.6%) compared with FET (79.7%) ($P = 0.0005$) and fresh embryo transfer groups (80.7%) ($P = 0.0013$). Analysis per protocol demonstrates that live birth rates at first embryo transfer were 56.2% in PET versus 42.4% in FET ($P = 0.09$), and 45.7% in fresh embryo transfer groups ($P = 0.17$). Cumulative live birth rates after 12 months were 71.2% in PET versus 55.4% in FET ($P = 0.04$), and 48.9% in fresh embryo transfer ($P = 0.003$). Pregnancy rates at the first embryo transfer in PET, FET and fresh embryo transfer arms were 72.5% versus 54.3% ($P = 0.01$) and 58.5% ($P = 0.05$), respectively. Implantation rates at first embryo transfer were 57.3% versus 43.2% ($P = 0.03$), and 38.6% ($P = 0.004$), respectively. Obstetrical outcomes, type of delivery and neonatal outcomes were similar in all groups.

Conclusions: Despite 50% of patients dropping out compared with 30% initially planned, per protocol analysis demonstrates statistically significant improvement in pregnancy, implantation and cumulative live birth rates in PET compared with FET and fresh embryo transfer arms, indicating the potential utility of PET guided by the ERA test at the first appointment.

Human Reproduction Open, Vol.00, No.0, pp. 1–6, 2021
doi:10.1093/hropen/hoab010

2021

human reproduction open

DEBATE

Endometrial Receptivity Analysis (ERA) test: an unproven technology

Zion Ben Rafael *

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Submitted on September 29, 2020; resubmitted on December 2, 2020; editorial decision on February 23, 2021

ABSTRACT: This article addresses the limitations of the endometrial receptivity array (ERA) methodology to increase implantation. Such limitations vary from the assumed inconsistency of the endometrial biopsy, the variable number of genes found to be dysregulated in endometrium samples without the embryonal-induced effect, the failure to account for the simultaneous serum progesterone level, and the expected low percentage of patients who may need this add-on procedure, to the difficulties in synchronising the endometrium with hormone replacements in successive cycles and the inherent perinatal risks associated with routine cryopreservation of embryos. Without a gold standard to compare, the claim that the window of implantation (WOI) might be off by ±12 h only requires a good argument for the advantage it provides to human procreation, knowing that embryos can linger for days before actual embedding starts and that the window is actually a few days. The intra-patient variations in the test need to be addressed. In summary, like all other add-ons, it is doubtful whether the ERA test use can significantly enhance implantation success rates.

Key words: ERA test / add-ons / ART / IVF / implantation failure / RIF

Fertility and Sterility asrm

2021

ABSTRACT ONLY | VOLUME 116, ISSUE 3, SUPPLEMENT , E101, SEPTEMBER 01, 2021

A RANDOMIZED CONTROLLED TRIAL COMPARING LIVE BIRTH FROM SINGLE EUPLOID FROZEN BLASTOCYST TRANSFER USING STANDARDIZED TIMING VERSUS TIMING BY ENDOMETRIAL RECEPTIVITY ANALYSIS

Nicole Doyle, MD, PhD • Samad Jahandideh, PhD • Micah J. Hill, DO • Eric A. Widra, M.D. • Michael Levy, M.D. • Kate Devine, MD Shady Grove Fertility Center

CONCLUSIONS: ERA does not improve OP from single euploid FBT in an unselected population. An additional RCT is needed to assess whether ERA is beneficial in the setting of recurrent implantation failure.

IMPACT STATEMENT: Patients and physicians hold great hope that personalized medicine will improve ART outcomes; however, ERA does not improve OP from FBT of a single euploid blastocyst.

2022

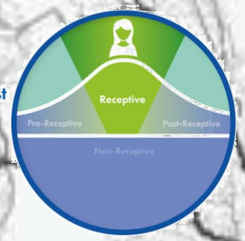
ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Use of the endometrial receptivity array to guide personalized embryo transfer after a failed transfer attempt was associated with a lower cumulative and per transfer live birth rate during donor and

Objective: To determine whether personalized embryo transfer (pET) guided by endometrial receptivity array (ERA) test improves reproductive outcomes for fresh embryo transfers (fsETs) or frozen embryo transfers (FETs) during autologous and donor cycles.
Design: A retrospective, observational, multicenter cohort study.
Setting: University-affiliated in vitro fertilization center.
Patient(s): The study included patients with a single previous failed transfer and yielded 3,239 autologous transfers and 2,133 donor transfers. Among autologous transfers, 255 were pET guided by ERA; among unguided autologous transfers, 1,122 and 1,862 transfers involved fresh or previously frozen embryos, respectively. Among donor transfers, 319 were ERA-guided; among unguided donor transfers, 1,175 and 639 involved fsETs or FETs, respectively.
Intervention(s): None.
Main Outcome Measure(s): Primary outcomes were live birth rate per embryo transfer and cumulative live birth rate on consecutive transfers until live birth or cessation of pregnancy. Secondary outcomes were implantation, pregnancy rate, clinical pregnancy rates per embryo transfer, and miscarriage rate per pregnancy.
Result(s): During both autologous or donor transfers, live birth rate and cumulative live birth rate were higher in FET and fsET than in pET groups, even with euploid transfers. Logistic regression analysis, considering possible confounders, indicated patients receiving pET had poorer outcomes than those undergoing FET and fsET in autologous and donor cycles. Implantation, pregnancy, and clinical pregnancy rates were lower in patients undergoing pET.
Conclusion(s): Using ERA to guide pET during either autologous or donor cycles after a failed transfer attempt did not improve reproductive outcomes. Conversely, worse outcomes were detected when ERA was used. (Fertil Steril® 2022;■:■–■. ©2022 by American Society for Reproductive Medicine.)

ERPeak℠

Endometrial Receptivity Test



FERT&i

(Es) ENDOMETRIAL SOLUTION

ER Map®

iGLS

ERA® Endometrial Receptivity Analysis

ALL THE ROADS LEAD ROME…

scientific reports

The human endometrium is receptive to the embryo for a specific period of time known as the window of implantation (WOI). During this period, the endometrium shows a specific gene expression profile suitable for endometrial function evaluation. ER Map is a molecular tool able to accurately predict endometrial receptivity status by transcriptomic analysis. In this retrospective study, including 2256 subfertile patients undergoing ART treatment, the clinical value of precise WOI determination is studied in detail. Results obtained when single embryo transfers (sET) were scheduled either within the WOI timeframe as established by ER Map, or deviating from this WOI, are assessed and compared. Data obtained showed that 34.18% (771/2256) of patients had a displaced WOI. Analysis of ART outcomes showed significantly higher pregnancy rates in transfers scheduled within the WOI predicted compared to transfers that deviated more than 12h from this WOI (44.35% vs 23.08%, $p < 0.001$). The deviation from the WOI had also an impact on the progression of pregnancy, with a significant increase in pregnancy loss (~twofold) observed in transfers that deviated more than 12h from the WOI predicted. These results indicate that the precise determination of the WOI and personalised embryo transfer can significantly improve clinical outcomes.

ORIGIN

Clinic
test f
receptivity
Japan

Yasuhir
Kohei Y
Mika Ha
Takaya[3] |
to Ishikawa[1,3] |

Abstract

Purpose: To assess the clinical efficacy of personalized embryo transfer (pET) guided by a new endometrial receptivity test, ERPeak[SM], in patients with recurrent implantation failure (RIF).

Methods: Recurrent implantation failure patients of all ages at two private Japanese clinics from April 2019 to June 2020 were retrospectively analyzed. The intervention group ($n = 244$) received pET in accordance with endometrial receptivity testing results and was compared to control group ($n = 306$) receiving standardized timing, non-personalized embryo transfer (npET). In propensity score matching analysis, the clinical pregnancy rate (CPR) and live birth rate (LBR) were compared between groups, and a subanalysis of advanced maternal age (AMA) (≥38 years old) versus non-AMA (<38 years old) patients was also conducted.

Results: The CPR and LBR of the pET group were significantly higher than those of the npET group (37.7% vs. 20.0%, adjusted OR: 2.64; 95%CI, 1.70–4.11, $p < 0.001$ and 29.9% vs. 9.7%, adjusted OR: 4.13; 95%CI, 2.40–7.13, $p < 0.001$, respectively). Furthermore, in the subanalyses, the CPR and LBR of the pET group were significantly higher than those of the npET group in both the AMA non-AMA patients.

Conclusions: The new ERPeak[SM] endometrial receptivity test is a useful alternative diagnostic tool for poor-prognosis patients, regardless of age.

KEYWORDS

advanced maternal age, endometrial receptivity test, personalized embryo transfer, recurrent implantation failure, window of implantation

PERSONALIZED MEDICINE

PERSONALIZED TREATMENTS

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

PHARMACOGENOMICS

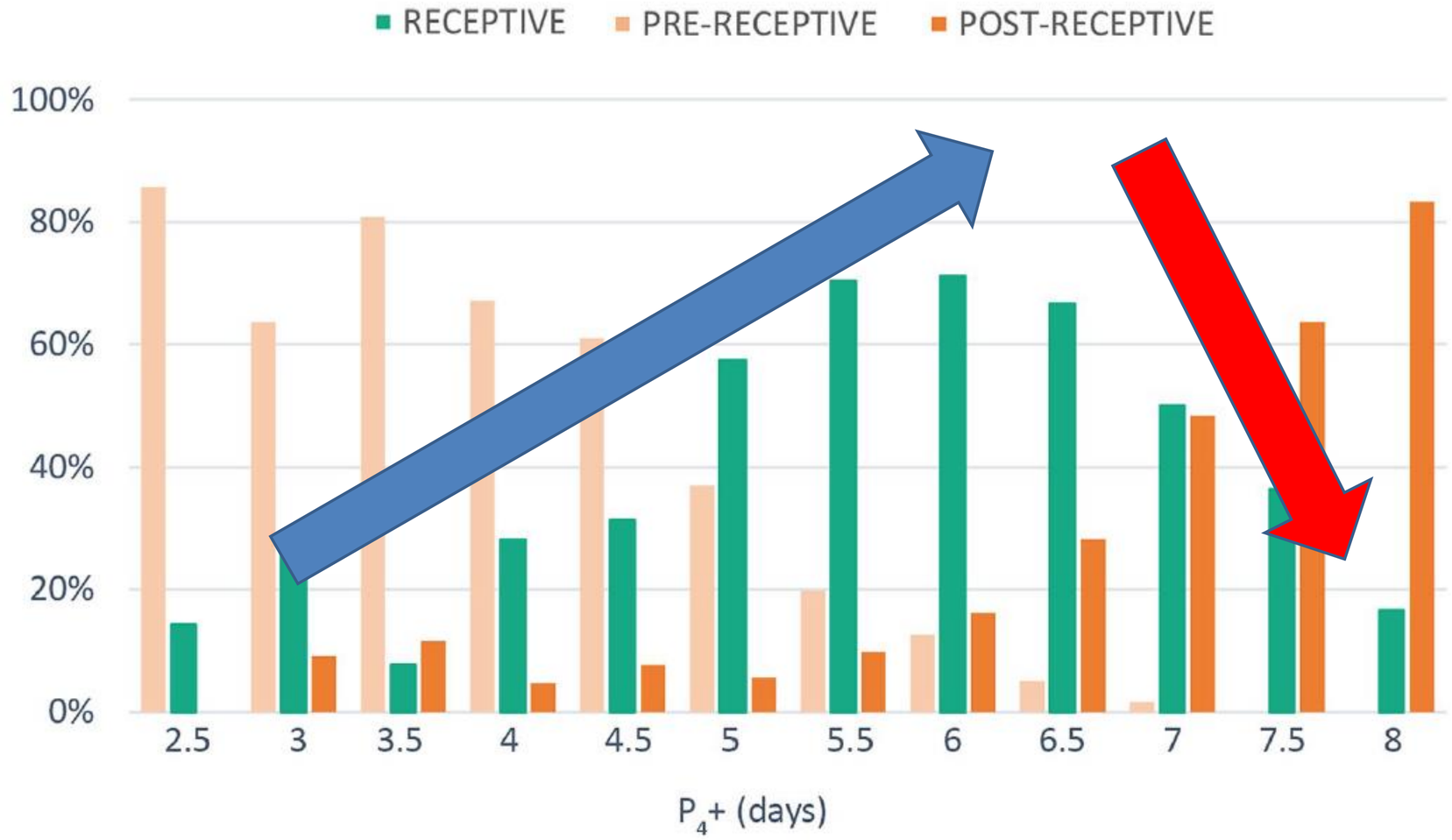


Figure 1. Endometrial receptivity status frequencies along different days of progesterone administration as assessed by ER Map. Frequencies of receptive, pre-receptive and post-receptive samples after a variable number of days of progesterone administration. N = 2828 biopsies.

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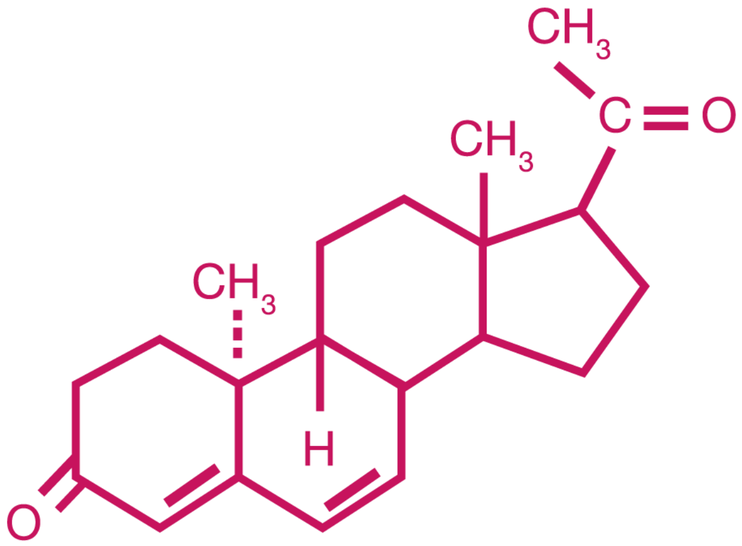
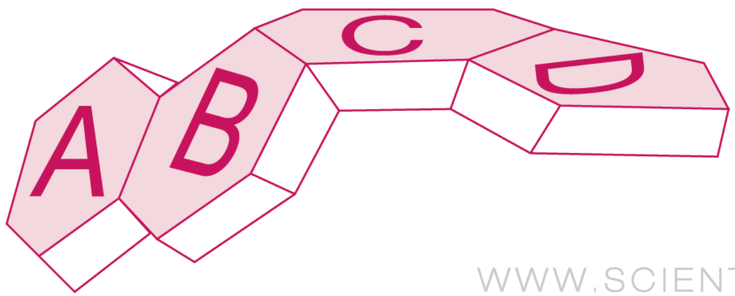
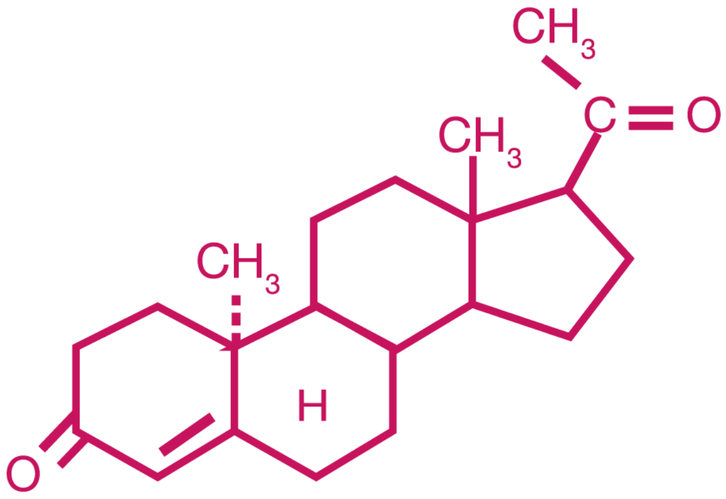
OTHER DRUGS

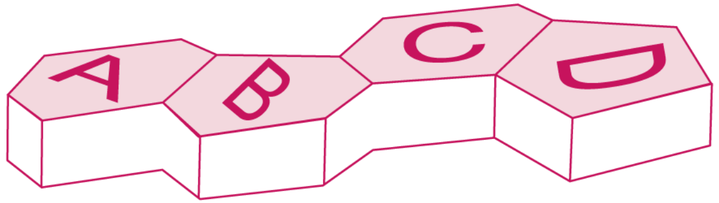
Dydrogesterone





Progesterone

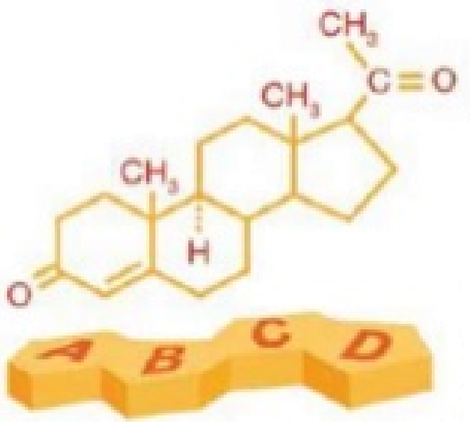




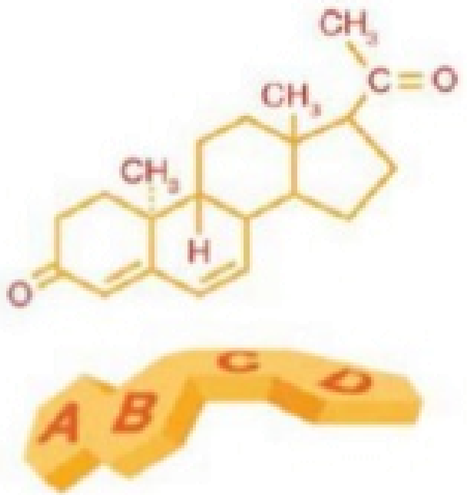
Structural Modification of Progesterone

- Dydrogesterone is retroprogesterone, stereoisomer of progesterone, with additional double bond between carbons 6 and 7[1]

Progesterone



Dydrogesterone



- Dydrogesterone, shaped by light, enhances progestogenic effects (improved bioavailability, and specificity and affinity for progesterone receptor)[2]

1. Kuhl H. Climacteric 2005; 8(Suppl 1): 3-63.
2. Schindler AE et al. Maturitas 2009; 65(Suppl 1): S3-S11.

Dihidrogesteronne has been used with patients with similar efficacy than natural progesterone

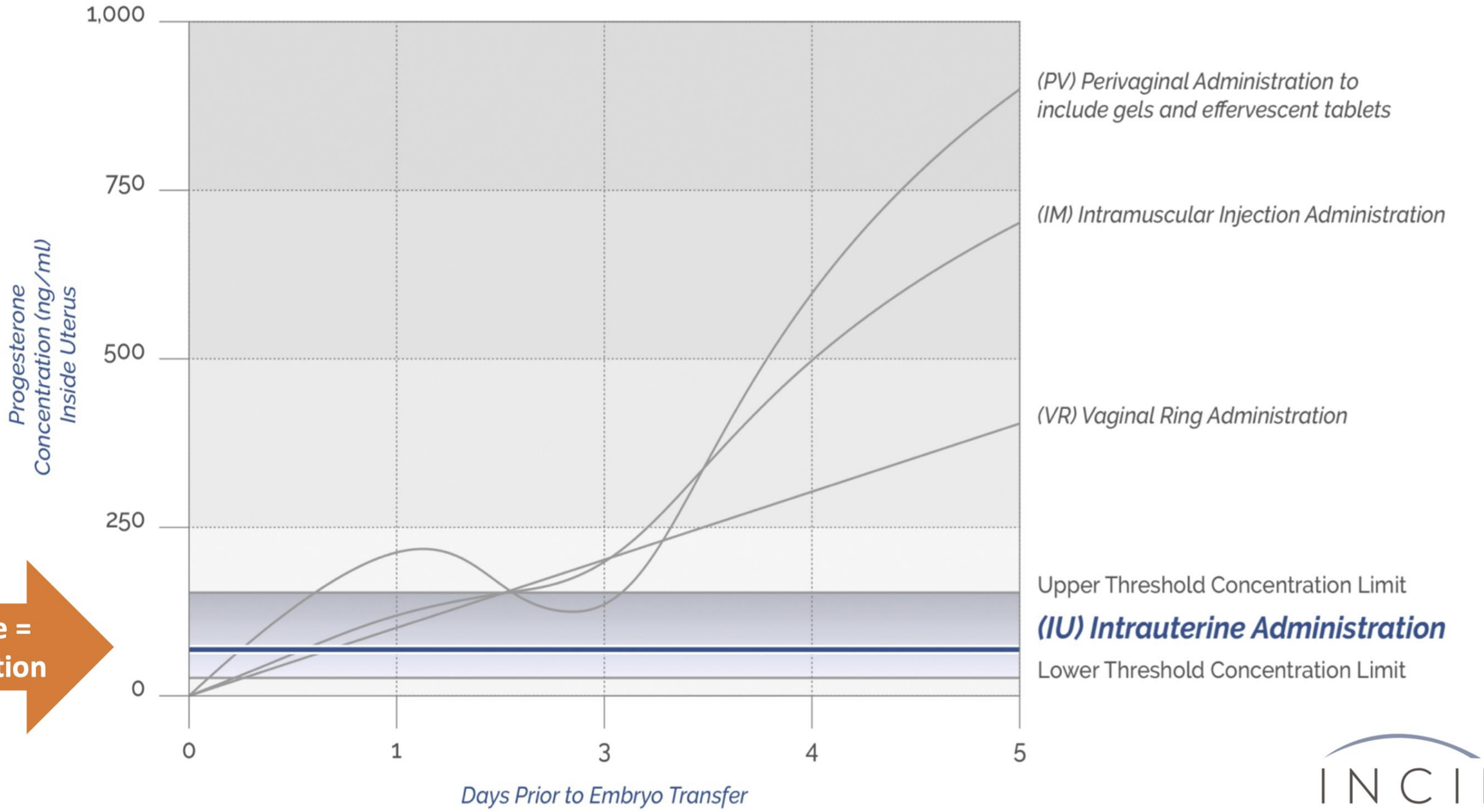
Oral administration avoid adverse effects on the Central Nervous System

More clinical studies are needed

Tournaye et al., 2017 A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. *Hum Reprod 32:1019-1027*.

Incintas' Discovery – How Progesterone Administration Affects Endometrial Hormone Levels

Endometrial gene expression is directly *and* indirectly correlated with Progesterone concentration; too little or too much P4 hinders implantation (failure to up-regulate and down-regulate, respectively).



Right quantity at right place = natural window of implantation

INCINTAS

Our Study: preliminary results

ER Test Clinical Results, Endometrial Biopsy Analysis

Mean Concentration (ngP4/g) Linear with Time, using conventional (PV) progesterone administration

"Pre-receptive"
Aprox 31.96 ng/g

"Receptive"
aprox 140.93 ng/g

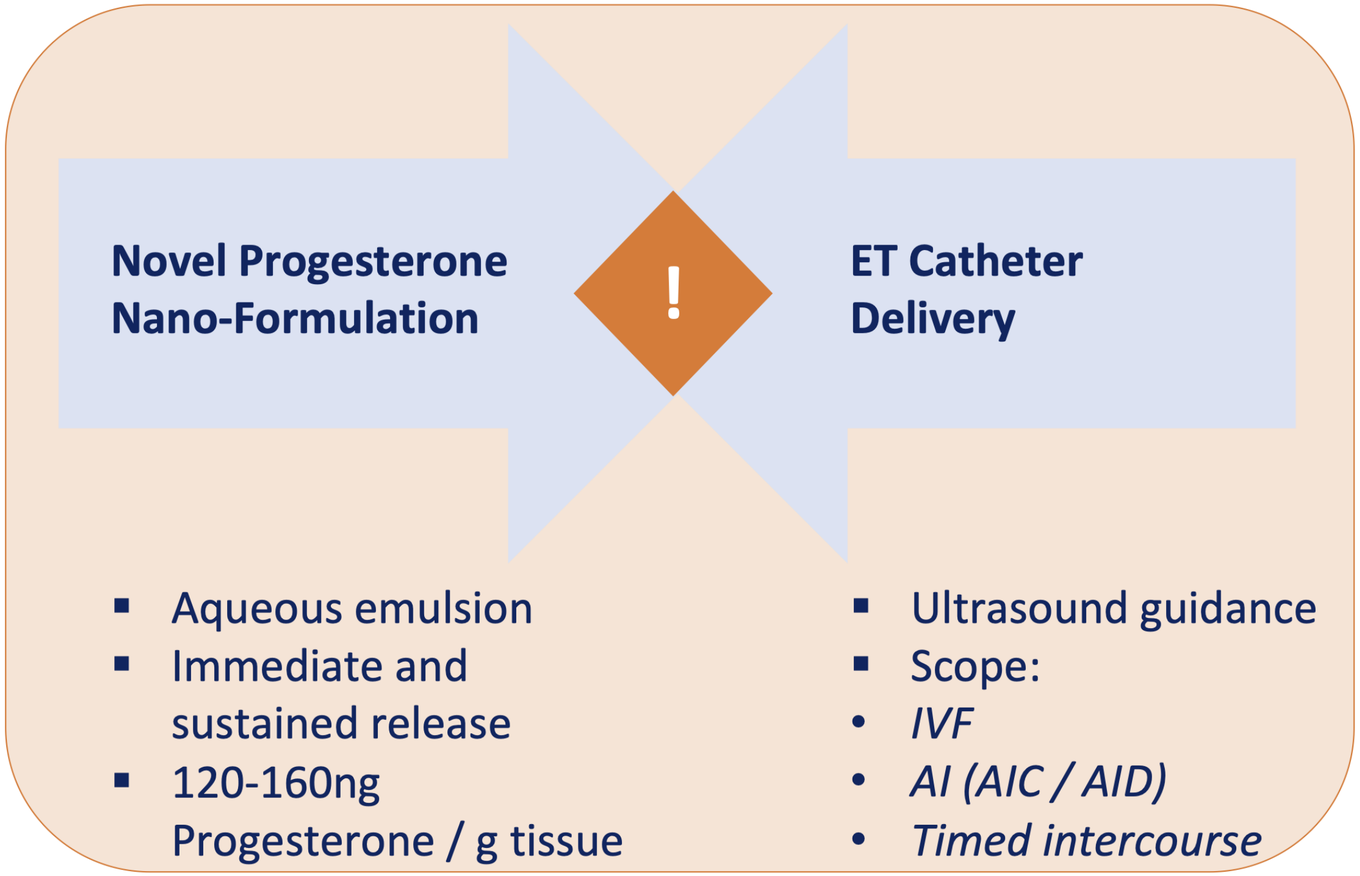
"Post-receptive"
aprox 316.87 ng/g

àNarrow "Window of Implantation"ß
(WOI Clinical Ave. = only 24 hrs.) (32 hrs. max.)

Conclusion:
Endometrial Gene Expression is P4 Concentration Dependent,
too little or too much P4 is detrimental to implantation.

Conventional uterine preparation methods establish a very short WOI and cannot sustain proper bioavailability

Our Proprietary Technology is a Novel Formulation and Delivery Method



INTELLECTUAL PROPERTY:

1. Modified **ET catheter with demarcation on flexible, internal cannula** to provide accurate aspiration and depth of penetration into the uterus (beyond the cervix)
2. Ability **to administer Progesterone directly on the uterine wall** to establish a longer window of implantation (claims protect wide progesterone concentration range for expansive formulation options. (Note: Includes Lubrizol's patented "LyoCell Technology")

- 2 US Patents Granted
- 1 EU Patent Granted, 1 EU Patent "Pending"

INCINTAS

Progesterone supplementation of luteal phase in ART cycles: classical versus innovative routes of administration

Take-home messages

- ✓ The efficacy of progesterone in fresh embryo transfer (ET) is now well established
- ✓ It doesn't exist a consensus in the minimal P concentration to define the right luteal function for FET and OD
- ✓ There are not evidences that IM progesterone produces better clinical outcomes than vaginal P, but the last one is more friendly for patients
- ✓ It is necessary more clinical trials to define the best treatment in terms of doses and timing including rescue strategies
- ✓ New types of progesterone and new method of application are being developed

jose.horcajadas@gmail.com

THANK YOU

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