Recent Developments in the Transmission of Human Life

19-21 January 2023

Berlin, Germany

Welcome to all Participants

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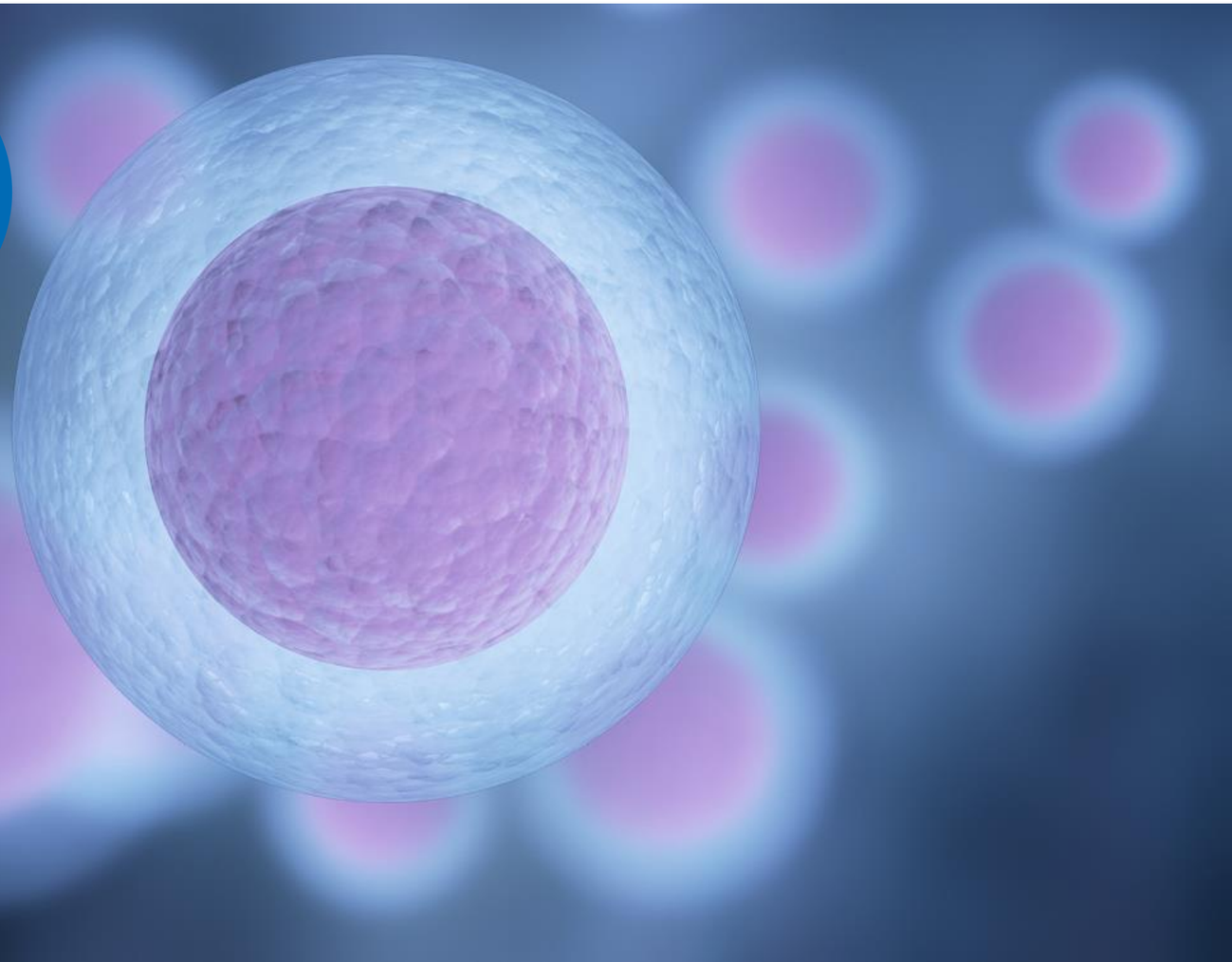
Recent Developments in the Transmission of Human Life

The gold standards of embryos implantation and ongoing pregnancy with special focus on endometrial adequacy

Andrea Borini

Bologna - Italy

9.baby
a GeneraLife network



Faculty Disclosure

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

Ferring, IBSA, Organon & Theramex

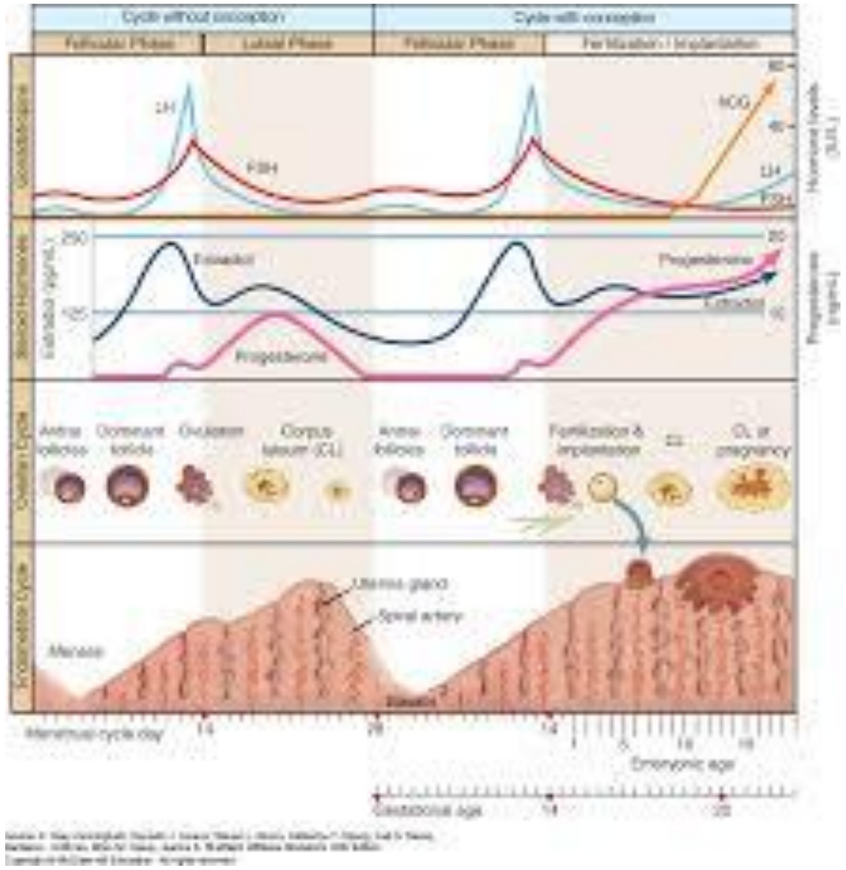
I have no potential conflict of interest to declare for this presentation

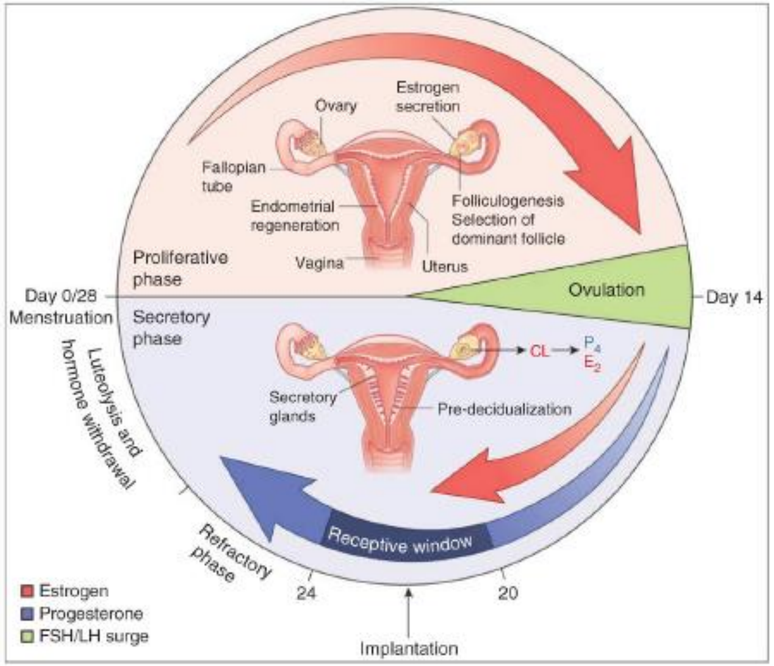
AGENDA

- Endometrium physiology and receptivity
- Endometrium in stimulated cycles
- Endometrial Thickness and pregnancy
- FET protocols
- Endometrial aging
- Take home message

ENDOMETRIAL PHYSIOLOGY

The ENDOMETRIUM is a highly dynamic tissue that plays a crucial role in the establishment and maintenance of normal pregnancy



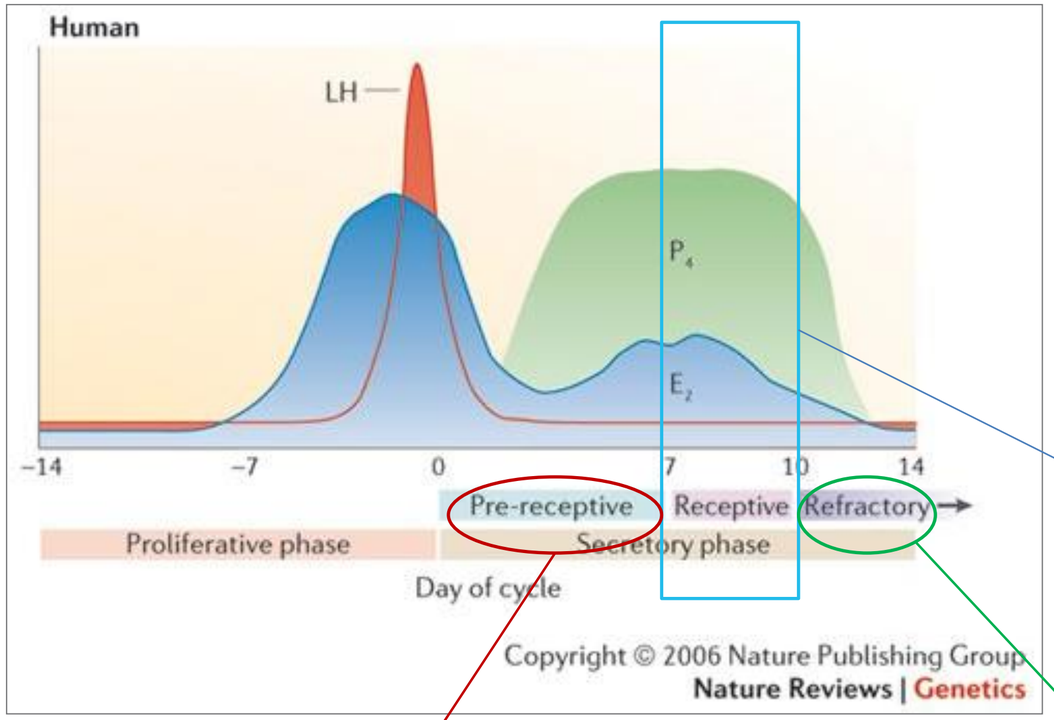


Ovarian ESTROGEN and PROGESTERONE regulates different phases of pregnancy by coordinating uterine cell specific effects.

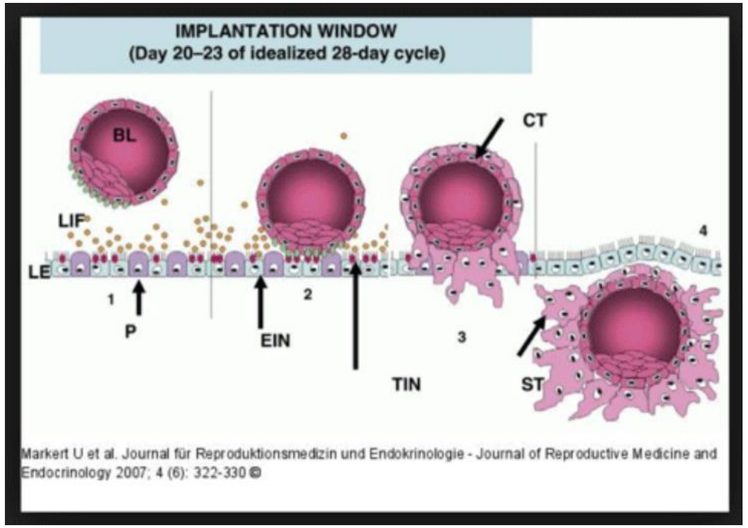
The human endometrium is a hormone-responsive mucosa that lines the uterine cavity and undergoes cyclic proliferation and differentiation to support embryo implantation

ENDOMETRIAL RECEPTIVITY

The uterus is receptive to blastocyst implantation during a spatio/temporally restricted window (WOI)



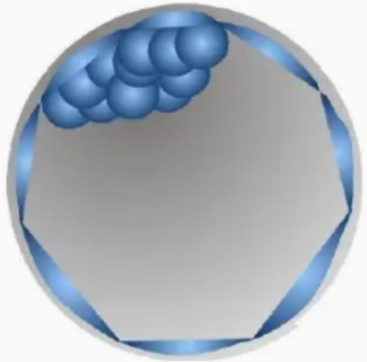
The uterus becomes receptive during the **Mid Secretory Phase**, which spans 7-10 days after ovulation

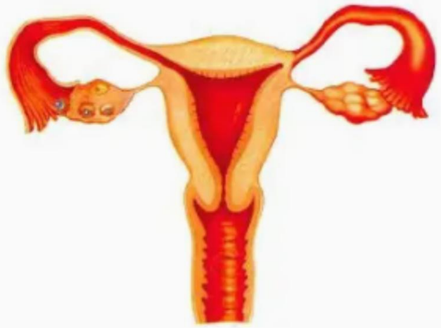


Durung the **Secretory Phase**, the uterus is considered prereceptive for the first 7 days following ovulation (day 0)

The **Non Receptive Phase**, comprises the rest of the secretory phase

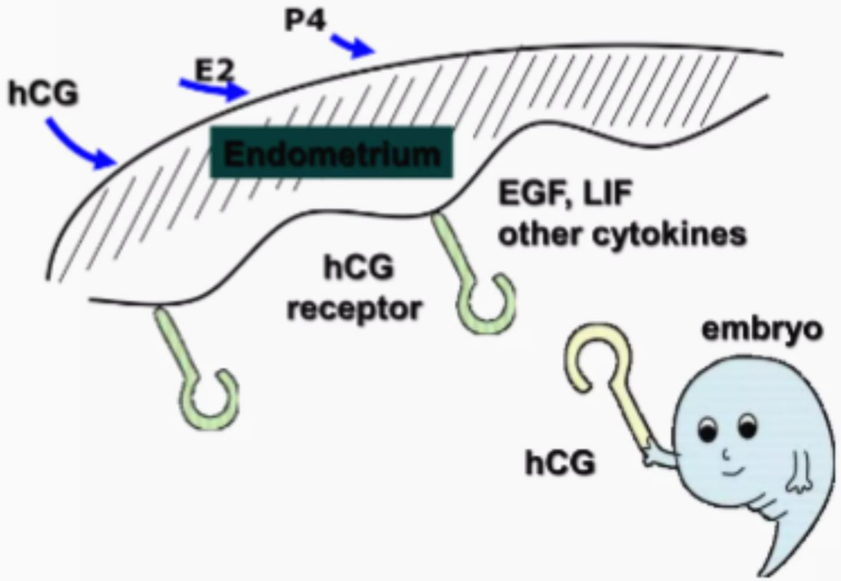
Who decides if the embryo can implant





Embryo or uterus?

Embryo-Maternal Communication



Implantation = **Good embryo** x **Good Endometrium**

IMPLANTATION MECHANISMS

The main causes of failure of IVF is failure

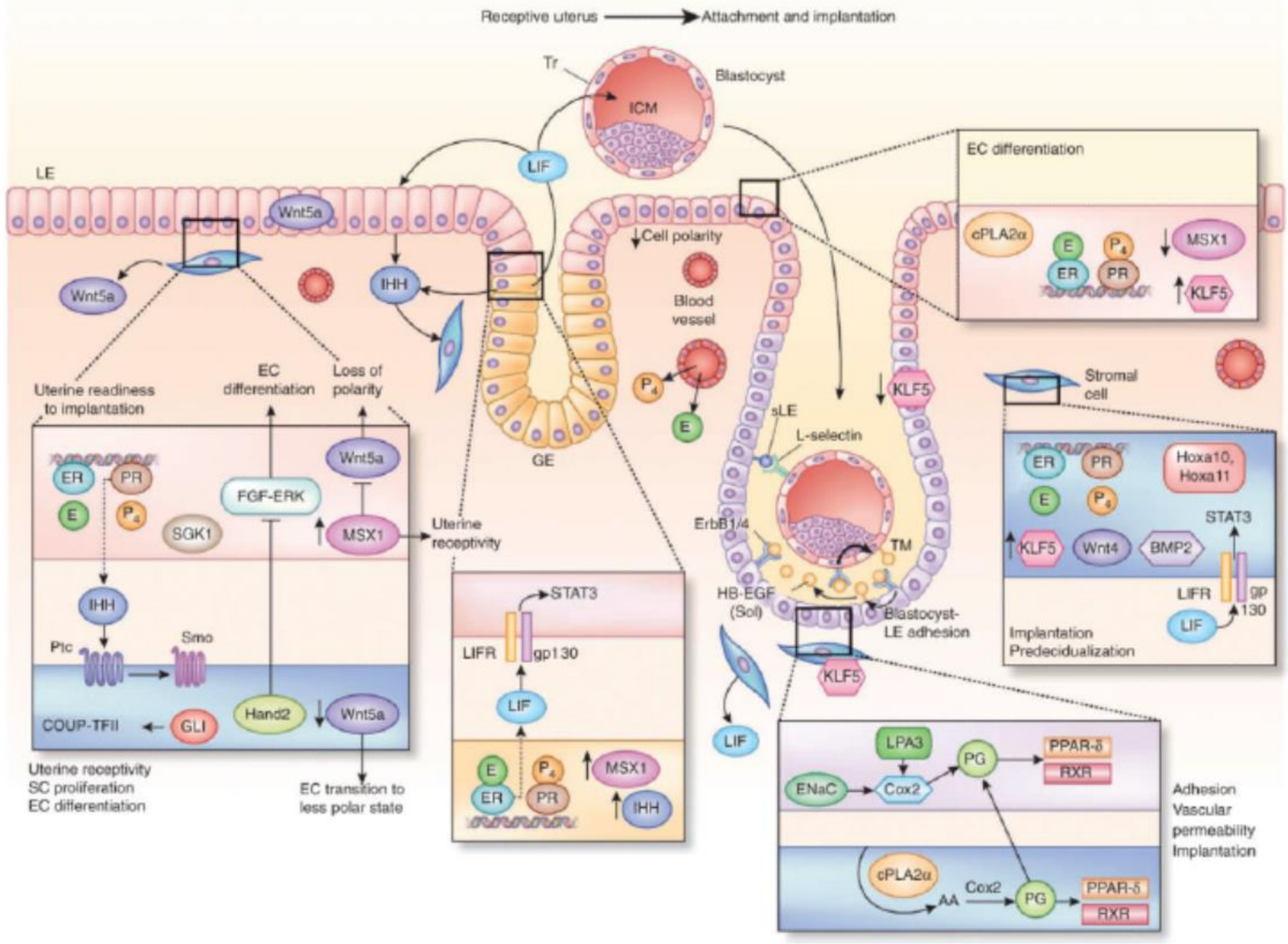
embryo implantation

- The quality of the embryo
- Endometrial receptivity
- The embryo/endometrial interface

Mechanisms of implantation: strategies for successful pregnancy **2012**

Jeeyeon Cha, **Xiaofei Sun**, and **Sudhansu K Dey**
Division of Reproductive Sciences, Perinatal Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA.

IMPLANTATION MECHANISMS



Signaling network for uterine receptivity and implantation.

A hybrid cartoon, based on mouse and human studies, portraying compartment- and cell-type–specific expression of molecules and their potential functions necessary for uterine receptivity, implantation and decidualization.

ENDOMETRIUM IN STIMULATED CYCLES
histology

- **Pre-ovulatory phase → accentuated proliferative aspects and early secretory changes** *(Marchini et al., 1991)*.
- **Peri-ovulatory phase → advanced endometrial maturation**
- **The day of oocyte retrieval → advancement of 2-4** (*Ubaldi et al.,1997: Lass et al., 1998)*
- **Day 2 following oocyte retrieval → discordant stromal maturation with precocious edema and vascular hypertrophy** *(Noci et al., 1997)*.
- **Mid-luteal biopsies → glandular-stromal dyssynchrony with a glandular delay** *(Seif et al., 1992; Meyer et al., 1999; Basir et al., 2001)*.

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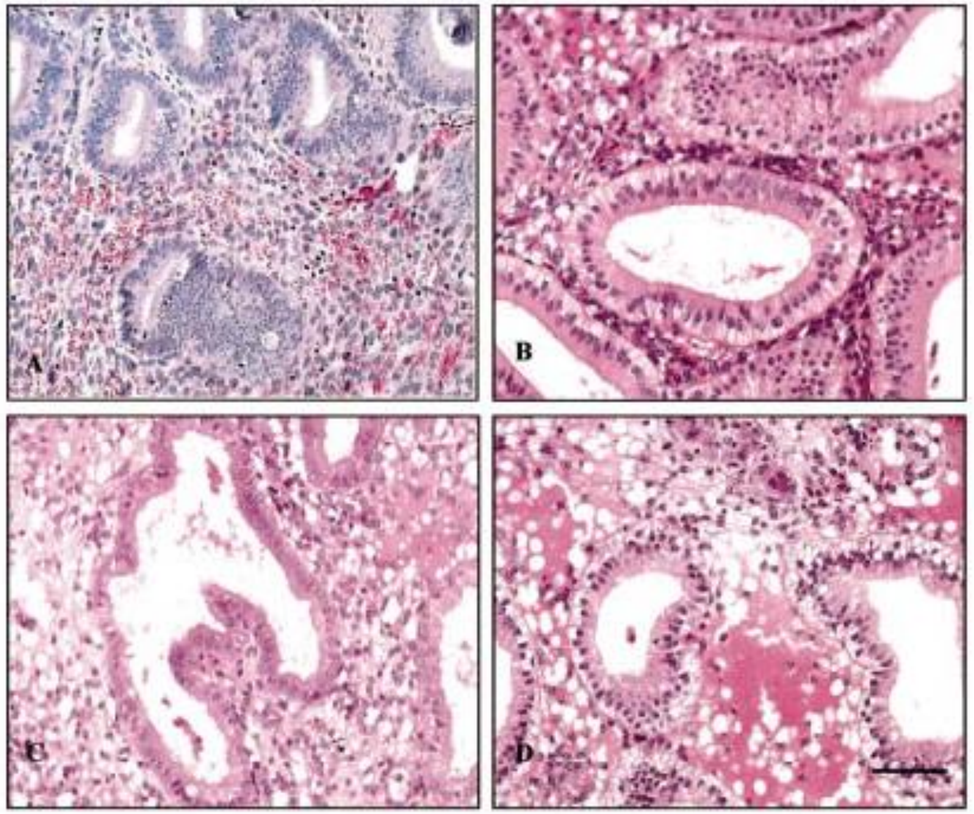
The endometrium in stimulated IVF cycles

NATURAL CYCLE



STIMULATED CYCLE

Figure 1. Histological maturation in natural and stimulated cycles. Light microscopy of the endometrium on luteal phase day 0 (**A**, **B**) and day 7 (**C**, **D**) of the luteal phase in natural (**A**, **C**) and stimulated (**B**, **D**) cycles. On the day of natural ovulation, a pseudostratified epithelium without vacuoles is seen (**A**). On the day of oocyte retrieval, the glandular cells show subnuclear vacuolization and very few mitotic figures (**B**). On day 7, stimulated endometria show glandular–stromal dyssynchrony with persistent vacuoles in the glands (**D**). Scale bar = 100 µm.

ENDOMETRIUM IN STIMULATED CYCLES

histology

- An early and increased **exposure to progesterone** of the endometrium in stimulated cycles may explain both **early secretory transformation** (*Fanchin et al., 1995)* and subsequent **mid-luteal glandular maturation arrest** *(Ezra et al.,1994)*.

- **Elevated serum E2** concentrations in stimulated cycles have also been associated with more frequent **glandular-stromal dyssynchrony** (*Basir et al., 2001)*.

- **HCG injection** to achieve final oocyte maturation is a further possible cause for disrupted endometrial luteal phase morphology (direct effect of hCG in terms of **advanced endometrial maturation** and **acquisition of a luteal phase phenotype**) *(Tang and Gurpide, 1993; Han et al., 1999; Fanchin et al., 2001)*.

- Finally, it has been demonstrated that **GnRH and its agonists** have **antiproliferative effects on the endometrium** *(Kim et al., 1999; Meresman et al., 2002)*.

ENDOMETRIUM IN STIMULATED CYCLES

steroid receptors

- In stimulated cycles, both **glandular and stromal PR** are found to be **reduced** **in the peri-ovulatory and luteal phase**.

- Data on **endometrial estrogen receptors** in stimulated cycles are less clear since **both overall decrease and glandular ER increase** has been described.

- A **decreased amount of both glandular and stromal ER and PR** was seen throughout the **luteal phase** in stimulated cycles (Develioglu et al., 1999).

- **Lower glandular and stromal mid-luteal PR expression** was found in supplemented than in non-supplemented cycles (Bourgain et al., 1994).

LUTEAL PHASE IN STIMULATED CYCLES

EVERYTHING DEPENDS ON ESTRADIOL !!

High E2 levels during late follicular phase of **stimulated cycles** will induce progesterone resistance

↓

more progesterone supplementation

Natural cycles or **artificial cycles** in which estradiol levels are very physiological

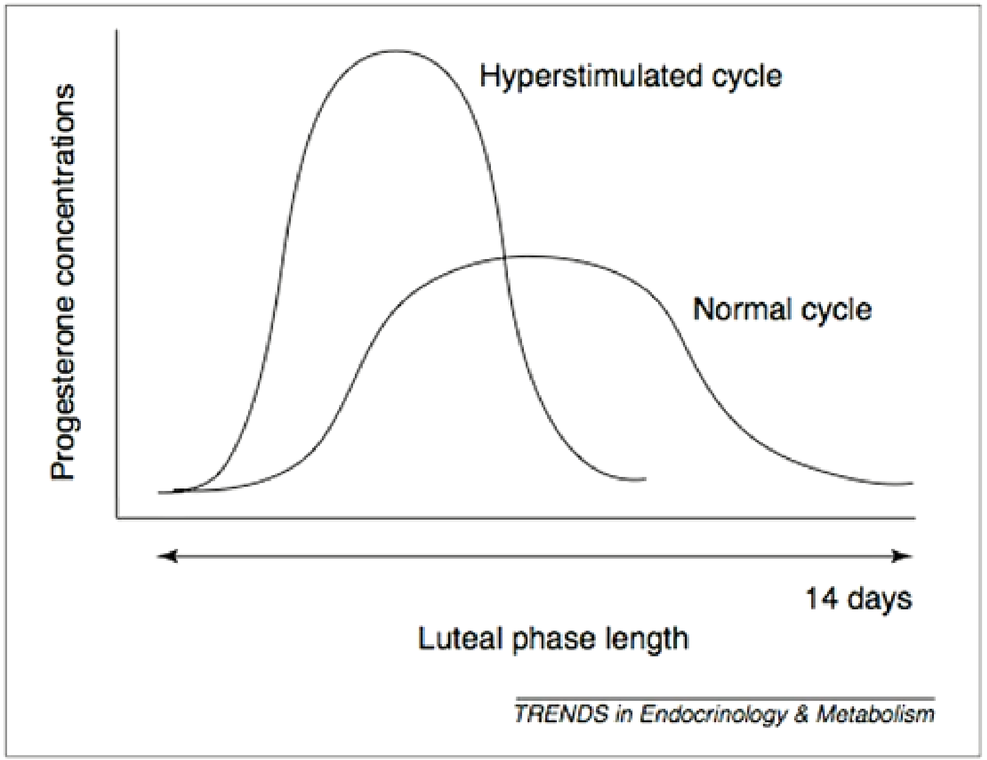
↓

less progesterone supplementation

LUTEAL EFFECTS OF PROGESTERONE

- Transform the endometrium into the secretory phase
- Regulates the window of implantation (WOI)
- Increases endometrial vascularization
- Immuno-modulator
- Reduces uterine contractions at peri-implantation

Luteal phase progesterone in natural vs HCG triggered cycle



Adapted from Jones-1996 by Fauser and Devroey - 2003

Correlation between mid luteal progesterone and reproductive outcomes

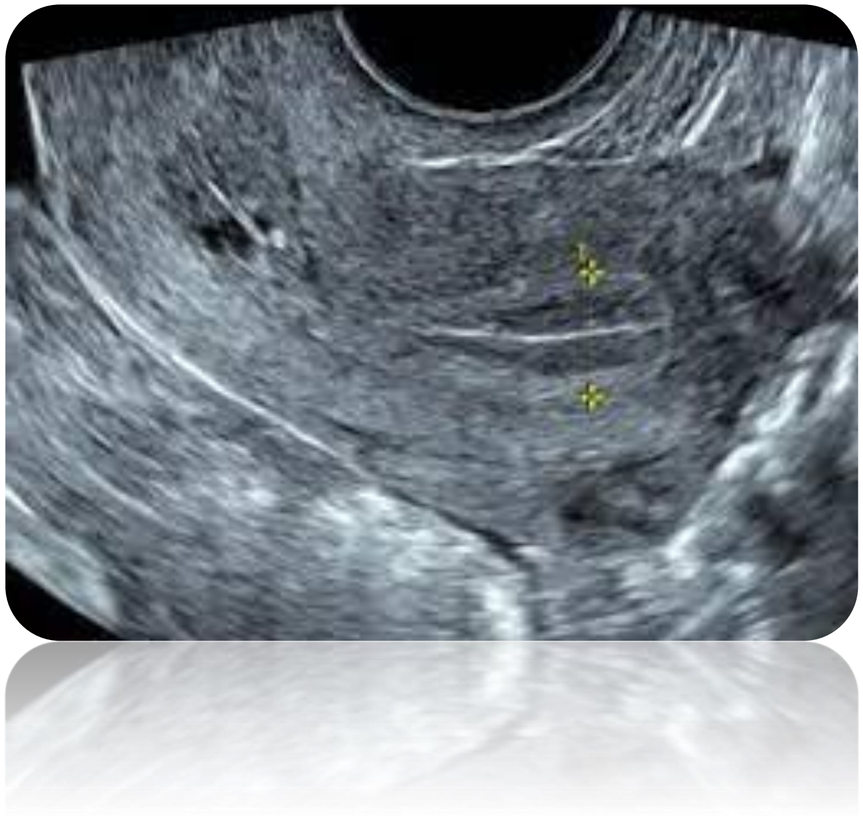
- 6.0 IU/l in natural cycle *(Tavaniotou A and Devroey P, 2003)*
- 1,5 IU/l – GnRHa trigger *(Humaidan P et al, 2005)*
- 0.2 IU/l – HCG trigger *(Humaidan P et al, 2005)*

LOWER LIMIT FOR NATURAL CONCEPTION : 9,4 ng/ml (30 mmol/l)

(Hull M et al, Fert Steril 1982)

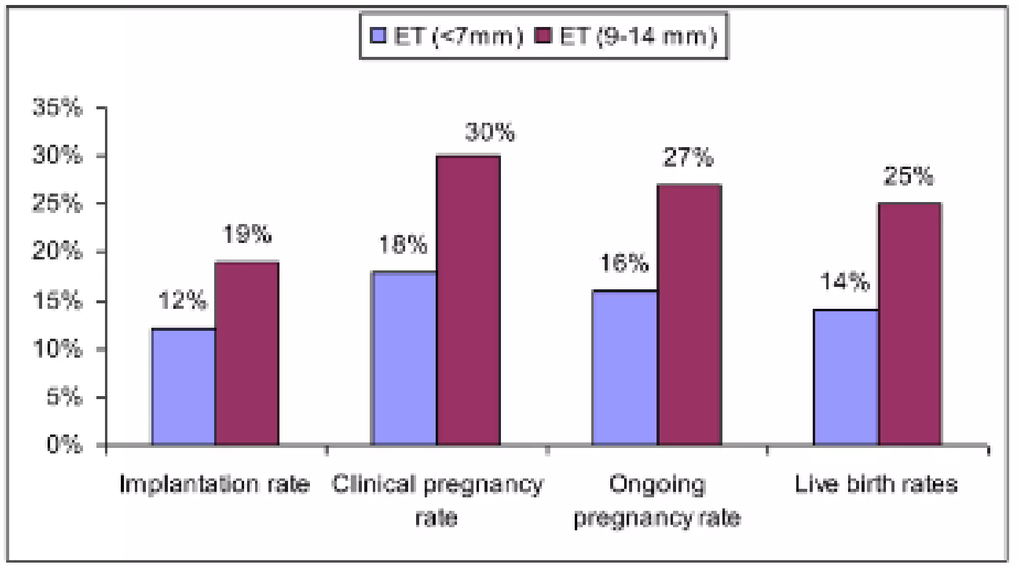
ENDOMETRIAL RECEPTIVITY DURING WOI DEPENDS ON

- Endometrial thickness
- Endometrial pattern
- Endometrial and
- Sub endometrial blood flow



- Endometrial thickness is directly correlated to increasing circulating oestrogens (Hershko-Klement and Tepper, 2016)
- Endometrial thickness is related to endometrial receptivity and can be a predictor of success in assisted reproduction (Momeni et al., 2011).

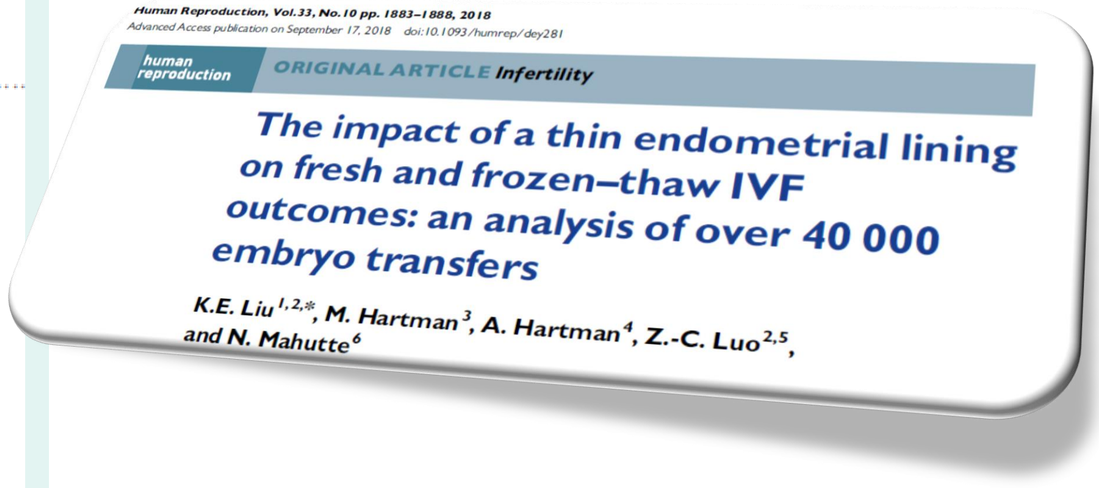
An endometrial thickness of 9-14 mm is associated with higher implantation & pregnancy rates as compared to endometrial thickening of < 7mm



Fertil Steril, 2008

Table I Clinical and live birth rates in autologous and donor fresh IVF-ET.

Endometrial thickness at trigger	# Embryo transfers	Incidence %	Clinical pregnancy rate (*n*)	Pregnancy loss rate (*n*)	Live birth rate (*n*)
≥8 mm	19 220	87.7	43.2 (8309)	22.0 (1831)	33.7 (6478)
7.0–7.9 mm	1837	8.4	34.6 (636)	26.4 (168)	25.5 (468)
6.0–6.9 mm	647	3.0	33.7 (218)	27.1 (59)	24.6 (159)
5.0–5.9 mm	155	0.7	25.8 (40)	30.0 (12)	18.1 (28)
4.0–4.9 mm	29	0.1	20.7 (6)	N/A[a]	N/A[a]
<4 mm	26	0.1	N/A[a]	N/A[a]	N/A[a]
Total	21 914	100%			
P for difference[b]			*P* < 0.0001	*P* = 0.01	*P* < 0.0001
P for trend[c]			<0.0001	0.002	<0.0001



Clinical pregnancy and live birth rates **decrease for each millimeter** of endometrial thickness below 8 mm in fresh IVF cycles and below 7 mm for frozen–thaw IVF cycles.

Table IV Clinical and live birth rates in autologous and donor frozen–thaw ET.

Peak endometrial thickness	# Embryo transfers	Proportion %	Clinical pregnancy rate (*n*)	Pregnancy loss rate (*n*)	Live birth rate (*n*)
≥8 mm	16263	85.9	38.4 (6245)	26.0 (1621)	28.4 (4624)
7.0–7.9 mm	2130	11.2	38.3 (816)	28.4 (232)	27.4 (584)
6.0–6.9 mm	413	2.2	31.7 (131)	25.2 (33)	23.7 (98)
5.0–5.9 mm	80	0.4	28.8 (23)	47.8 (11)	15.0 (12)
4.0–4.9 mm	33	0.2	27.3 (9)	22.2 (2)	21.2 (7)
<4 mm	23	0.3	N/A[a]	N/A[a]	N/A[a]
Total	18942	100			
P for difference[b]			0.02	0.09	0.01
P for trend[c]			0.007	0.1	0.002

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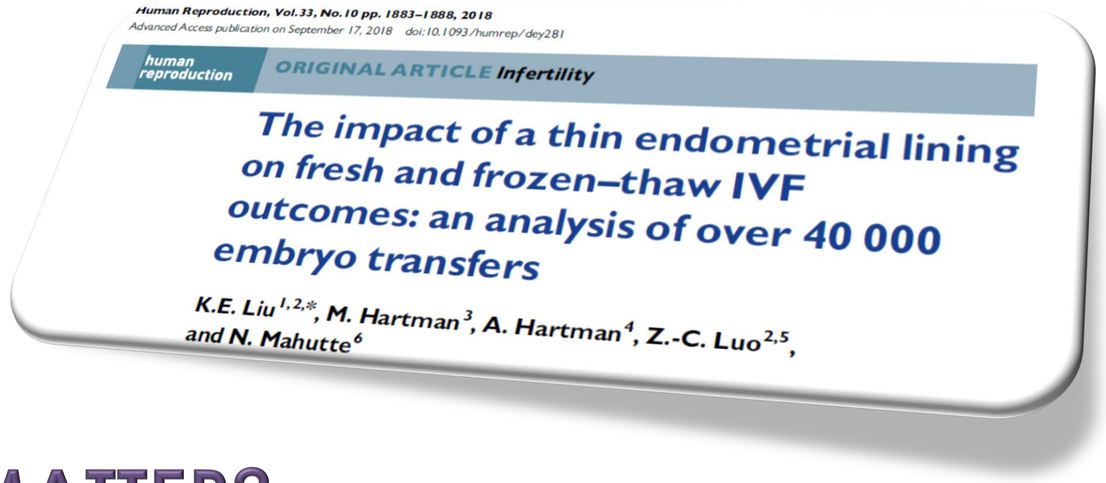

DOES IT REALLY MATTER?

- The likelihood of achieving an endometrial thickness ≥8 mm **decreased with age** (89.7, 87.8 and 83.9% in women <35, 35–39 and ≥40, respectively) ($P < 0.0001$).
- Nevertheless, viable pregnancy rates remain reasonably acceptable in patients with an endometrial thickness between 4 and 6 mm

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- 9 prospective and 21 retrospective studies
- a total of 88,056 cycles
- outcomes: pregnancy rate, implantation rate, abortion rate, live births or ongoing pregnancies, and ectopic pregnancy rate

LOWER EMT WAS ASSOCIATED WITH LOWER INCIDENCE OF PREGNANCY RATE, IMPLANTATION RATE, AND LIVE BIRTH OR ONGOING PREGNANCY RATE IRRESPECTIVELY FOR WOMEN RECEIVED FRESH OR FROZEN CYCLES

Sonographic parameters such as endometrial thickness (EMT), endometrial pattern, endometrial volume, and endometrial and subendometrial blood flow are employed for the identification of endometrial receptivity (Fanchin, 2001; Wang et al., 2010).

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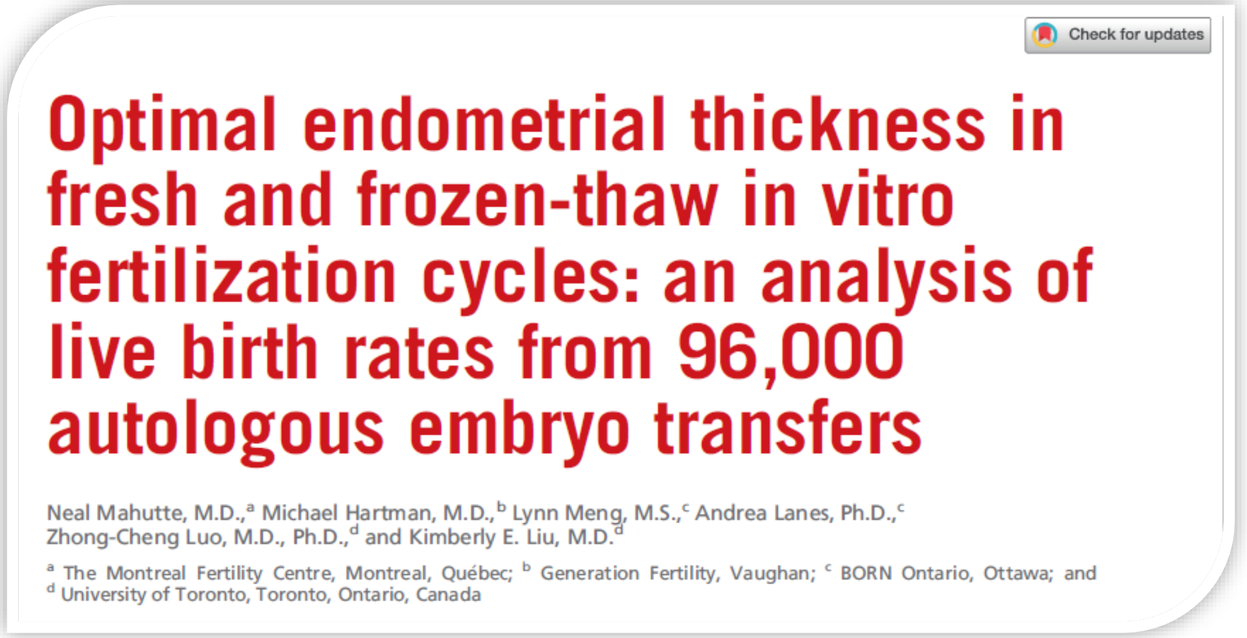

Check for updates

Optimal endometrial thickness in fresh and frozen-thaw in vitro fertilization cycles: an analysis of live birth rates from 96,000 autologous embryo transfers

Neal Mahutte, M.D.,[a] Michael Hartman, M.D.,[b] Lynn Meng, M.S.,[c] Andrea Lanes, Ph.D.,[c] Zhong-Cheng Luo, M.D., Ph.D.,[d] and Kimberly E. Liu, M.D.[d]

[a] The Montreal Fertility Centre, Montreal, Québec; [b] Generation Fertility, Vaughan; [c] BORN Ontario, Ottawa; and [d] University of Toronto, Toronto, Ontario, Canada

- Retrospective cohort study.
- between Jan 2013 and Dec 2019
- 43,383 fresh and 53,377 frozen ET
- 33 Canadian clinics
- Main Outcome Measure(s): Clinical pregnancy, pregnancy loss, and live birth rates.

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TABLE 1

Clinical outcomes in fresh IVF-ET cycles by endometrial thickness

Endometrial thickness (mm)	Clinical pregnancy rate	Live birth rate	Pregnancy loss rate	Mean term singleton birth weight in grams (SD)
≥18	44.9% (105/234)	33.8% (79/234)	34.7% (42/121)	3,400 (427)
16–17.9	47.6% (288/605)	37.7% (228/605)	31.7% (106/334)	3,310 (395)
14–15.9	43.8% (966/2,207)	33.7% (743/2,207)	34.3% (388/1,131)	3,399 (420)
12–13.9	43.0% (2,899/6,739)	33.4% (2,250/6,739)	34.0% (1,159/3,409)	3,351 (434)
10–11.9	41.1% (5,620/13,672)	31.8% (4,345/13,672)	34.0% (2,239/6,584)	3,337 (430)
8–9.9	37.5% (5,415/14,444)	28.1% (4,059/14,444)	37.5% (2,432/6,491)	3,317 (427)
6–7.9	31.0% (1,574/5,084)	22.1% (1,126/5,084)	42.2% (822/1,948)	3,262 (438)
4–5.9	24.4% (97/398)	15.8% (63/398)	54.3% (75/138)	3,215 (547)
*P**	<.001	<.001	<.001	<.001

SD = Standard deviation.
* *P* values for differences in pregnancy outcome rates across endometrial thickness strata.

TABLE 2

Clinical outcomes in FET cycles by endometrial thickness

Endometrial thickness (mm)	Clinical pregnancy rate	Live birth rate	Pregnancy loss rate	Mean term singleton birth weight in grams (SD)
≥18	44.1% (60/136)	30.9 (42/136)	41.7% (30/72)	3,496 (432)
16–17.9	45.0% (159/353)	32% (113/353)	38.9% (72/185)	3,529 (563)
14–15.9	42.1% (604/1,434)	29.2% (419/1,434)	41.6% (299/718)	3,474 (450)
12–13.9	41.9% (2,134/5,094)	30.7% (1,566/5,094)	38.9% (998/2,564)	3,486 (441)
10–11.9	42.3% (5,728/13,539)	30.8% (4,169/13,539)	40.8% (2,875/7,044)	3,452 (442)
8–9.9	40.7% (10,218/25,089)	29.4% (7,375/25,089)	41.3% (5,197/12,572)	3,451 (445)
7–7.9	39.3% (2,476/6,302)	28.4% (1,791/6,302)	41.9% (1,293/3,084)	3,407 (424)
6–6.9	31.5% (334/1,059)	22.6% (239/1,059)	46.0% (204/443)	3,378 (440)
<6	29.1% (108/371)	15.1% (56/371)	62.2% (92/148)	3,412 (394)
*P**	<.001	<.001	<.001	<.001

SD = Standard deviation.
* *P* values for differences in pregnancy outcome rates across endometrial thickness strata.

In cycles with a **fresh** embryo transfer, live birth rates increase significantly until an endometrial thickness of **10–12 mm**, while in **FET** cycles live birth rates plateau after **7–10 mm**.

However, an endometrial thickness <6 mm was associated clearly with a dramatic reduction in live birth rates in fresh and frozen embryo transfer cycles.

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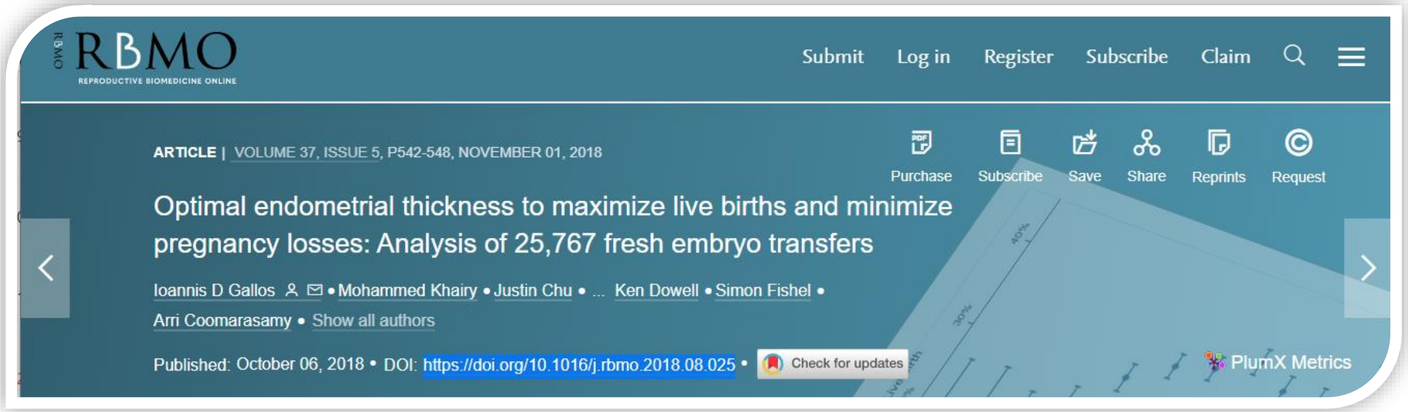
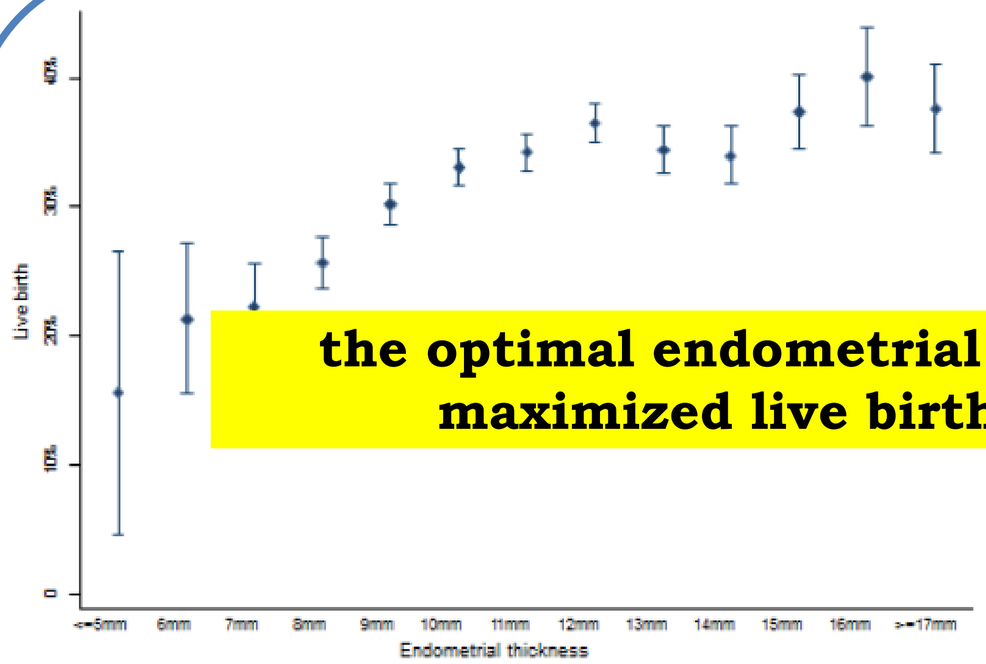
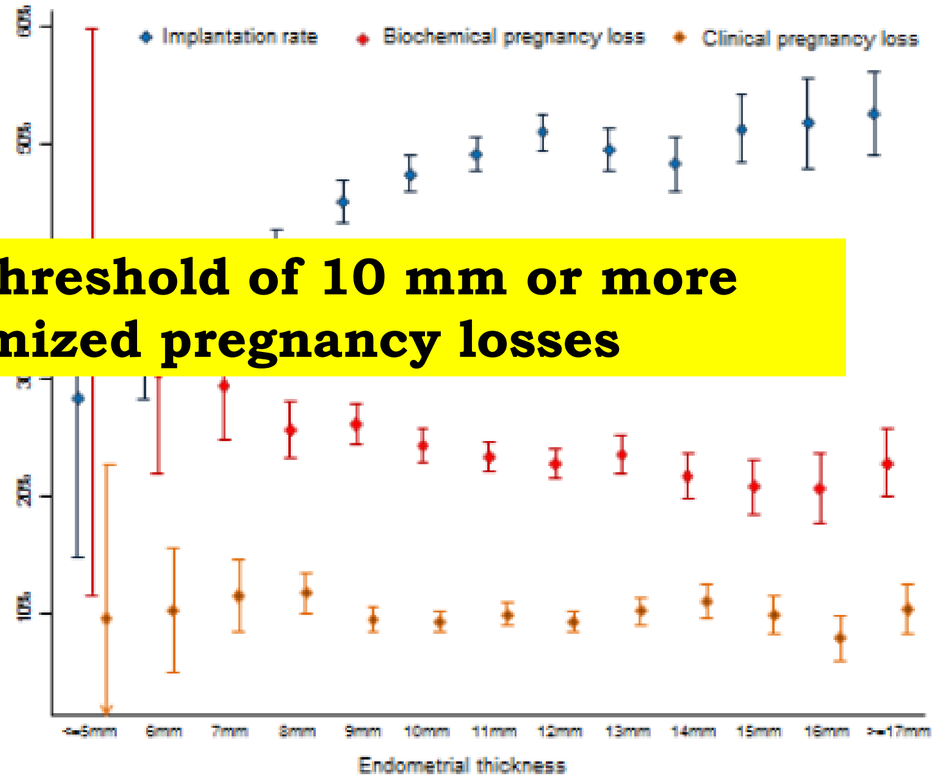
2018



- 25,767 IVF cycles
- UK between 2007 and 2016.
- LBR per embryo transfer.



the optimal endometrial thickness threshold of 10 mm or more maximized live births and minimized pregnancy losses



Live birth rate significantly increased from 15.6% (95% CI 6.4% to 29.4%) with an endometrial thickness of 5 mm or less, to 33.1% (95% CI 31.6% to 34.5%) with an endometrial thickness of 10 mm.

CLINICAL IMPORTANCE OF ENDOMETRIUM

Successful implantation depends on a close dialog between the blastocyst and the endometrium

Thin endometrium may be because of:

1. **Endometrial resistance to cirulating oestrogen**
2. **Reduced blood flow to the endometrium**
3. **Over -exposure to testosterone**
4. **Permanent damage to the basal endometrium**

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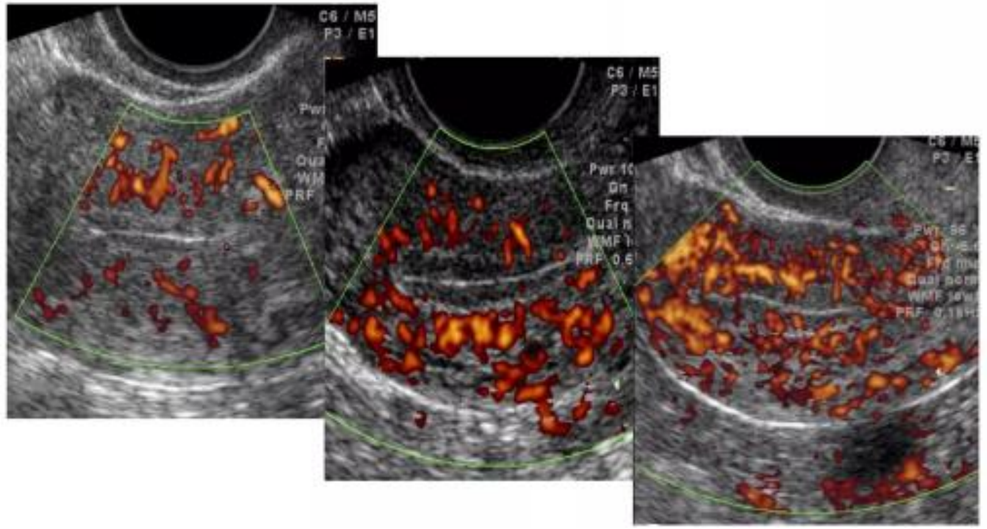
Higher uterine flow rates is associated with a positive pregnancy outcome , while absent diastolic flow is associated with no conception

- **Good uterine blood flow is very important for endometrial growth.**
- Any resistance to blood flow impairs growth of glandular epithelium & results in decrease in VEGF which in turn further causes poor flow to endometrium

- Estrogen produces a vasodilatory effect on the uterine arteries
- RI, PI of uterine artery drops with increasing estradiol levels.



No pregnancy seen if the PI of uterine is > 3

Steer et al : Human Reproduction. 1990;5:391

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An endometrial receptivity scoring system basing on the endometrial thickness, volume, echo, peristalsis, and blood flow evaluated by ultrasonography

Chun-hui Zhang[1†], Cheng Chen[1†], Jia-rui Wang[1†], Yue Wang[2], Si-xi Wen[1], Yan-pei Cao[1] and Wei-ping Qian[1*]

- **retrospective study**
- **562 patients at first (FET) cycles**
- **From March 2021 to August 2021**

Transvaginal 3D ultrasound on the day of ET to evaluate endometrial receptivity (endometrial thickness, echogenicity, volume, movement and blood flow.

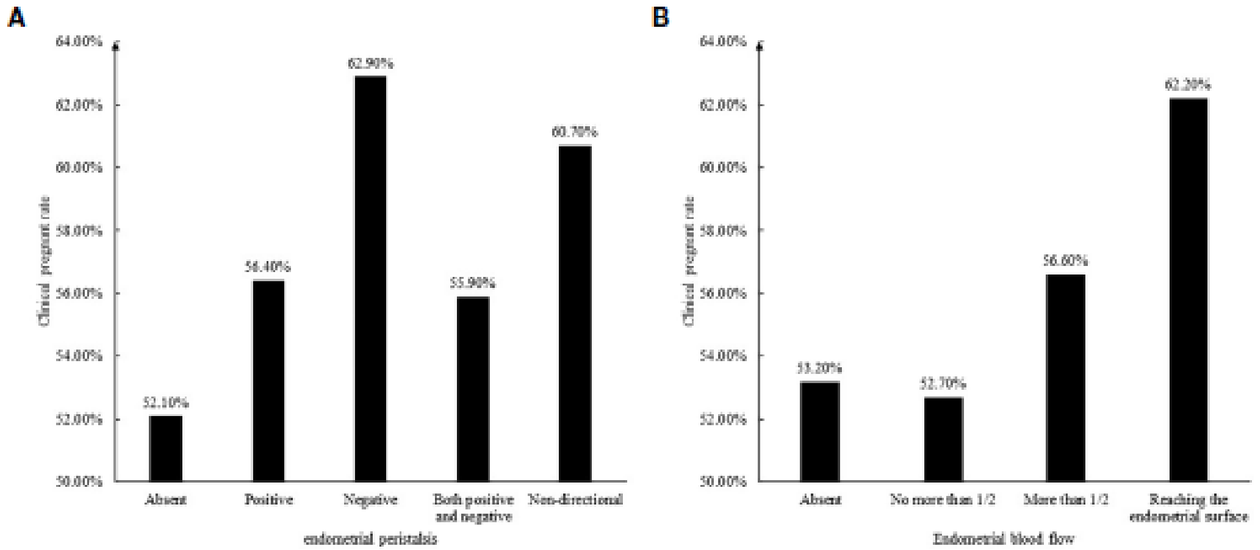

FIGURE 2
(A) The relationship between endometrial peristalsis and clinical pregnant rate. **(B)** The relationship between endometrial blood flow and clinical pregnant rate.

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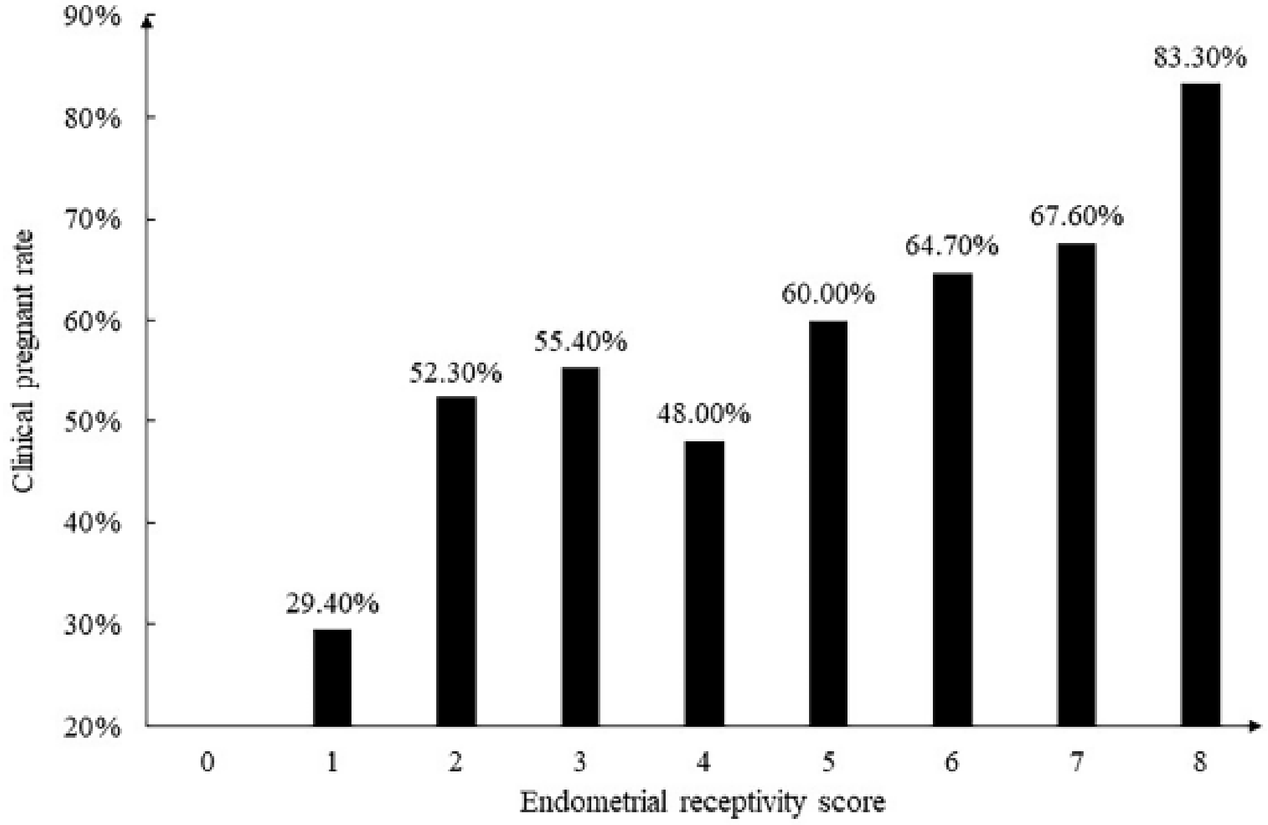
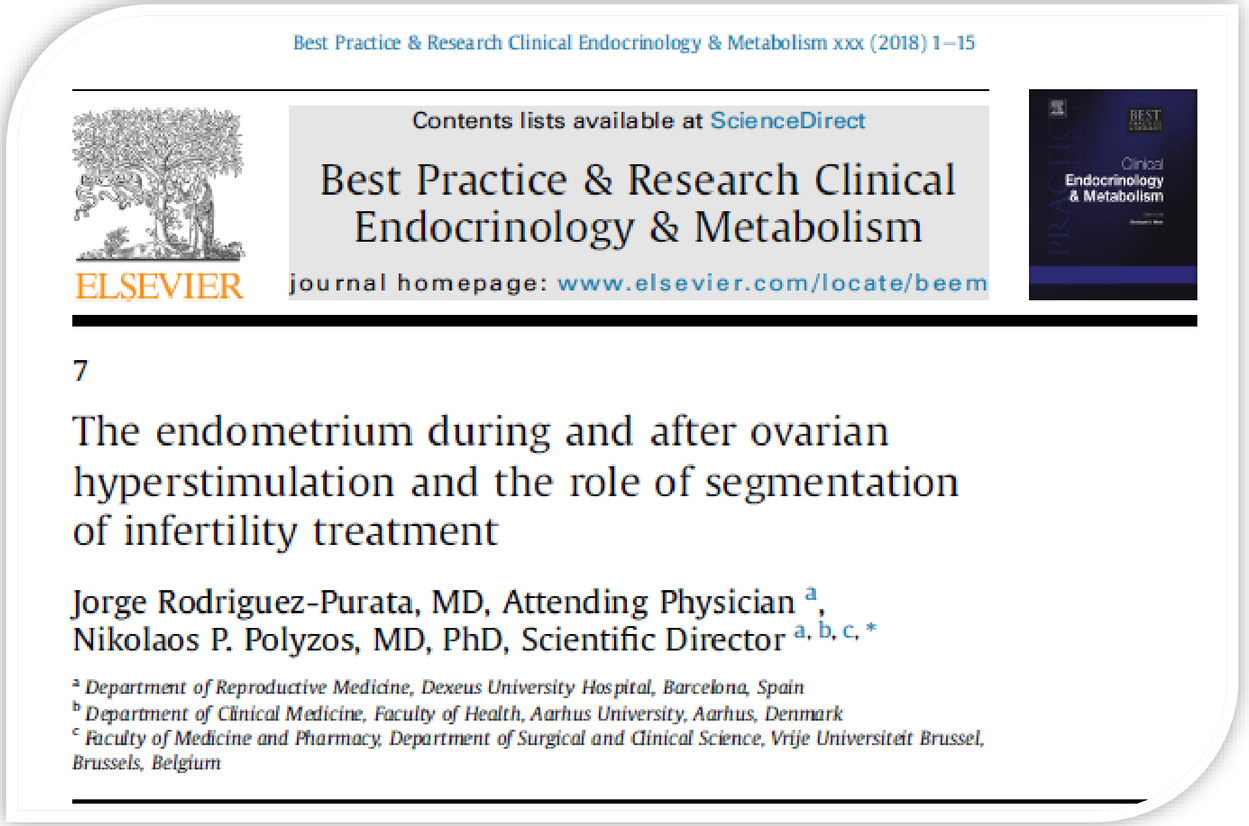
Endometrial receptivity scoring system

Score	0	1	2
Endometrial thickness	<8 mm	8-14 mm	>14 mm
Endometrial volume	<3 ml	>3 ml	
Echo of the functional layer of endometrium	Heterogeneous	Homogeneous	
Endometrial central echogenic line	Absent	Present	
Endometrial peristalsis	Absent, Positive, Both positive and negaive	Non-directional	Negative
Endometrial blood flow	Absent, No more than 1/2	More than 1/2	Reaching the endometrial surface



When the endometrial receptivity score is greater than or equal to 5, the clinical pregnancy rate exceeds 60% in the frozen-thawed embryo transfer cycle.

Segmentation of IVF treatment: is it the key for a “healthy” endometrium?



Best Practice & Research Clinical Endocrinology & Metabolism xxx (2018) 1–15

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The endometrium during and after ovarian hyperstimulation and the role of segmentation of infertility treatment

Jorge Rodriguez-Purata, MD, Attending Physician [a],
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embryo transfer may be performed in a more physiologic uterine environment in a later cycle

Segmentation of IVF treatment: is it the key for a “healthy” endometrium?

Practice points

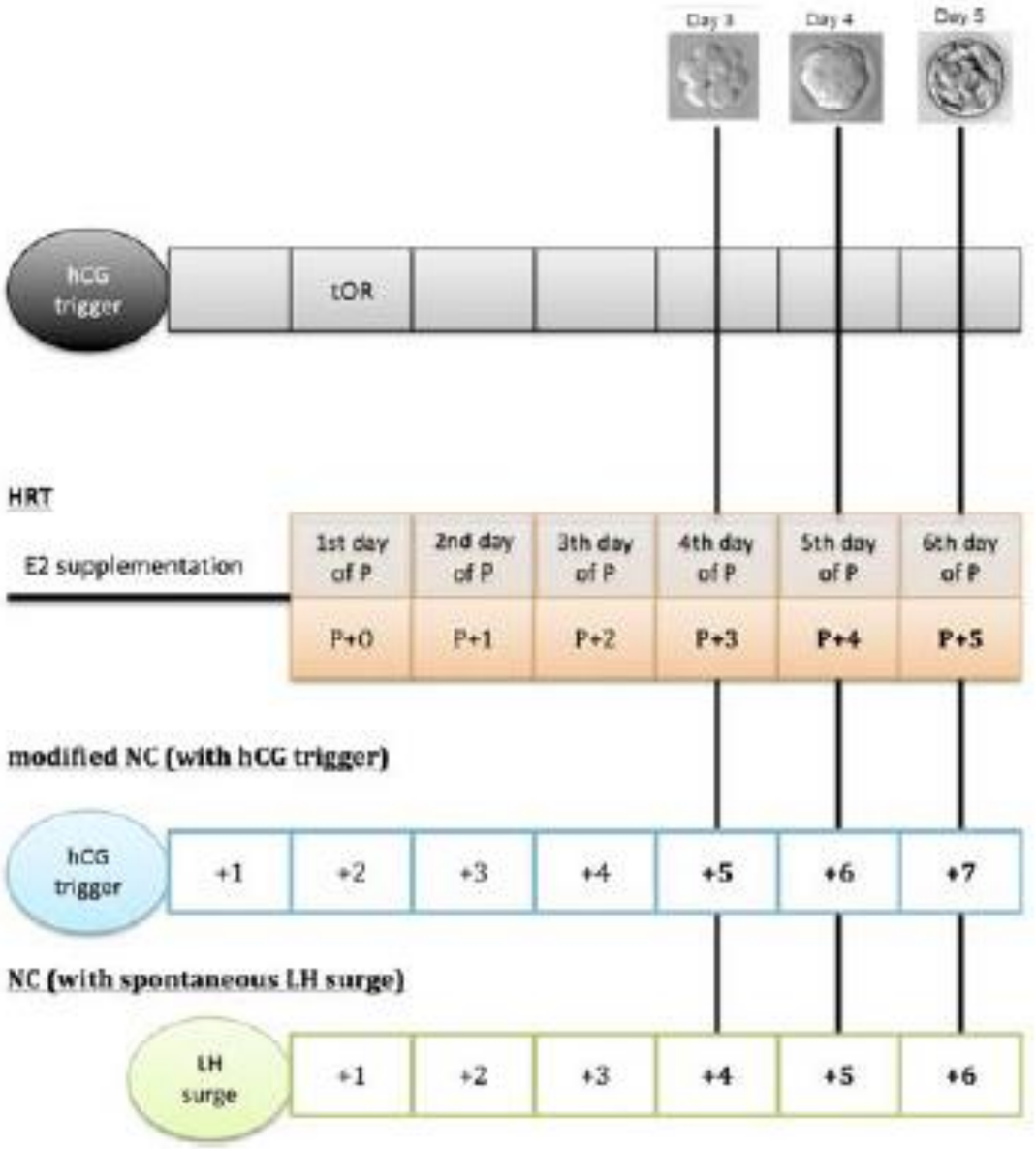
- The freeze-all’ strategy, cryopreservation of the entire cohort of embryos and transfer in a subsequent synthetic cycle has been the key towards an OHSS-free clinic.
- There is evidence that the supraphysiologic levels of estradiol and progesterone during COH could lead to morphologic and biochemical modifications, and consequently impair endometrial receptivity.
- Recent studies have demonstrated that uterine peristaltic wave frequency at oocyte retrieval and two days later were significantly higher in stimulated cycles when compared to natural cycles.
- High responder patients are the group of patients that benefit the most from a freeze-all strategy.
- It is still unclear if normo-responding patients benefit in terms of pregnancy outcome from a freeze-all strategy as compared to traditional IVF.
- Segmentation should not be routinely recommended in low responding patients unless other practical or clinical reasons point in this direction, i.e. progesterone elevation during COH.

FET PROTOCOLS

Table 1 Cycle characteristics for frozen embryo transfer preparation

	Estrogen	Timing of transfer	Progesterone
Ovulatory Cycles			
Natural cycles	Follicular development	LH surge	Corpus luteum
Modified natural cycles	Follicular development	hCG trigger	Corpus luteum with or without supplemental progesterone
Stimulated cycles	Follicular development	hCG trigger or LH surge	Corpus luteum with or without supplemental progesterone
Programmed Cycles			
Programmed cycles	Exogenous estrogen (oral, vaginal, transdermal)	Initiation of progesterone	Intramuscular and/or vaginal progesterone

FET PROTOCOLS



Human Reproduction, Vol.32, No.11 pp. 2234–2242, 2017
Advanced Access publication on September 8, 2017 doi:10.1093/humrep/dex285

human reproduction REVIEW *Infertility*

Frozen embryo transfer: a review on the optimal endometrial preparation and timing

S. Mackens[1], S. Santos-Ribeiro[1,2], A. van de Vijver[1], A. Racca[1,3], L. Van Landuyt[1], H. Tournaye[1], and C. Blockeel[1,4,*]

In terms of embryo transfer timing, we propose to start progesterone intake on the theoretical day of oocyte retrieval in HRT and to perform blastocyst transfer at hCG + 7 or LH + 6 in modified or true NC, respectively. As individual timing of the WOI becomes increasingly substantiated by diagnostics tools, subsequent time corrections might offer further opportunities to increase FET success rates.

FET PROTOCOLS

Preparation of endometrium for frozen embryo replacement cycles: a systematic review and meta-analysis

J Assist Reprod Genet (2016) 33:1287–1304
DOI 10.1007/s10815-016-0787-0

REVIEW

Hakan Yarali[1,2] · Mehtap Polat[2] · Sezcan Mumusoglu[1] · Irem Yarali[2] · Gurkan Bozdag[1]

33 studies (11 RCTs)
Natural Cycle (NC) and modified Natural Cycle (mNC; with hCG trigger)
Artificial Cycle (AC) with or without pituitary suppression

LBR:

- No difference between NC and mNC
- No difference between NC and AC
- No difference between AC
- No difference between mNC and AC with or without pituitary suppression
- LBR ↑ in AC with pituitary suppression than NC

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

Optimal endometrial preparation for frozen embryo transfer cycles: window of implantation and progesterone support

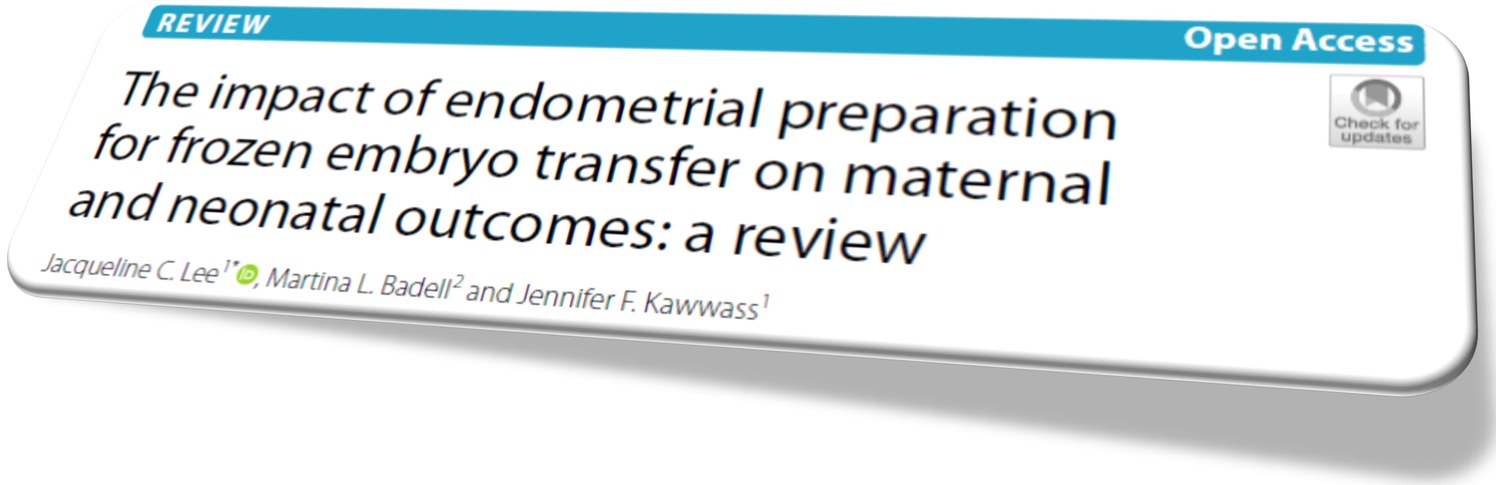
2016

Robert F. Casper, M.D.[a] and Elena H. Yanushpolsky, M.D.[b]

1. Natural FET cycles benefit from vaginal P supplementation starting after ET. They are most appropriate for patients with regular ovulatory cycles who are able to comply with strict regimen of frequent urine and blood hormonal measurements.
2. Modified natural FET cycles require ultrasound monitoring and blood hormonal measurements for optimal timing of hCG trigger. Luteal phase support with P does not appear to be necessary because of the luteotrophic effect of hCG. P support after ET could be optional and should use the most convenient and cost effective P preparation.
3. Programmed FET cycles are the most convenient with respect to limited monitoring requirements and ease and flexibility of scheduling. However, they have not been shown to be superior to properly timed natural or modified natural FET protocols. The optimal form of P supplementation has not been established from available data. Patients' preference and convenience, as well as costs should be considered when choosing either vaginal or IM P preparations.
4. Alternative options for P supplementation in FET cycles—SC and oral—should be evaluated with adequately powered randomized trials.

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

2022


REVIEW Open Access

The impact of endometrial preparation for frozen embryo transfer on maternal and neonatal outcomes: a review

Jacqueline C. Lee[1*], Martina L. Badell[2] and Jennifer F. Kawwass[1]

Check for updates

hypertensive disorders of pregnancy (4% vs. 3%, aOR 1.43; 95% CI, 1.14–1.80],

preeclampsia (12.8% vs. 3.9%, aOR 3.55, 95% CI, 1.20–11.94)

preeclampsia with severe features (9.6% vs. 0.8%, aOR 15.05, 95% CI 2.59–286.27)

placenta accreta (0.9% vs 0.1%, aOR 6.91; 95% CI, 2.87–16.66)

cesarean section (44.5% vs. 33.7%, aOR 1.69; 95% CI, 1.55–1.84)

postpartum hemorrhage (19.4% vs. 7.9%, aOR 2.63; 95% CI, 2.20–3.13)

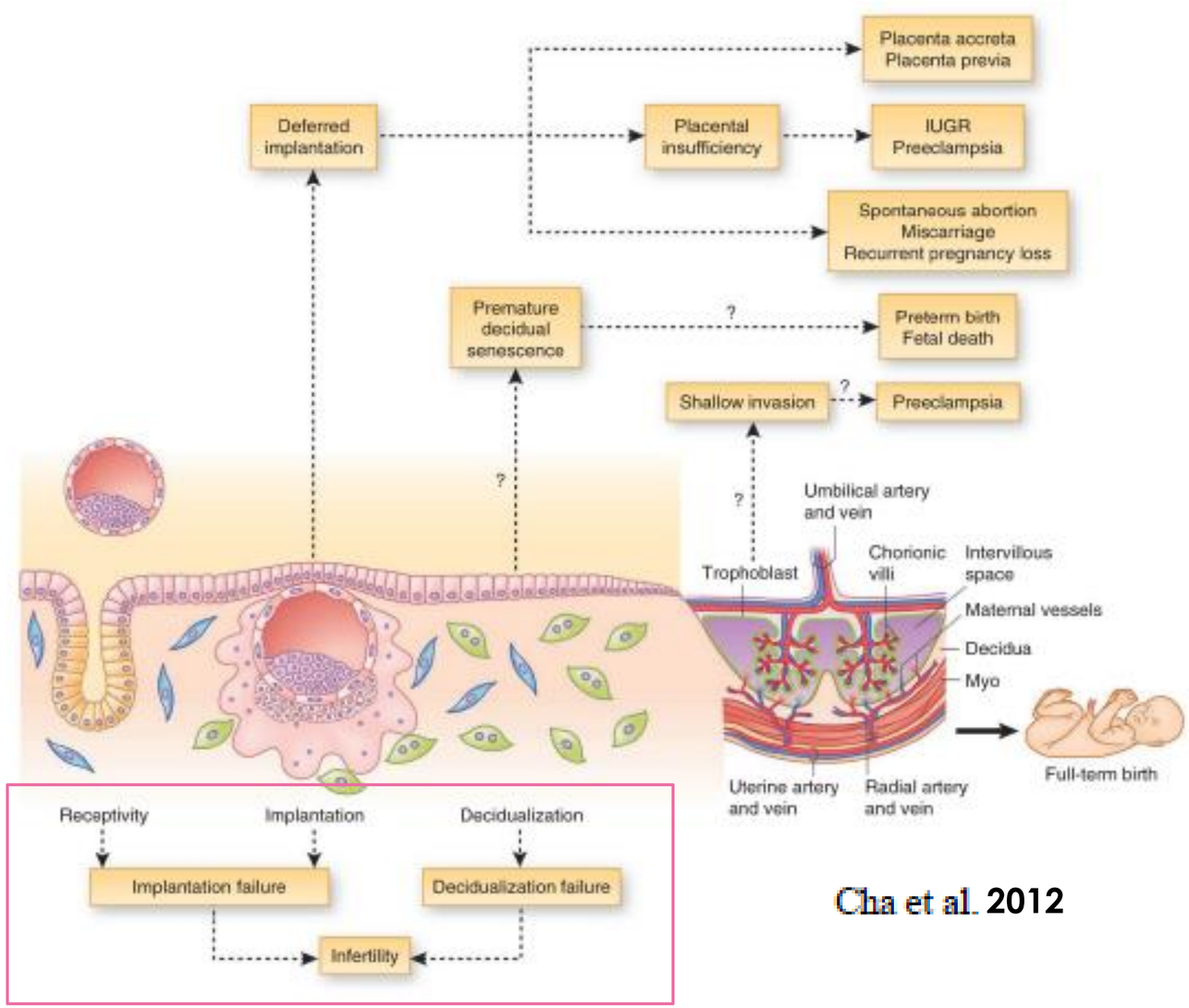
post term birth (8.9% vs. 5.8%, aOR 1.59; 95% CI, 1.27–2.01)

macrosomia (8.9% vs. 4.7%, aOR 1.62; 95% CI, 1.26–2.09)

low birth weight (4.5% vs. 2.8%, aOR 1.49, 95% CI 1.09–2.06)

preterm birth (7.9% vs. 4.6%, aOR 1.78, 95% CI 1.39–2.28)

COMPROMISING THE PREGNANCY OUTCOME



Cha et al. 2012

August 2022

- **Retrospective cohort study**
- **Patients with (307)and without (2284) ERA before euploid single FET**
- **primary outcome: LB;**
- **secondary outcomes biochemical and CPR**

Result(s)

125 patients (40.7%) were ERA receptive, and 182 (59.3%) were ERA nonreceptive. After adjusting for the number of the previously failed FETs, there was no difference in the proportion of receptive and nonreceptive ERA results. There were **no statistically significant differences in live births in patients with ERA-receptive vs. ERA-nonreceptive results** (48.8% and 41.7%, respectively; adjusted odds ratio 1.17; 95% CI, 0.97–1.40). There were **no statistically significant differences in live births in patients with or without ERA testing results before FET** (44.6% and 51.3%, respectively; adjusted odds ratio 0.87; 95% CI, 0.73–1.04).

Conclusion(s)

Patients with an increasing number of previous failed euploid FET cycles are not at an increased risk of a displaced window of implantation. Patients categorized as receptive vs. nonreceptive and those without ERA testing results have comparable FET success rates.

Journal of Assisted Reproduction and Genetics (2018) 35:1301–1305
https://doi.org/10.1007/s10815-018-1190-9

ASSISTED REPRODUCTION TECHNOLOGIES

2022

Does the endometrial receptivity array really provide personalized embryo transfer?

Rawad Bassil[1] · Robert Casper[1,2] · Nivin Samara[1] · Tzu-Bou Hsieh[1] · Eran Barzilay[3] · Raoul Orvieto[3,4] · Jigal Haas[1,3]

- single-center retrospective cohort study,
- 53 good prognosis patients (0–2 previous frozen embryo transfers) , 41 FET
- endometrial biopsy for both the ERA test and histological assessment before blastocyst transfer

Table 3 Ongoing pregnancy rates according to the Noyes histologic dating and ERA results

ERA ($n = 41$)	Ongoing pregnancy rate	Ongoing pregnancy rate (NOYES)	Results by NOYES and % of agreement with ERA		Control group (503)	p value
Receptive (14)	7/14 (50%)	2/4 (50%)	4	Receptive	Pregnancy rate: 177/503 (35.2%)	NS
		5/10 (50%)	10	Non-receptive		
Non-receptive before the adjustment (27)	9/27 (33.3%)	5/12 (41.6%)	12	Receptive		
		4/15 (26.6%)	15	Non-receptive		

*53 patients went through ERA biopsy but twelve patients did not undergo FET, therefore only 41 patients are included in the pregnancy outcome analysis

Conclusions Performing the ERA test in a mock cycle prior to a FET does not seem to improve the ongoing pregnancy rate in good prognosis patients. Further large prospective studies are needed to elucidate the role of ERA testing in both good prognosis patients and in patients with recurrent implantation failure.

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

2022

Review > Fertil Steril. 2022 Nov 19;S0015-0282(22)02039-8. doi: 10.1016/j.fertnstert.2022.11.012.
Online ahead of print.

Endometrial Receptivity Array Before Frozen Embryo Transfer Cycles: A Systematic Review and Meta-analysis

Sara E Arian [1], Kamran Hessami [2], Ali Khatibi [3], Alvin K To [4], Alireza A Shamshirsaz [2], William Gibbons [5]

- **meta-analysis.**
- **8 studies on 2,784 patients**
- **(831 ERA and 1,953 without ERA)**

Objective: To investigate the impact of ERA prior to frozen embryo transfer (FET) in patients undergoing IVF.

Main outcome(s): The primary outcomes of the study were livebirth rate and/or ongoing pregnancy rate. Implantation rate, biochemical pregnancy rate, clinical pregnancy rate, and miscarriage rate were considered secondary outcomes.

Conclusion(s) and relevance: The findings of the current meta-analysis did not reveal a significant change in the rate of pregnancy after IVF cycles using ERA and it is not clear whether ERA can increase the pregnancy rate or not.

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

2021


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

human reproduction open

DEBATE

Endometrial Receptivity Analysis (ERA) test: an unproven technology

Zion Ben Rafael *

Adelson School of Medicine, Ariel, University, Israel

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.

The message to the patients should be that failures occur more often than not, and if no special obstacle to pregnancy exists, when stimulation, embryo culture and endometrial width appear to be normal, **there is no need to resort to unproven costly add-ons**, and, if patients agree, they need to persevere with their similar trials for five or more cycles, which will leave only a small fraction of patients in need other, albeit unproven, solutions.

ENDOMETRIAL AGING

Effect of age on endometrial receptivity

- Embryo implantation rates declines in a linear fashion through the age.
- Abnormal receptivity in aging subjects may be due to decreased levels of P receptors promoted by the low levels of E2 receptors (*Meldrum 1993*).
- No conclusive evidence of age related histological changes in the endometrium (*Sauer 1993*).
- No difference in implantation, pregnancy, miscarriage or live birth rates between younger and older patients receiving oocytes from the same donors (*Abdalla 1997*).

Human Reproduction vol.8 no.12 pp.2088–2092, 1993

Oocyte donation: comparison between recipients from different age groups

C.Flamigni[1,3], A.Borini[2], F.Violini[1,2], L.Bianchi[1,2] and L.Serrao[2]

Table V. Results in different age groups

Group	A (21–35 years)	B (36–40 years)	C (41–49 years)	D (50–61 years)
Patients	37	11	33	10
Transfers	53	17	57	14
Embryos transferred	141	46	165	38
Mean (range)	3 (1–5)	3 (1–4)	3 (2–5)	3 (2–4)
Pregnancies	24	5	13	4
Gestational sacs	32	8	17	4
Abortions	0	1	3	0
Pregnancy rate/patient (%)	65[a]	45	39[b]	40
Pregnancy rate/transfer (%)	45[c]	29[d]	23[e]	29[f]
Implantation rate (%)	23[g]	17[h]	10[i]	10[l]
Abortion rate (%)	0	20	23	0

[a,b]$P = 0.02$; [c,e]$P = 0.01$; [c,d,f]$P > 0.05$; [g,i]$P = 0.003$; [g,h,l]$P > 0.05$.

There were significant differences in the pregnancy and implantation rates according to the age of the recipients. These data seem to demonstrate a lesser likelihood of pregnancy and implantation in older recipients because of increasing uterine age.

SCIENTIFIC SEMINARS
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*Oocyte donation program: pregnancy and implantation rates in women of different ages sharing oocytes from single donor**

Andrea Borini, M.D.†‡§ Andrea Maccolini, M.D.‡
Liana Bianchi, M.D.‡ Monica Cattoli, M.D.‡
Flavia Violini, M.D.‡ Carlo Flamigni, M.D.†

Reproductive Medicine Unit, Department of Obstetrics and Gynaecology, University of Bologna, and Tecnobios, Center for Reproductive Health, Bologna, Italy

1996

Table 1 Comparison Between Donors, Recipients ≤ 39 Years, and Recipients Between 40 and 49 Years of Age

Groups per age of patients	Donors ≤35 years	Recipients Group A ≥39 years	Recipients Group B Between 40 and 49 years
Patients	47	57	57
Transfers	33	57	57
Oocytes*	499 (10.6 ± 4.5)	235 (4.1 ± 1.0)	236 (4.1 ± 1.0)
Embryos transferred*	102 (3.0 ± 0.7)	137 (2.4 ± 0.7)	134 (2.3 ± 0.8)
Clinical pregnancies	16	27	14
Abortions	1	4	1
Gestational sacs	26	34	20
Pregnancy rate per transfer (%)†	48.4	47.3	24.5
Abortion rate (%)	6.2	14.8	7
Implantation rate (%)‡	25.4	24.8	14.9

* Values in parentheses are means ± SD.
† Pregnancy rate is significantly higher in group A than in group B, $P = 0.01$ and in the donors than group B, $P = 0.03$.
‡ Implantation rate is significantly higher in group A than in group B, $P = 0.05$.

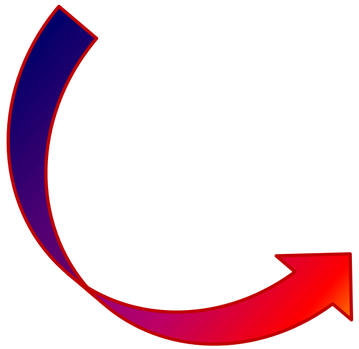
This study seems to suggest that there are differences in pregnancy and implantation rates in recipients of different ages because of uterine receptivity. Fertility therefore does not depend merely on oocyte age and quality but also on uterine age.

Age and Uterine Receptiveness: Predicting the Outcome of Oocyte Donation Cycles

Sérgio Reis Soares, Carlos Troncoso, Ernesto Bosch, Vicente Serra, Carlos Simón, José Remohí, and Antonio Pellicer

Parameters of oocyte donation cycles in the four age groups studied

	Age groups (yr)			
	<40	40–44	45–49	>49
No. of cycles	1615	1068	358	48
Mean donor's age (yr)[a]	26.0 ± 4.1	25.9 ± 4.3	26.0 ± 4.4	25.5 ± 4.2
PR (%)[a]	48.8	51.0	45.5	35.4
Singleton PR (%)[a]	58.8	58.9	68.7	52.9
Multiple PR (%)[a]	41.2	41.1	31.3	47.1
IR (%)[b]	20.7	20.7	17.2	13.2
MR (%)[c]	15.3	19.0	22.0	35.3
Mean no. of replaced embryos[a]	2.8 ± 0.7	2.8 ± 0.7	2.8 ± 0.7	2.9 ± 0.6
Mean no. of good-quality embryos[a]	1.6 ± 0.6	1.5 ± 0.4	1.7 ± 0.5	1.5 ± 0.5
Duration of E2 therapy (wk)[a]	5.1 ± 2.5	5.1 ± 2.5	5.0 ± 2.5	5.3 ± 2.8



	Age groups (yr)	
	<45	≥45
No. of OD cycles	2683	406
Mean donor's age (yr)[a]	26.0 ± 4.3	25.5 ± 4.2
PR (%)[b]	49.8 (1333/2683)	44.4 (180/406)
IR (%)[c]	20.7 (1555/7512)	16.8 (191/1137)
MR (%)[d]	16.8 (224/1333)	23.3 (42/180)
Mean no. of replaced embryos[a]	2.8 ± 0.7	2.8 ± 0.7
Mean no. of good-quality embryos replaced[a]	1.6 ± 0.6	1.7 ± 0.5
Duration of E2 therapy (wk)[a]	5.1 ± 2.5	5.0 ± 2.5

- **Retrospective study**
- **3089 cycles of oocyte donation with embryo transfer**
- **Single-center study**
- **Recipients' age (yr): 38.9±5. 2**

J Clin Endocrinol Metab, 2005

Fertil Steril. 1995 Feb;63(2):258-61.

Pregnancies in postmenopausal women over 50 years old in an oocyte donation program.

Borini A[1], Bafaro G, Violini F, Bianchi L, Casadio V, Flamigni C.

Retrospective study
34 pts; 61 cycles of oocyte donation
55 transfer
Single-center study
Recipients' age (yr): 50 to 62 yrs

Outcome of pregnancies

N of pregnancies	18
Singletons	16
Twins	1
Triplets	1
N of abortions	1
Abortion rate (%)	5,5
N of deliveries	12
N of ongoing pregnancies	5
Complications	7
Gestational diabetes	2
Moderate pre-eclampsia	2
Severe pre-eclampsia	3

	Recipients	Donors	
Patients	34	50	
Mean age	53 (50-62)	30 (22-35)	
Cycles	61	51	
Transfers	55	44	
Embryos-Oocytes transferred	116	139	
Pregnancies	18	17	
Abortions	1	1	
Gestational sacs	21	23	
Pregnancy rate per transfer (%)	32,7	38,6	NS
Abortion rate (%)	5,5	5,8	
Implantation rate (%)	18	16,5	

The aging of uterus after HRT allows implantation as well as in young women, and is able to carry pregnancy to term apparently without any problems.

STEM CELLS

Human Reproduction Update, Vol.22, No.2 pp. 137–163, 2016
Advanced Access publication on November 9, 2015 doi:10.1093/humupd/dmv051
human reproduction update

Endometrial stem/progenitor cells: the first 10 years

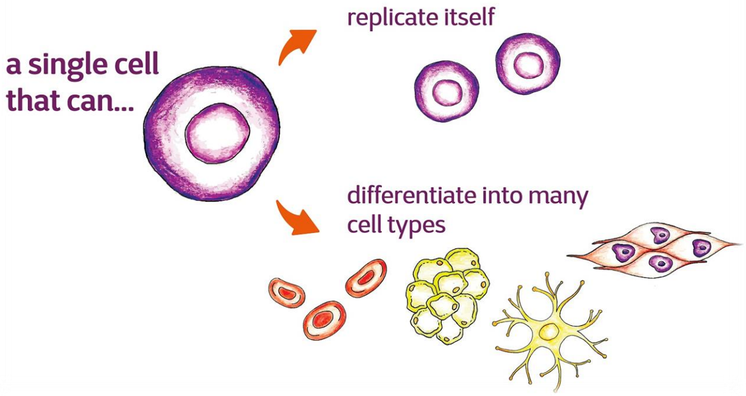
2016

Caroline E. Gargett[1,2,*], Kjiana E. Schwab[1], and James A. Deane[1,2]

The human endometrium not only regenerates each month as part of the menstrual cycle, but also following parturition, almost complete resection and in postmenopausal women taking estrogen-based hormone replacement therapy *(Gargett et al., 2012)*.
The atrophic endometrium of postmenopausal women regenerates to a thickness similar to premenopausal endometrium by the administration of estradiol valerate for 8 weeks *(Ettinger et al., 1997; Ulrich et al., 2014c)*

Table VII Endometrial diseases in which endometrial stem/progenitor cells may play a role.

Endometrial disease	Description
Adenomyosis	A benign disease involving extensive growth and invasion of basalis endometrial tissue into the uterine myometrium with associated smooth muscle hyperplasia, resulting in an enlarged uterus and painful, heavy or prolonged periods
Asherman's syndrome and intrauterine adhesions (IUAs)	An acquired uterine condition characterized by complete obliteration of the endometrium with fibrotic intrauterine adhesions (IUAs) causing amenorrhea and infertility. IUA is a less severe condition involving partial replacement of the endometrium with fibrous tissue, causing hypomenorrhea, infertility and pregnancy loss. It results from trauma to the basalis endometrium following dilation and curettage (D&C) due to miscarriage, abortion or retained placenta in a setting of low estrogen and/or infection
Endometriosis	A benign disease affecting reproductive aged women in whom endometrial tissue grows outside the uterine cavity, most often in the pelvic cavity, around/on the ovaries and in the rectovaginal septum, resulting in inflammation, infertility and severe pelvic pain
Thin dysfunctional endometrium	Endometrial tissue that does not respond to estrogen stimulation and fails to reach at least 7 mm in thickness necessary for embryo implantation and maintenance of an ongoing pregnancy



2013

CURRENT OPINION

Regenerating endometrium from stem/progenitor cells: is it abnormal in endometriosis, Asherman's syndrome and infertility?

James A. Deane*, Rosa C. Gualano*, and Caroline E. Gargett

Repeated endometrial biopsy may activate endometrial stem/progenitor cells to regenerate a thick endometrium suitable for implantation.

(..) transplant of autologous CD9+, CD44+ and CD90+ bone marrow cells comprising fibroblasts and MSCs was administered into the uterine cavity of a patient with Asherman's syndrome.

KEY POINTS

- Human endometrium contains small populations of stem/progenitor cells, which are self-renewing, multipotent, highly proliferative and able to regenerate endometrium in a mouse transplant model.
- Human embryonic stem cells can be induced to generate endometrial epithelium, recapitulating endometrial development and demonstrating possible clinical uses.
- Mouse studies have identified a role for mesenchymal-to-epithelial transition in postpartum endometrial epithelial regeneration.
- The recent identification of specific markers and enrichment methods for endometrial stem/progenitor cells is facilitating research on endometrial disorders such as endometriosis, although these have identified heterogeneous populations whose phenotypes and hierarchical relationships require clarification.
- Stem/progenitor cells can be isolated from routine endometrial biopsy or menstrual blood and may be used autologously to regenerate endometrium in disorders of inadequate proliferation, such as Asherman's syndrome.

Original Article

Autologous stem cell transplantation in refractory Asherman's syndrome: A novel cell based therapy

Neeta Singh,
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Tulika Seth,
Meenakshi Shankar,
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Received: 15.01.2014
Review completed: 26.03.2014
Accepted: 26.05.2014

ABSTRACT

BACKGROUND: There is substantial evidence that adult stem cell populations exist in human endometrium, and hence it is suggested that either endogenous endometrial stem/progenitor cells can be activated or bone marrow derived stem cells can be transplanted in the uterine cavity for endometrial regeneration in Asherman's syndrome (AS). **AIMS AND OBJECTIVES:** The objective was to evaluate the role of sub-endometrial autologous stem cell implantation in women with refractory AS in attaining menstruation and fertility. **SETTING:** Tertiary care referral center. **DESIGN:** Prospective case series. **MATERIALS AND METHODS:** Six cases of refractory AS with failed standard treatment option of hysteroscopic adhesiolysis in the past were included. Mononuclear stem cells (MNCs) were implanted in sub-endometrial zone followed by exogenous oral estrogen therapy. Endometrial thickness (ET) was assessed at 3, 6, and 9 months. **RESULTS:** Descriptive statistics and statistical analysis of study variables was carried out using STATA version 9.0. The mean MNC count was 103.3×106 (± 20.45) with mean CD34+ count being 203,642 ($\pm 269,274$). Mean of ET (mm) at 3 months (4.05 ± 1.40), 6 months (5.46 ± 1.36) and 9 months (5.48 ± 1.14) were significantly ($P < 0.05$) increased from pretreatment level (1.38 ± 0.39). Five out of six patients resumed menstruation. **CONCLUSION:** The autologous stem cell implantation leads to endometrial regeneration reflected by restoration of menstruation in five out of six cases. Autologous stem cell implantation is a promising novel cell based therapy for refractory AS.

Granulocite Colony Stimulating Factor (GCSF)

First use in 4 patients with dramatic improvement in ET

Successful treatment of unresponsive thin endometrium

CASE REPORT 2011

Norbert Gleicher, M.D.,[a,b] *Andrea Vidali, M.D.,*[c] *and David H. Barad, M.D., M.S.*[a,d]

Result(s): We report successful endometrial expansion to at least minimal thickness of 7 mm after uterine perfusion with G-CSF in four patients previously resistant to treatment with estrogen and vasodilators. All four patients therefore reached ET, and all four also conceived, although one pregnancy required termination because of intramural, corneal ectopic location. Endometrial expansion to minimal thickness occurred within approximately 48 hours from infusion.

OTHER 65 STUDIES ON GCSF

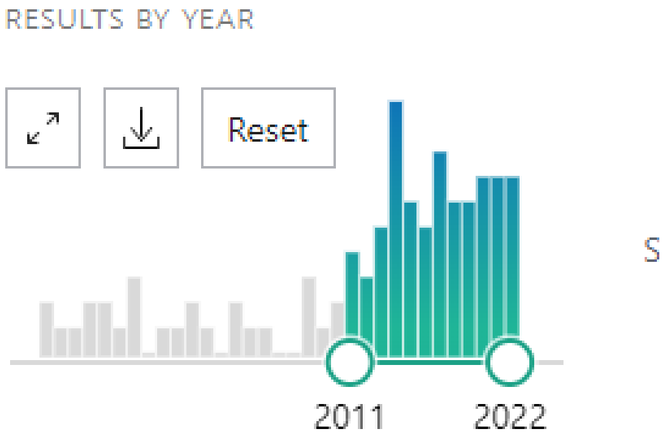
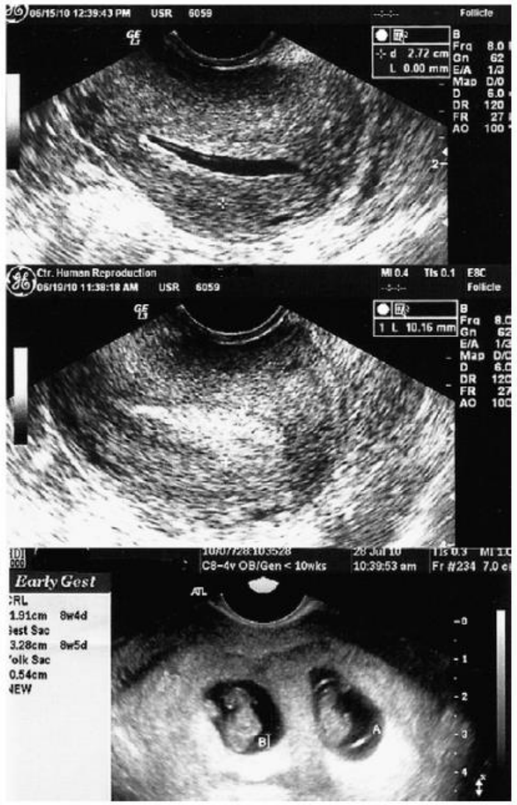


FIGURE 1

Ultrasound studies in patient 1. (**A**) Very thin endometrium (depending on area of measurement, 3.0–4.0 mm), surrounding an entirely fluid-filled endometrial cavity on day −5 before ET. (**B**) Same endometrium 4 days later, 1 day before ET (day −1). (**C**) Twin pregnancy at approximately 8 weeks, 3 days gestational age.



Gleicher. Thin endometrium. Fertil Steril 2011.

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

Human Endometrial Reconstitution From Somatic Stem Cells: The Importance of Niche-Like Cells

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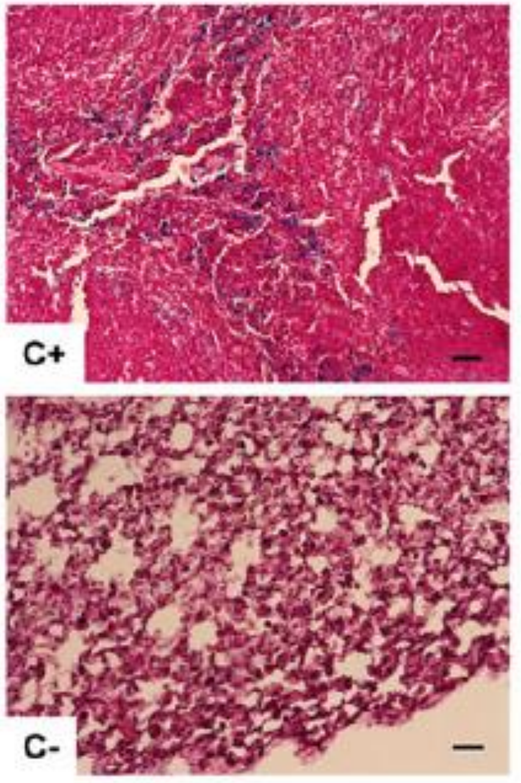
2019



Abstract

Endometrial regeneration has long been proposed to be mediated by stem cells, but the isolation of endometrial stem cells has been hampered by a lack of validated markers. Specific markers would enable isolation of these stem cells, thereby promoting advancements in regenerative medicine for the treatment of endometrial diseases and dysfunctions. We sought to investigate the regenerative ability of human endometrial positive for sushi domain containing 2/intercellular adhesion molecule 1 ($SUSD2^+$/$ICAM1^+$) cells and Side Population cell lines in a xenograft mice model. The injection of total endometrial cell suspensions and Side Population cell lines under kidney capsules induced neoformation of human endometrium verified by the presence of typical endometrial markers (vimentin, cytokeratin 18, and progesterone receptor) by immunofluorescence. Total endometrial cell types promoted a better reconstitution in comparison to injecting $ICAM1^+$ and $SUSD2^+$ cells alone. The endometrial fraction is probably acting as a niche, resulting in increased reconstruction efficiency of pure fractions. Human engrafted cells were localized near blood vessels and induced the proliferation of surrounding cells. Our results suggest that human endometrial Side Population, a heterogeneous population possibly harboring endometrial stem cells, has the optimum capacity to regenerate endometrial-like tissue. In contrast, cells positive for single stem cell markers SUSD2 and ICAM1 have minimally functional regenerative capacities in the absence of niche-like cells.

TAKE HOME MESSAGE

- Embryo implantation is a major rate-limiting step in the success of ART. A variety of factors can impact embryo implantation including endometrial differentiation, embryo quality and the method of embryo transfer.

- A thin endometrium is associated with implantation failure.

- Results of several clinical studies concerning oocytes donation have shown that there is a decline in conception rate with increasing recipient age.

- In the last decade, the role of bone marrow-derived and endogenous stem/progenitor cells in endometrial proliferative disorders, including endometriosis, adenomyosis, thin dysfunctional endometrium and Asherman's syndrome, has been established.

FUTURE THERAPY ?

THANK YOU

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