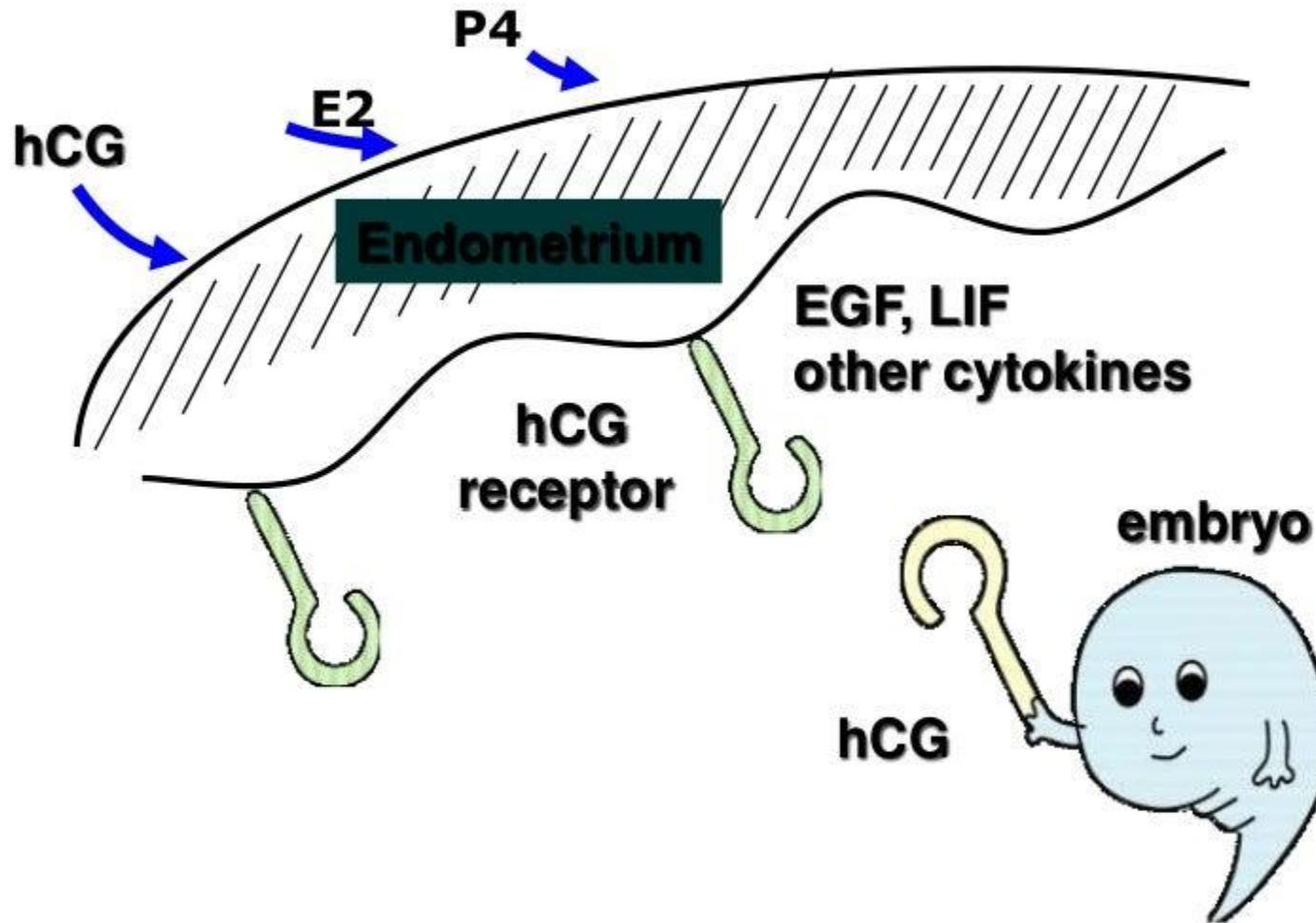


*Thin endometrium*

# IVF Success Rate- 40%



# Embryo-Maternal Communication



**Implantation**

**= Good embryo x**

**Good Endometrium**

# Receptive Endometrium requires

1. *Estrogen priming-*  
needed for endometrial proliferation and development of P4 receptors

2. *Time-related progesterone* induced secretory changes in the endometrium

- *Other molecules*
- IGFBP-1
- Prolactin
- Laminin, type IV  
Collagen, Fibronectin,  
Heparin sulphate
- Integrin, Cadherin,  
Adheren, Secretin
- LIF, IL-6, IL-11, VEGF,  
CSF, TGF- $\beta$ , TNF- $\alpha$

# Ideal way to measure the endometrial receptivity

- Sensitive and specific
- Accurate
- Noninvasive
- Cheap
- Accepted by patients
- Easily available

*Yet to identify*

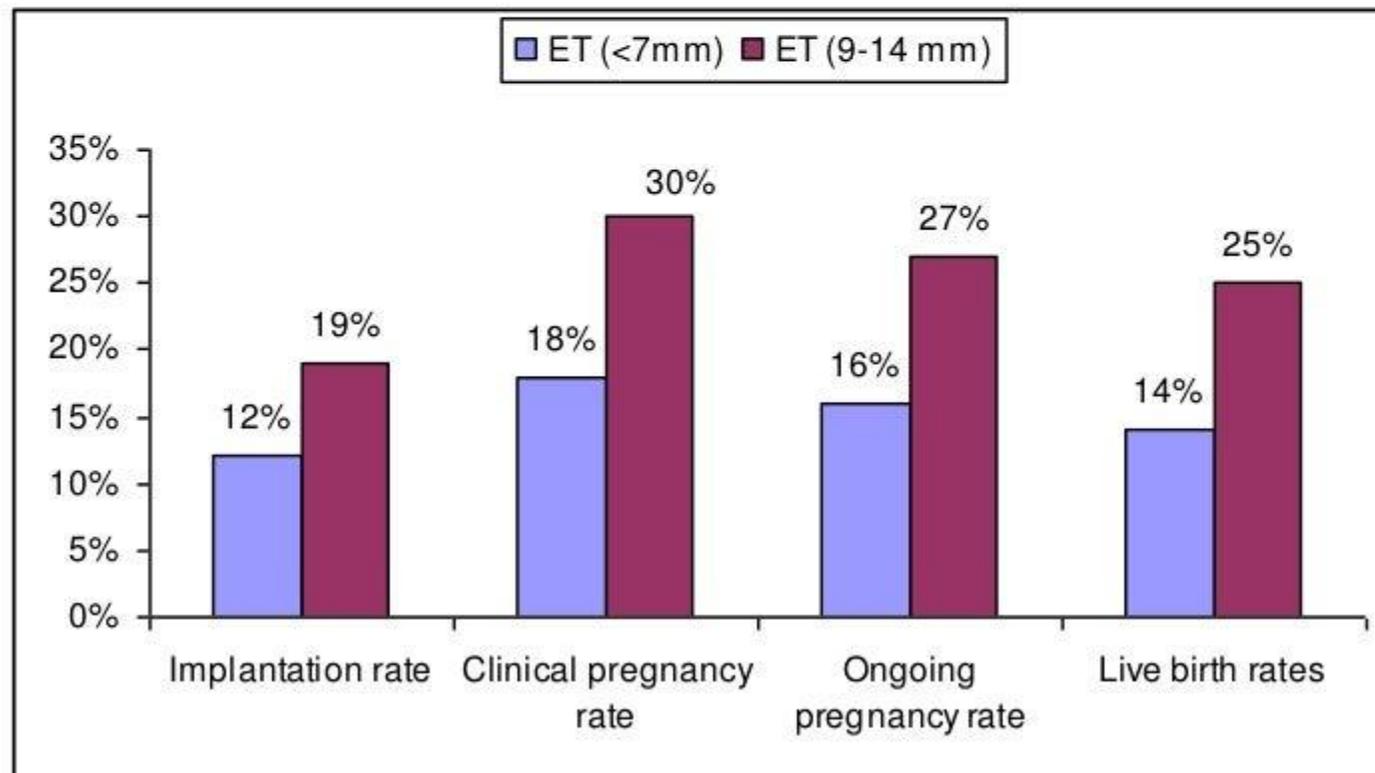
# Endometrial Thickness by Ultrasound

- While the benefit of ultrasound to characterize follicular development is well documented, **its value in endometrial evaluation is less clear** (Hershko-Klement and Tepper, 2016).
- 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).
- **In 10% cases, the ideal image for measurement is difficult to obtain** due to the presence of fibroids, adenomyosis, polyps, uterine orientation, body habitus, previous surgeries and patient intolerance (Goldstein, 2004).



# Ideal Endometrial Thickness

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



# What is thin endometrium?

- Considerable controversy (Chen et al., 2010; De Geyter et al., 2000; Detti et al., 2008; Zhao et al., 2012, 2014).

# The impact of a thin endometrial lining on fresh and frozen–thaw IVF outcomes: an analysis of over 40 000 embryo transfers

K.E. Liu<sup>1,2,\*</sup>, M. Hartman<sup>3</sup>, A. Hartman<sup>4</sup>, Z.-C. Luo<sup>2,5</sup>,  
and N. Mahutte<sup>6</sup>

**Table 1** 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 <sup>a</sup>	N/A <sup>a</sup>
<4 mm	26	0.1	N/A <sup>a</sup>	N/A <sup>a</sup>	N/A <sup>a</sup>
Total	21 914	100%			
<i>P</i> for difference <sup>b</sup>			<i>P</i> < 0.0001	<i>P</i> = 0.01	<i>P</i> < 0.0001
<i>P</i> for trend <sup>c</sup>			<0.0001	0.002	<0.0001

<sup>a</sup>Data for cell counts <6 was suppressed and not available (N/A).

<sup>b</sup>*P* values in Chi-square tests for differences in all groups with available data.

<sup>c</sup>*P* values in Cochran–Armitage tests for trends in rates across endometrial thickness strata in all groups with available data.

## The impact of a thin endometrial lining on fresh and frozen–thaw IVF outcomes: an analysis of over 40 000 embryo transfers

K.E. Liu<sup>1,2,\*</sup>, M. Hartman<sup>3</sup>, A. Hartman<sup>4</sup>, Z.-C. Luo<sup>2,5</sup>,  
and N. Mahutte<sup>6</sup>

- 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.**



REVIEW

Management of thin endometrium in assisted reproduction: a clinical practice guideline from the Canadian Fertility and Andrology Society



- In **fresh IVF-embryo transfer** cycles, patients should be counselled that **endometrial thickness <8 mm** may have a negative impact on pregnancy and live birth rates
- In **frozen IVF-embryo transfer** cycles, patients should be counselled that **endometrial thickness <7 mm** may have a negative impact on pregnancy and live birth rates.

# Incidence of “thin endometrium”

- In ovarian stimulation cycles- 38–66%; in IVF is 1-2.5%. (*Asante et al., 2013; Chen et al., 2012; Wolff et al., 2013; Jeon et al., 2013*).
- Based on retrospective and prospective observational studies.
- Ovarian stimulation cycles are more likely to proceed despite the thin endometrium whilst IVF cycles are more likely to be cancelled.

# How does it affect implantation

- Poor growth of glandular epithelium
- Decreased VEGF expression
- Poor vascular development
- High resistance in radial arteries  $\rightarrow$   $\downarrow$  VEGF  $\rightarrow$   $\downarrow$  blood flow  $\rightarrow$  thin endometrium  $\rightarrow$   $\uparrow$  vascular resistance

# Does it really matter?

Human Reproduction, Vol.33, No.10 pp. 1883–1888, 2018  
Advanced Access publication on September 17, 2018 doi:10.1093/humrep/dey281

human  
reproduction

ORIGINAL ARTICLE *Infertility*

## The impact of a thin endometrial lining on fresh and frozen–thaw IVF outcomes: an analysis of over 40 000 embryo transfers

K.E. Liu<sup>1,2,\*</sup>, M. Hartman<sup>3</sup>, A. Hartman<sup>4</sup>, Z.-C. Luo<sup>2,5</sup>,  
and N. Mahutte<sup>6</sup>

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

# How thin is the “thin endometrium”?

Human Reproduction, Vol.33, No.10 p. e1, 2018

doi:10.1093/humrep/dey297

human  
reproduction

EDITOR'S CHOICE

## More than 1200 embryo transfers with an endometrial thickness below 7 mm

J.L.H. (Hans) Evers\*

Editor-in-Chief

\*Correspondence address. E-mail: [eshre.editorialoffice@oup.com](mailto:eshre.editorialoffice@oup.com)

The impact of a thin endometrium has been a longstanding topic of lively debate among IVF clinicians. Kimberly Liu *et al.* (2018) from Toronto, Canada, now have reviewed over 40,000 fresh and frozen IVF cycles. They show that live birth rates decreased and pregnancy loss rates increased with each millimeter decline of endometrial thickness below 8 mm in fresh transfer cycles. In frozen transfer cycles, live birth rates decreased below 7 mm, but no significant difference in pregnancy loss rates was found. The likelihood of achieving an endometrial thickness over 8 mm decreased with age. Yet, live birth rates remained fair (15–21%) in patients with an endometrial thickness of

5–6 mm in fresh and 4–6 mm in frozen cycles. Data were 'suppressed and not available' for 49 embryo transfers in women with an endometrium below 4 mm.

### Reference

Liu KE, Hartman M, Hartman A, Luo Z-C, Manhutte N. The impact of a thin endometrial lining on fresh and frozen-thaw IVF outcomes: an analysis of over 40,000 embryo transfers. *Hum Reprod* 2018. DEY281.

# Causes of Thin Endometrium

1. Asherman Syndrome
2. Clomiphene Citrate- Prolonged Use
3. Postpartum Endometritis
4. Septic Abortion
5. Pelvic Radiation
6. Chemotherapy
7. In-utero Diethylstilbestrol
8. Hypothalamic Hypogonadism
9. Fibroids
10. Müllerian Anomalies
11. Premature Ovarian Insufficiency
12. Hyperandrogenaemia
13. Iatrogenic
- 14. Idiopathic**

- Studies of patients with thin endometrium often exclude patients with uterine pathology; therefore, the **true incidence of uterine pathology is not well reported.**

# First step

## Find out the cause

- Uterine cavity assessment by hysteroscopy or sonohysterogram may be performed (*Consensus Opinion*)
- Uterine assessment may identify patients who may benefit from surgical management.
- Most studies have not identified endometritis as a contributing factor ([Garcia-Velasco et al., 2016](#)),
- No studies on the treatment of endometritis in patients with thin endometrium could be identified.

# Treat the cause

- May have **more detrimental effect than the thin endometrium itself**
  1. Endometritis
  2. Intrauterine Adhesion
  3. Endometriosis
  4. Hydrosalpinx

# Thin ET in Fresh Cycle

- Change Stimulation protocol
- Add Estradiol
- Add adjuvants
- Freeze all

# Fresh Cycle- Blame or Change

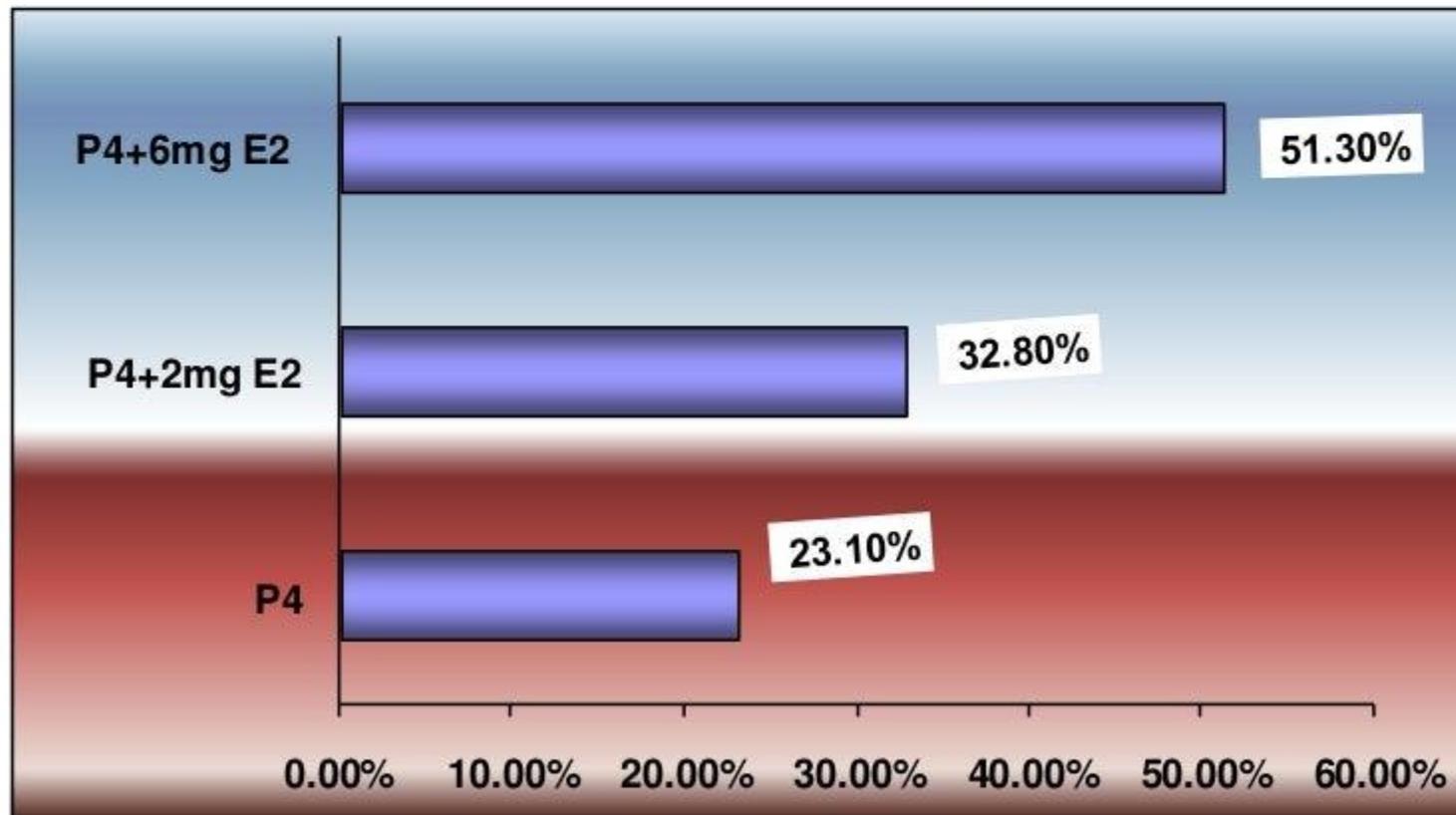
- In ovarian stimulation treatment cycles, there is **insufficient evidence** to recommend changing stimulation medications or a specific stimulation medication to improve the endometrial thickness
- **Quality of evidence- Weak**

Canadian Fertility and Andrology Society Guideline, 2019

# Fresh Cycle- Add Estrogen

*Addition of luteal estrogen supplementation in stimulated cycles improves the pregnancy rates & hence improves IVF embryo transfer rates \*\**

**\*\* Fertil Steril. 2005 May;83(5):1372-6**



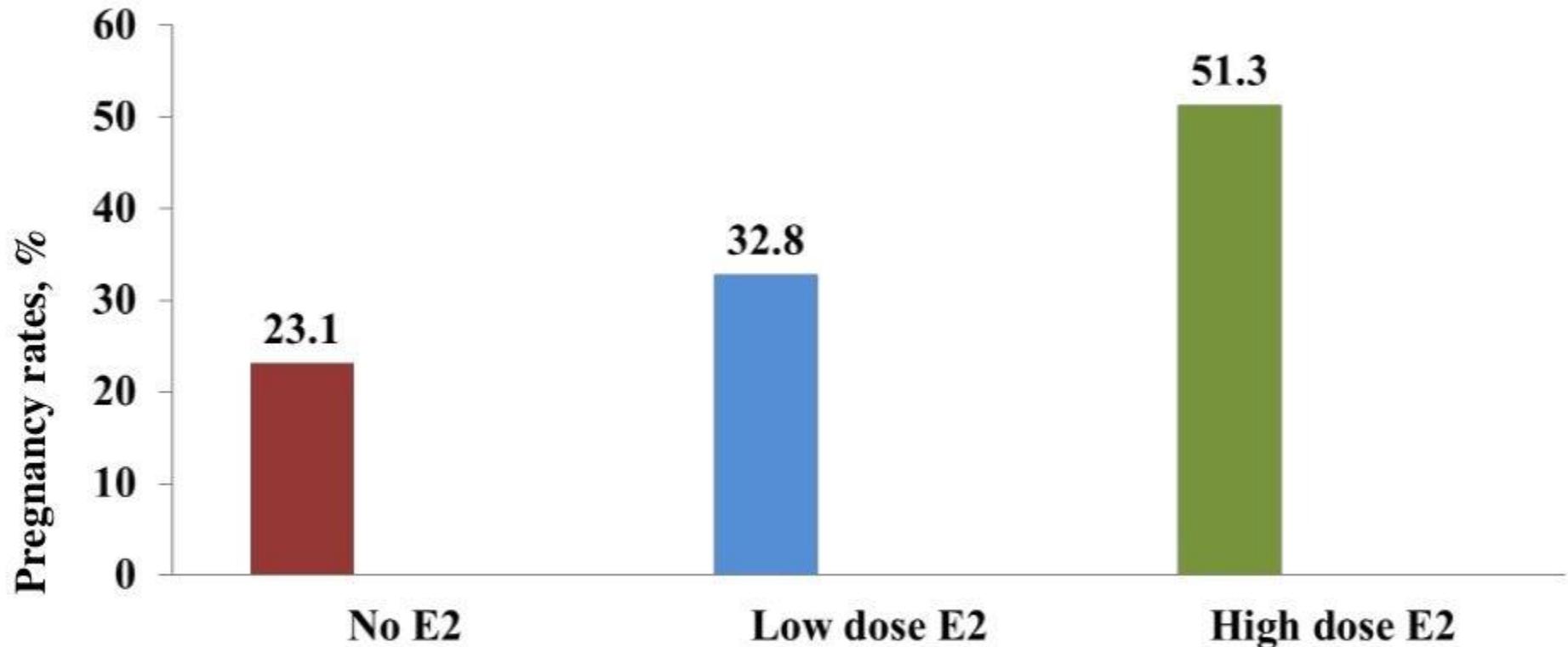
## Luteal phase support for assisted reproduction cycles (Review)

van der Linden M, Buckingham K, Farquhar C, Kremer JAM, Metwally M

- Progesterone vs progesterone with oestrogen
- 16 RCTs, 2577 women
- **There was no evidence of a difference between the groups** in rates of live birth or ongoing pregnancy (OR 1.12, 95% CI **0.91 to 1.38**, nine RCTs, 1651 women, I<sup>2</sup> = 0%, low-quality evidence) or OHSS (OR 0.56, 95% CI **0.2 to 1.63**, two RCTs, 461 women, I<sup>2</sup> = 0%, **low-quality evidence**)

# Estrogen in Agonist Cycle

## Pregnancy rates with E2 supplementation



Significantly higher IR and PR were found in patients who received low dose E<sub>2</sub> (2 mg) compared with no E<sub>2</sub>, but the best outcomes were found significantly in the group with high dose E<sub>2</sub> (6 mg) supplementation.

ORIGINAL ARTICLE

## Effects of oestradiol for luteal phase support in fresh embryo transfer cycles: A retrospective cohort study

Wei Zhao, Yifeng Liu, Peng Xu, Yiqing Wu, Kai Chen, Xiaoyan Guo, Fan Zhang, Yun Huang, Linlin Zhu, Runjv Zhang, Dan Zhang 

First published: 12 May 2018 | <https://doi.org/10.1111/cen.13740>

- Any benefit of oestradiol supplementation for luteal phase support appears to correlate with the serum oestradiol level on the day of hCG trigger.
- **Oestradiol supplementation is beneficial for improving live birth rate in cycles with oestradiol levels less than 5000 pmol/L, but is not recommended in cycles with oestradiol levels over 10 000 pmol/L.**

**SUMMARY OF FINDINGS: LUTEAL OESTRADIOL COMPARED WITH NO TREATMENT FOR PATIENTS WITH THIN ENDOMETRIUM UNDERGOING IVF-EMBRYO TRANSFER (FRESH OR FROZEN)**

Outcomes	Anticipated absolute effects <sup>a</sup>		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with no treatment	Risk with luteal oestradiol				
Clinical pregnancy rate	233 per 1000	280 per 1000 (152-520)	RR 1.20 (0.65-2.23)	117 (one observational study)	⊕○○○ Very low <sup>b,c</sup>	
Live birth rate	133 per 1000	173 per 1000 (75-413)	RR 1.30 (0.56-3.10)	117 (one observational study)	⊕○○○ Very low <sup>b,c</sup>	
Clinical pregnancy rate with frozen embryo transfer compared with fresh embryo transfer	43 per 1000	383 per 1000 (50-1000)	RR 8.80 (1.15-67.80)	36 (one observational study)	⊕○○○ Very low <sup>d</sup>	
Live birth rate with frozen embryo transfer compared with fresh embryo transfer	0 per 1000	0 per 1000 (0-0)	RR 18.90 (1.13-316.10)	36 (one observational study)	⊕○○○ Very low <sup>d</sup>	

Patient or population: patients with thin endometrium undergoing IVF-embryo transfer (fresh or frozen).

Intervention: luteal oestradiol.

Comparison: no treatment.

GRADE, Grading of Recommendations, Assessment, Development and Evaluations framework; CI, confidence interval; RR, risk ratio.

<sup>a</sup> The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

<sup>b</sup> Demir et al. (2013); unclear how it was determined who received which treatment.

<sup>c</sup> Few events.

<sup>d</sup> Chen et al. (2006); unclear how patients were selected to receive fresh or frozen embryo transfer.

Studies included:

Chen, M.J., Yang, J.H., Peng, F.H., Chen, S.U., Ho, H.N., Yang, Y.S., 2006. Extended estrogen administration for women with thin endometrium in frozen-thawed in-vitro fertilization programs. *J. Assist. Reprod. Genet.* 23, 337-342.

Demir, B., Dilbaz, S., Cinar, O., Ozdegirmenci, O., Dede, S., Dundar, B., Goktolga, U., 2013. Estradiol supplementation in intracytoplasmic sperm injection cycles with thin endometrium. *Gynecol. Endocrinol.* 29, 42-45.

# Thin Endometrium in Fresh Cycle

- In patients with thin endometrium undergoing fresh IVF-embryo transfer cycles, **we suggest against the use of luteal oestradiol** to improve pregnancy rates. \*
- In fresh IVF-embryo transfer cycles, patients with thin endometrium can be offered **elective cryopreservation of embryos** and transfer in a subsequent cycle.\*

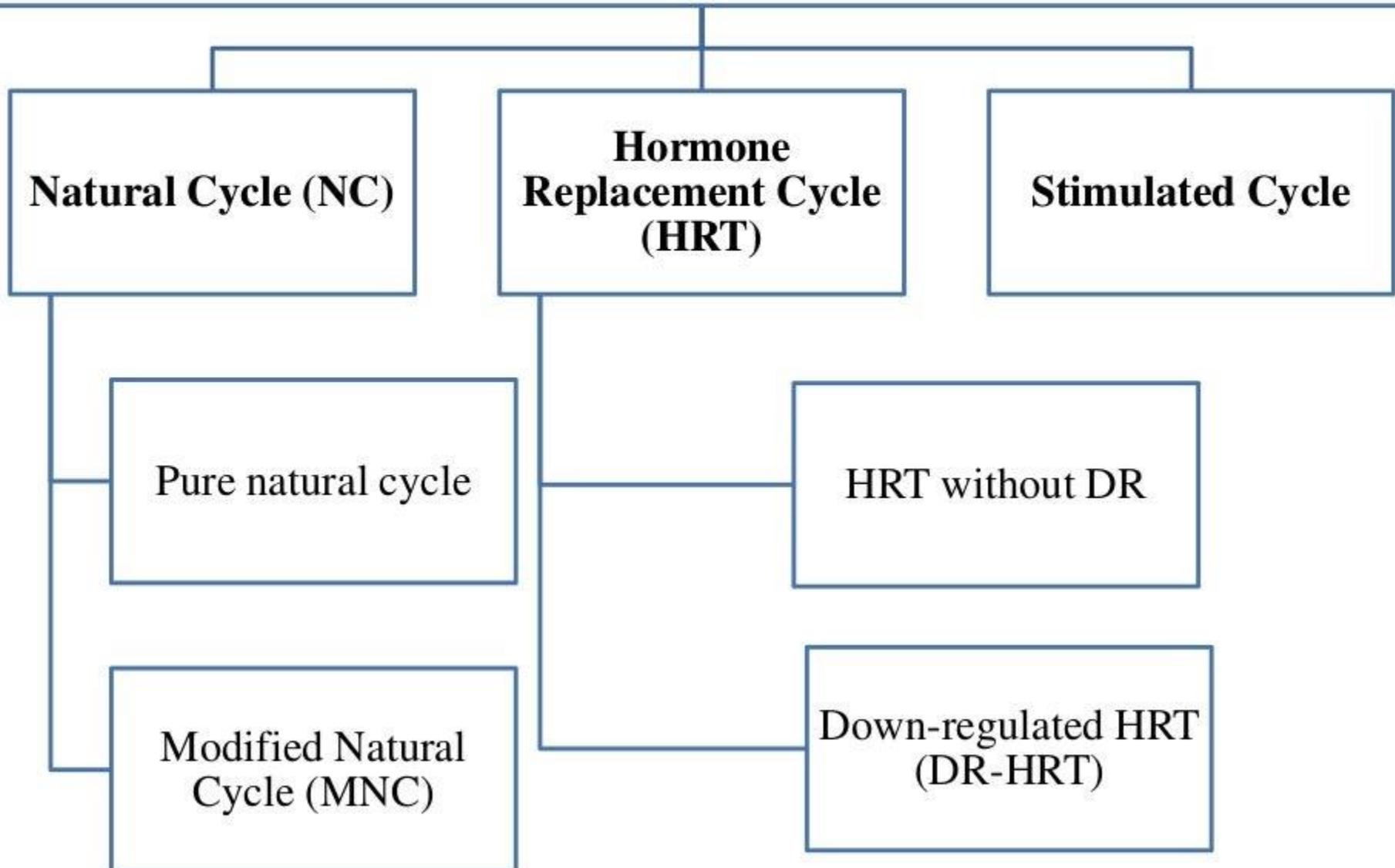
\*Canadian fertility and Andrology Society Guideline, 2019

# Fresh Cycle- Adjuvants

- In ovarian stimulation treatment cycles, there is insufficient evidence to recommend the use of adjuvants to improve endometrial thickness or pregnancy rates.

**Canadian Fertility and Andrology Society Guideline, 2019**

# Which Endometrial Preparation for FET?



# Which Endometrial Preparation is the best?

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<sup>1</sup>, S. Santos-Ribeiro<sup>1,2</sup>, A. van de Vijver<sup>1</sup>, A. Racca<sup>1,3</sup>,  
L. Van Landuyt<sup>1</sup>, H. Tournaye<sup>1</sup>, and C. Blockeel<sup>1,4,\*</sup>

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<sup>2</sup>Department of Obstetrics, Gynaecology and Reproductive Medicine, Santa Maria University Hospital, Avenida Professor Egas Moniz, Lisbon 1649-035, Portugal <sup>3</sup>Academic Unit of Obstetrics and Gynecology, IRCCS AOU San Martino—IST, University of Genova, Largo R. Benzi 10, 16132 Genova, Italy <sup>4</sup>Department of Obstetrics and Gynaecology, School of Medicine, University of Zagreb, Petrova 13, 10000 Zagreb, Croatia

\*Correspondence address. Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Laarbeeklaan 101-1090 Brussels, Belgium.  
E-mail: [Christophe.Blockeel@uzbrussel.be](mailto:Christophe.Blockeel@uzbrussel.be)

Submitted on June 6, 2017; resubmitted on August 6, 2017

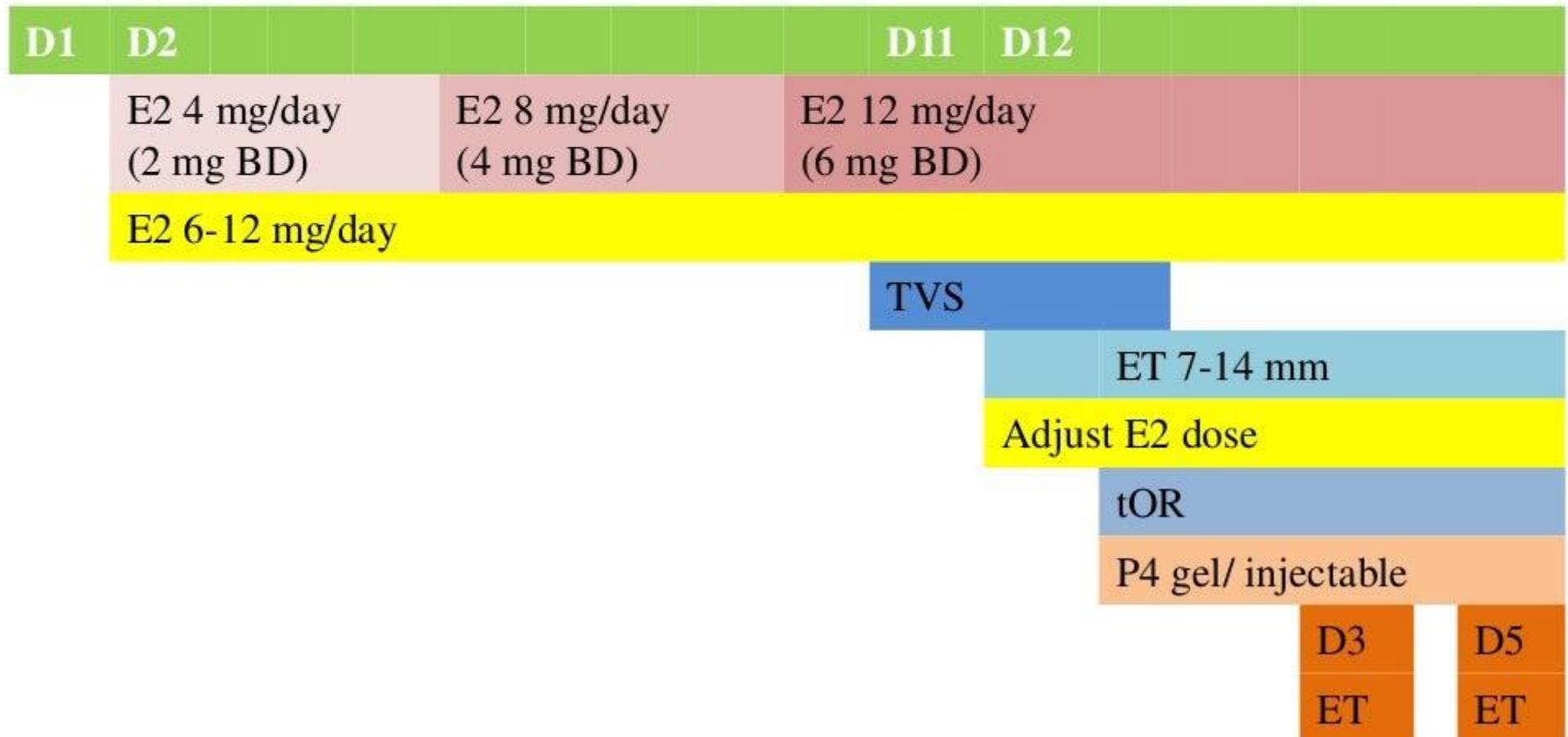
- **The number of high quality randomized controlled trials (RCTs) is scarce** and, hence, **the evidence for the best protocol for FET is poor.**
- In terms of embryo transfer timing, we propose to start progesterone intake on the theoretical day of oocyte retrieval in HRT and to perform blastocyst transfer at hCG + 7 or LH + 6 in modified or true NC, respectively.

# Canadian Fertility and Andrology Society Guideline, 2019

- For patients with a history of thin endometrium in ART treatment undergoing endometrial preparation for embryo transfer, there is **insufficient evidence that any specific protocol (natural cycle or hormone replacement)** for endometrial preparation provides better pregnancy outcomes.

# Hormone Replacement Cycle (Artificial Cycle)

- Exogenous supply of Estrogen & Progesterone that equals the effects of ovarian hormones on the endometrial tissue is required [Gupta SA et al, 2018](#)



# Superiority of Estradiol valerate over other estrogens

<b>Ethinyl Estradiol</b>	<ul style="list-style-type: none"> <li>↑ Triglyceride</li> <li>↑PRA → Hypertension</li> <li>↑ Factor VII → ↑ Coagulation</li> </ul>
<b>Conjugated Estrogen</b>	<ul style="list-style-type: none"> <li>Inter-batch variability</li> <li>Allergic reaction</li> <li>↑PRA → Hypertension</li> <li>↑ Factor VII → ↑ Coagulation</li> </ul>
<b>Estriol</b>	<ul style="list-style-type: none"> <li>1/6 estrogenic activity</li> <li>↑ LDL</li> </ul>
<b>Estradiol Transdermal Patch</b>	<ul style="list-style-type: none"> <li>Inconsistency between products</li> <li>Skin reaction</li> <li>Problem in humid atmosphere</li> </ul>
<b>Estradiol Transdermal Gel</b>	<ul style="list-style-type: none"> <li>↓Bioavailability</li> <li>Skin reaction</li> </ul>

# Duration of Estrogen Therapy

- Endometrial receptivity (ER) is tolerant to a wide duration of E2 treatment
- Uterine preparation consisting of 6 mg EV can be extended as long as 5 weeks with no significant decrease in ER

*Journal of Assisted Reproduction & genetics ,vol 18 ,No 4,april 2001  
Fertil steril 1995 jun ;63(6):1284-6*

- Long duration of E2 therapy is not deleterious
- Vaginal micronized E2 achieves higher endometrial concentration

*Hum Reprod 2002*

- Decreasing the length of E2 therapy is beneficial in terms of cost and time to pregnancy

Chen, M.J., Yang, J.H., Peng, F.H., Chen, S.U., Ho, H.N., Yang, Y.S.  
Extended estrogen administration for women with thin endometrium in  
frozen-thawed in-vitro fertilization programs. *J. Assist. Reprod. Genet.*  
2006; 23: 337–342

In patients with endometrial thickness <8 mm

In this prospective cohort study, 23 patients  
proceeded with a fresh embryo transfer and one  
patient conceived **but no live births resulted.**

Thirteen patients underwent a frozen embryo  
transfer with hormone replacement. Oestradiol  
was continued until endometrial thickness  
reached 8 mm (**range 14–82 days, mean 30  
days**). Five patients conceived and delivered (risk  
ratio 18.9, **95% confidence interval 1.13–316.1**).

## Prolonged estrogen (E2) treatment prior to frozen-blastocyst transfer decreases the live birth rate

Mathilde Bourdon<sup>1,2,†</sup>, Pietro Santulli<sup>1,2,†,9</sup>, Fleur Kefelian<sup>1</sup>,  
Laurine Vienet-Legue<sup>1</sup>, Chloé Maignien<sup>1</sup>, Khaled Pocate-Cheriet<sup>4</sup>,  
Jacques de Mouzon<sup>1,5</sup>, Louis Marcellin<sup>1,2,3</sup>, and Charles Chapron<sup>1,3</sup>

<sup>1</sup>Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Assistance Publique—Hôpitaux de Paris (AP-HP), Hôpital Universitaire Paris Centre, Centre Hospitalier Universitaire (CHU) Cochin, Department of Gynaecology Obstetrics I and Reproductive Medicine 52 avenue de l'Observance, 75014 Paris, France; <sup>2</sup>INSERM U1154, Département 'Services gynécologie, procréation, infertilité et infirmières', Université Paris Descartes, Sorbonne Paris Cité, 22 rue Mechain, 75014 Paris, France; <sup>3</sup>Institut Cochin, INSERM U1184, Département de Génétique, Développement et Cancer, Université Paris Descartes, Sorbonne Paris Cité, 22 rue Mechain, 75014 Paris, France; <sup>4</sup>Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Assistance Publique—Hôpitaux de Paris (AP-HP), Hôpital Universitaire Paris Centre, Centre Hospitalier Universitaire (CHU) Cochin, Service d'Histologie Embryologie Biologie de la Reproduction, 52 avenue de l'Observance, 75014 Paris, France; <sup>5</sup>Epidémiologie, Paris, France

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Submitted on August 2, 2017; resubmitted on January 23, 2018; accepted on February 7, 2018

## Fertility and Sterility.



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June 2019 Volume 111, Issue 6, Pages 1177–1185.e3

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### Endometrial preparation before the transfer of single, vitrified-warmed, euploid blastocysts: does the duration of estradiol treatment influence clinical outcome?

Lucky Sekhon, M.D.<sup>a,b,†</sup>, Jessica Feuerstein, M.D.<sup>a</sup>, Stephanie Pan, M.S.<sup>b</sup>, Jessica Overbey, M.S.<sup>b</sup>, Joseph A. Lee, B.A.<sup>a</sup>, Christine Britton-Jones, Ph.D.<sup>a</sup>, Eric Filmer, M.D.<sup>a,b</sup>, Daniel E. Stein, M.D.<sup>a,c</sup>, Tanmay Mukherjee, M.D.<sup>a,b</sup>, Lawrence Grunfeld, M.D.<sup>a,b</sup>, Benjamin Sandler, M.D.<sup>a,b</sup>, Alan B. Copperman, M.D.<sup>a,b</sup>

PlumX Metrics

DOI: <https://doi.org/10.1016/j.fertnstert.2019.02.024> |

Check for updates

# Use of Adjuvants

- Sildenafil- oral/ vaginal
- Aspirin
- L-Arginine
- Vitamin E
- Pentoxify
- G-CSF
- Platelet rich plasma (PRP)
- Stem cells

*All Empirical*

# Aspirin

## SUMMARY OF FINDINGS: ASPIRIN COMPARED WITH NO TREATMENT FOR PATIENTS WITH THIN ENDOMETRIUM UNDERGOING IVF-EMBRYO TRANSFER (FRESH OR FROZEN)

Outcomes	Anticipated absolute effects <sup>a</sup> (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with no treatment	Risk with aspirin				
Clinical pregnancy rate: cohort studies	733 per 1000	872 per 1000 (755–1000)	RR 1.19 (1.03–1.38)	390 (one observational study)	⊕○○○ Very low <sup>b</sup>	
Clinical pregnancy rate, EMT <8 mm: RCT	308 per 1000	600 per 1000 (240–1000)	RR 1.95 (0.78–4.86)	28 (one RCT)	⊕○○○ Very low <sup>c,d,e</sup>	
Live birth rate, EMT <8 mm: RCT	308 per 1000	462 per 1000 (175–1000)	RR 1.50 (0.57–4.00)	28 (one RCT)	⊕○○○ Very low <sup>c,d,e</sup>	

Patient or population: patients with thin endometrium undergoing IVF-embryo transfer (fresh or frozen).

Intervention: aspirin.

Comparison: no treatment.

EMT, endometrial thickness; RCT, randomized controlled trial; GRADE, Grading of Recommendations, Assessment, Development and Evaluations framework; CI, confidence interval; RR, risk ratio.

<sup>a</sup> The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

<sup>b</sup> Frattarelli et al. (2006) combined data for all adjuvant treatments, not just aspirin, so many confounders.

<sup>c</sup> Not blinded, no placebo.

<sup>d</sup> Only oocyte recipient patients.

<sup>e</sup> Small event size.

Studies included:

Frattarelli, J.L., Miller, B.T., Scott, R.T. 2006. Adjuvant therapy enhances endometrial receptivity in patients undergoing assisted reproduction. *Reprod. Biomed. Online* 12, 722-729.

Weckstein, L.N., Jacobson, A., Galen, D., Hampton, K., Hammel, J., 1997. Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective, randomized study. *Fertil. Steril.* 68, 927-930.

# Sildenafil

- Many case series reported the use of sildenafil for patients with thin endometrium for fresh and frozen IVF embryo transfers. (Sher and Fisch, 2000, 2002; Zinger et al., 2006)
- One small observational study reported a benefit in pregnancy rates (Takasaki et al., 2010)
- One RCT of 80 patients failed to detect a difference in pregnancy rates in patients undergoing frozen embryo transfers. However, the study did show an improvement in endometrial thickness (9.8 mm versus 8 mm;  $P < 0.001$ ) (Dehghani Firouzabadi et al., 2013).

# Sildenafil in Thin ET

## SUMMARY OF FINDINGS: SILDENAFIL CITRATE COMPARED WITH NO TREATMENT FOR PATIENTS WITH THIN ENDOMETRIUM UNDERGOING IVF-EMBRYO TRANSFER (FRESH OR FROZEN)

Outcomes	Anticipated absolute effects <sup>a</sup> (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with no treatment	Risk with silde- nafil citrate				
Clinical pregnancy rate: observational studies	0 per 1000	0 per 1000 (0-0)	RR 11.00 (0.69-174.00)	22 (one observational study)	⊕○○○ Very low <sup>b</sup>	
Endometrial thickness >8 mm: observational studies	100 per 1000	1000 per 1000 (129-1000)	RR 19.40 (1.29-294.00)	22 (one observational study)	⊕⊕○○ Low <sup>c</sup>	
Pregnancy rate: RCT	200 per 1000	325 per 1000 (151-698)	RR 1.625 (0.757-3.489)	80 (one RCT)	⊕○○○ Very low <sup>c,d,e</sup>	

Patient or population: patients with thin endometrium undergoing IVF-embryo transfer (fresh or frozen).

Intervention: sildenafil citrate.

Comparison: no treatment.

GRADE, Grading of Recommendations, Assessment, Development and Evaluations framework; RCT, randomized controlled trial; CI, confidence interval; RR, risk ratio.

<sup>a</sup> The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

<sup>b</sup> Takasaki et al. (2010) compared IVF patients with sildenafil with natural cycle or human menopausal gonadotropins + intrauterine insemination patients as control group.

<sup>c</sup> Not blinded, no allocation concealment.

<sup>d</sup> History of previously poor endometrium was not well defined.

<sup>e</sup> Small sample size in control and intervention groups.

Studies included:

Dehghani Firoozabadi, R., Davar, R., Hojat, F., Mahdavi, M., 2013. Effect of sildenafil citrate on endometrial preparation and outcome of frozen-thawed embryo transfer cycles: a randomized clinical trial. *Iran. J. Reprod. Med.* 11, 151-158.

Takasaki, A., Tamura, H., Miwa, I., Taketani, T., Shimamura, K., Sugino, N., 2010. Endometrial growth and uterine blood flow: a pilot study for improving endometrial thickness in the patients with a thin endometrium. *Fertil. Steril.* 93, 1851-1858.

# Pentoxifylline

- 400 mg/day
- Several case series ([Acharya et al., 2009](#); [Ledee-Bataille et al., 2002](#); [Letur-Konirsch et al., 2002](#); [LeturKonirsch and Delanian, 2003](#)).
- No controlled studies for pentoxifylline.

# Tocopherol and L-Arginine

- Several papers have also evaluated supplements such as vitamins C and E (500 IU/day), and L-arginine (6 g/day) ([Kitaya et al., 2014](#); [Takasaki et al., 2010](#)).
- These studies have been small and poorly controlled.

# G-CSF

- **Case series-** Improved endometrial thickness and pregnancy rate (Gleicher et al., 2011).
- **Subsequent case series-** conflicting results (Check et al., 2014; Kunicki et al., 2014; Lee et al., 2016; Lucena and Moreno-Ortiz, 2013; Tehraninejad et al., 2015)
- **Cohort studies-** G-CSF intrauterine infusion had a thicker endometrium, but no difference was seen in the pregnancy and live birth rates (Kunicki et al., 2017; Eftekhar et al., 2014; Xu et al., 2015).
- **Retrospective cohort study** - an increase in pregnancy rate, but this was not statistically significant (Li et al., 2014)
- **Double-blinded placebo-controlled RCT-** clinical pregnancy rate and mean endometrial thickness were not significantly different in the G-CSF group compared with the control group. However, this study looked at all patients undergoing IVF, not just patients with thin endometrium. (Barad et al., 2014)

# Evaluation of the role G-CSF in thin endometrium

Study	Dose of GCSF	Duration of therapy	Results
Nobert Gleicher et al 2011	1 ml 30 MU (300mcg)	2-7 days before embryo transfer (ET)by ET catheter	Dramatic improvement in endometrial thickness all four patients conceived with one intramural ectopic pregnancy.
Y Kim et al 2012	1 ml 30MU (300mcg)	On the day of hCG injection	Significantly higher endometrial thickness (85% showed improvement), implantation and ongoing pregnancy rate
Maryam Eftekhar 2014	1 ml 30 MU (300mcg)	12 <sup>th</sup> – 13 <sup>th</sup> day of cycle but <b>repeated</b> once more if endometrial thickness below 7 mm within 48 – 72 hours.	No difference in endometrial thickness Chemical pregnancy rate and clinical pregnancy rate were found to be better (39.30%vs, 14.30% & 32.10%vs. 12.00% respectively )

**SUMMARY OF FINDINGS: GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF) COMPARED WITH NO TREATMENT FOR PATIENTS WITH THIN ENDOMETRIUM UNDERGOING IVF-EMBRYO TRANSFER (FRESH OR FROZEN)**

Outcomes	Anticipated absolute effects <sup>a</sup> (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with no treatment	Risk with G-CSF				
Live birth rate: observational studies	129 per 1000	186 per 1000 (86-400)	RR 1.441 (0.669-3.102)	144 (two observational studies)	⊕○○○ Very low <sup>b,c,d</sup>	
Clinical pregnancy rate: observational studies	166 per 1000	278 per 1000 (184-422)	RR 1.678 (1.108-2.540)	332 (four observational studies)	⊕○○○ Very low <sup>b,c,d</sup>	
Clinical pregnancy rate: RCT	235 per 1000	233 per 1000 (128-423)	OR 0.990 (0.545-1.800)	141 (one RCT)	⊕⊕○○ Low <sup>d,e</sup>	

Patient or population: patients with thin endometrium undergoing IVF-embryo transfer (fresh or frozen).

Intervention: G-CSF.

Comparison: no treatment.

GRADE, Grading of Recommendations, Assessment, Development and Evaluations framework; RCT, randomized controlled trial; CI, confidence interval; RR, risk ratio; OR, odds ratio.

<sup>a</sup> The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

<sup>b</sup> In some studies, patients were co-treated with aspirin or sildenafil. Some studies used patient choice to decide if they received G-CSF or not.

<sup>c</sup> Low event rates.

<sup>d</sup> Most studies published in major journals showed beneficial effect of G-CSF, even in small sample sizes.

<sup>e</sup> Looked at all IVF patients, not just patients with thin endometrium.

Studies included:

Barad, D.H., Yu, Y., Kushnir, V.A., Shohat-Tal, A., Lazzaroni, E., Lee, H.J., Gleicher, N., 2014. A randomized clinical trial of endometrial perfusion with granulocyte colony-stimulating factor in in vitro fertilization cycles: impact on endometrial thickness and clinical pregnancy rates. *Fertil. Steril.* 101, 710-715.

Eftekhari, M., Sayadi, M., Arabjehani, F., 2014. Transvaginal perfusion of G-CSF for infertile women with thin endometrium in frozen ET program: a non-randomized clinical trial. *Iran. J. Reprod. Med.* 12, 661-666.

Kunicki, M., Lukaszuk, K., Liss, J., Skowronska, P., Szczyptanska, J., 2017. Granulocyte colony stimulating factor treatment of resistant thin endometrium in women with frozen-thawed blastocyst transfer. *Syst. Biol. Reprod. Med.* 63, 49-57.

Li, Y., Pan, P., Chen, X., Li, L., Li, Y., Yang, D., 2014. Granulocyte colony-stimulating factor administration for infertile women with thin endometrium in frozen embryo transfer program. *Reprod. Sci.* 21, 381-385.

Xu, B., Zhang, Q., Hao, J., Xu, D., Li, Y., 2015. Two protocols to treat thin endometrium with granulocyte colony-stimulating factor during frozen embryo transfer cycles. *Reprod. Biomed. Online* 30, 349-358.

# Safety of G-CSF

- No side effects have been reported with G-CSF intrauterine infusion
- Systemic G-CSF
  - ❑ increased risk of therapy-related myeloid neoplasm, although this risk is deemed to be small ([Lyman et al., 2010](#)).
  - ❑ Sickle cell crisis and multi-organ failure in patients who have used G-CSF with sickle cell syndromes ([Abboud et al., 1998](#); [Adler et al., 2001](#)).
  - ❑ Bone pain ([Kuderer et al., 2007](#))

# Electroacupuncture

- May improve blood flow, reduce the PI in the uterine arteries

**Huang Ho M et al, 2009; Stener Victoran et al, 1996**

# Platelet rich Plasma (PRP)

- Described in patients with thin endometrium resulting from Asherman syndrome ([Aghajanova et al., 2016](#); [Chang et al., 2015](#); [Gargett and Healy, 2011](#); [Nagori et al., 2011](#); [nazari et al., 2016](#); [Santamaria et al., 2016](#); [Singh et al., 2014](#); [Zadehmodarres et al., 2017](#)).
- Preliminary studies are promising for a population which has a poor prognosis and few options for treatment
- Further research and controlled studies are required

# Stem Cell

- Case series ([Gargett et al., 2012](#); [Taylor HS, 2004](#))
- Invasive and expensive

# hCG and GnRH Agonist

- Case series reported endometrial thickness, and pregnancy and live birth rates with the use of HCG in frozen embryo transfers in patients with a history of thin endometrium (Davar et al., 2016; Papanikolaou et al., 2013).
- There have been **no controlled studies on hCG.**
- RCT on the use of adjuvant GnRH agonists at the time of oocyte retrieval and embryo transfer for patients with endometrial thickness- found a **beneficial effect;** however, the **biological plausibility is uncertain and the results have not been replicated.** (Qublan et al., 2008).

# Scratching

- Systematic review of 5 RCTs
- No benefits ([Santamaria et al., 2016](#))

# Canadian Fertility and Andrology Society Guideline, 2019

- In patients with thin endometrium undergoing embryo transfer cycles, **we suggest** **AGAINST** the use of aspirin, vaginal sildenafil, G-CSF, pentoxifylline, HCG, gonadotropin-releasing hormone agonists, platelet-rich plasma or stem cells to improve pregnancy rates
- **Quality of evidence- weak**

# Thin Endometrium in Non IVF

- Most of these studies have been retrospective and small.
- Most studies have **not shown an effect of thin endometrium** on outcomes (Chen et al., 2012; Kolibianakis et al., 2004; Weiss et al., 2017)
- Very low pregnancy rate with endometrial thickness  $\leq 7$  mm (Jeon et al., 2013)
- Prospective study of 168 patients, comparable pregnancy rates in clomiphene citrate cycles for endometrial thickness  $<6$ ,  $6-7.9$  and  $\geq 8$  mm (Kolibianakis et al., 2004)
- Absolute pregnancy and live birth rates are much lower with ovarian stimulation/ IUI compared with IVF, which may account for the lack of effect.

# Counter the antiestrogenic effect of CC

## Effect of estradiol valerate on endometrium thickness during clomiphene citrate-stimulated ovulation

*Aim:* The aim of this study was to examine the effects of estradiol valerate (EV) on the thickness of clomiphene citrate (CC)-stimulated endometrium.

*Material and Methods:* Thirty-four normal ovulatory women were randomized double-blindly into two groups to receive CC 100 mg/day on day 2–6 of the treatment cycle, and either vitamin B (placebo) or EV 6 mg/day on day 10–14 of the cycle. The endometrial thickness, endometrial pattern, numbers of mature follicles, and maximal diameters of preovulatory follicles were evaluated by transvaginal sonographic examination.

*Results:* Thirty women completed both treatment cycles. Two other participants dropped out during the treatment due to side-effects (headache). The average endometrial thickness of the group treated with CC + placebo became slightly thinner when compared to the thickness at the baseline (9.04 vs 9.52 mm;  $P = 0.24$ ). The CC + placebo and the CC + EV resulted in similar endometrial pattern, ovulation day, numbers of mature follicles, and sizes of the leading follicles before ovulation. However, an addition of EV into the CC cycle significantly increased the average endometrial thickness (10.7 mm vs 9.04 mm;  $P < 0.001$ ).

*Conclusions:* We concluded that the addition of 6 mg/day EV following the CC treatment can prevent the endometrial thinning without perturbing folliculogenesis and ovulation.



# Effect of clomiphene citrate on endometrial thickness, ovulation, pregnancy and live birth in anovulatory women: systematic review and meta-analysis

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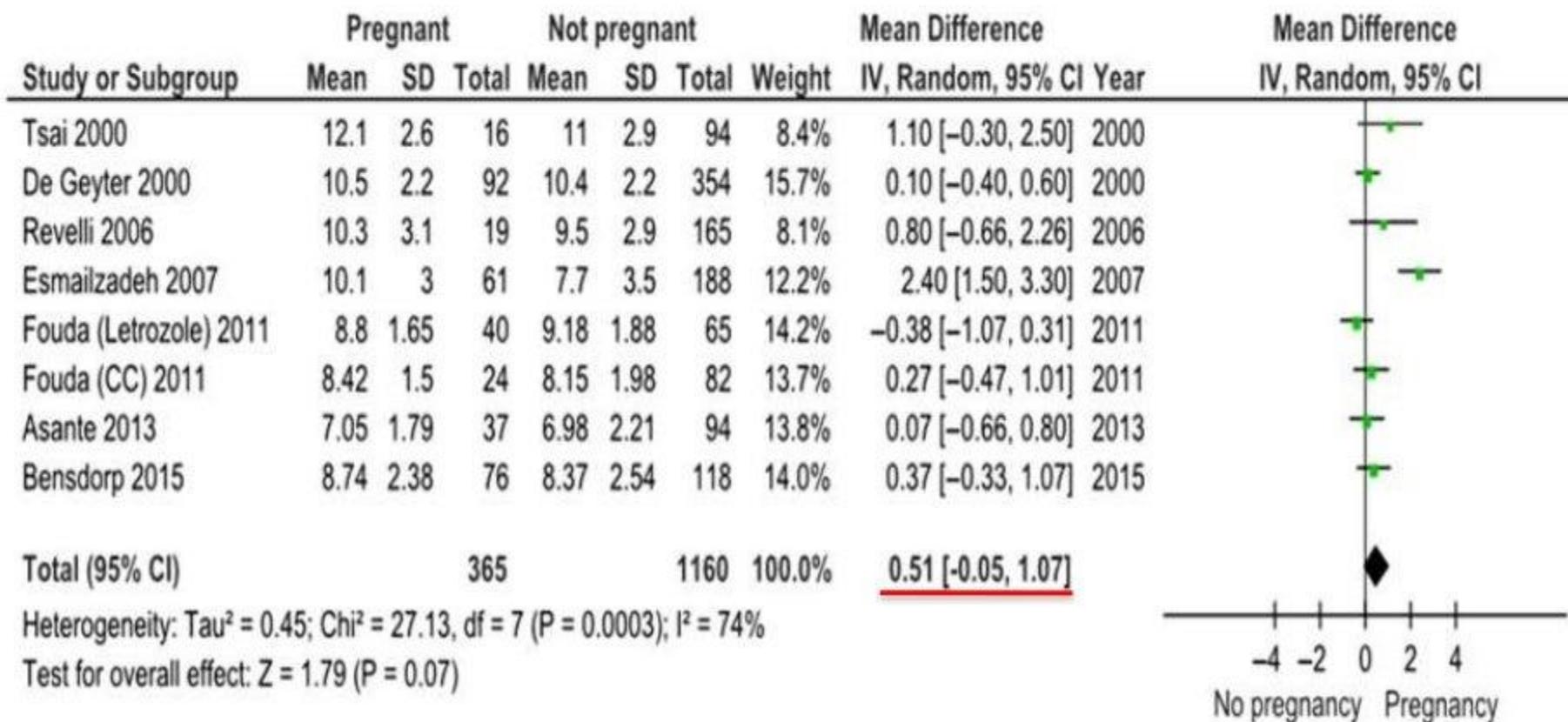
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**KEYWORDS:** anovulation; clomiphene; endometrial thickness; ovulation induction; PCOS

- We retrieved 1718 articles of which 33 RCTs
- In women with WHO group II ovulatory disorders, **ovulation induction with CC might result in lower EMT than other ovulation induction regimens.** Whether *the lower EMT caused the lower pregnancy and live birth rates remains to be elucidated.* Letrozole seems to be beneficial for these women. However, our findings should be interpreted with caution as the quality of evidence was very low.

Weiss, N.S., van Vliet, M.N., Limpens, J., Hompes, P.G.A., Lambalk, C.B., Mochtar, M.H., van der Veen, F., Mol, B.W.J., van Wely, M. Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis. *Hum. Reprod.* 2017; 32: 1009–1018

- Meta-analysis included 1525 women in 7 studies [2 RCT and 5 cohort studies]



### **CC vs Gonadotrophins**

CC- Significantly thinner

EMT (MD:  $-0.33$ , 95% CI:  $-0.64$  to  $-0.01$ ;  $I^2 = 0\%$ ).

### **CC + Gonadotrophins vs Letrozole**

CC+ Gn- Significantly thinner EMT

(MD:  $-0.79$ , 95% CI:  $-1.37$  to  $-0.20$ ;  $I^2 = 84\%$ )

### **CC vs Letrozole**

CC- thinner EMT -no longer statistically significant (MD:  $-0.84$ , 95% CI:  $-1.97$  to  $0.28$ ;  $I^2 = 86\%$ ).

### **Letrozole vs Gonadotrophins**

Letrozole- Significantly thinner

EMT ( MD:  $-1.31$ , 95% CI:  $-2.08$  to  $-0.53$ ;  $I^2 = 0\%$ )

## Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis

N.S. Weiss<sup>1,2</sup>, M.N. van Vliet<sup>1</sup>, J. Limpens<sup>3</sup>, P.G.A. Hompes<sup>2</sup>, C.B. Lambalk<sup>2</sup>, M.H. Mochtar<sup>1</sup>, F. van der Veen<sup>1</sup>, B.W.J. Mol<sup>4</sup>, and M. van Wely<sup>1,\*</sup>

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Submitted on October 5, 2016; resubmitted on December 9, 2016; accepted on January 16, 2017

- Our results suggest that the differences in EMT between women who get pregnant and those that do not are too small to be useful as a tool to guide treatment for the individual woman.
- Therefore, canceling IUI cycles with thin endometrial lining because of the presumed negative effect of the thin EMT—of which we have found no proof—may lead to the very effect one tries to avoid, i.e. **non-conception by the simple and easy to understand mechanism of not inseminating.**



## REVIEW

## Management of thin endometrium in assisted reproduction: a clinical practice guideline from the Canadian Fertility and Andrology Society



- Patients undergoing ovarian stimulation with thin endometrium may be counselled **that the effect on pregnancy rates is unclear.**
- In ovarian stimulation treatment cycles, there is **insufficient evidence to recommend changing stimulation medications** or a specific stimulation medication.
- In ovarian stimulation treatment cycles, there **is insufficient evidence to recommend the use of adjuvants** to improve endometrial thickness or pregnancy rates.

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Article in Press

## Clinical adjuncts in in vitro fertilization: a growing list

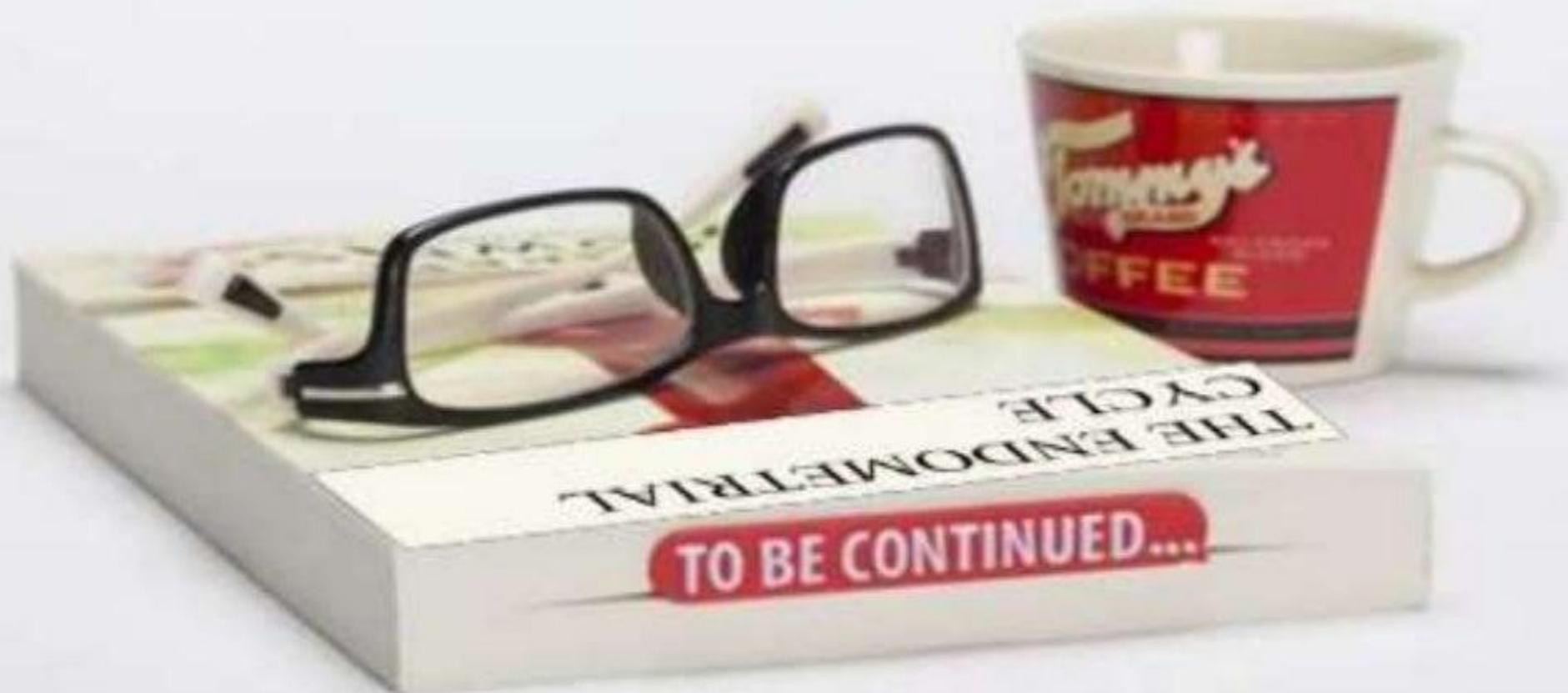
[Mohan S. Kamath](#), M.S.<sup>a,\*</sup>  , [Mariano Mascarenhas](#), M.S.<sup>b</sup>, [Sebastian Franik](#), M.D.<sup>c</sup>, [Emily Liu](#), F.R.A.N.Z.C.O.G.<sup>d</sup>, [Sesh Kamal Sunkara](#), M.D.<sup>e</sup>

DOI: <https://doi.org/10.1016/j.fertnstert.2019.09.019>

 Article Info

- Large, well-designed, randomized trials must be conducted to evaluate the effectiveness and safety of these interventions.

**One of the most challenging problems faced in Rx of infertility is to deal with thin endometrium**



**Neither there are clear cut remedies nor any consensus regarding management of thin endometrium**

# Take Home Message

- Thin endometrium is an infrequent but challenging occurrence in assisted reproduction.
- Balance the prognosis for patients if they proceed with treatment with a thin endometrium or consider alternative treatments.
- Currently, there is minimal evidence to support any specific protocols or adjuvants to significantly improve pregnancy outcomes

# Ovarian stimulation cycles

- Patients undergoing ovarian stimulation with thin endometrium may be counselled that the effect on pregnancy rates and outcomes is unclear.
- In ovarian stimulation treatment cycles, there is insufficient evidence to recommend changing stimulation medications or a specific stimulation medication
- In ovarian stimulation treatment cycles, there is insufficient evidence to recommend the use of adjuvants to improve endometrial thickness or pregnancy rates.

# Fresh IVF-embryo transfer

- In fresh IVF-embryo transfer cycles, patients should be counselled that endometrial thickness  $<8$  may have a negative impact on pregnancy and live birth rates.
- In fresh IVF-embryo transfer cycles, patients with thin endometrium can be offered elective cryopreservation of embryos and transfer in a subsequent cycle.

# Frozen IVF-embryo transfer cycles

- In fresh IVF-embryo transfer cycles, patients should be counselled that endometrial thickness  $<7\text{mm}$  may have a negative impact on pregnancy and live birth rates
- For patients with a history of thin endometrium in ART treatment undergoing endometrial preparation for embryo transfer, there is insufficient evidence that any specific protocol (natural cycle or hormone replacement) for endometrial preparation provides better pregnancy outcomes.

If you can't explain it **simply**, you don't understand it well enough.

– Albert Einstein

*Thank you*

