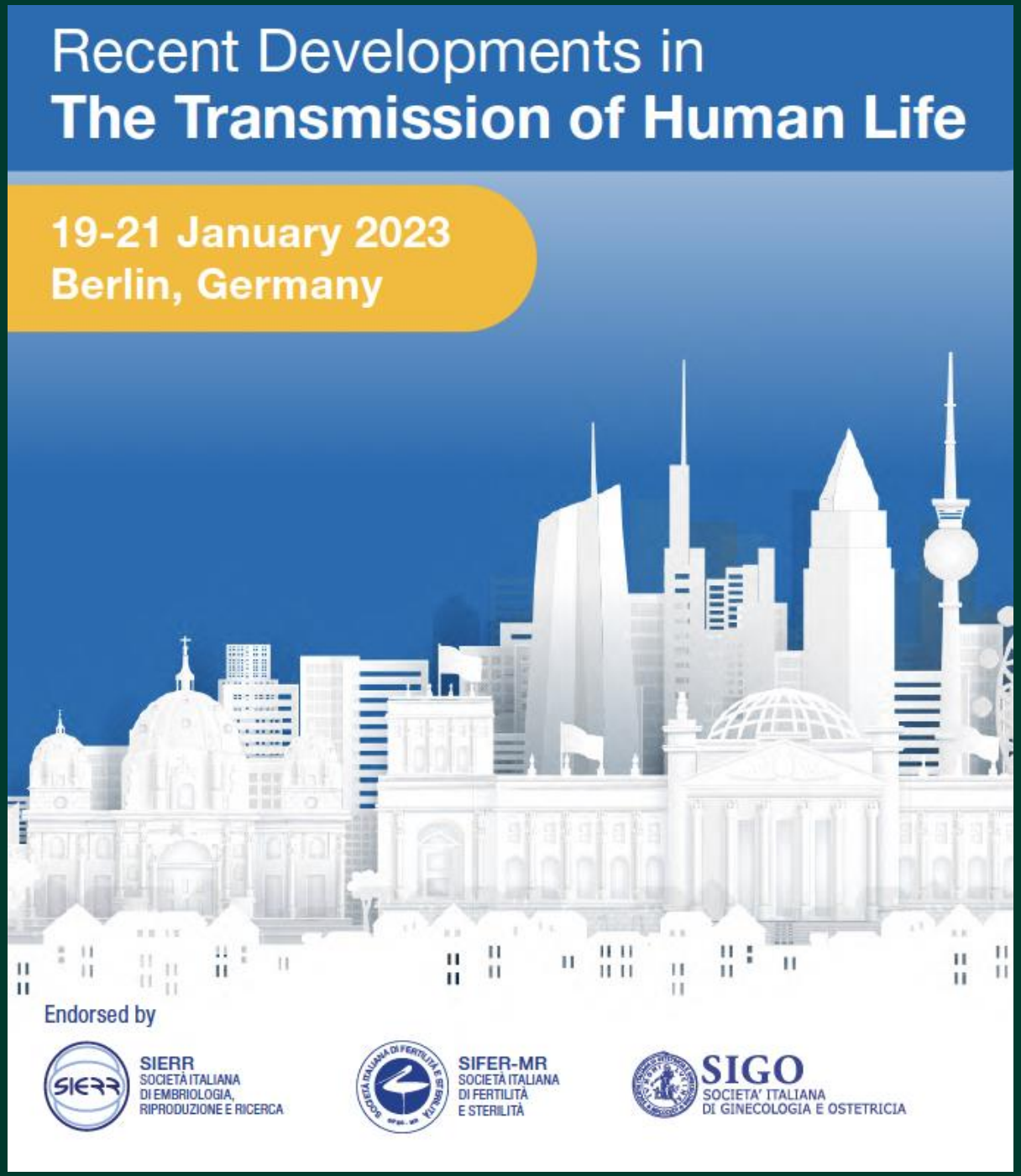

GeneraLife

Endometrial preparation for delayed embryo transfer. Synchronization with: GnRH, Progestins etc. Facts and Opinions

Filippo Maria Ubaldi, MD, PhD

Scientific Director GeneraLife

Centers for Reproductive Medicine

Conflict of interest disclaimer

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- Honoraria or consultation fees:
  Cook, IBSA, Gedeon Richter, Merck, Organon, Ferring

- Stakeholder of GENERA HEALTH CARE

Agenda

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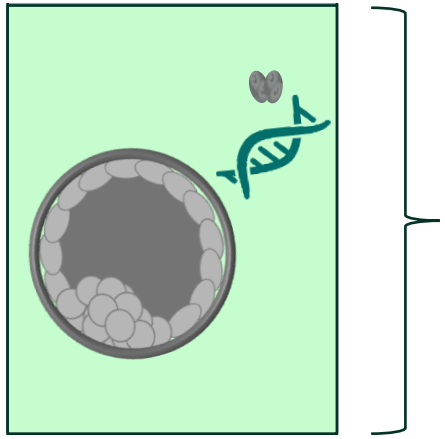
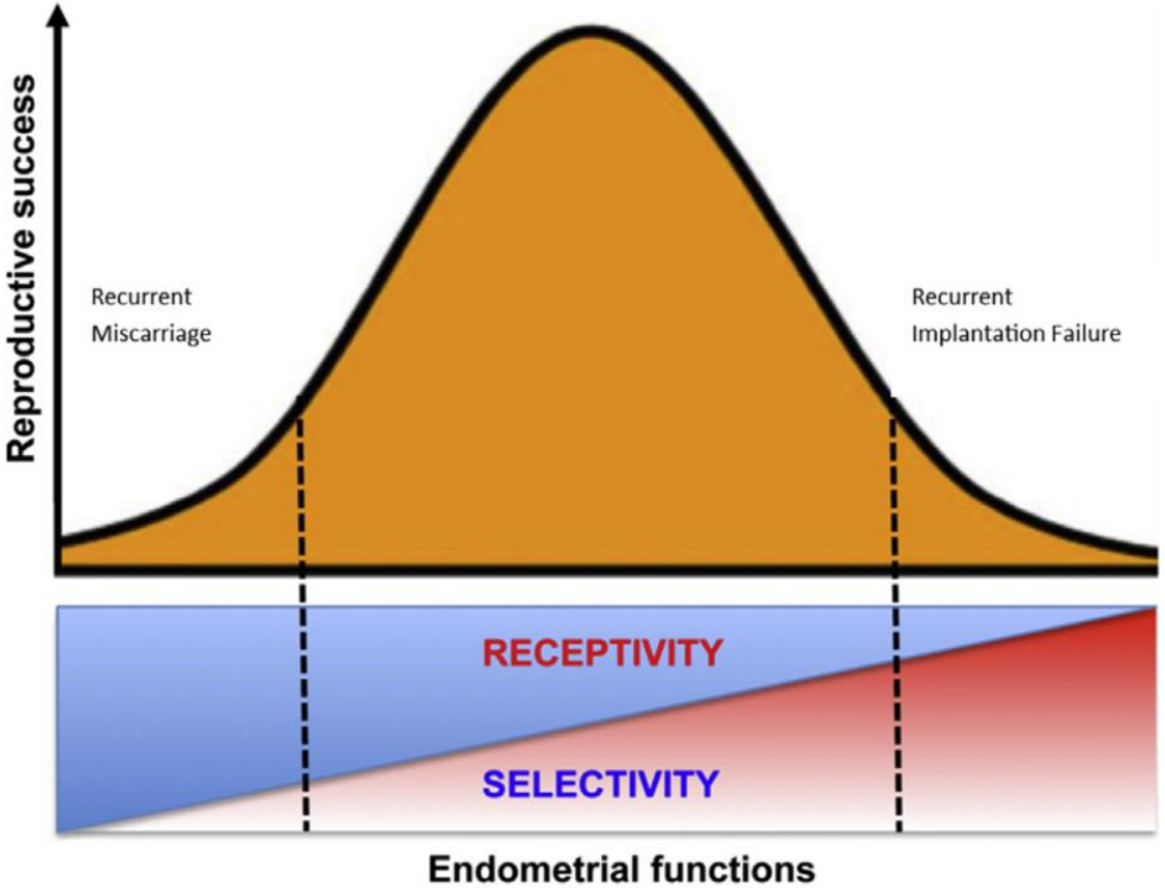
1. Introduction

The “Black Box” of implantation



Implantation rates of euploid blastocyst remain ***around 50%***

Endometrial selectivity/receptivity



Endometrium as a biosensor of embryo quality:

- ***Selectivity:*** recognize and reject embryos with reduced development potential;
- ***Receptivity:*** provide an optimal environment for the embryo to implant.

- To be reproductively successful, the maternal endometrium ***must be receptive as well as selective***, meaning acquiring the ability to mount a secretory response that is tailored to an individual embryo.
- The purpose of a tailored maternal response is either to support further development of high-quality embryos or to trigger early disposal of an unwanted conceptus.

Macklon and Brosens, Biology of Reproduction, 2014

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2. Endometrium in spontaneous and stimulated cycles

Physiology of the Endometrium and Regulation of Menstruation

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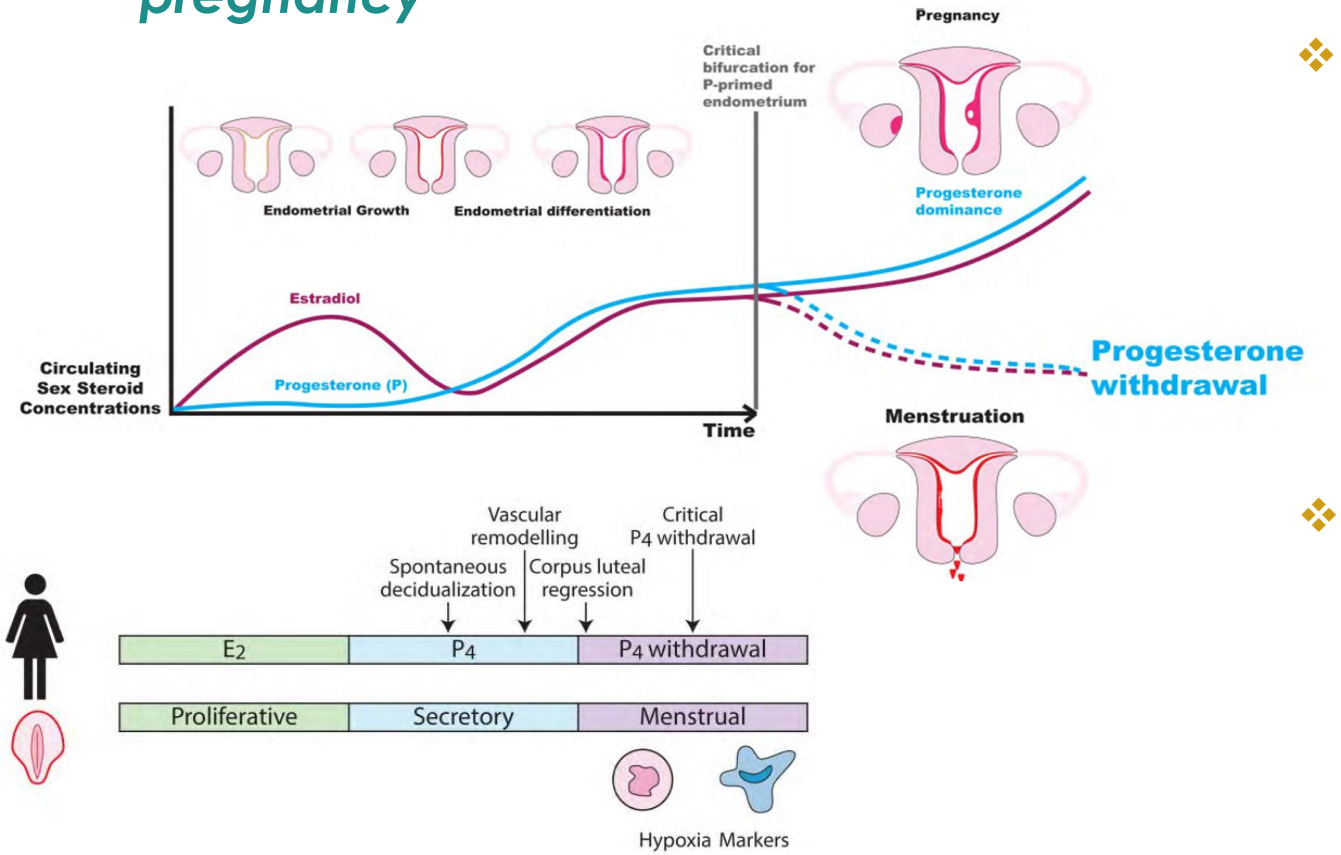
- The physiological functions of the uterine endometrium are ***preparation for implantation maintenance of pregnancy if implantation occurs***, and ***menstruation in the absence of pregnancy***



Critchley HOD et al, Physiol Rev, 2020

- Following ovulation, the endometrium undergoes secretory transformation driven by P_4 in the presence of E_2 achieving a state of receptivity lasting 3-5 days.

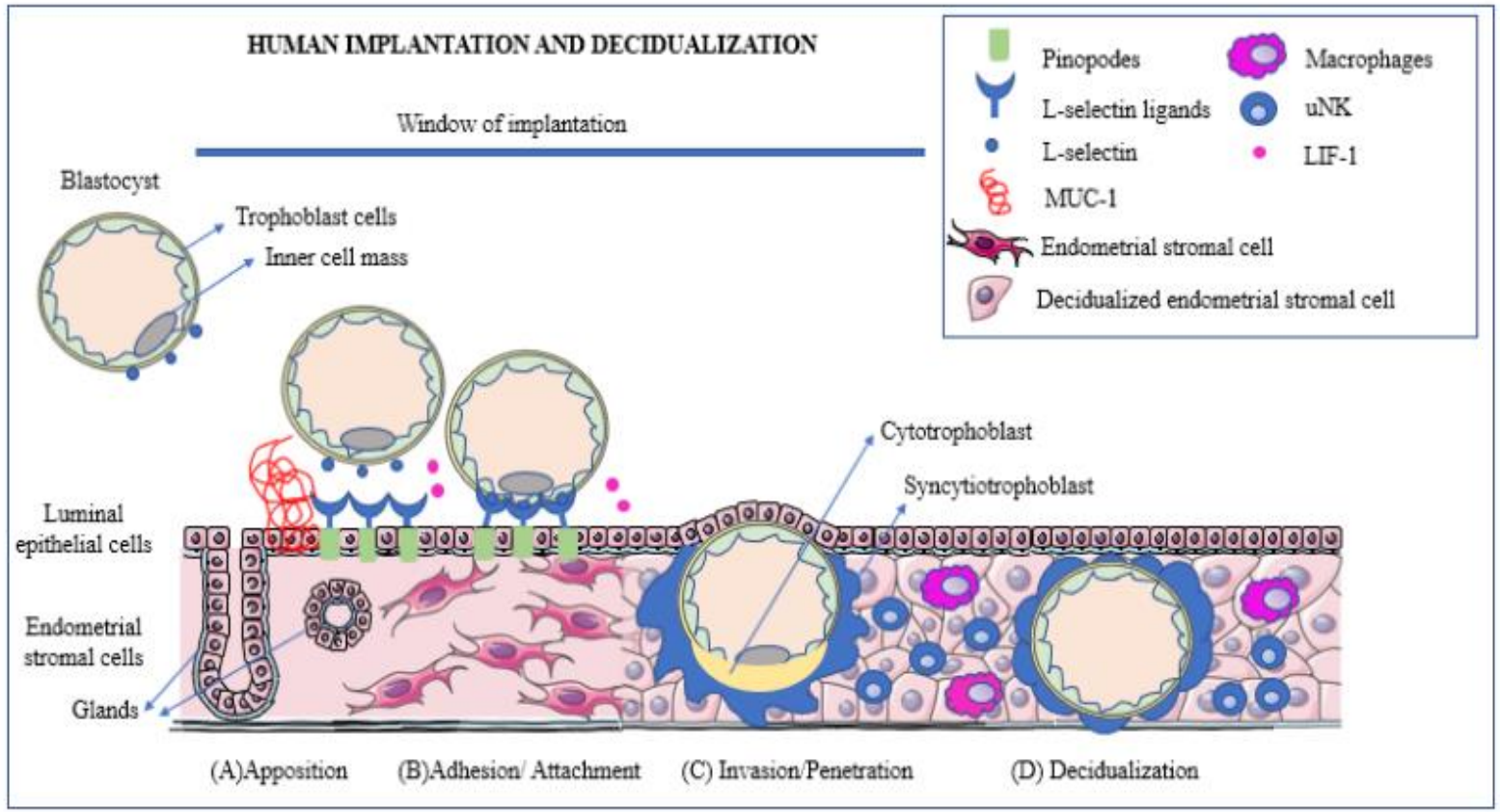
Navot & Bergh 1991

- P_4 induces differentiation of both epithelial and stromal cells (decidualization) and changes in the vasculature, in the extra-cellular matrix and leucocyte content of the tissue.

Salamonsen et al 2009

Dynamics of Human Implantation

During the ***window of implantation***, the endometrium expresses several genes that enable the process of implantation to occur



Ochoa-Bernal, M.A. et al, Int. J. Mol. Sci, 2020

Implantation could be divided into different phases: ***apposition, adhesion /attachment, invasion/penetration and immune regulation***

Once implantation is initiated and the embryo breaches the luminal epithelium, ***the stromal cells surrounding the embryo transform into decidualized cells***

Controlled Ovarian Stimulation (COS) alters Endometrial Gene Expression Profiles

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Supraphysiological concentrations of E_2 and P can dramatically impact the timing of endometrial development and the achievement of receptivity

Fauser and Devroey, Trends Endocrinol Metab, 2003

Modifications of endometrial receptor dynamics:

- glandular and stromal PGRs expression is reduced in the periovulatory, and luteal phases compared with natural cycles
- E2 receptors expression data are conflicting: overall decrease and glandular upregulation have been described

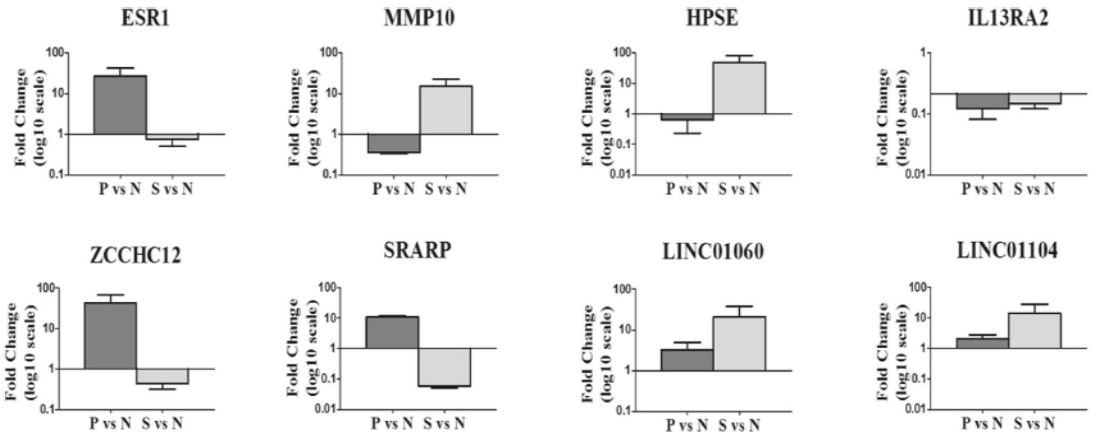
Noci et al, Eur J Obstet Gynecol Reprod Biol, 1997; Bourgain et al, Fertil Steril, 2002

Journal of Assisted Reproduction and Genetics (2020) 37:21–32
https://doi.org/10.1007/s10815-019-01616-5

ASSISTED REPRODUCTION TECHNOLOGIES

Transcriptome sequencing of endometrium revealed alterations in mRNAs and lncRNAs after ovarian stimulation

Lingxiu Li[1] · Peng Wang[1] · Shan Liu[1] · Xueyan Bai[1] · Binbin Zou[2] · Yuan Li[1]



Supraphysiological E_2 levels from ovarian stimulation had a ***marked impact on endometrial transcriptome*** profiles and ***may result in a shift of the WOI***

Higher follicular phase serum P_4 alters endometrial receptivity

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Journal of Assisted Reproduction and Genetics (2020) 37:33–43
https://doi.org/10.1007/s10815-019-01623-6

REPRODUCTIVE PHYSIOLOGY AND DISEASE

Effects of high progesterone in in-vitro fertilization cycle on DNA methylation and gene expression of adhesion molecules on endometrium during implantation window

Yujing Xiong[1,2,3] · Linli Hu[1] · Tao Zhang[3] · Mengying Wang[4] · Hui Xu[3] · Tin Chiu Li[3] · Yingpu Sun · Chi Chiu Wang[3,5,6]

N = 40

- high P group **(HP)** (P≥1.5 ng/mL, 20 patients)
- normal P group **(NP)** (P<1.5 ng/mL, 20 patients)

→ Endometrial biopsy 7 days after hCG administration

Conclusions:

DNA hypermethylation and low expression of adhesion molecules on endometrium were associated with high P during implantation window, which may contribute to the underlying epigenetic mechanism in the failure of IVF treatment

Human Reproduction, Vol.26, No.7 pp. 1813–1825, 2011
Advanced Access publication on May 2, 2011 doi:10.1093/humrep/der126

human reproduction ORIGINAL ARTICLE *Infertility*

Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis

E. Labarta[1,*], J.A. Martínez-Conejero[2], P. Alamá[1], J.A. Horcajadas[2], A. Pellicer[1], C. Simón[1,2], and E. Bosch[1]

Elevated P levels on the day of hCG administration can induce significant alterations in the gene expression profile of the endometrium

↓

140 genes significantly dysregulated related to cell adhesion,developmental processes, the immune system and others, which are all required for normal endometrial function development.

Controlled ovarian hyperstimulation COH and the window of implantation

The WOI is advanced during COH, but the magnitude of anticipation may vary

- In normoresponders, the anticipation would be modest, allowing normal implantation of the cleavage-stage embryos, interfering with the implantation of the blastocysts

(From: Viganò P. et al., 2020)

- In cycles with hyper-response an early rise of P and in those responding more to COH, the anticipation may be more marked and the detrimental effects would become evident also at cleavage stage. Of note, ovarian hyper-response and early P rise commonly coexist

(From: Viganò P. et al., 2020)

Fatemi, H.M. et al, Curr Opin Obstet Gynecol, 2015

COH affects vaginal and endometrial microbiota in IVF cycles

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Journal of Assisted Reproduction and Genetics (2020) 37:2315–2326
https://doi.org/10.1007/s10815-020-01878-4

ASSISTED REPRODUCTION TECHNOLOGIES

Check for updates

Controlled ovarian stimulation and progesterone supplementation affect vaginal and endometrial microbiota in IVF cycles: a pilot study

Andrea Carosso[1] · Alberto Revelli[1] · Gianluca Gennarelli[1] · Stefano Canosa[1] · Stefano Cosma[1] · Fulvio Borella[1] · Annalisa Tancredi[1] · Carlotta Paschero[1] · Lara Boatti[2] · Elisa Zanotto[3] · Francesca Sidoti[3] · Paolo Bottino[3] ·

N = 15

pre-COH Vaginal and endometrial microbiota analysis

post-COH Vaginal and endometrial microbiota analysis

- Vaginal swabs and endometrial biopsies
- NGS analysis

10 most abundant bacteria in vaginal and endometrial microbiota pre-COH and post-COH

Bacterial genus	Vagina pre-COS	Vagina post-COS	Endometrium pre-COS	Endometrium post-COS
Lactobacillus	71.5 ± 40.6	61.1 ± 44.2	27.4 ± 34.5	25.0 ± 29.9
Gardnerella	10.0 ± 19.2	6.5 ± 10.2	6.1 ± 13.5	10.1 ± 15.2
Prevotella	3.5 ± 8.9	12.0 ± 19.4	3.4 ± 9.5	4.7 ± 7.4*
Propionibacterium	0.1 ± 0.3	0.3 ± 0.6	11.5 ± 13.5	10.2 ± 8.9
Pseudomonas	0.0 ± 0.1	0.0 ± 0.1	10.3 ± 16.7	7.8 ± 12.7
Atopobium	5.7 ± 10.6	5.6 ± 9.4	0.7 ± 1.6	5.8 ± 12.0*
Delftia	0.5 ± 1.7	0.1 ± 0.3	6.0 ± 7.9	5.1 ± 7.7
Pelomonas	0.2 ± 0.7	0.1 ± 0.1	5.5 ± 5.4	5.4 ± 5.0
Veillonella	2.5 ± 6.7	2.8 ± 6.2	2.3 ± 6.2	1.6 ± 4.2
Escherichia coli/Shigella spp.	1.4 ± 5.6	2.0 ± 7.8	2.5 ± 8.8	1.1 ± 2.7

Values are expressed as percentage ± SD
* $p < 0.05$ pre-COS vs. post-COS

Conclusions:

"COS and P supplementation significantly change the composition of vaginal and endometrial microbiota. The greater instability could affect both endometrial receptivity and placentation. If these findings are confirmed, they may provide a further reason to encourage the freeze-all strategy".

Carosso, J Assist Reprod Genet, 2020

Agenda

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3. Endometrial preparation in frozen ET cycles

The development of embryo and endometrium should be synchronized

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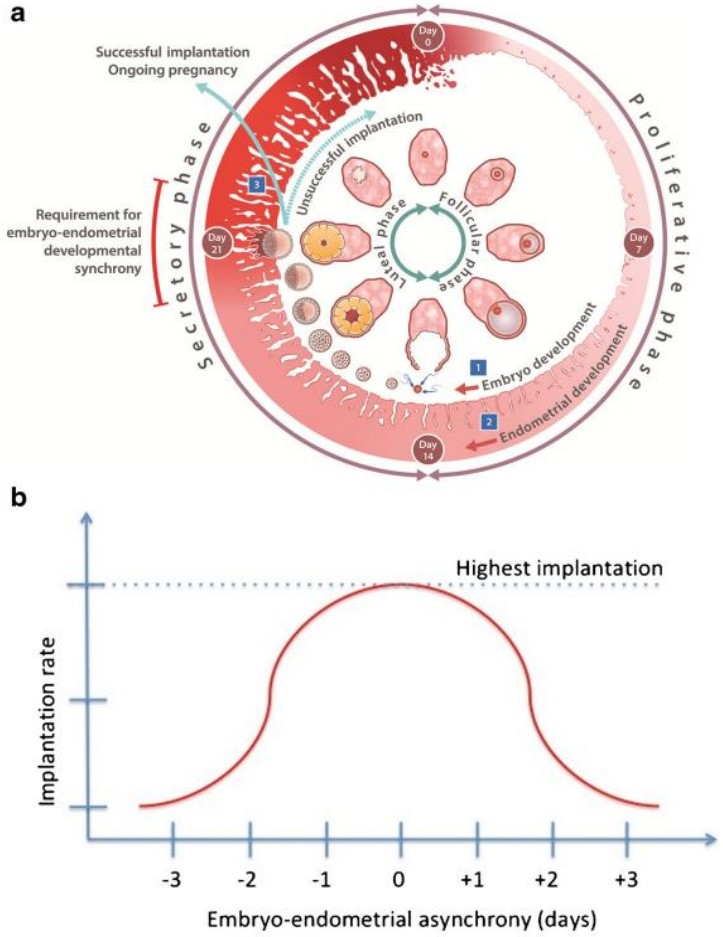
A ***functional embryo***, a ***receptive endometrium*** and a ***synchrony*** between the ***embryo and the endometrium*** are the three pre-requisites for successful implantation



Stimulated cycle

- Cycles stimulated with GN and ovulation induced with hCG

Natural cycle

- Spontaneous LH surge (NC FET)
- hCG administ. (modified-NC FET)

Artificial cycle

- Exogenous E2 and P (HR FET) with or without GnRH-a co-treatment

Wan-Tinn Teh et al, JARG, 2016

Cycles stimulated with gonadotropins and ovulation induced with hCG

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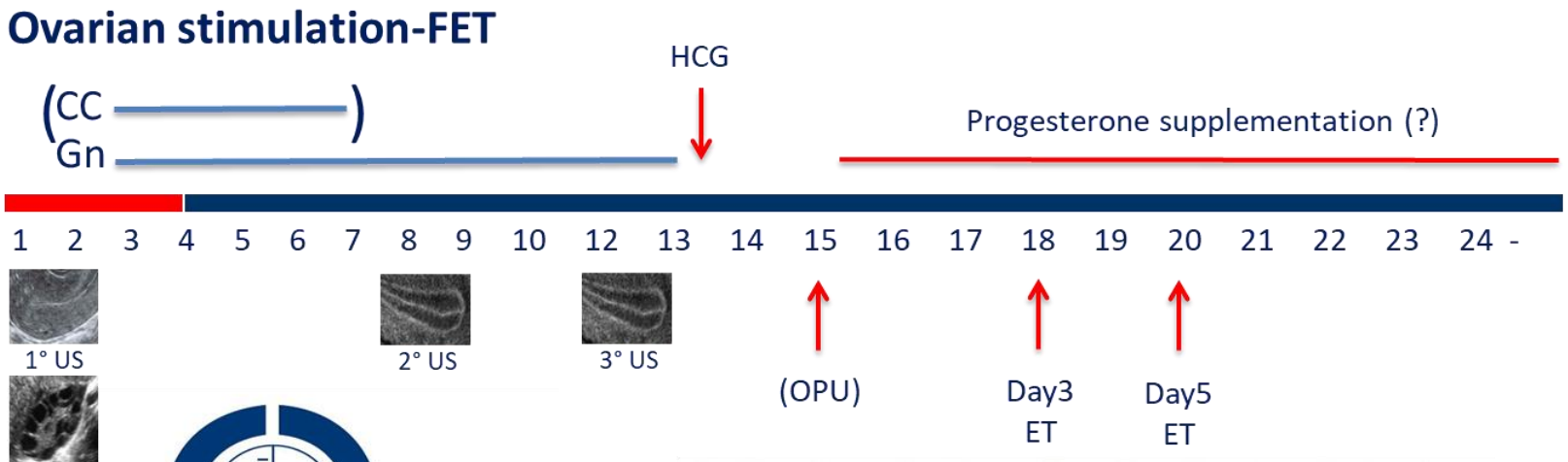

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Cycle regimens for frozen-thawed embryo transfer (Review)

Ghobara T, Vanderkerchove P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

Analysis 3.1. Comparison 3 Oestrogen and progesterone FET versus FSH ovulation induction FET, Outcome 1 Clinical pregnancy rate.

Review: Cycle regimens for frozen-thawed embryo transfer

Comparison: 3 Oestrogen and progesterone FET versus FSH ovulation induction FET

Outcome: 1 Clinical pregnancy rate

Study or subgroup	FSH n/N	O + P n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Wright 2006	11/100	12/94		100.0 %	0.84 [0.35, 2.02]
Total (95% CI)	**100**	**94**		**100.0 %**	**0.84 [0.35, 2.02]**

Total events: 11 (FSH), 12 (O + P)

Heterogeneity: not applicable

Test for overall effect: Z = 0.38 (P = 0.70)

0.1 0.2 0.5 1 2 5 10

Programmed cycles (HR) vs stimulated cycles (with FSH, letrozole or clomiphene citrate)

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Intervention: **Stimulated cycle**

Comparison: **Programmed cycle**

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Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with programmed	Risk with Stimulated cycle				
Live birth rate	240 per 1000	285 per 1000 (134 to 507)	OR 1.26 (0.49 to 3.26)	100 (1 RCT)	⊕⊝⊝⊝ VERY LOW [a b]	Letrozole stimulation versus programmed cycle
Clinical pregnancy rate	191 per 1000	278 per 1000 (210 to 360)	OR 1.63 (1.12 to 2.38)	656 (5 RCTs)	⊕⊕⊝⊝ LOW [a c]	
Miscarriage rate	87 per 1000	70 per 1000 (33 to 140)	OR 0.79 (0.36 to 1.71)	355 (3 RCTs)	⊕⊝⊝⊝ VERY LOW [a b]	
Multiple pregnancy rate						Not reported in any study
Cycle cancellation rate						Not reported in any study
Endometrial thickness (mm)	The mean endometrial thickness (mm) was 8.7 mm	MD -0.05 mm (-0.19 lower to 0.10 higher)	-	362 (2 RCTs)	⊕⊕⊝⊝ LOW [a c]	Letrozole stimulation versus programmed cycle
Other adverse effects						Not reported in any study

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

LBR:

Very low-quality evidence

→ *No differences*

CPR:

Low-quality evidence

→ *Improved CLR*

MR:

Very low-quality evidence

→ *No differences*

Glujovsky et al., Cochrane Library, 2020

Natural or Modified Natural Cycle and HR for endometrial preparation in FRET cycles

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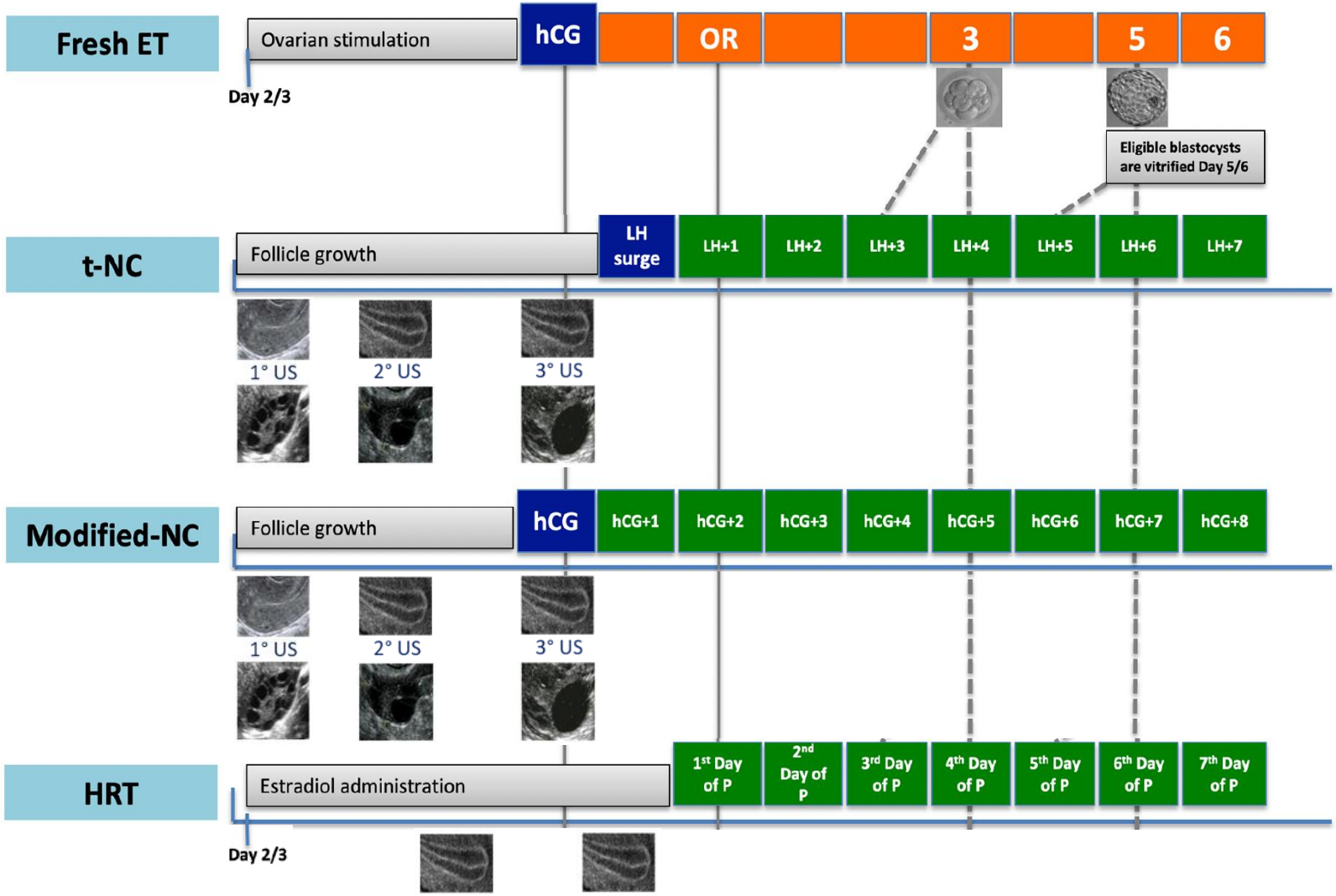


- Stimulated cycles for Fresh ET

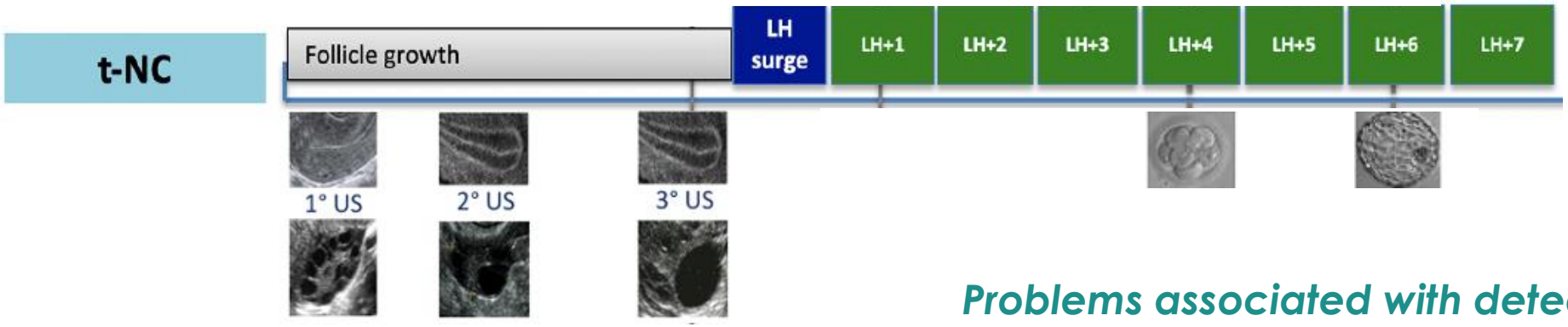
- t-NC with LP support
- t-NC without LP support

- Modified-NC with LP support
- Modified-NC without LP support

- HRT with GnRH-a suppression
- HRT without GnRH-a suppression

Modified from Mumusoglu et al., FENDO, 2021

True-NC for endometrial preparation in FRET cycles



Pregnancy rates are closely dependent on timely identification of ovulation and calculation of endometrial receptivity

(Harper, Baillieres Clin Obstet Gynaecol, 1992; Tabibzadeh, Mol Hum Reprod, 1998)

LH monitoring in either blood or urine

Problems associated with detection of spontaneous LH surge:

a. Variation in time of its occurence between cycles and between patients *Park et al, Fertil Steril, 2007*
b. At least daily determination, better twice a day *Miller and Soules, Obstet Gynecol, 1996*
c. Large variation in thresholds of LH in urine kits and risk of up to 30% of false negative testing *Guermandi et al, Obstet Gynecol, 2001; O'Connor, Hum Reprod, 2006*
d. Risk of unexpected ovulation and difficulty in planning thawing and transfer with cycle cancellation

Modified Natural Cycle for endometrial preparation in FRET cycles

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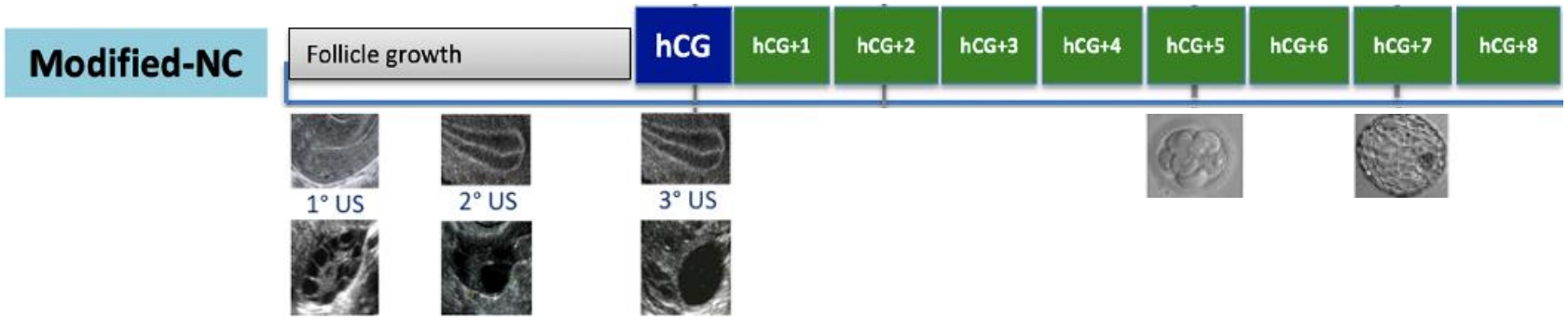

HCG triggering of ovulation to overcome LH monitoring:

a. no LH monitoring
b. 2-3 ultrasound evaluations of the dominant follicle
c. HCG administered when follicle is 17-18 mm
d. final oocyte maturation and ovulation will take place 36-38 h later

Modified NC and NC-FET: is the luteal phase supplementation needed?

True-NC and M-NC-FET: luteal phase supplementation?

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

No luteal support (RCT)

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

TABLE 3

Treatment outcomes in spontaneous LH and hCG group.

	Spontaneous LH (n = 61)	hCG group (n = 63)	Difference, % (95% CI)	*P* value
Ongoing pregnancy rate–ET (%)	31.1 (19)	14.3 (9)	16.9 (2.1–30.9)	.025
Miscarriage rate–ET (%)	0 (0)	3.2 (2)	−3.2 (−10.9 to 3.2)	NS
Biochemical rate–ET (%)	3.3 (2)	3.2 (2)	0.1 (−7.9 to 8.3)	NS
Positive hCG–ET(%)	34.4 (21)	20.6 (13)	13.8 (−1.9 to 28.7)	NS

Note: CI = confidence interval; NS = not significant.

Fatemi. Natural cycle vs. hCG induced for frozen ET. Fertil Steril 2010.

Conclusion(s): The results suggest the superiority of the natural cycle as compared with the natural cycle controlled by hCG administration in cryothawed ET cycles. (Fertil Steril® 2010;94:2054–8. ©2010 by American Society for Reproductive Medicine.)

True-NC and M-FET: luteal phase supplementation?

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Luteal phase progesterone increases live birth rate after frozen embryo transfer

Luteal support (RCT)

Kerstin Bjuresten, B.S.,[a] *Britt-Marie Landgren, M.D., Ph.D.,*[a] *Outi Hovatta, M.D., Ph.D.,*[a] *and Anneli Stavreus-Evers, Ph.D.*[b]

	Progesterone	No progesterone	*P* value
No. of transfers	n = 219	n = 216	.8921
No. of embryos transferred	n = 290	n = 293	.9067
No. of embryos transferred (mean)	n = 1.32	n = 1.36	—
No. of single embryo transfers	n = 148	n = 139	.5423
No. of transfers with good-quality embryos	n = 164	n = 178	.3706
No. of transfers with lower-quality embryos	n = 126	n = 116	.3706
No. of blastocyst transfers	n = 3	n = 9	.1497
No. of IVF transfers	n = 110	n = 105	.7728
No. of ICSI embryos	n = 109	n = 112	.7728
Positive hCG rate	0.35 (76 of 219)	0.28 (60 of 216)	.1458
Miscarriage rate	0.03 (7 of 219)	0.03 (6 of 216)	.7977
Clinical pregnancy rate	0.32 (69 of 219)	0.25 (54 of 216)	.1614
Clinical abortion rate	0.02 (4 of 219)	0.05 (10 of 216)	.1105
Live birth rate (at least one live infant)	0.30 (65 of 219)	0.20 (44 of 216)	.0272*

Result(s): Live birth rate were significantly greater in women receiving vaginal progesterone as luteal phase support after frozen–thawed embryo transfer in natural cycles compared with those who did not take progesterone. There were no differences in biochemical pregnancy rate, pregnancy rate, or spontaneous abortion rate.

Conclusion(s): Progesterone supplementation improves live birth rate after embryo transfer in natural cycles.
(Fertil Steril® 2011;95:534–7. ©2011 by American Society for Reproductive Medicine.)

True-NC and M-NC-FET: luteal phase supplementation?

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Human Reproduction Update, Vol.19, No.5 pp. 458–470, 2013
Advanced Access publication on July 2, 2013 doi:10.1093/humupd/dmt030

human reproduction update

What is the optimal means of preparing the endometrium in frozen–thawed embryo transfer cycles? A systematic review and meta-analysis

Eva R. Groenewoud[1,*], Astrid E.P. Cantineau[1], Boudewijn J. Kollen[2], Nick S. Macklon[3], and Ben J. Cohlen[4]

"Based on the conflicting results of the previously mentioned studies we conclude that currently there is too little evidence supporting a positive effect of luteal phase support in patients undergoing t-NC-FET.

In modified NC, luteal phase support is strongly suggested"

Endometrial synchronization for Embryo Transfer

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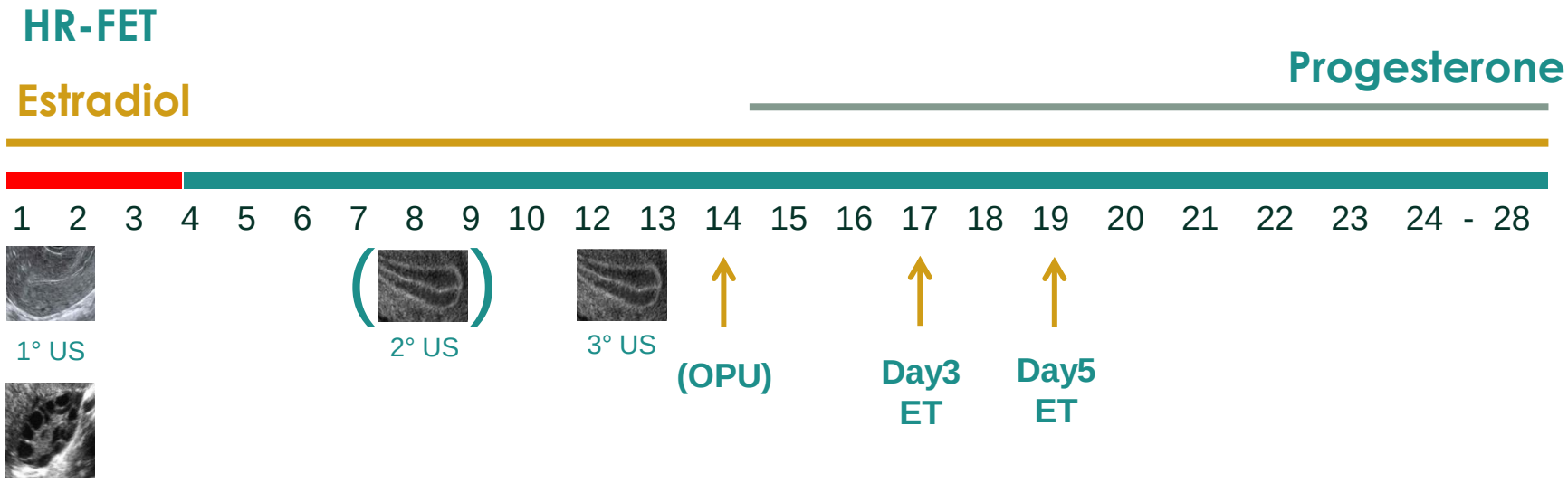

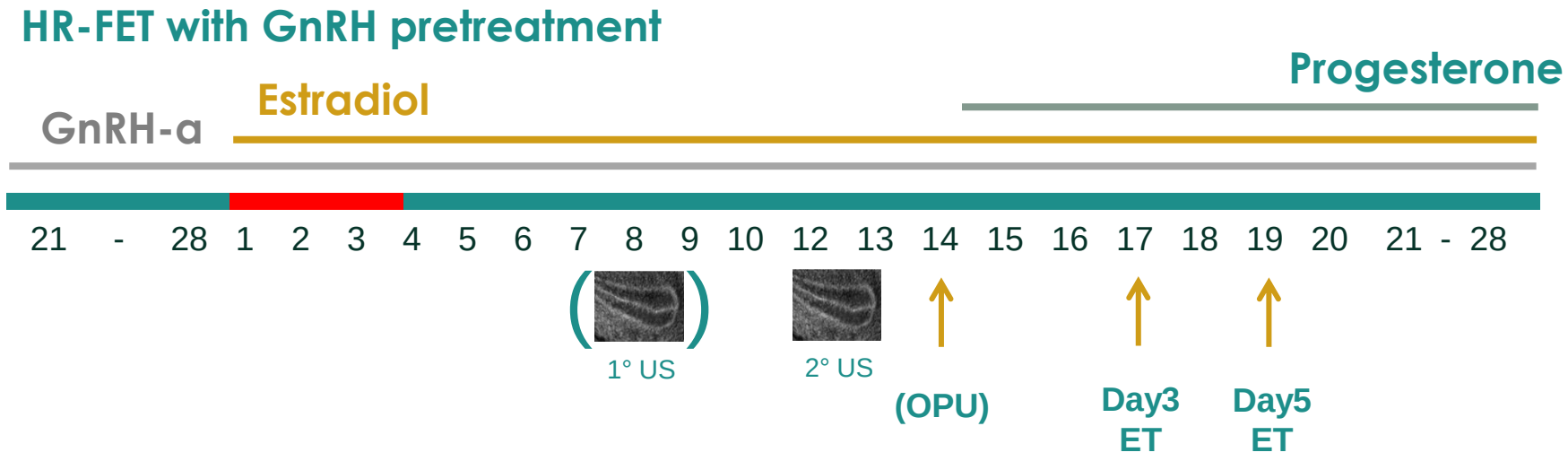

Endometrial synchronization for Embryo Transfer

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HR-FET** with or without GnRH vs **t-NC or M-NC FET

Cons

- *medication needed* ⟹ *less "physiological"*

Pros

- *cycles easier to plan making it popular among many doctors*

Is anyone of these approaches superior to the other

?

Programmed cycles (HR) versus natural cycles

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Intervention: Natural cycle
Comparison: Programmed cycle

} 6 RCT — 830 NC cycles / 860 HR cycles

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Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with programmed cycle	Risk with Natural cycle				
Live birth rate	233 per 1000	228 per 1000 (184 to 280)	OR 0.97 (0.74 to 1.28)	1285 (4 RCTs)	⊕⊝⊝⊝ VERY LOW [a b c]	
Clinical pregnancy rate	347 per 1000	296 per 1000 (248 to 350)	OR 0.79 (0.62 to 1.01)	1249 (5 RCTs)	⊕⊝⊝⊝ VERY LOW [a b d]	
Miscarriage rate	50 per 1000	32 per 1000 (13 to 82)	OR 0.64 (0.25 to 1.63)	485 (3 RCTs)	⊕⊝⊝⊝ VERY LOW [a e]	
Multiple pregnancy rate						Not reported in any study
Cycle cancellation rate	365 per 1000	256 per 1000 (202 to 320)	OR 0.60 (0.44 to 0.82)	734 (1 RCT)	⊕⊕⊕⊝ MODERATE [b]	
Endometrial thickness (mm)	The mean difference endometrial thickness (mm) was 0.42	MD 0.22 higher (0.25 lower to 0.69 higher)	-	485 (3 RCTs)	⊕⊕⊝⊝ LOW [a d]	
Other adverse effects						Not reported in any study

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

LBR:
Very low-quality evidence
→ *No differences*

CPR:
Very low-quality evidence
→ *No differences*

MR:
Very low-quality evidence
→ *No differences*

Glujovsky et al., Cochrane Library, 2020

NC and M-NC cycles vs HR cycle. Systematic review and network meta-analysis – Live birth rate

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Journal of Assisted Reproduction and Genetics (2021) 38:1913–1926
https://doi.org/10.1007/s10815-021-02125-0

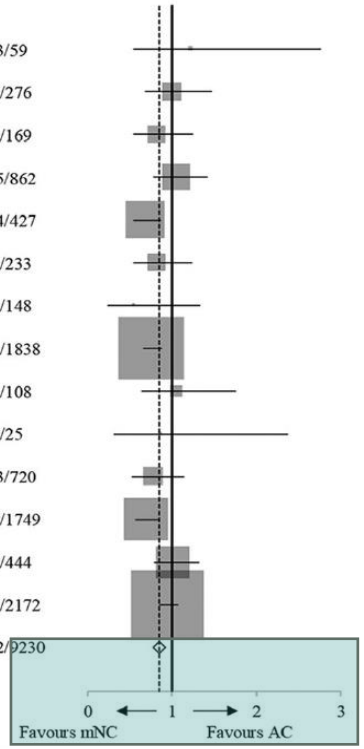
REVIEW

Endometrial preparation for frozen–thawed embryo transfer cycles: a systematic review and network meta-analysis

Hanglin Wu[1] · Ping Zhou[2] · Xiaona Lin[2] · Shasha Wang[2] · Songying Zhang[2]

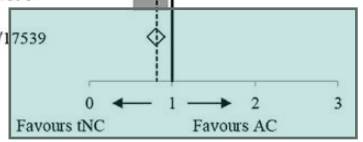
Study	No of events/total AC	No of events/total mNC	Odds ratio (95% CI)	Weight (%)
Al Krayem 2018	18/70	13/59	1.22 (0.54, 2.77)	1.4
An 2020	76/338	62/276	1.00 (0.68, 1.47)	5.2
Cerrillo 2017	78/280	54/169	0.82 (0.54, 1.25)	4.5
Givens 2009	77/262	245/862	1.05 (0.77, 1.42)	7.4
Guan 2016	271/794	184/427	0.68 (0.54, 0.87)	10.0
Guo 2016	59/167	93/233	0.82 (0.54, 1.24)	4.6
Hancke 2012	7/55	31/148	0.55 (0.23, 1.34)	1.2
Huang 2018	524/1666	690/1838	0.76 (0.66, 0.88)	16.9
Kalem 2018	67/224	31/108	1.06 (0.64, 1.76)	3.3
Kang 2018	16/49	9/25	0.86 (0.31, 2.37)	0.9
Kawamura 2007	42/136	263/720	0.78 (0.52, 1.15)	5.0
Levi Setti 2020	151/585	587/1749	0.69 (0.56, 0.85)	11.8
Tomas 2012	500/2858	77/444	1.01 (0.78, 1.32)	9.0
Ye 2020	978/2293	953/2172	0.95 (0.85, 1.07)	18.8
Total (95% CI)	2864/9777	3292/9230	0.85 (0.77, 0.93)	100

Random effects analysis, Heterogeneity: I^2=33.5%



Study	No of events/total AC	No of events/total tNC	Odds ratio (95% CI)	Weight (%)
Al Krayem 2018	18/70	22/80	0.91 (0.44, 1.89)	2.8
Cardellicchio 2017	17/55	67/196	0.86 (0.45, 1.64)	3.3
Cardenas Armas 2019	240/934	50/163	0.78 (0.54, 1.12)	5.9
Cerrillo 2017	78/280	40/121	0.78 (0.49, 1.24)	4.9
Dor 1991	2/42	7/56	0.35 (0.07, 1.78)	0.7
El Bahja 2013	2/24	17/132	0.61 (0.13, 2.85)	0.8
Jing 2019	1025/2611	3872/8425	0.76 (0.69, 0.83)	9.2
Levi Setti 2020	151/585	135/561	1.10 (0.84, 1.44)	7.2
Loh 1999	6/161	8/51	0.21 (0.07, 0.63)	1.4
Melnick 2017	18/48	41/65	0.35 (0.16, 0.76)	2.6
Pan 2020	110/225	375/683	0.79 (0.58, 1.06)	6.7
Tomas 2012	500/2858	211/1168	0.96 (0.81, 1.15)	8.3
Veleva 2013	37/312	268/1276	0.51 (0.35, 0.73)	5.9
Wang 2019	120/315	60/166	1.09 (0.74, 1.61)	5.6
Zheng 2015	1274/2506	276/654	1.42 (1.19, 1.69)	8.4
Mubarak 2019	265/1531	279/1221	0.71 (0.59, 0.85)	8.2
Pakes 2020	188/997	496/2033	0.72 (0.60, 0.87)	8.2
Pang 2020	19/76	25/98	0.97 (0.49, 1.94)	3.0
Wang 2020	126/396	150/390	0.75 (0.56, 1.00)	6.9
Total (95% CI)	4196/14026	6399/17539	0.81 (0.70, 0.93)	100

Random effects analysis, Heterogeneity: I^2=75.6%



Hormonal Replacement vs Modified-NC for endometrial preparation in frozen euploid blastocyst transfers: *retrospective study - GeneraLife*

GeneraLife
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	Artificial cycle *LBR per euploid blastocyst SET*	**Modified natural cycle** *LBR per euploid blastocyst SET*
AA - day5	282/497, 56.7%	169/277, 61.0%
AA - day6	174/390, 44.6%	101/195, 51.8%
AA - day7	5/16, 31.3%	2/8, 25.0%
AB, BA - day 5	20/38, 52.6%	11/26, 42.3%
AB, BA - day 6	33/85, 38.8%	13/33, 39.4%
AB, BA - day 7	3/12, 25.0%	0/6, 0%
BB, AC, CA - day5	9/21, 42.9%	12/22, 54.5%
BB, AC, CA - day6	16/59, 27.1%	15/45, 33.3%
BB, AC, CA - day7	3/7, 42.9%	1/4, 25.0%
CC, BC, CB - day5	6/14, 42.9%	3/10, 30.0%
CC, BC, CB - day6	11/45, 24.4%	8/32, 25.0%
CC, BC, CB - day7	3/27, 11.1%	1/15, 6.7%
TOTAL	**565/1211, 46.7%**	**336/673, 49.9%**

HR FRET cycles: 1211

M-NC FRET cycles: 673

LBR per euploid blastocyst Single Embryo Transfer:

No statistically significant difference

Petriglia et al., Human Reprod, 2021

GnRH agonist compared to control for women undergoing ET with frozen or fresh embryos derived from donor oocytes

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Intervention: **GnRH agonist pretreatment cycle**

Comparison: **Control (without GnRH-a pretreatment)**

THE COCHRANE COLLABORATION®

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with GnRH agonists				
Live birth rate	85 per 1000	197 per 1000 (100 to 351)	OR 2.62 (1.19 to 5.78)	234 (1 RCT)	⊕⊕⊝⊝ LOW [a b]	
Clinical pregnancy rate	184 per 1000	199 per 1000 (151 to 264)	OR 1.08 (0.82 to 1.43)	1289 (8 RCTs)	⊕⊕⊝⊝ LOW [c d]	In frozen-embryo transfers
Miscarriage rate	30 per 1000	26 per 1000 (11 to 58)	OR 0.85 (0.36 to 2.00)	828 (4 RCTs)	⊕⊕⊝⊝ LOW [d e]	
Multiple pregnancy rate						Not reported in any study
Cycle cancellation cycles	60 per 1000	30 per 1000 (13 to 69)	OR 0.49 (0.21 to 1.17)	530 (2 RCTs)	⊕⊕⊝⊝ LOW [d e]	
Endometrial thickness (mm)	The mean endometrial thickness (mm) was 9.4 mm	MD 0.08 mm lower (0.33 lower to 0.16 higher)	-	697 (4 RCTs)	⊕⊕⊝⊝ LOW [d e]	
Other adverse effects						Not reported in any study

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Glujovsky et al., Cochrane Library, 2020

LBR:

Low-quality evidence

→ *Improved LBR*

CPR:

Fresh and frozen-thawed ET

Low-quality evidence

→ *No differences*

MR:

Low-quality evidence

→ *No differences*

HR FRET cycles: GnRH agonists versus GnRH antagonists

GeneraLife
Catalysts of life

Intervention: **GnRH agonist pretreatment cycle**

Comparison: **GnRH antagonist control cycle**

THE COCHRANE COLLABORATION®

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with GnRH antagonists	Risk with GnRH agonists				
Live birth rate						Not reported in any study
Clinical pregnancy rate	681 per 1000	570 per 1000 (473 to 658)	OR 0.62 (0.42 to 0.90)	473 (1 RCT)	⊕⊕⊕⊖ MODERATE [a]	
Miscarriage rate	86 per 1000	66 per 1000 (35 to 123)	OR 0.75 (0.38 to 1.49)	473 (1 RCT)	⊕⊕⊖⊖ LOW [a b]	
Multiple pregnancy rate	254 per 1000	190 per 1000 (133 to 267)	OR 0.69 (0.45 to 1.07)	473 (1 RCT)	⊕⊕⊖⊖ LOW [a b]	
Cycle cancellation rate						Not reported in any study
Endometrial thickness (mm)						Not reported in any study
Other adverse effects						Not reported in any study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

Glujovsky et al., Cochrane Library, 2020

CPR:

Moderate-quality evidence

↳ ***Improved LBR***

MR:

Low-quality evidence

↳ ***No differences***

Multiple pregnancy rate:

Low-quality evidence

↳ ***No differences***

Effects of GnRH agonist pretreatment on FRET outcomes in HR cycles: a meta-analysis

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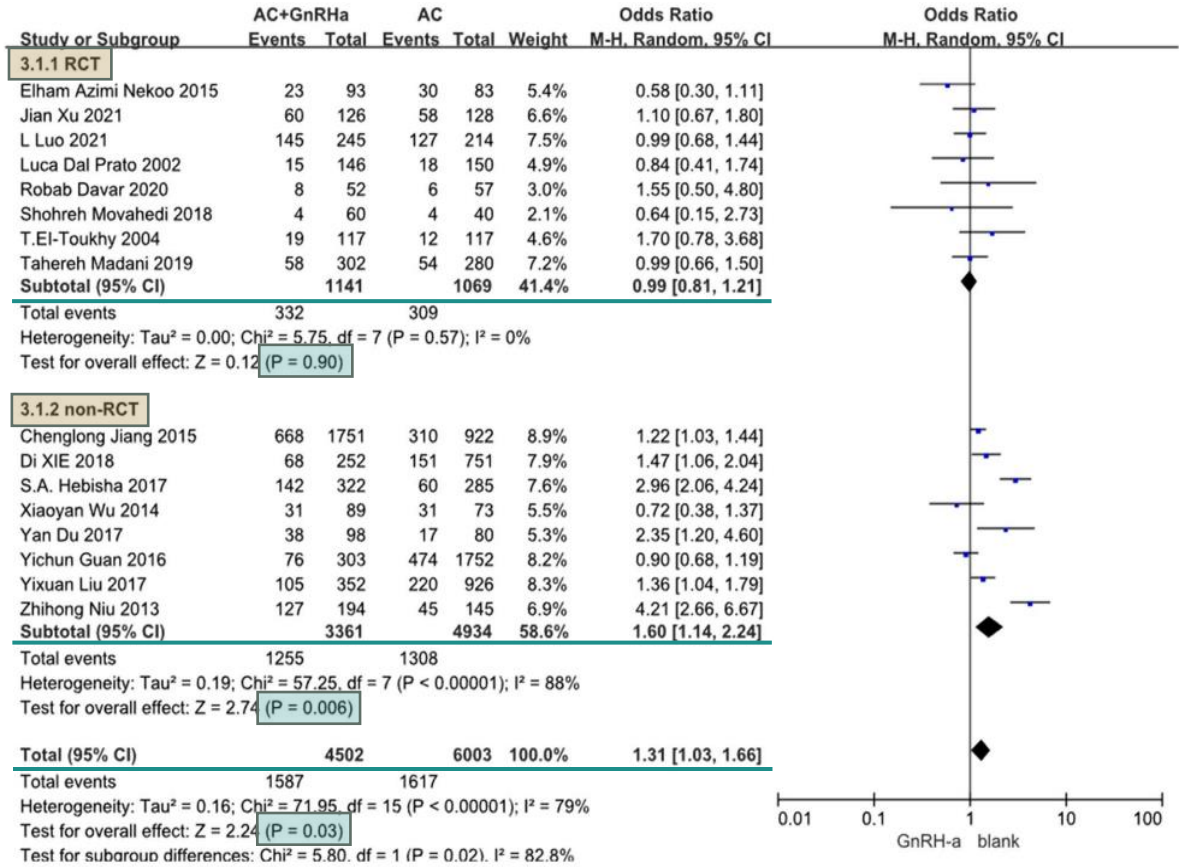
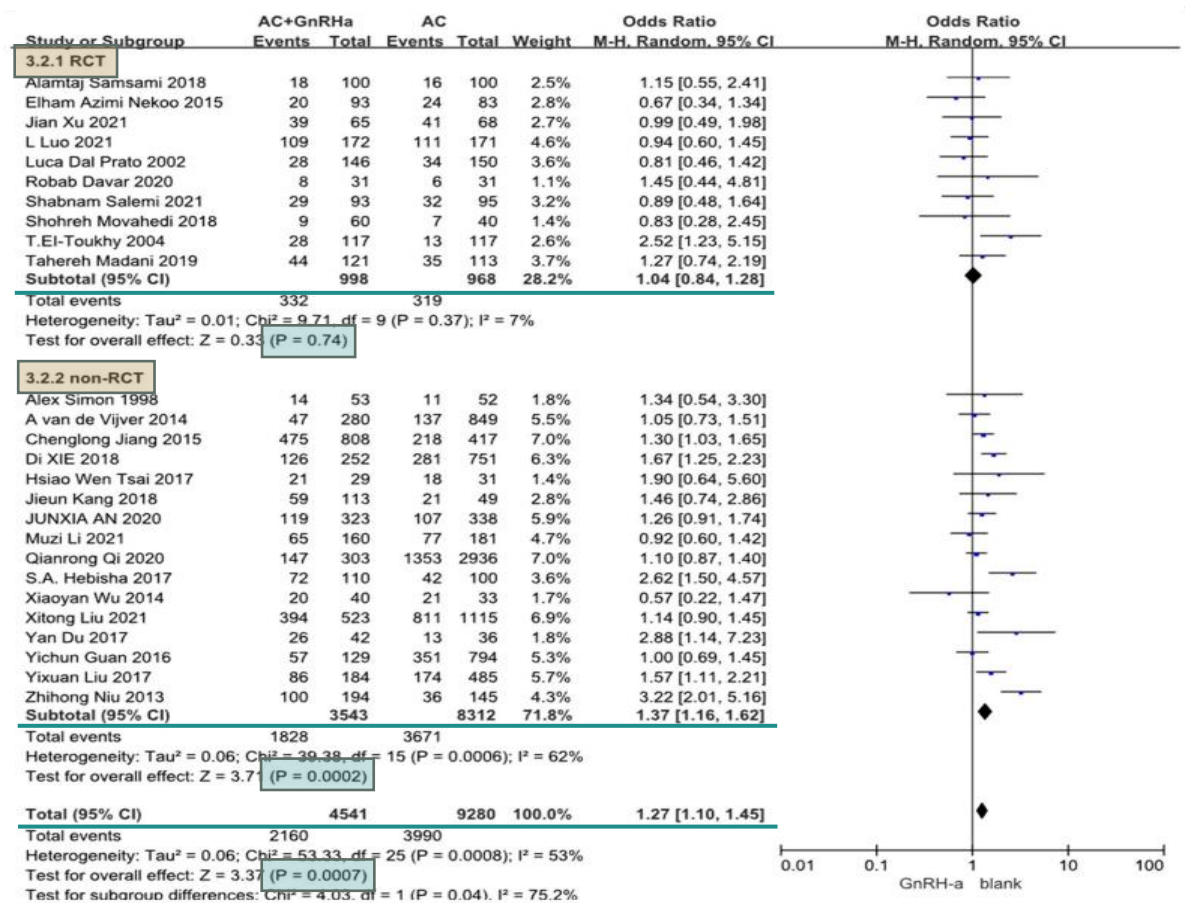
Forest plot of implantation rate



Forest plot of clinical pregnancy rate



Li et al, Archives of Gynecology and Obstetrics, 2022

Effects of GnRH agonist pretreatment on FRET outcomes in HR cycles

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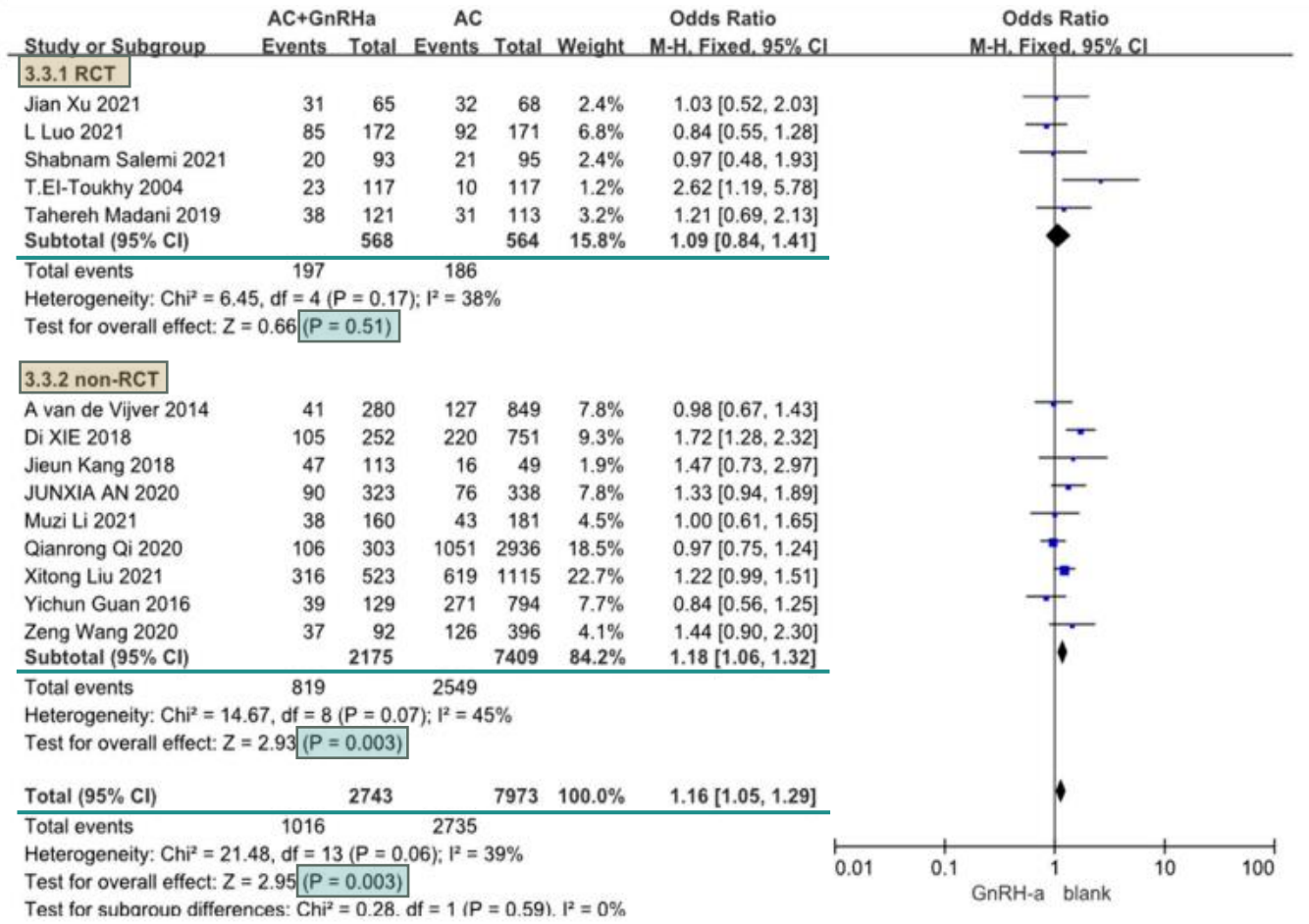
Forest plot of Live Birth rate



- ***GnRHa pretreatment*** in FRET ***can improve implantation, clinical pregnancy, and live birth rates***, especially in patients with ***repeated implantation failure***.
- ***GnRHa pretreatment seems to improve*** FRET outcomes, though with a ***higher preterm birth rate.***

Li et al, Archives of Gynecology and Obstetrics, 2022

Effects of HR with and without GnRH-a pretreatment on FRET outcomes in patients with adenomyosis and endometriosis

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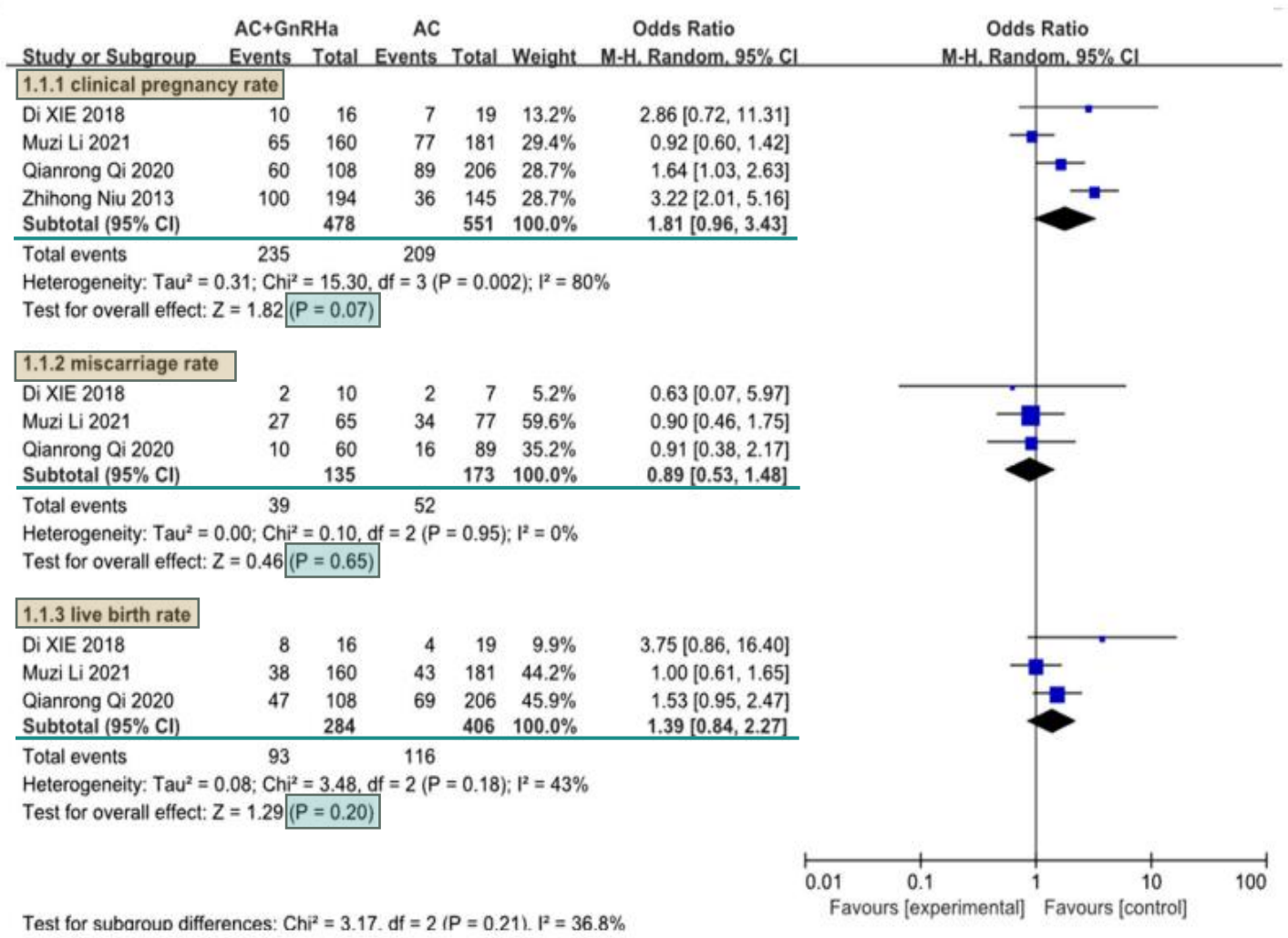
Forest plot of CPR,MR and LBR

1 single dose of GnRH-a



The inactivation of adenomyosis by an ultralong pituitary downregulation regime promptly resulted in successful pregnancy

Tremellen K, Russell P, J Obstet Gynaecol, 2011

GnRHa treatment before HRT was not associated with the altered CPR, MR or LBR in patients with endometriosis and adenomyosis

1. The degree of endometriosis and adenomyosis was not clearly reported in these studies
2. For ***severe adenomyosis***, ***one injection*** of GnRH-a ***is probably not sufficient***

Li et al, Archives of Gynecology and Obstetrics, 2022

Effects of HR with and without GnRH-a pretreatment on FRET outcomes in patients with PCOS

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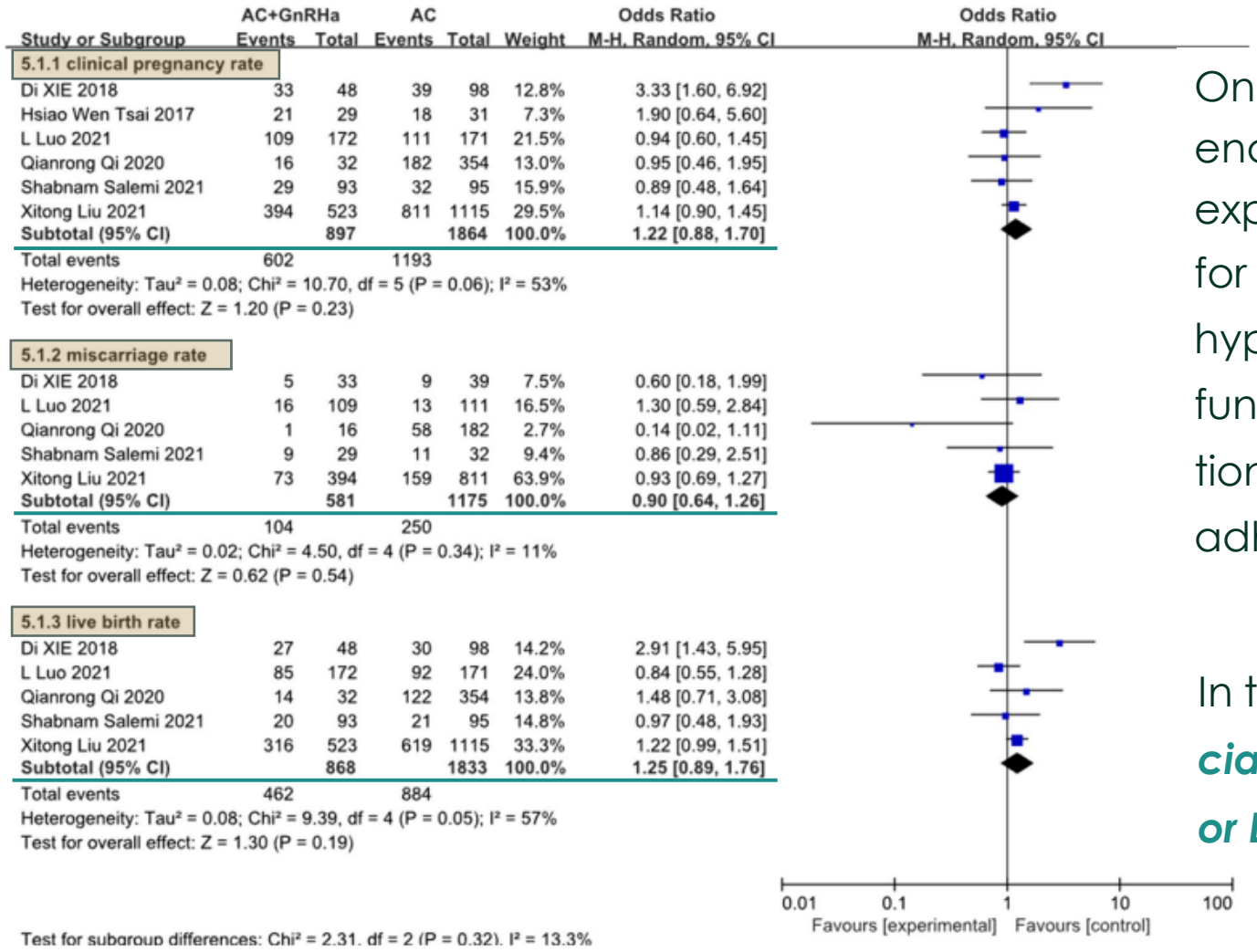
Forest plot of CPR, MR and LBR



One of the factors resulting in infertility in PCOS is endometrial dysfunction. A possible mechanism explaining the benefits of GnRH-a pretreatment for PCOS is suppression of LH levels, E2 levels, hyper-androgenic levels, and GnRH–HCG axis function with inhibition of endometrial inflammation and enhanced expression of endometrial adhesion molecules

In this study, ***GnRH-a pretreatment was not associated with the significant changes in CPR, MR, or LBR in PCOS***

Li et al, Archives of Gynecology and Obstetrics, 2022

Effects of HR with and without GnRH-a pretreatment on FRET outcomes in patients with PCOS: a RCT

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TABLE 3 COMPARISON OF THE STUDIED OUTCOMES AND PREGNANCY COMPLICATIONS BETWEEN THE GROUPS

Characteristics		Group A (n = 93)	Group B (n = 95)	P-value	OR/ mean difference	95% CI	
						Lower	Upper
Total dose of oestradiol administered, mg		89.68 ± 1.45	93.12 ± 1.12	0.06	−3.44	−7.04	0.17
Endometrial thickness, mm		9.66 ± 1.15	9.38 ± 1.38	0.13	0.29	−0.09	0.65
Embryo transfer, n		2.13 ± 0.39	2.12 ± 0.32	0.78	0.02	−0.09	0.12
Cycle Outcome	Implantation rate	0.58 ± 0.04	0.51 ± 0.03	0.18	0.07	−0.03	0.16
	Clinical pregnancy	29 (31.2%)	32 (33.7%)	0.71	0.89	0.48	1.64
	Miscarriage	9 (9.7%)	11 (11.6%)	0.75	0.86	0.34	2.17
	Live birth	20 (21.7%)	21 (22.1 %)	0.92	0.97	0.48	1.93
Multiple pregnancy		8 (8.6%)	3 (3.2%)	0.13	2.89	0.74	11.24
Multiple live birth		6 (6.5%)	3 (3.2%)	0.30	2.11	0.51	8.72
Medical complications during pregnancy	Preeclampsia	0	2 (9/5%)	0.30	0.20	0.01	4.22
	GDM	2 (10.0%)	4 (19.1%)	0.43	0.50	0.89	2.79
	PROM	3 (15.0%)	1 (4.8%)	0.33	3.13	0.32	30.68
	Preterm labour	6 (30.0%)	3 (14.3%)	0.30	2.11	0.51	8.72
Neonatal anomaly	Cardiac	1 (5.0%)	1 (4.8%)	0.98	1.02	0.06	16.58
	Cleft palate	1 (5.0%)	0	0.49	3.09	0.13	77.01
	Urogenital	0	1 (4.8%)	0.50	0.34	0.01	8.38

Values are reported as means ± SD.

Chi-square and independent sample t-test were used for all statistical analysis.

$P < 0.05$ is statistically significant.

- ***Group A (n = 93)*** had pituitary suppression before steroid hormone administration
- ***Group B (n = 95)*** commenced steroid supplementation without prior pituitary desensitization.

Endometrial preparation for FET with and without ovarian suppression by GnRH agonist provides similar results

Salemi et al, RBMO, 2021

Agenda

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4. Obstetric and neonatal outcomes

True-NC vs HR cycle. Systematic review and meta-analysis – obstetric and neonatal outcomes

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Journal of Assisted Reproduction and Genetics (2021) 38:1913–1926
https://doi.org/10.1007/s10815-021-02125-0

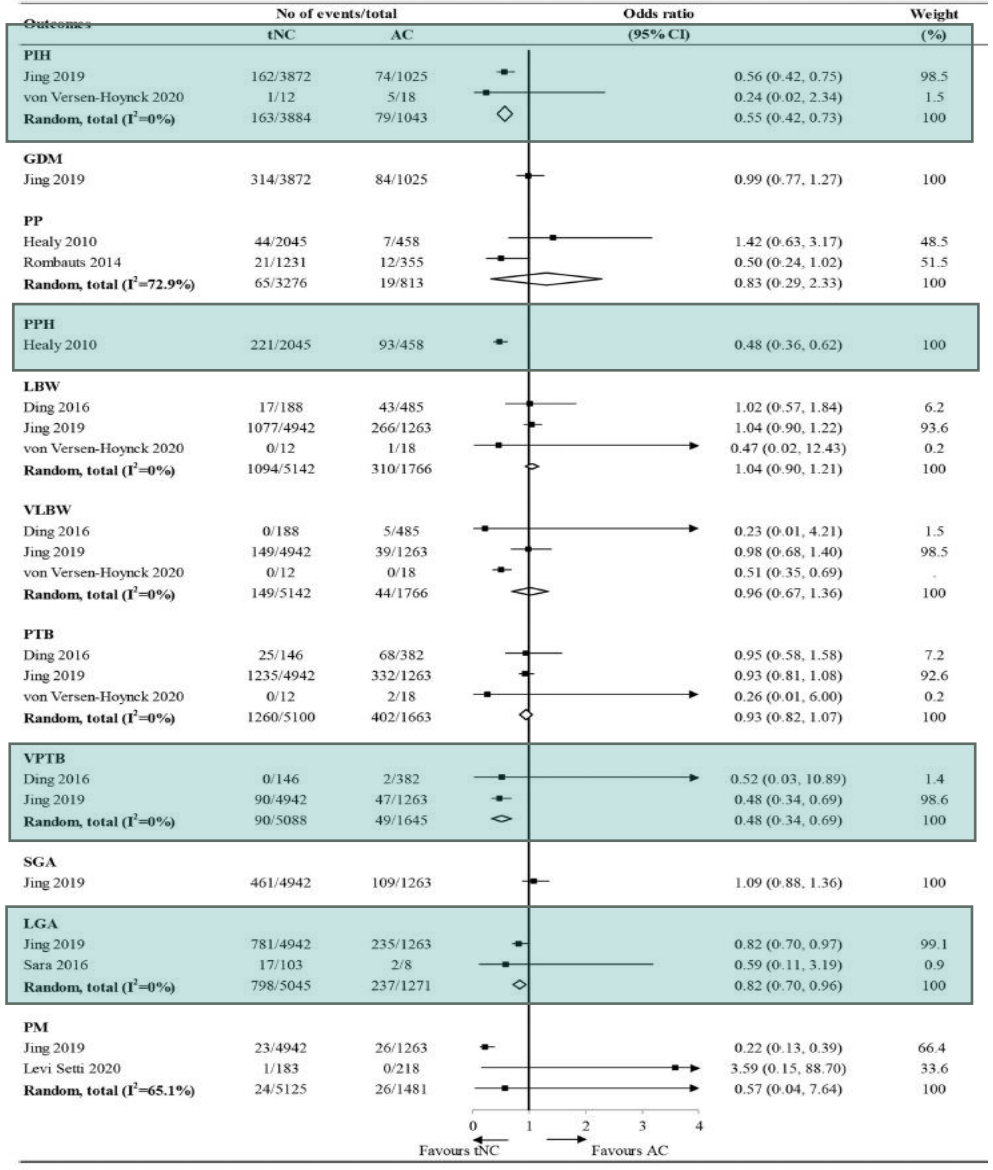
REVIEW

Endometrial preparation for frozen–thawed embryo transfer cycles: a systematic review and network meta-analysis

Hanglin Wu[1] · Ping Zhou[2] · Xiaona Lin[2] · Shasha Wang[2] · Songying Zhang[2]

True-NC associated with reduced risks of:

- Pregnancy Induced Hypertension
- Post-Partum Haemorrhage
- Very Pre-Term Birth
- Large for Gestational Age



Modified-NC vs HR cycle. Systematic review and meta-analysis – obstetric and neonatal outcomes

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Journal of Assisted Reproduction and Genetics (2021) 38:1913–1926
https://doi.org/10.1007/s10815-021-02125-0

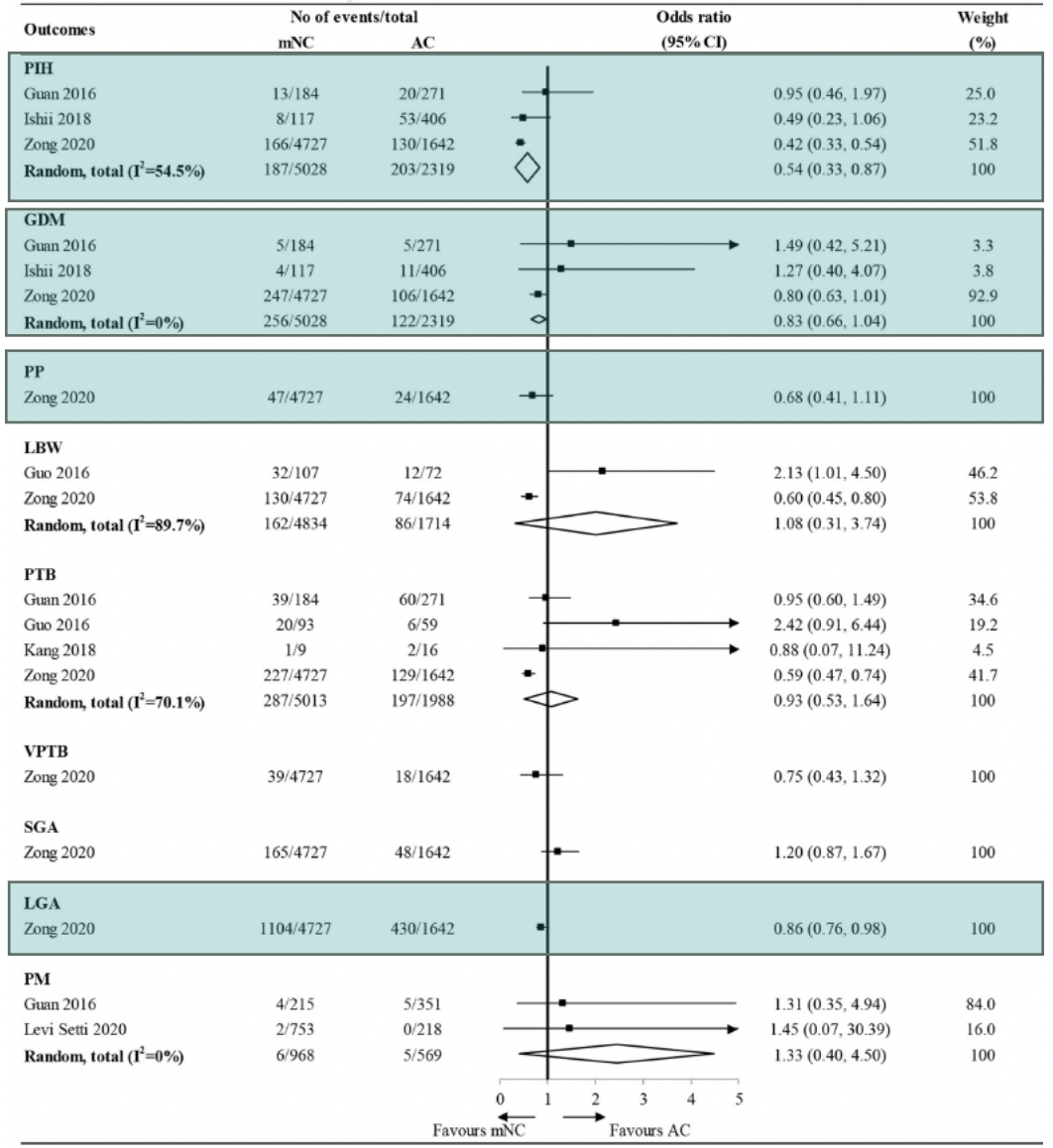
REVIEW

Endometrial preparation for frozen–thawed embryo transfer cycles: a systematic review and network meta-analysis

Hanglin Wu[1] · Ping Zhou[2] · Xiaona Lin[2] · Shasha Wang[2] · Songying Zhang[2]

M-NC associated with reduced risks of:

- Pregnancy Induced Hypertension
- Gestational Diabetes Mellitus
- Placenta Previa
- Large for Gestational Age



True-NC and M-NC vs HR cycle. Danish Register-based cohort study: obstetric and neonatal outcomes

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Fertility and Sterility® Vol. 115, No. 4, April 2021

Adverse obstetric and perinatal outcomes in 1,136 singleton pregnancies conceived after programmed frozen embryo transfer (FET) compared with natural cycle FET

Louise Laub Asserhøj, M.D.,[a,b] Anne Lærke Spangmose, M.D.,[a] Anna-Karina Aaris Henningsen, M.D.,[a] Tine Dalsgaard Clausen, M.D., Ph.D.,[c] Søren Ziebe, D.M.Sc.,[a] Rikke Beck Jensen, M.D., Ph.D.,[b] and Anja Pinborg, D.M.Sc.[a]

HR cycles associated with Higher risk:

- Hypertensive Disorders in Pregnancy
- Preeclampsia
- Postpartum hemorrhage
- Cesarean section
- Very PTB

Multiple logistic regression analyses: obstetric and perinatal outcomes in singleton deliveries in Denmark from 2006 to 2014 conceived after programmed FET (n = 357), mNC-FET (n = 611), and tNC-FET (n = 168).

	Treatment			Programmed FET versus mNC-FET		Programmed FET versus tNC-FET	
Outcome	Programmed FET n (%)	mNC-FET n (%)	tNC-FET n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Obstetric							
HPD	37 (10.4)	32 (5.2)	12 (7.1)	2.10 (1.28–3.42)	1.99 (1.20–3.29)	1.50 (0.76–2.97)	1.63 (0.75–3.53)
Preeclampsia	33 (9.2)	20 (3.3)	11 (6.5)	3.01 (1.70–5.33)	2.86 (1.61–5.10)	1.46 (0.72–2.95)	1.57 (0.72–3.43)
Eclampsia	1 (0.3)	0 (0.0)	0 (0.0)	NA	NA	NA	NA
PPROM	50 (14.0)	64 (10.5)	24 (14.3)	1.39 (0.94–2.07)	1.27 (0.84–1.93)	0.98 (0.58–1.65)	1.03 (0.59–1.81)
Placenta previa	7 (2.0)	10 (1.6)	5 (3.0)	1.20 (0.45–3.19)	1.24 (0.47–3.24)	0.65 (0.20–2.09)	0.66 (0.21–2.06)
Placental abruption	5 (1.4)	6 (1.0)	1 (0.6)	1.43 (0.43–4.73)	1.48 (0.45–4.85)[b]	0.42 (0.05–3.64)	NA
Induction of labor	149 (41.7)	181 (29.6)	50 (29.8)	1.71 (1.30–2.24)	1.71 (1.29–2.26)	1.75 (1.18–2.59)	1.65 (1.07–2.54)
Postpartum hemorrhage	137 (38.4)	150 (24.5)	29 (17.3)	1.91 (1.44–2.54)	2.22 (1.64–2.99)	2.99 (1.90–4.70)	2.32 (1.43–3.75)
Cesarean section	123 (34.5)	164 (26.8)	49 (29.2)	1.45 (1.09–1.92)	1.57 (1.17–2.12)	1.28 (0.86–1.91)	1.27 (0.82–1.97)
Perinatal							
Child's sex, female)	165 (46.2)	288 (47.1)	84 (50.0)	0.97 (0.75–1.26)	0.99 (0.76–1.30)	0.86 (0.60–1.25)	0.91 (0.61–1.35)
Post-term birth	12 (3.4)	9 (1.5)	11 (6.6)	2.34 (0.98–5.61)	2.14 (0.89–5.16)[c]	0.50 (0.22–1.16)	0.70 (0.29–1.65)
Preterm birth	26 (7.4)	45 (7.4)	19 (11.4)	0.99 (0.60–1.64)	1.02 (0.61–1.71)[b]	0.62 (0.33–1.16)	0.68 (0.35–1.32)
Very preterm birth	11 (3.1)	7 (1.2)	7 (4.2)	2.76 (1.06–7.18)	2.95 (1.06–8.23)[b]	0.74 (0.28–1.93)	0.85 (0.32–2.21)
Birth weight > 4,000 g	84 (23.7)	126 (20.7)	37 (22.2)	1.19 (0.87–1.63)	1.20 (0.86–1.66)	1.09 (0.76–1.69)	1.10 (0.67–1.80)
Birth weight > 4,500 g	6 (3.6)	19 (3.1)	22 (6.2)	2.05 (1.10–3.85)	1.75 (0.93–3.28)[c]	1.77 (0.71–4.46)	2.28 (0.81–6.44)
Small for gestational age[d]	14 (4.0)	14 (2.3)	6 (3.6)	1.74 (0.82–3.69)	1.58 (0.72–3.47)[b]	1.10 (0.41–2.91)	0.91 (0.30–2.76)
Large for gestational age[d]	21 (6.0)	30 (5.0)	10 (6.1)	1.21 (0.68–2.15)	1.13 (0.64–2.00)	0.98 (0.45–2.14)	1.07 (0.45–2.54)

Obstetric and neonatal complications for singleton births based on endometrial preparation protocols

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AJOG Global Reports November 2022

Original Research ajog.org

Endometrial preparation and maternal and obstetrical outcomes after frozen blastocyst transfer

Kazumi Takeshima, MD, PhD; Kenji Ezoe, PhD; Sachie Onogi, MD; Nami Kawasaki, MS; Tomoko Kuroda, MD, PhD; Keiichi Kato, MD, PhD

CONCLUSION: The risk of ***hypertensive disorders of pregnancy, placenta accreta, cesarean delivery, preterm delivery, and low birthweight*** was ***higher in HR cycles than in NC***, whereas the risk of ***congenital anomalies was similar between both cycles***. Further follow-up is needed to investigate these risks and to explore alternative endometrial preparation methods

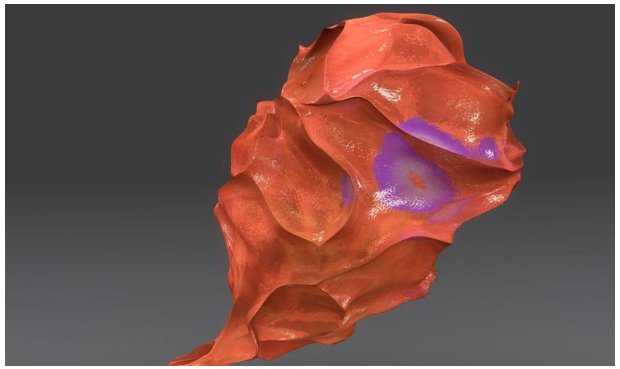
Ovulation cycles (OV): 51.700 cycles - 30.998 singleton pregnancies

HR cycles: 5.318 cycles - 2.488 singleton pregnancies

Logistic regression analysis of pregnancy complications

Adverse maternal outcomes	Group	OR (95% confidence intervals)	*P* value	aOR[a] (95% confidence intervals)	*P* value
Pregnancy complications[a]	OV 5.0	1.07 (0.97–1.17)	.1743	1.05 (0.95–1.16)	.3133
	HR	1.39 (1.17–1.64)	.0001	1.55 (1.30–1.84)	<.0001
Hypertensive disorders of pregnancy[a]	OV 5.0	1.10 (0.94–1.30)	.2257	1.09 (0.92–1.28)	.2929
	HR	1.84 (1.42–2.38)	<.0001	2.17 (1.67–2.81)	<.0001
Gestational diabetes mellitus[a]	OV 5.0	1.10 (0.95–1.28)	.1786	1.09 (0.94–1.28)	.2210
	HR	1.14 (0.86–0.15)	.3417	1.26 (0.94–1.69)	.1094
HELLP syndrome[a]	OV 5.0	0.64 (0.28–1.43)	.2782	0.66 (0.28–1.51)	.3270
	HR	1.31 (0.37–4.53)	.6684	1.54 (0.42–5.64)	.5125
Preterm premature rupture of membranes[a]	OV 5.0	0.92 (0.53–1.60)	.7855	0.91 (0.52–1.58)	.7428
	HR	1.51 (0.62–3.68)	.7855	1.61 (0.65–3.94)	.2956
Low-lying placenta[a]	OV 5.0	0.86 (0.61–1.21)	.4110	0.83 (0.59–1.17)	.2990
	HR	0.74 (0.35–1.55)	.4372	0.74 (0.35–1.56)	.4360
Placenta previa[a]	OV 5.0	1.15 (0.92–1.43)	.2111	1.12 (0.90–1.41)	.2914
	HR	1.08 (0.70–1.67)	.7096	1.06 (0.67–1.68)	.7809
Placenta accreta[a]	OV 5.0	0.88 (0.40–1.95)	.7700	0.72 (0.33–1.60)	.4336
	HR	3.54 (1.41–8.89)	.0071	3.85 (1.54–9.60)	.0038
Placental abruption[a]	OV 5.0	0.83 (0.48–1.41)	.4965	0.88 (0.52–1.50)	.6585
	HR	0.67 (0.20–2.22)	.5211	0.91 (0.32–2.62)	.8721

Pregnancy outcomes after frozen-thawed embryo transfer in the absence of corpus luteum



Absence of Corpus luteum

Abnormal placentation

Cause

- reduced vasoactive products: relaxin and vascular endothelial growth factor levels (important in initial placentation)
- reduced angiogenic and nonangiogenic circulatory endothelial progenitor cells
- Increased mean arterial pressure during pregnancy

The absence of the corpus luteum is partly responsible for the increased risk of hypertensive disorders

Waschkies et al., Front Med, 2021; Singh et al, FS 2020

Conclusions

- It is not possible, based on the current published literature, to recommend one endometrial preparation method in FET over another with or without any pretreatment with regard to pregnancy rates
- Hormonal replacement endometrial preparation protocols induces an increased risk of Gestational hypertension, Preeclampsia, Placenta accreta, Postpartum haemorrhage, VLBW and SGA
- Future prospective RCTs should not only address pregnancy rates but also consider convenience and cost efficiency and safety for the patients and the offsprings

Thank you for your attention

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