Recent Developments in **The Transmission of Human Life**



GeneraLife

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

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

Stakeholder of GENERA HEALTH CARE

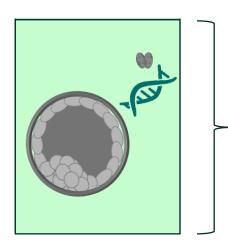




1. Introduction

The "Black Box" of implantation



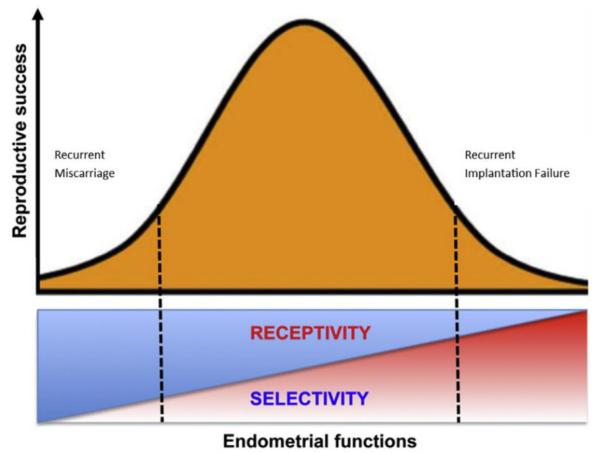


Implantation rates of euploid blastocyst remain **around 50%**

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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.



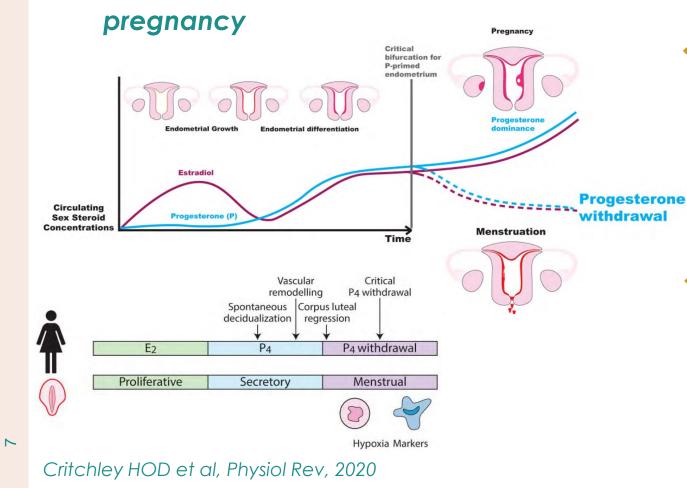


2. Endometrium in spontaneous and stimulated cycles

Physiology of the Endometrium and Regulation of Menstruation



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



 Following ovulation, the endometrium undergoes secretory transformation driven by P₄ in the presence of E₂ achieving a state of receptivity lasting 3-5 days.

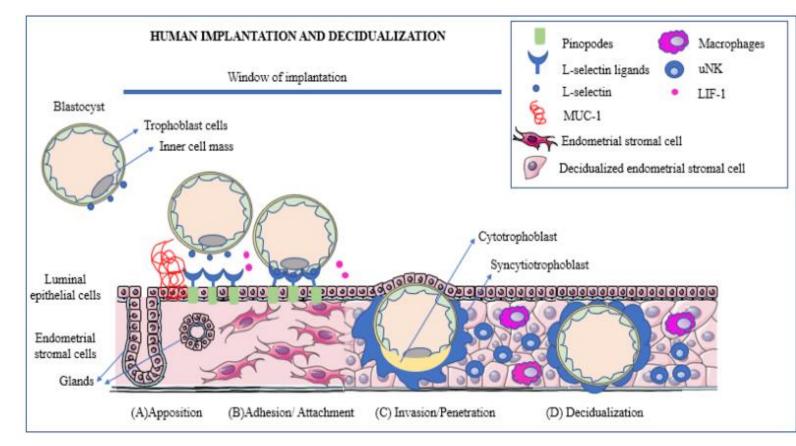
Navot & Bergh 1991

P₄ induces differentiation of both epithelial and stromal cells (decidualization) and changes in the vasculature, in the extracellular matrix and leucocyte content of the tissue.

Salamonsen et al 2009



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



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

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

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Controlled Ovarian Stimulation (COS) alters Endometrial Gene Expression Profiles



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

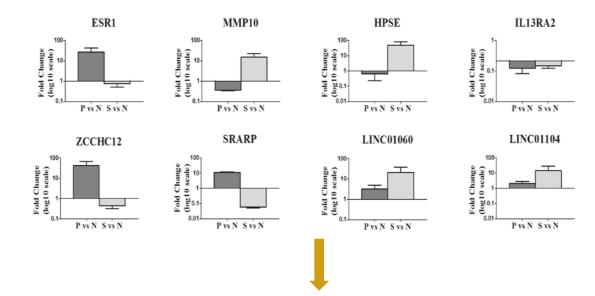
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Journal of Assisted Reproduction and Genetics (2020) 37:21–32 https://doi.org/10.1007/s10815-019-01616-5

ASSISTED REPRODUCTION TECHNOLOGIES

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

Lingxiu Li¹ • Peng Wang¹ • Shan Liu¹ • Xueyan Bai¹ • Binbin Zou² • Yuan Li¹



Supraphysiological E₂ **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 P₄ alters endometrial receptivity

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 Hu¹ · Tao Zhang³ · Mengying Wang⁴ · Hui Xu³ · Tin Chiu Li³ · Yingpu Sun Chi Chiu Wang^{3,5,6}



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 GeneraLife

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

human reproduction ORIGINA

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-Conejero², P. Alamá¹, J.A. Horcajadas², A. Pellicer¹, C. Simón^{1,2}, and E. Bosch¹

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

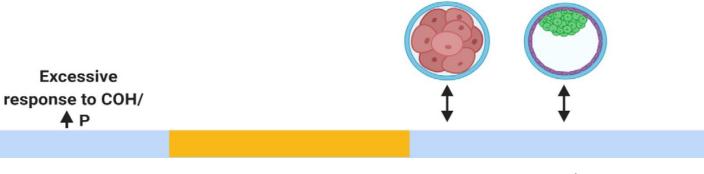


- In normoresponders, the anticipation would be modest, allowing normal implantation of the cleavage-stage embryos, interfering with the implantation of the blastocysts
- In cycles with hyper-response an early rise of P and in those responding more to COH, the anticipation may be more marked and the 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)

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COH affects vaginal and endometrial microbiota in IVF cycles

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 N = 15

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

Andrea Carosso¹ • Alberto Revelli¹ • Gianluca Gennarelli¹ • Stefano Canosa¹ • Stefano Cosma¹ • Fulvio Borella¹ • Annalisa Tancredi¹ · Carlotta Paschero¹ · Lara Boatti² · Elisa Zanotto³ · Francesca Sidoti³ · Paolo Bottino³

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

pre-COH Vaginal and endometrial microbiota analysis

- post-COH Vaginal and endometrial microbiota analysis
- Vaginal swabs and endometrial biopsies

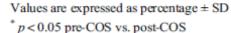
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NGS analysis

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





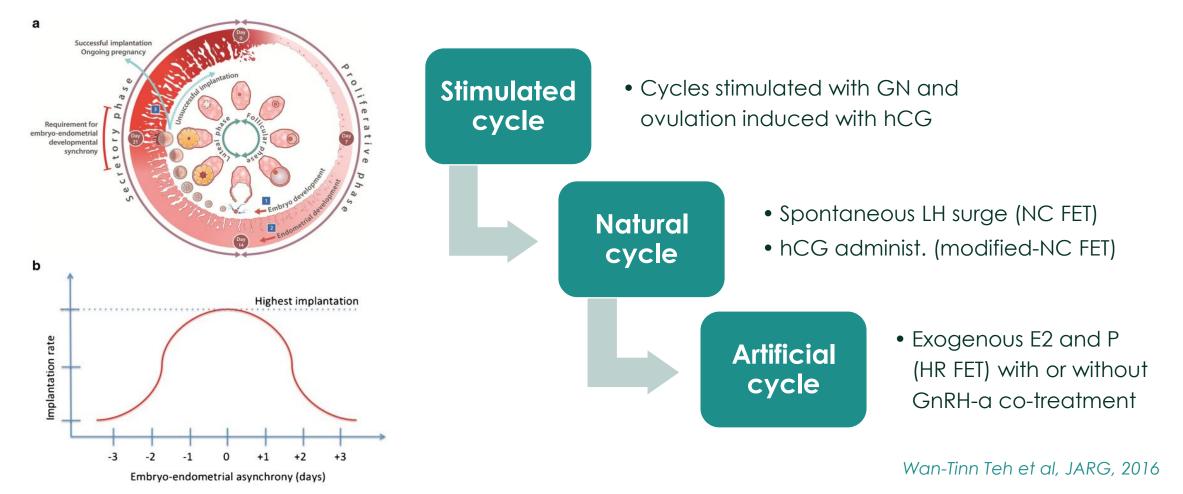


3. Endometrial preparation in frozen ET cycles

The development of embryo and endometrium should be synchronized

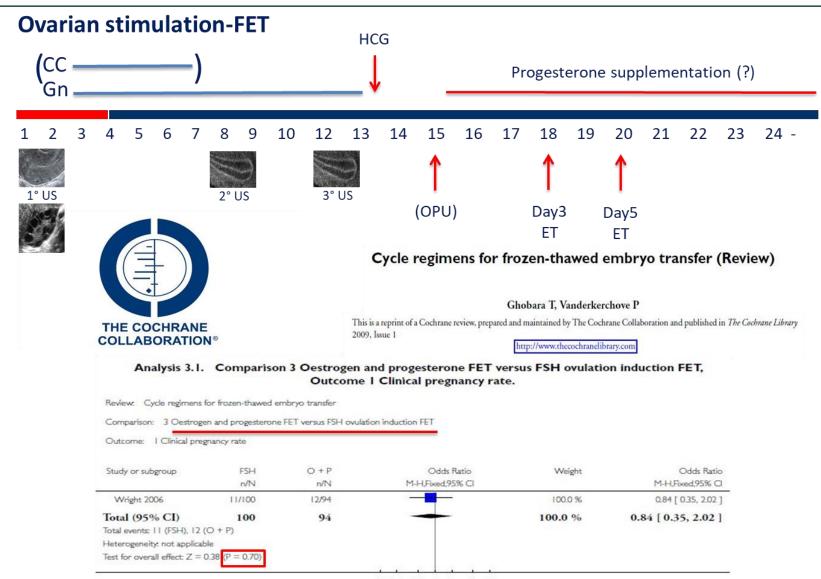


A functional embryo, a receptive endometrium and a synchrony between the embryo and the endometrium are the three pre-requisites for successful implantation



Cycles stimulated with gonadotropins and ovulation induced with hCG





0.1 0.2 0.5 1 2 5 10

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



Intervention: Stimulated cycle **Comparison:** Programmed cycle THE COCHRANE LBR: COLLABORATION Outcomes Anticipated absolute effects* (95% CI) Relative effect Nº of partici-Quality of the Comments Very low-quality evidence (95% CI) pants evidence (studies) (GRADE) Risk with pro-**Risk with Stimulated cy**grammed cle No differences Live birth rate OR 1.26 100 Letrozole stimulation versus 240 per 1000 285 per 1000 0000 (134 to 507) (1 RCT) programmed cycle (0.49 to 3.26) VERY LOW a b Clinical pregnancy rate 191 per 1000 278 per 1000 OR 1.63 656 0000 **CPR**: (210 to 360) (1.12 to 2.38) (5 RCTs) LOW^{ac} Low-quality evidence 70 per 1000 OR 0.79 355 Miscarriage rate 87 per 1000 0000 (33 to 140) (0.36 to 1.71) (3 RCTs) VERY LOW a b Improved CLR Not reported in any study Multiple pregnancy rate Cycle cancellation rate Not reported in any study Endometrial thickness Letrozole stimulation versus The mean endome-MD -0.05 mm 362 0000 trial thickness (-0.19 lower to 0.10 higher) (2 RCTs) (mm) LOWac programmed cycle MR: (mm) was 8.7 mm 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).

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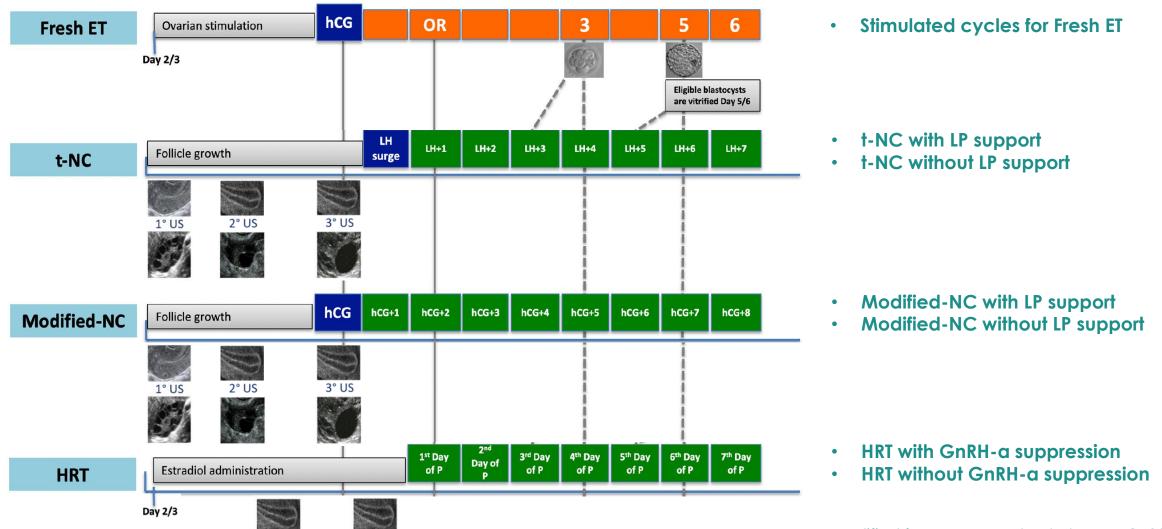
Glujovsky et al., Cochrane Library, 2020

Very low-quality evidence No differences

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

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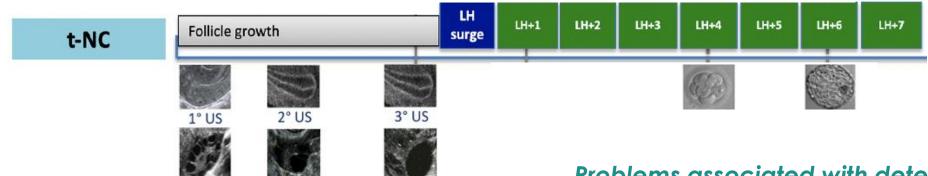




Modified from Mumusoglu et al., FENDO, 2021

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

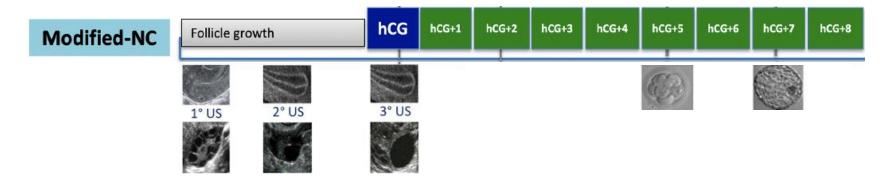
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Problems associated with detection of spontaneous LH surge:

- 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





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?



No luteal support (RCT)

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

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

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							

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?



Luteal support (RCT)

Luteal phase progesterone increases live birth rate after frozen embryo transfer

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?



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

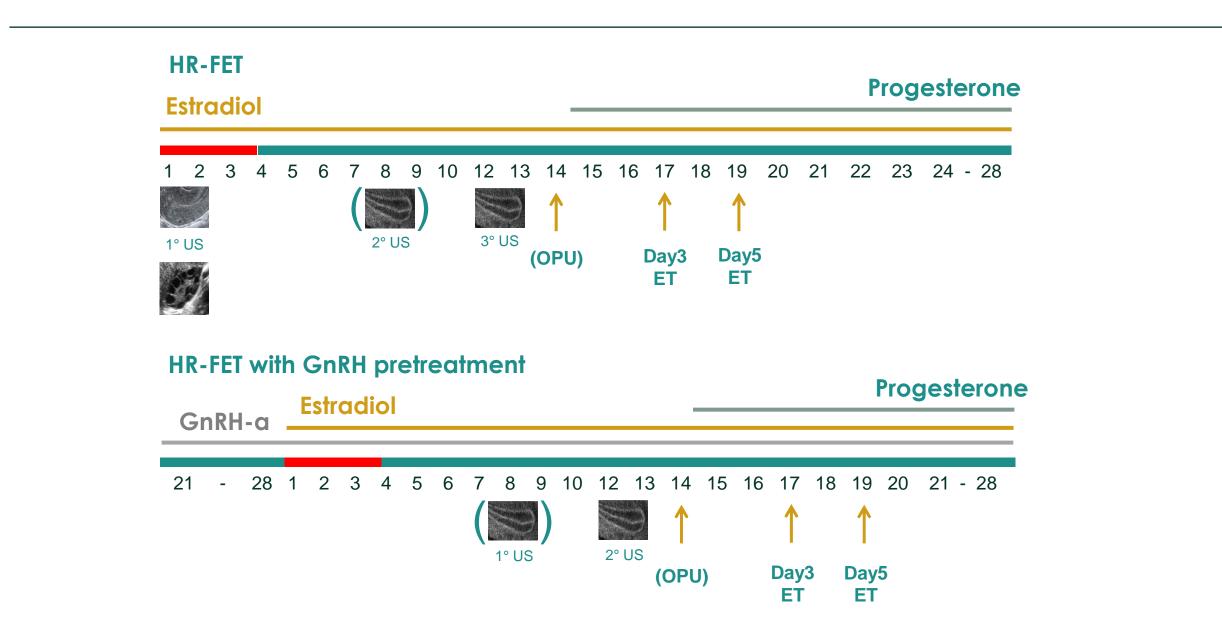
Eva R. Groenewoud^{1,*}, Astrid E.P. Cantineau¹, Boudewijn J. Kollen², Nick S. Macklon³, and Ben J. Cohlen⁴

"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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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



	Natural c		830 I RCT	NC cycles				
Comparisor	n: Program	med cycle		HR cycles		THE COCHRANE COLLABORATION®	LBR:	
Outcomes	Anticipated absolute effects* (95% CI)			№ of partici-	Quality of the evidence	Comments	Very lov	v-quality evidence
	Risk with pro- grammed cycle	Risk with Natural cycle	(95% CI)	pants (studies)	(GRADE)			No differences
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		CPR:	
Miscarriage rate	50 per 1000	32 per 1000 (13 to 82)	OR 0.64 (0.25 to 1.63)	485 (3 RCTs)	⊕⊙⊙⊙ VERY LOWª e		Very lov	v-quality evidence
Multiple pregnancy rate						Not reported in any study		No differences
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		MR:	
Other adverse effects						Not reported in any study	very lov	v-quality evidence
*The risk in the interven	ntion group (and its 95% co	onfidence interval) is based on the ass	umed risk in the comp	arison group and th	e relative effect of t	he intervention (and		No differences

*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

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

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 Wu¹ • Ping Zhou² • Xiaona Lin² • Shasha Wang² • Songying Zhang²

n 2020 Ferrillo 2017 Sivens 2009 Juan 2016	No of eve	nts/total	Odds ratio	Weight	
Study	AC	mNC	(95% CI)	(%)	
			11		
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 analysi	s, Heterogeneity: I ² =3.	3.5% Favour	$0 \longleftarrow 1 \longrightarrow 2 \qquad 3$ s mNC Favours AC		

Study	No of eve	nts/total	Odds ratio		Weight
Cardellicchio 2017 Cardenas Armas 2019 Cerrillo 2017 Dor 1991 El Bahja 2013 ing 2019 evi Setti 2020 oh 1999	AC	tNC	(95% CI)	(%)	
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	\diamond	0.81 (0.70, 0.93)	100
Random effects analysis, I	Heterogeneity: I ² =75	5.6% Favour	$0 \leftarrow 1 \rightarrow 2 \qquad 3$ s tNC Favours AC		



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



	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, <u>CB - day</u> 7	3/27, 11.1%	1/15, 6.7%
TOTAL	565/1211, 46.7%	336/673, 49.9%

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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

Intervention: GnRH agonist pretreatment cycle

Comparison: Control (without GnRH-a pretreatment)

Outcomes	Anticipated absolute	effects [*] (95% CI)	Relative effect (95% CI)	№ of partici- pants	Quality of the evidence	Comments
	Risk with control	Risk with GnRH agonists		(studies)	(GRADE)	
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)	⊕⊕⊝⊝ DOM c q	In frozen-em- bryo 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 endome- trial 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).

LBR: Low-quality evidence

CPR:

THE COCHRANE COLLABORATION

> **Fresh and frozen-thawed ET** Low-quality evidence

GeneraLife

No differences

MR:

Low-quality evidence No differences

Glujovsky et al., Cochrane Library, 2020

HR FRET cycles: GnRH agonists versus GnRH antagonists



Intervention: GnRH agonist pretreatment cycle Comparison: GnRH antagonist control cycle

Outcomes	Anticipated abso	olute effects [*] (95% CI)	Relative effect (95% CI)	№ of partici- pants	Quality of the evidence	Comments
	Risk with Risk with GnRH ag GnRH antago-nists nists			(studies)	(GRADE)	
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).

CPR:

COLLABORATION



Improved LBR

MR:

Low-quality evidence



Multiple pregnancy rate:

Low-quality evidence



No differences

Glujovsky et al., Cochrane Library, 2020

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



Forest plot of implantation rate

	AC+Gn	RHa	AC			Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI	
3.1.1 RCT							CONTRACTOR CONTRACTOR CONTRACTOR (CONTRACTOR)	
Elham Azimi Nekoo 2015	23	93	30	83	5.4%	0.58 [0.30, 1.11]		
Jian Xu 2021	60	126	58	128	6.6%	1.10 [0.67, 1.80]	+	
Luo 2021	145	245	127	214	7.5%	0.99 [0.68, 1.44]	+	
uca Dal Prato 2002	15	146	18	150	4.9%	0.84 [0.41, 1.74]		
Robab Davar 2020	8	52	6	57	3.0%	1.55 [0.50, 4.80]		
Shohreh Movahedi 2018	4	60	4	40	2.1%	0.64 [0.15, 2.73]		
T.EI-Toukhy 2004	19	117	12	117	4.6%	1.70 [0.78, 3.68]	+	
Fahereh Madani 2019	58	302	54	280	7.2%	0.99 [0.66, 1.50]	+	
Subtotal (95% CI)		1141		1069	41.4%	0.99 [0.81, 1.21]	•	
Total events	332		309					
Heterogeneity: Tau ² = 0.00	; Chi ² = 5.7	75. df =	7 (P = 0.5	57); ² =	0%			
Test for overall effect: Z = 0	0.12 (P = 0)	.90)	5. T					
3.1.2 non-RCT								
Chenglong Jiang 2015	668	1751	310	922	8.9%	1.22 [1.03, 1.44]	-	
Di XIE 2018	68	252	151	751	7.9%	1.47 [1.06, 2.04]		
S.A. Hebisha 2017	142	322	60	285	7.6%	2.96 [2.06, 4.24]		
Xiaoyan Wu 2014	31	89	31	73	5.5%	0.72 [0.38, 1.37]		
Yan Du 2017	38	98	17	80	5.3%	2.35 [1.20, 4.60]		
richun Guan 2016	76	303	474	1752	8.2%	0.90 [0.68, 1.19]	-	
Yixuan Liu 2017	105	352	220	926	8.3%	1.36 [1.04, 1.79]		
Zhihong Niu 2013	127	194	45	145	6.9%	4.21 [2.66, 6.67]		
Subtotal (95% CI)		3361		4934	58.6%	1.60 [1.14, 2.24]		
Fotal events	1255		1308					
Heterogeneity: Tau ² = 0.19	; Chi ² = 57	.25, df =	7 (P < 0	.00001); l ² = 88%			
Test for overall effect: Z = 2	2.74 (P = 0)	.006)						
Total (95% CI)		4502		6003	100.0%	1.31 [1.03, 1.66]	•	
Total events	1587		1617				· ^	
Heterogeneity: Tau ² = 0.16		95 df =		0 0000	1) $l^2 = 79^{\circ}$	26		
Test for overall effect: Z = 2		No. Contraction of the local sectors of the local s	1011 4	0.0000	1,1 - 15	<i>·</i> •	0.01 0.1 1 10	10
Test for subaroup difference		/					GnRH-a blank	

Forest plot of clinical pregnancy rate

	AC+Gn		AC			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% CI	M-H, Random, 95% Cl
3.2.1 RCT							
Alamtaj Samsami 2018	18	100	16	100	2.5%	1.15 [0.55, 2.41]	
Elham Azimi Nekoo 2015	20	93	24	83	2.8%	0.67 [0.34, 1.34]	
Jian Xu 2021	39	65	41	68	2.7%	0.99 [0.49, 1.98]	
L Luo 2021	109	172	111	171	4.6%	0.94 [0.60, 1.45]	-+
Luca Dal Prato 2002	28	146	34	150	3.6%	0.81 [0.46, 1.42]	-+-
Robab Davar 2020	8	31	6	31	1.1%	1.45 [0.44, 4.81]	
Shabnam Salemi 2021	29	93	32	95	3.2%	0.89 [0.48, 1.64]	
Shohreh Movahedi 2018	9	60	7	40	1.4%	0.83 [0.28, 2.45]	
T.EI-Toukhy 2004	28	117	13	117	2.6%	2.52 [1.23, 5.15]	
Tahereh Madani 2019	44	121	35	113	3.7%	1.27 [0.74, 2.19]	+
Subtotal (95% CI)		998		968	28.2%	1.04 [0.84, 1.28]	•
Total events	332		319				
Heterogeneity: Tau ² = 0.01	: Chi ² = 9.7	/1. df = 1	9 (P = 0.3	37); l ² =	7%		
Test for overall effect: Z = 0							
3.2.2 non-RCT							
Alex Simon 1998	14	53	11	52	1.8%	1.34 [0.54, 3.30]	- -
A van de Vijver 2014	47	280	137	849	5.5%	1.05 [0.73, 1.51]	+
Chenglong Jiang 2015	475	808	218	417	7.0%	1.30 [1.03, 1.65]	-
Di XIE 2018	126	252	281	751	6.3%	1.67 [1.25, 2.23]	
Hsiao Wen Tsai 2017	21	29	18	31	1.4%	1.90 [0.64, 5.60]	
Jieun Kang 2018	59	113	21	49	2.8%	1.46 [0.74, 2.86]	+
JUNXIA AN 2020	119	323	107	338	5.9%	1.26 [0.91, 1.74]	+
Muzi Li 2021	65	160	77	181	4.7%	0.92 [0.60, 1.42]	-
Qianrong Qi 2020	147	303	1353	2936	7.0%	1.10 [0.87, 1.40]	+
S.A. Hebisha 2017	72	110	42	100	3.6%	2.62 [1.50, 4.57]	
Xiaoyan Wu 2014	20	40	21	33	1.7%	0.57 [0.22, 1.47]	
Xitong Liu 2021	394	523	811	1115	6.9%	1.14 [0.90, 1.45]	+-
Yan Du 2017	26	42	13	36	1.8%	2.88 [1.14, 7.23]	
Yichun Guan 2016	57	129	351	794	5.3%	1.00 [0.69, 1.45]	+
Yixuan Liu 2017	86	184	174	485	5.7%	1.57 [1.11, 2.21]	
Zhihong Niu 2013	100	194	36	145	4.3%	3.22 [2.01, 5.16]	
Subtotal (95% CI)	100	3543	50	8312	71.8%	1.37 [1.16, 1.62]	•
Total events	1828	0010	3671	0012	111070		1. The second
Heterogeneity: Tau ² = 0.06		38 df -		0 0006	- 12 = 62%		
Test for overall effect: Z = 3			15 (1 -	0.0000	,1 - 02 /		
		4541		9280	100.0%	1.27 [1.10, 1.45]	•
Total (95% CI)							

Test for subaroup differences: Chi* = 4.03. at = 1 (P = 0.04). I2 = 75.2%

Li et al, Archives of Gynecology and Obstetrics, 2022

Effects of GnRH agonist pretreatment on FRET outcomes in HR cycles



Forest plot of Live Birth rate

	AC+Gn	RHa	AC			Odds Ratio		0	dds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	М-Н.	Fixed, 95% C		
3.3.1 RCT											
Jian Xu 2021	31	65	32	68	2.4%	1.03 [0.52, 2.03]					
L Luo 2021	85	172	92	171	6.8%	0.84 [0.55, 1.28]			-		
Shabnam Salemi 2021	20	93	21	95	2.4%	0.97 [0.48, 1.93]		5	-		
T.EI-Toukhy 2004	23	117	10	117	1.2%	2.62 [1.19, 5.78]					
Tahereh Madani 2019	38	121	31	113	3.2%	1.21 [0.69, 2.13]			+		
Subtotal (95% CI)		568		564	15.8%	1.09 [0.84, 1.41]			•		
Total events	197		186	5			-				
Heterogeneity: Chi ² = 6.4	45, df = 4 (P = 0.17	7); l ² = 38	%							
Test for overall effect: Z	= 0.66 (P =	= 0.51)									
3.3.2 non-RCT											
A van de Vijver 2014	41	280	127	849	7.8%	0.98 [0.67, 1.43]			-		
Di XIE 2018	105	252	220	751	9.3%	1.72 [1.28, 2.32]					
Jieun Kang 2018	47	113	16	49	1.9%	1.47 [0.73, 2.97]					
JUNXIA AN 2020	90	323	76	338	7.8%	1.33 [0.94, 1.89]					
Muzi Li 2021	38	160	43	181	4.5%	1.00 [0.61, 1.65]					
Qianrong Qi 2020	106	303	1051	2936	18.5%	0.97 [0.75, 1.24]			+		
Xitong Liu 2021	316	523	619	1115	22.7%	1.22 [0.99, 1.51]			-		
Yichun Guan 2016	39	129	271	794	7.7%	0.84 [0.56, 1.25]			-		
Zeng Wang 2020	37	92	126	396	4.1%	1.44 [0.90, 2.30]			<u>t-</u>		
Subtotal (95% CI)	0.50	2175	2004	7409	84.2%	1.18 [1.06, 1.32]	_		٠		
Total events	819		2549	Sec.							
Heterogeneity: Chi ² = 14	.67, df = 8	(P = 0.0)	$(77); 1^2 = 4$	5%							
Test for overall effect: Z	= 2.93 (P =	= 0.003)									
Total (95% CI)		2743		7973	100.0%	1.16 [1.05, 1.29]			+		
Total events	1016		2735	š							
Heterogeneity: Chi ² = 21				39%			0.01	0.1	-	10	100
Test for overall effect: Z							0.01	0.1 GnRF	1 I-a blank	10	10

Test for subaroup differences: Chi² = 0.28. df = 1 (P = 0.59). l² = 0%

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



Forest plot of CPR,MR and LBR

Study or Subgroup 1.1.1 clinical pregnancy Di XIE 2018 Muzi Li 2021 Qianrong Qi 2020 Zhihong Niu 2013 Subtotal (95% CI) Total events		16 160	7	Total	Weight	M-H. Random, 95% Cl		M-H. Random, 95% Cl	
Di XIE 2018 Muzi Li 2021 Qianrong Qi 2020 Zhihong Niu 2013 Subtotal (95% CI)	10 65 60	160		10					
Muzi Li 2021 Qianrong Qi 2020 Zhihong Niu 2013 Subtotal (95% CI)	65 60	160		10					
Qianrong Qi 2020 Zhihong Niu 2013 Subtotal (95% CI)	60	10.7.7.7.		19	13.2%	2.86 [0.72, 11.31]			
Zhihong Niu 2013 Subtotal (95% CI)	1.1573.0		77	181	29.4%	0.92 [0.60, 1.42]			
Subtotal (95% CI)	100	108	89	206	28.7%	1.64 [1.03, 2.63]			
	100	194	36	145	28.7%	3.22 [2.01, 5.16]			
Total events	00110404	478	00202	551	100.0%	1.81 [0.96, 3.43]		-	
	235		209				·		
Heterogeneity: Tau ² = 0.	31; Chi ²	= 15.30	, df = 3 (F	P = 0.0	02); l ² = 80)%			
Test for overall effect: Z	= 1.82 (F	P = 0.07)						
1.1.2 miscarriage rate									
Di XIE 2018	2	10	2	7	5.2%	0.63 [0.07, 5.97]			
Muzi Li 2021	27	65	34	77	59.6%	0.90 [0.46, 1.75]			
Qianrong Qi 2020	10	60	16	89	35.2%	0.91 [0.38, 2.17]			
Subtotal (95% CI)	2264	135		173	100.0%	0.89 [0.53, 1.48]	_	•	
Total events	39		52			26 D. D. D.	-		
Heterogeneity: Tau ² = 0.	00; Chi ²	= 0.10,	df = 2 (P	= 0.95); l ² = 0%				
Test for overall effect: Z	= 0.46 (F	P = 0.65)						
1.1.3 live birth rate									
Di XIE 2018	8	16	4	19	9.9%	3.75 [0.86, 16.40]		<u> </u>	
Muzi Li 2021	38	160	43	181	44.2%	1.00 [0.61, 1.65]			
Qianrong Qi 2020	47	108	69	206	45.9%	1.53 [0.95, 2.47]		-	
Subtotal (95% CI)		284		406	100.0%	1.39 [0.84, 2.27]		◆	
Total events	93		116						
Heterogeneity: Tau ² = 0.	08; Chi ²	= 3.48,	df = 2 (P	= 0.18); l ² = 43%	Ê.			
Test for overall effect: Z									
									404
							0.01 0.1	1 10 erimental] Favours [control]	100

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

- 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

0.01

Favours [experimental] Favours [control]



Forest plot of CPR, MR and LBR

	AC+Gn	RHa	AC			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.1.1 clinical pregnancy	rate						
Di XIE 2018	33	48	39	98	12.8%	3.33 [1.60, 6.92]	
Hsiao Wen Tsai 2017	21	29	18	31	7.3%	1.90 [0.64, 5.60]	
L Luo 2021	109	172	111	171	21.5%	0.94 [0.60, 1.45]	
Qianrong Qi 2020	16	32	182	354	13.0%	0.95 [0.46, 1.95]	
Shabnam Salemi 2021	29	93	32	95	15.9%	0.89 [0.48, 1.64]	
Xitong Liu 2021	394	523	811	1115	29.5%	1.14 [0.90, 1.45]	T
Subtotal (95% CI)		897		1864	100.0%	1.22 [0.88, 1.70]	•
Total events	602		1193				
Heterogeneity: Tau ² = 0.0)8; Chi ² =	10.70, d	if = 5 (P =	: 0.06);	I ² = 53%		
Test for overall effect: Z =	: 1.20 (P =	= 0.23)					
5.1.2 miscarriage rate	1						
Di XIE 2018	5	33	9	39	7.5%	0.60 [0.18, 1.99]	
L Luo 2021	16	109	13	111	16.5%	1.30 [0.59, 2.84]	
Qianrong Qi 2020	1	16	58	182	2.7%	0.14 [0.02, 1.11]	
Shabnam Salemi 2021	9	29	11	32	9.4%	0.86 [0.29, 2.51]	
Xitong Liu 2021	73	394	159	811	63.9%	0.93 [0.69, 1.27]	-
Subtotal (95% CI)	10	581	155	1175		0.90 [0.64, 1.26]	
Total events	104		250				1
Heterogeneity: Tau ² = 0.0		4.50. df		0.34): 1	² = 11%		
Test for overall effect: Z =			. (.				
	,	,					
5.1.3 live birth rate							
Di XIE 2018	27	48	30	98	14.2%	2.91 [1.43, 5.95]	
L Luo 2021	85	172	92	171	24.0%	0.84 [0.55, 1.28]	
Qianrong Qi 2020	14	32	122	354	13.8%	1.48 [0.71, 3.08]	
Shabnam Salemi 2021	20	93	21	95	14.8%	0.97 [0.48, 1.93]	
Xitong Liu 2021	316	523	619	1115	33.3%	1.22 [0.99, 1.51]	
Subtotal (95% CI)		868		1833	100.0%	1.25 [0.89, 1.76]	•
Total events	462		884				
Heterogeneity: Tau ² = 0.0			= 4 (P =	0.05); l	² = 57%		
Test for overall effect: Z =	= 1.30 (P =	= 0.19)					

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

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Li et al, Archives of Gynecology and Obstetrics, 2022

Test for subaroup differences: Chi² = 2.31. df = 2 (P = 0.32). I² = 13.3%

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



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

Characteristics		Group A (<i>n</i> = 93)	Group B (n = 95)	P-value	OR/ mean difference	95% CI	
						Lower	Upper
Total dose of oestradiol adminis- tered, 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, <i>n</i>		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	Preeclampsia	0	2 (9/5%)	0.30	0.20	0.01	4.22
pregnancy	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.

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- 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

Agenda



4. Obstetric and neonatal outcomes

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



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 Wu¹ • Ping Zhou² • Xiaona Lin² • Shasha Wang² • Songying Zhang²

True-NC associated with reduced risks of:

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

Outcomes	No of eve	ats/total	Odds ratio	Weight	
Outconk 3	tNC	AC	(95% CI)		(%)
PIH					
Jing 2019	162/3872	74/1025		0.56 (0.42, 0.75)	98.5
von Versen-Hoynck 2020	1/12	5/18		0.24 (0.02, 2.34)	1.5
Random, total (I ² =0%)	163/3884	79/1043	♦	0.55 (0.42, 0.73)	100
GDM					
Jing 2019	314/3872	84/1025	+	0.99 (0.77, 1.27)	100
PP					
Healy 2010	44/2045	7/458		1.42 (0.63, 3.17)	48.5
Rombauts 2014	21/1231	12/355		0.50 (0.24, 1.02)	51.5
Random, total (I ² =72.9%)	65/3276	19/813	<	0.83 (0.29, 2.33)	100
РРН		1000000			-
Healy 2010	221/2045	93/458	•	0.48 (0.36, 0.62)	100
LBW		10000 x200000			
Ding 2016	17/188	43/485	1	1.02 (0.57, 1.84)	6.2
Jing 2019	1077/4942	266/1263	- T	1.04 (0.90, 1.22)	93.6
von Versen-Hoynck 2020	0/12	1/18	•	0.47 (0.02, 12.43)	0.2
Random, total (I ² =0%)	1094/5142	310/1766	Î	1.04 (0.90, 1.21)	100
VLBW			92011 H200		
Ding 2016	0/188	5/485	•	0.23 (0.01, 4.21)	1.5
Jing 2019	149/4942	39/1263	- 1	0.98 (0.68, 1.40)	98.5
von Versen-Hoynck 2020	0/12	0/18	-	0.51 (0.35, 0.69)	
Random, total (I ² =0%)	149/5142	44/1766	4	0.96 (0.67, 1.36)	100
РТВ	12.250 motors	10220-00			1.0-2362400
Ding 2016	25/146	68/382		0.95 (0.58, 1.58)	7.2
Jing 2019	1235/4942	332/1263		0.93 (0.81, 1.08)	92.6
von Versen-Hoynck 2020	0/12	2/18	•	0.26 (0.01, 6.00)	0.2
Random, total (I ² =0%)	1260/5100	402/1663	<u> </u>	0.93 (0.82, 1.07)	100
VPTB	0/146	2/202		0.52 (0.02, 10.02)	
Ding 2016	0/146	2/382	-	0.52 (0.03, 10.89)	1.4
Jing 2019	90/4942 90/5088	47/1263 49/1645	•	0.48 (0.34, 0.69)	98.6 100
Random, total (I ² =0%)	90/5088	49/1045		0.48 (0.34, 0.69)	100
SGA Jing 2019	461/4942	109/1263	-	1.09 (0.88, 1.36)	100
	401/4942	109/1203		1.09 (0.86, 1.30)	100
LGA Jing 2019	781/4942	235/1263		0.82 (0.70, 0.97)	99.1
Sara 2016	17/103	2/8		0.59 (0.11, 3.19)	0.9
	798/5045	237/1271	~	0.82 (0.70, 0.96)	100
Random, total (1²=0%)	/98/3043	237/12/1		0.82 (0.70, 0.96)	100
PM	2214042	24/12/2	-	0.00 (0.10.0.00)	
Jing 2019	23/4942	26/1263	-	0.22 (0.13, 0.39)	66.4
Levi Setti 2020	1/183	0/218	-	3.59 (0.15, 88.70)	33.6
Random, total (1 ² =65.1%)	24/5125	26/1481		0.57 (0.04, 7.64)	100
			0 1 2 3 4		

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



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REVIEW

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

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M-NC associated with reduced risks of:

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

Ortoone	No of eve	nts/total	Odds ratio		Weight	
Outcomes	mNC	AC	(95% CI)		(%)	
PIH						
Guan 2016	13/184	20/271		95 (0.46, 1.97)	25.0	
Ishii 2018	8/117	53/406		49 (0.23, 1.06)	23.2	
Zong 2020	166/4727	130/1642	• 0	42 (0.33, 0.54)	51.8	
Random, total (I ² =54.5%)	187/5028	203/2319	0.:	54 (0.33, 0.87)	100	
GDM						
Guan 2016	5/184	5/271		49 (0.42, 5.21)	3.3	
Ishii 2018	4/117	11/406		27 (0.40, 4.07)	3.8	
Zong 2020	247/4727	106/1642		80 (0.63, 1.01)	92.9	
Random, total (I ² =0%)	256/5028	122/2319	• 0.	83 (0.66, 1.04)	100	
PP						
Zong 2020	47/4727	24/1642		68 (0.41, 1.11)	100	
LBW						
Guo 2016	32/107	12/72	- 2.	13 (1.01, 4.50)	46.2	
Zong 2020	130/4727	74/1642	- 0.	60 (0.45, 0.80)	53.8	
Random, total (I ² =89.7%)	162/4834	86/1714		08 (0.31, 3.74)	100	
РТВ						
Guan 2016	39/184	60/271		95 (0.60, 1.49)	34.6	
Guo 2016	20/93	6/59	▶ 2.	42 (0.91, 6.44)	19.2	
Kang 2018	1/9	2/16	• 0.8	38 (0.07, 11.24)	4.5	
Zong 2020	227/4727	129/1642	■ 0.:	59 (0.47, 0.74)	41.7	
Random, total (I ² =70.1%)	287/5013	197/1988	0.9	93 (0.53, 1.64)	100	
VPTB						
Zong 2020	39/4727	18/1642		75 (0.43, 1.32)	100	
SGA						
Zong 2020	165/4727	48/1642	1.1	20 (0.87, 1.67)	100	
LGA						
Zong 2020	1104/4727	430/1642	• 0.1	86 (0.76, 0.98)	100	
PM						
Guan 2016	4/215	5/351		31 (0.35, 4.94)	84.0	
Levi Setti 2020	2/753	0/218	→ 1.4	5 (0.07, 30.39)	16.0	
Random, total (I ² =0%)	6/968	5/569		33 (0.40, 4.50)	100	
			0 1 2 3 4 5			
		Favour	s mNC Favours AC			

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



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

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HR cycles associated with Higher risk:

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

		Treatment		Programmed FI	ET 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 (0.70–1.69)	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	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)	

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).

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



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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

Endometrial preparation and maternal and obstetrical outcomes after frozen blastocyst transfer

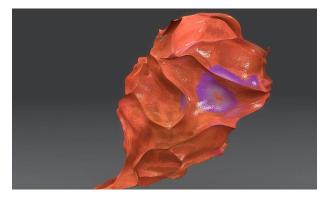
Kazumi Takeshima, MD, PhD; Kenji Ezoe, PhD; Sachie Onogi, MD; Nami Kawasaki, MS; Tomoko Kuroda, MD, PhD; Keiichi Kato, MD, PhD

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

Adverse maternal outcomes	Group	OR (95% confidence intervals)	<i>P</i> value	aOR ^a (95% confidence intervals)	<i>P</i> 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

6

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





- 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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