
MARCH 19 - 23
PCRS 2025
PACIFIC WAVES - EXPLORING SCIENTIFIC FRONTIERS IN AN EVOLVING SOCIETY
INDIAN WELLS, CA
PACIFIC COAST
REPRODUCTIVE
SOCIETY

Frozen Embryo Transfer: Exploring the Roles of the Corpus luteum and Relaxin in Pregnancy Outcomes

Frauke von Versen-Höynck, MD, MSc

Hannover Medical School, Germany

Disclosure Slide

Neither I nor members of my immediate family have any actual or potential financial interests to disclose relating to the content of this presentation.

Assessment Statement:

This session underscores how the absence of a corpus luteum in frozen embryo transfer (FET) cycles affects hormonal pathways and pregnancy outcomes, highlighting corpus luteum hormone‘s role in maternal adaptation and the need for clinical strategies to optimize reproductive health.

Expected Learning Outcomes:

1. Recognize the role of the corpus luteum in reproductive physiology
2. Demonstrate knowledge about the hormonal differences between FET cycle protocols
3. Review recent evidence linking the absence of the corpus luteum in FET cycles to increased risks of complications such as preeclampsia
4. Examine the influence of the corpus luteum on maternal adaptation to pregnancy

Presentation outline

Physiological and clinical background

Corpus luteum, ART and pregnancy outcomes

FET – The dilemma of choice

Research perspectives and open questions

Presentation outline

Physiological and clinical background

Corpus luteum, ART and pregnancy outcomes

FET – The dilemma of choice

Research perspectives and open questions

Differences in pregnancy outcomes of Frozen (FET) and Fresh Embryo Transfer

FET risk LOWER than fresh transfer

- Low birth weight
- Very low birth weight
- Very preterm birth
- Small for gestational age
- Placenta previa
- Placental abruption
- Perinatal mortality

FET risk HIGHER than fresh transfer

- **Pregnancy-induced hypertension / preeclampsia**
- Postpartum hemorrhage
- Large for gestational age

Sha 2018, *Fertil Steril; 31 studies*

Preeclampsia

Increased Preeclampsia Risk and Reduced Aortic Compliance With In Vitro Fertilization Cycles in the Absence of a Corpus Luteum

Frauke von Versen-Höynck,* Amelia M. Schaub,* Yueh-Yun Chi, Kuei-Hsun Chiu, Jing Liu, Melissa Lingis, R. Stan Williams, Alice Rhoton-Vlasak, Wilmer W. Nichols, Raquel R. Fleischmann, Wendy Zhang, Virginia D. Winn, Mark S. Segal, Kirk P. Conrad,† Valerie L. Baker†

von Versen-Höynck et al., *Hypertension 2019*

Preeclampsia

Maternal Vascular Health in Pregnancy and Postpartum After Assisted Reproduction

Frauke von Versen-Höynck, Sebastian Häckl, Elif Seda Selamet Tierney, Kirk P. Conrad, Valerie L. Baker, Virginia D. Winn

Preeclampsia

Increased Preeclampsia Risk and Reduced Aortic Compliance With In Vitro Fertilization Cycles in the Absence of a Corpus Luteum

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Original Article

Absent or Excessive Corpus Luteum Number Is Associated With Altered Maternal Vascular Health in Early Pregnancy

Frauke von Versen-Höynck, Purnima Narasimhan, Elif Seda Selamet Tierney, Nadine Martinez, Kirk P. Conrad, Valerie L. Baker, Virginia D. Winn

von Versen-Höynck et al., *Hypertension 2019 & 2020*

Preeclampsia

Human Reproduction Update, pp. 1–14, 2021
https://doi.org/10.1093/humupd/dmab037
human reproduction update

Effects of different frozen embryo transfer regimens on abnormalities of fetal weight: a systematic review and meta-analysis

Kendal Rosalik[1], Samantha Carson[2], Justin Pilgrim[2], Jacqueline Luizzi[3], Gary Levy[2], Ryan Heitmann[4], and Bruc

Journal of Assisted Reproduction and Genetics
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 Wa

RBMO

REVIEW

Lower risk of
n natura
mb

erse perinatal outcomes
rtificial frozen–thawed
les: a systematic review

is medical degree from Valparaiso School of Medicine,
ent of Obstetrics and Gynecology, Universitat
tly, his main research project is on safety in assisted
aternal and perinatal outcomes after IVF.
rinós[1,3,4],

ajog.org

Clinical Opinion

Potential role of the corpus luteum in maternal cardiovascular adaptation to pregnancy and preeclampsia risk

Kirk P. Conrad, MD; Frauke von Versen-Höynck, MD; Valerie L. Baker, MD

Gynecological Endocrinology

GYNECOLOGICAL ENDOCRINOLOGY

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/igy

Stimulated cycle versus artificial cycle embryo transfer in patients with polycystic ovary syndrome: a Meta-analysis

Mei Fang Zeng , Xin Zhou & Jin Liang Duan

To cite this article: Mei Fang Zeng , Xin Zhou & Jin Liang Duan (2021): Stimulated cycle ve
artificial cycle for frozen embryo transfer in patients with polycystic ovary syndrome: a Meta-
analysis, Gynecological Endocrinology, DOI: 10.1080/09513590.2020.1867976

With Alte

Should any use of artificial cycle regimen for frozen-thawed embryo transfer in women capable of ovulation be abandoned: yes, but what's next for FET cycle practice and research?

Frauke von Versen-Höynck [1] and Georg Griesinger [2,*]

·docrinology (2022) 20:62
·o/s12958-022-00931-4

REVIEW

sur Systematic review update and meta-analysis
N. of randomized and non-randomized controlled
trials of ovarian stimulation versus artificial cycle
for endometrial preparation prior to frozen
embryo transfer in women with poly
syndrome

Reproductive Biology and Endocrinology

Open Access

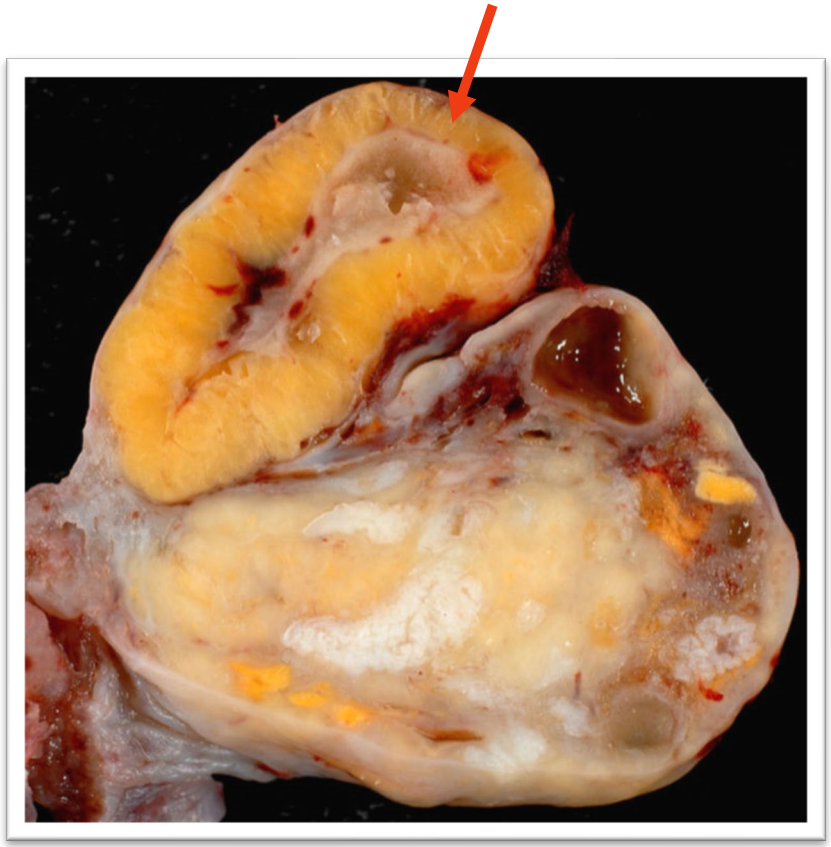
CURRENT OPINION

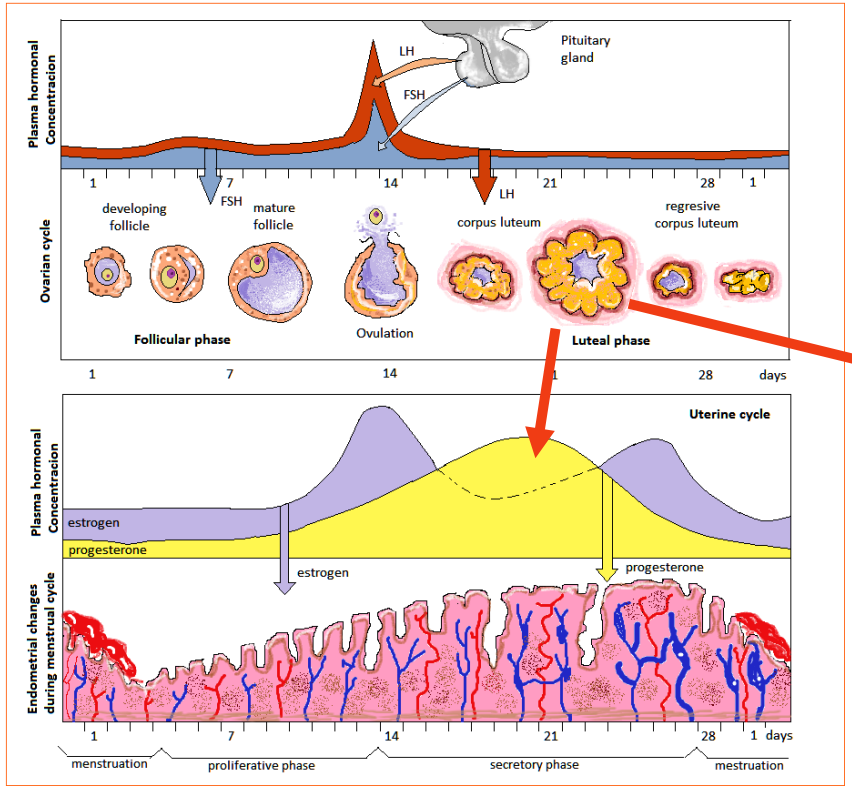
The future of frozen-thawed embryo transfer in hormone replacement therapy cycles

Kristine Løssl[a], Anne Lærke Spangmose[a], Louise Laub Asserhøj[a], Tine Vrist Dam[a] and Anja Pinborg[a,b]

Frauke von Versen-Höynck, Purnima Narasimhan, Elif Seda Selamet
Kirk P. Conrad, Valerie L. Baker, Virginia D. Winn

Corpus luteum



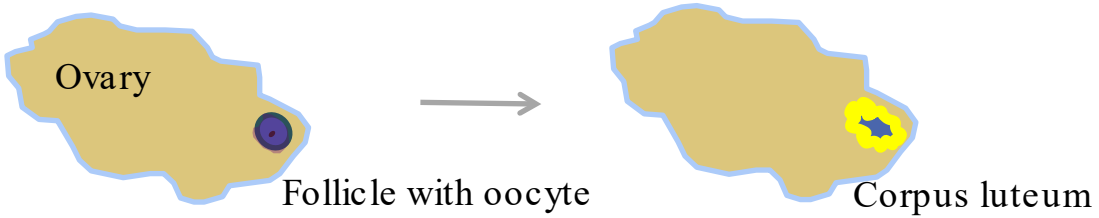


www.flickr.com, Ed Uthman

Physiologic background

Physiologic background

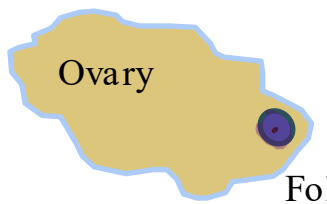
Unassisted



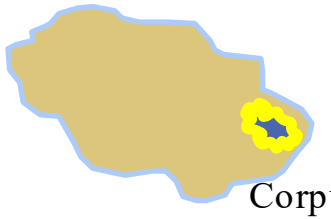
HRT; hormone replacement therapy, VEGF; vascular endothelial growth factor

Physiologic background

Unassisted



Follicle with oocyte



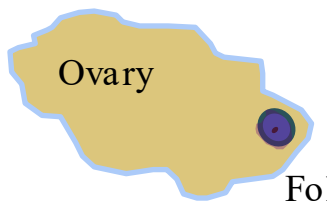
Corpus luteum

Vasoactive products:
Estradiol, progesterone
Estrogen metabolites
VEGF
Pro-Renin, Inhibin
Relaxin
…?

HRT; hormone replacement therapy, VEGF; vascular endothelial growth factor

Physiologic background

Unassisted



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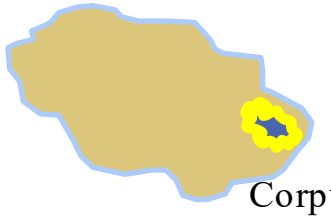

Corpus luteum

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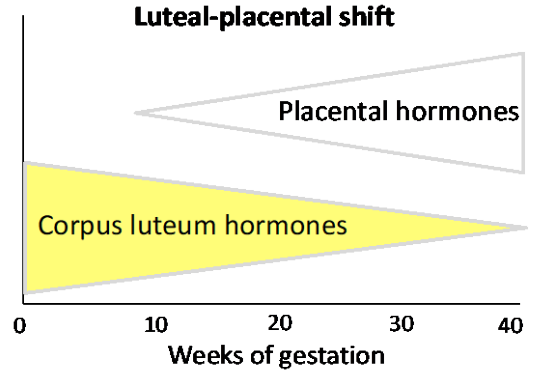

HRT; hormone replacement therapy, VEGF; vascular endothelial growth factor

Physiologic background

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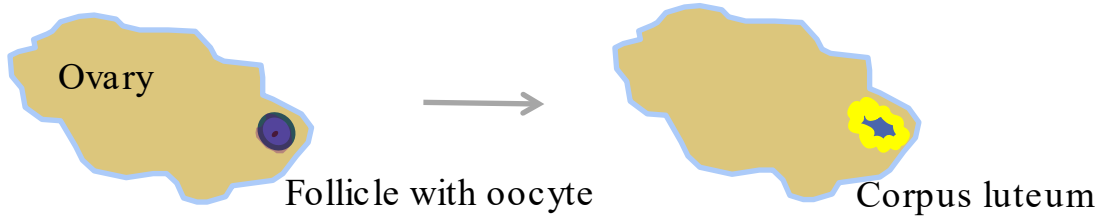

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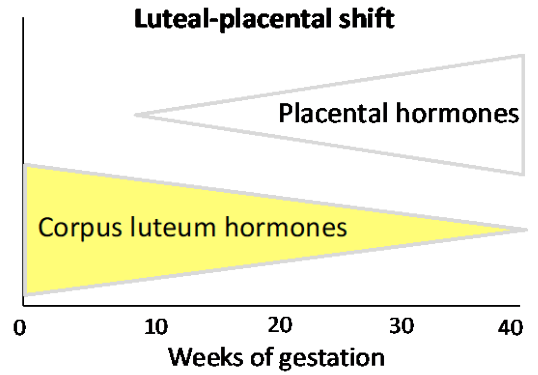


Assisted

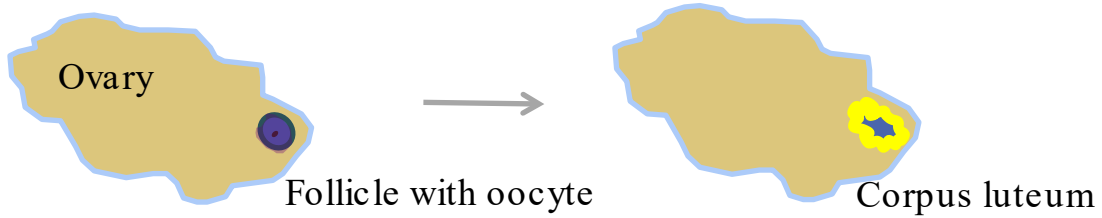
Fresh embryo transfer

Frozen embryo transfer

HRT; hormone replacement therapy, VEGF; vascular endothelial growth factor

Physiologic background

Unassisted



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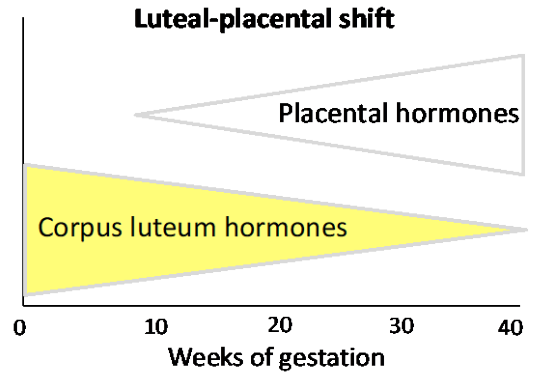
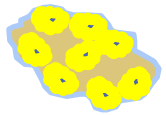


Assisted

Fresh embryo transfer



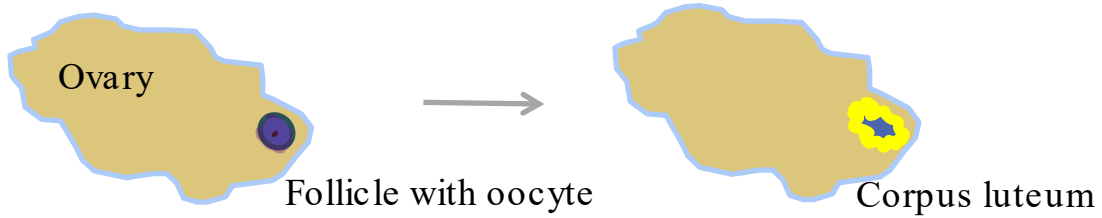
multiple corpora lutea

Frozen embryo transfer

HRT; hormone replacement therapy, VEGF; vascular endothelial growth factor

Physiologic background

Unassisted



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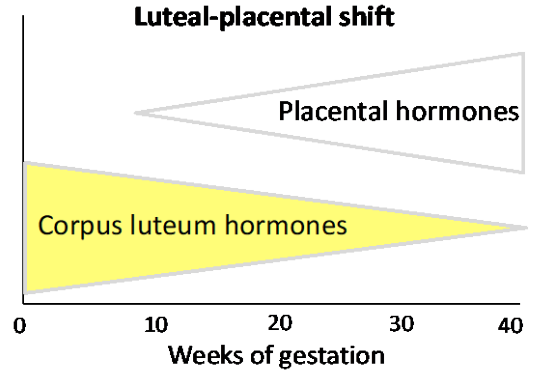
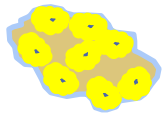


Assisted

Fresh embryo transfer



multiple corpora lutea

Frozen embryo transfer

1) Ovulatory

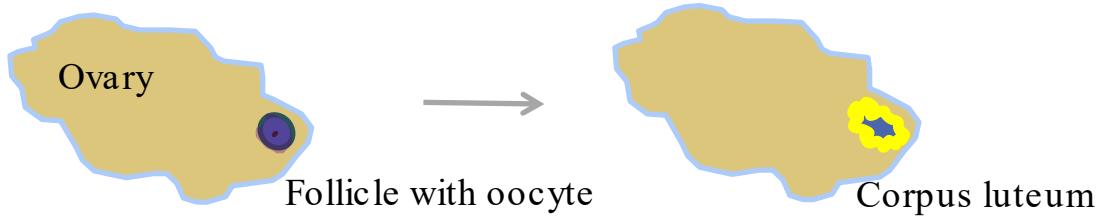
Corpus luteum

Natural cycle
Ovulation induction cycle
(clomiphene, letrozole, gonadotrophins)

HRT; hormone replacement therapy, VEGF; vascular endothelial growth factor

Physiologic background

Unassisted



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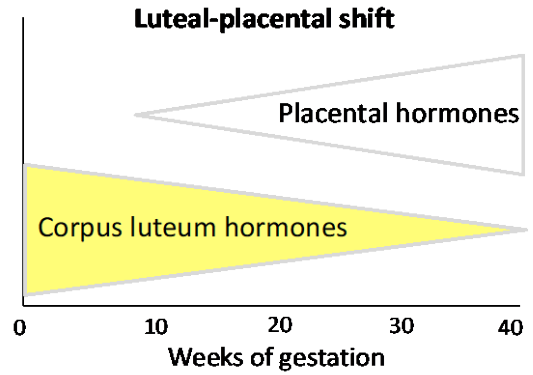
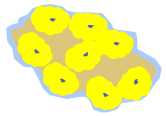


Assisted

Fresh embryo transfer



multiple corpora lutea

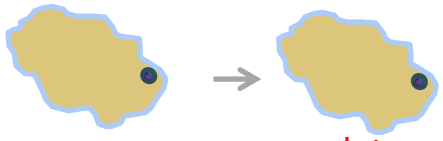
Frozen embryo transfer

1) Ovulatory

Corpus luteum

Natural cycle
Ovulation induction cycle
(clomiphene, letrozole, gonadotrophins)

2) Anovulatory



no corpus luteum

Programmed/artificial/HRT cycle
(estradiol, progesterone)

HRT; hormone replacement therapy, VEGF; vascular endothelial growth factor

Presentation outline

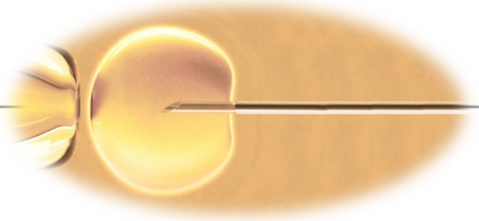
Physiological and clinical background

Corpus luteum, ART and pregnancy outcomes

FET – The dilemma of choice

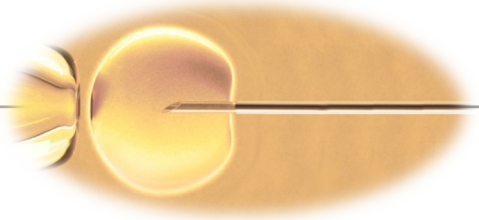
Research perspectives and open questions

Research question



Assisted Reproduction → **Adverse obstetrical outcomes; e.g. preeclampsia**

Research question



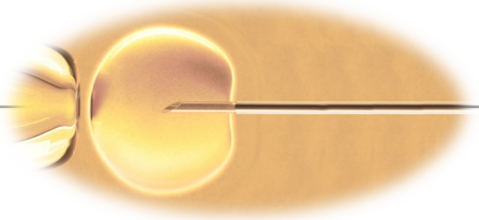
Assisted Reproduction

Fresh embryo transfer

Adverse obstetrical outcomes; e.g. preeclampsia

Frozen embryo transfer ↑ ↑

Research question



Assisted Reproduction

Fresh embryo transfer

Adverse obstetrical outcomes; e.g. preeclampsia

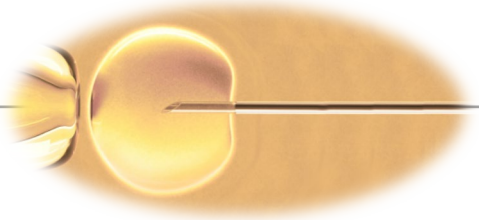
Frozen embryo transfer ↑ ↑

<u>Hypotheses:</u>

The presence/absence of corpora lutea at conception impacts:

1. **Preeclampsia risk**
2. **Maternal vascular adaptation in pregnancy**

Research question



Assisted Reproduction

Fresh embryo transfer

→

Adverse obstetrical outcomes;
e.g. preeclampsia

Frozen embryo transfer ↑ ↑

Hypotheses:

The presence/absence of corpora lutea at conception impacts:

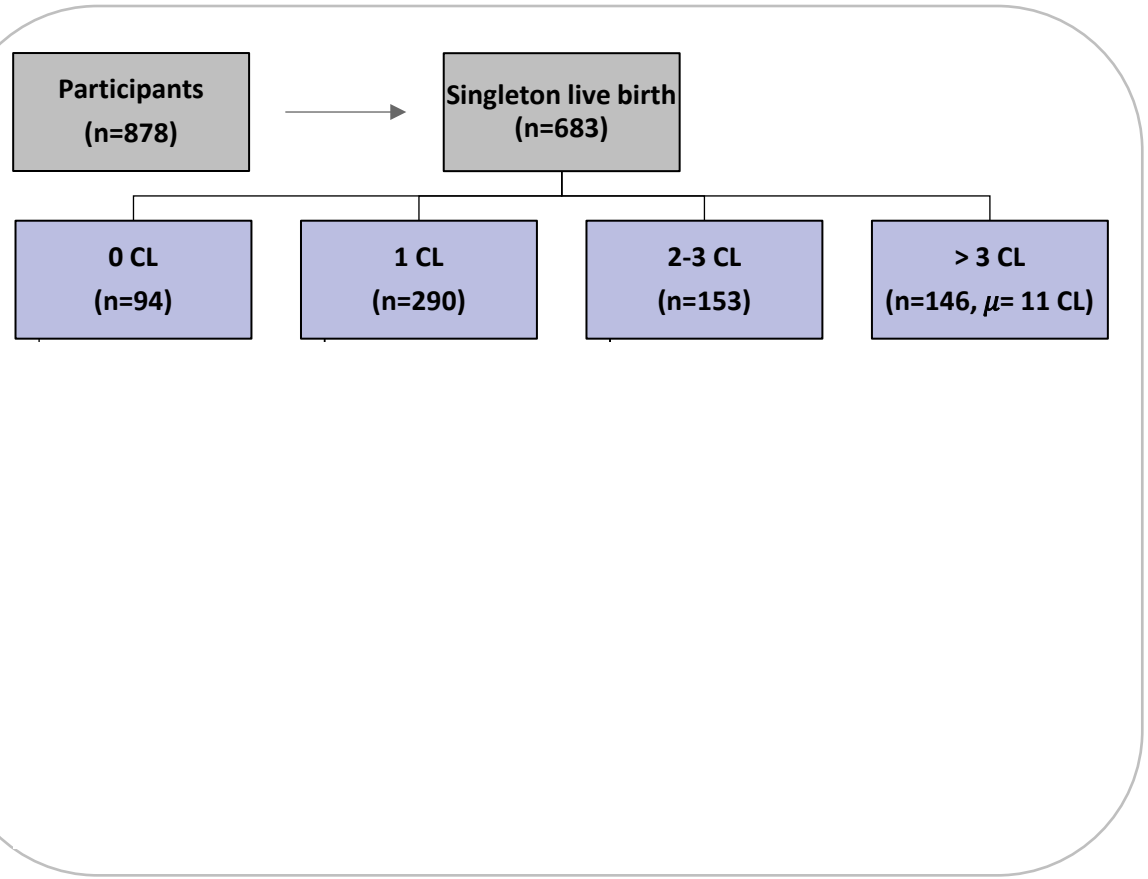
1. **Preeclampsia risk**
2. **Maternal vascular adaptation in pregnancy**

Study design

Recruitment

6-8 wks

Delivery



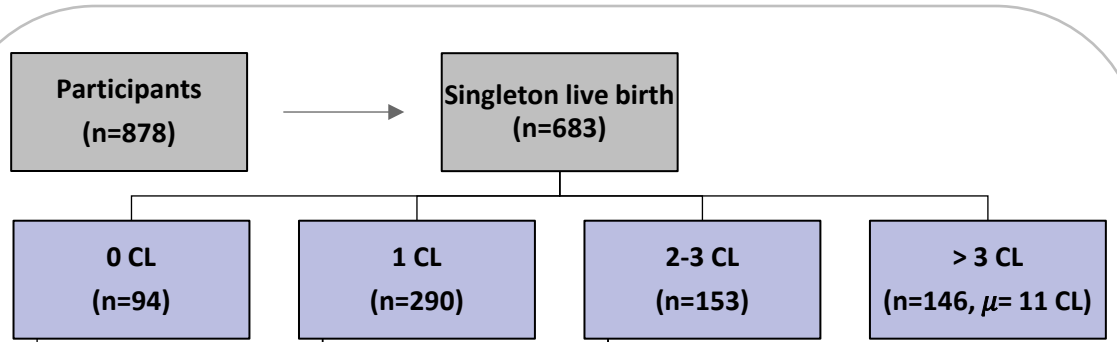
von Versen-Höynck et al., *Hypertension 2019*

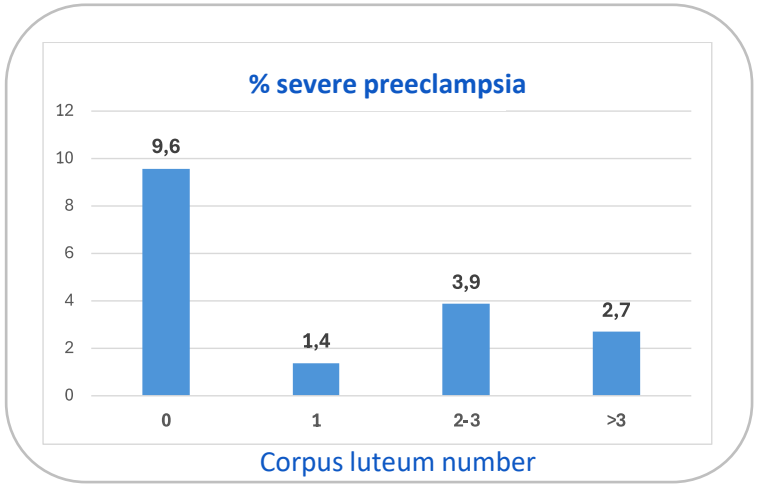
CL; corpus luteum, FET; Frozen embryo transfer, IUI; intrauterine insemination

Study results

Recruitment

6-8 wks **Delivery**





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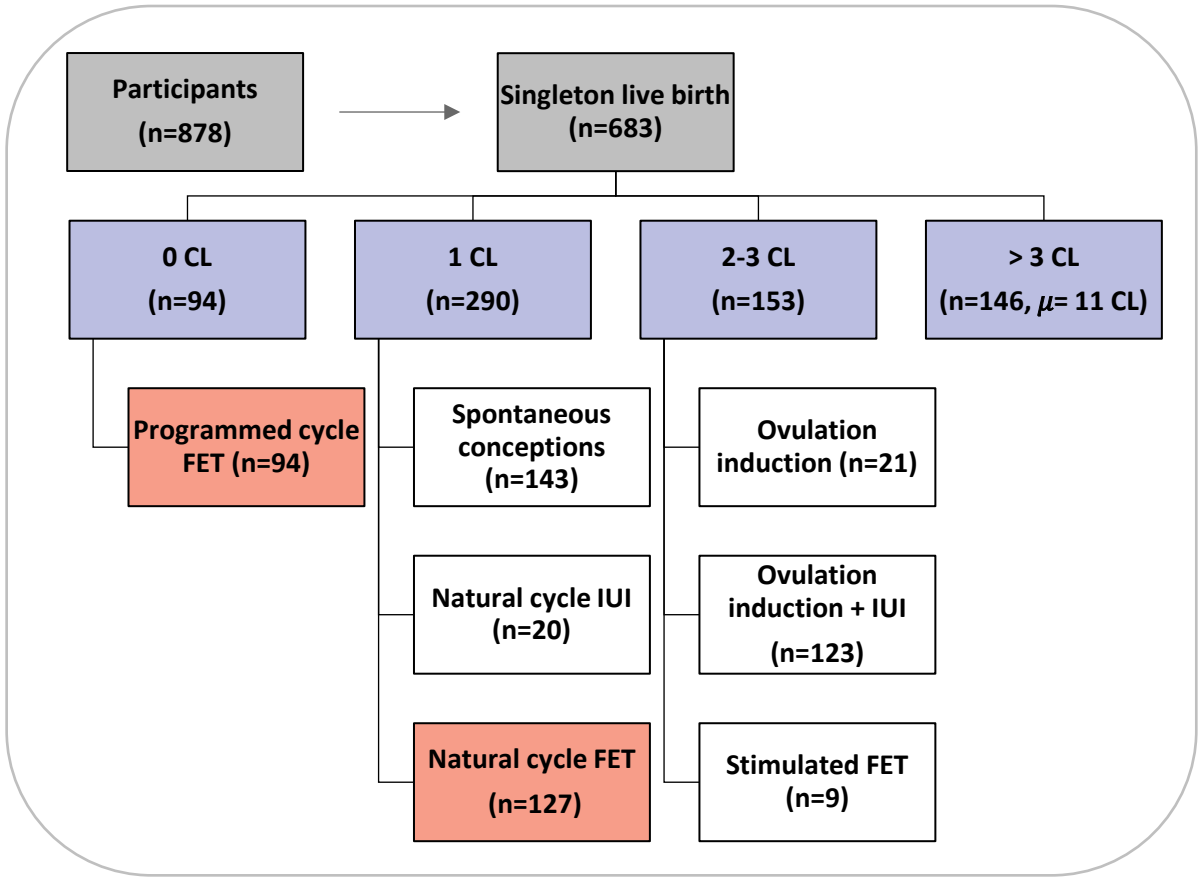
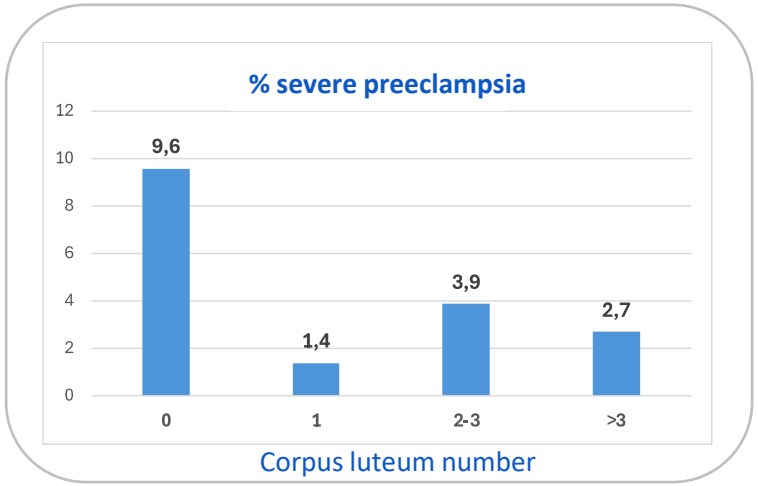
Study results

Recruitment

6-8 wks → Delivery





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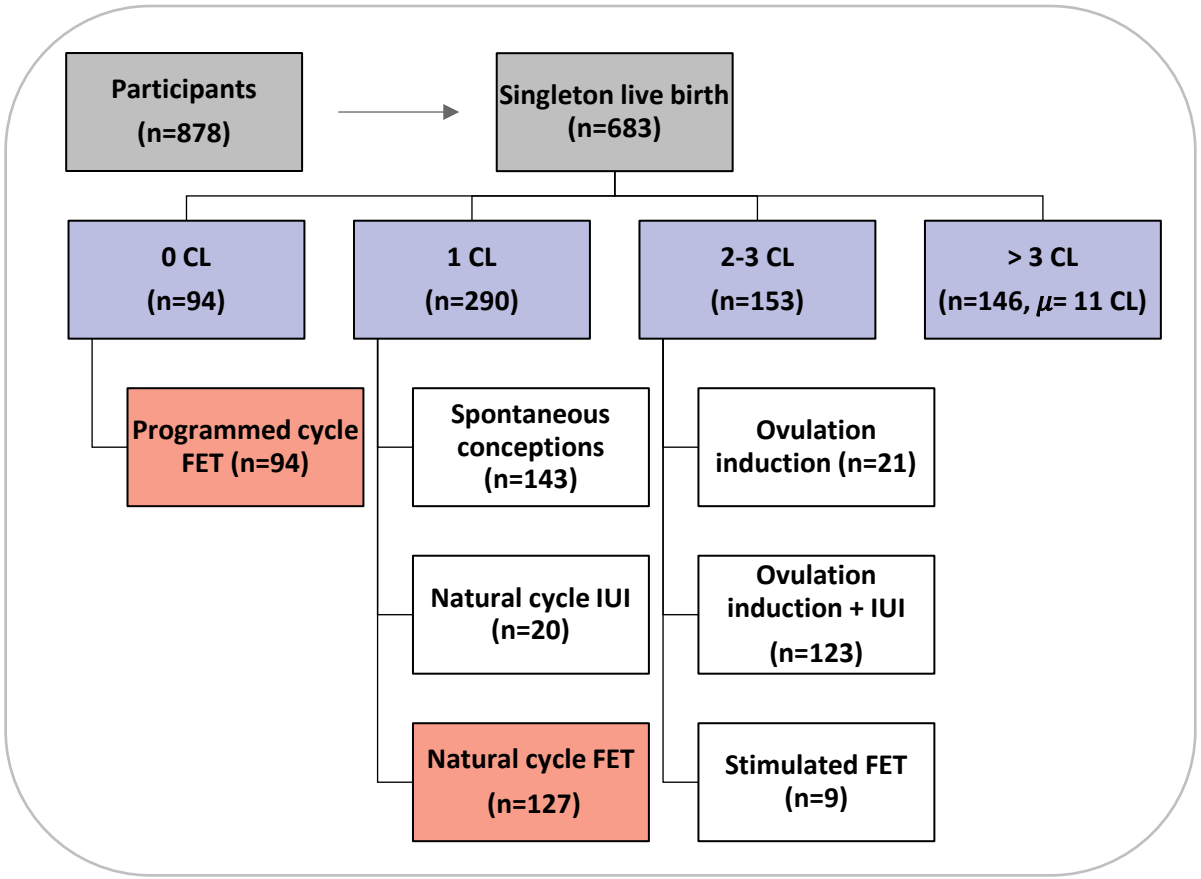

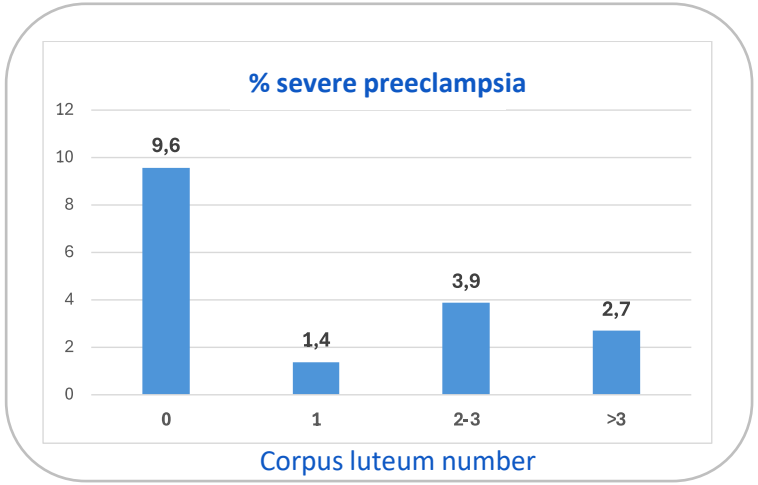

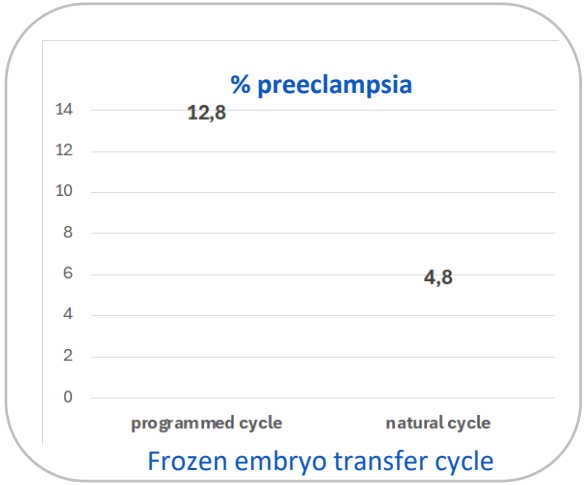

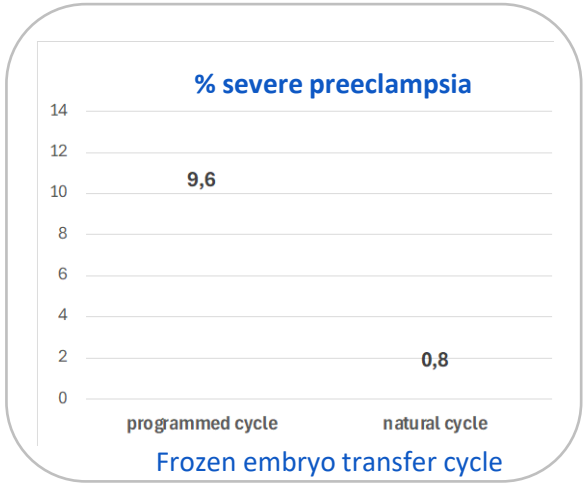

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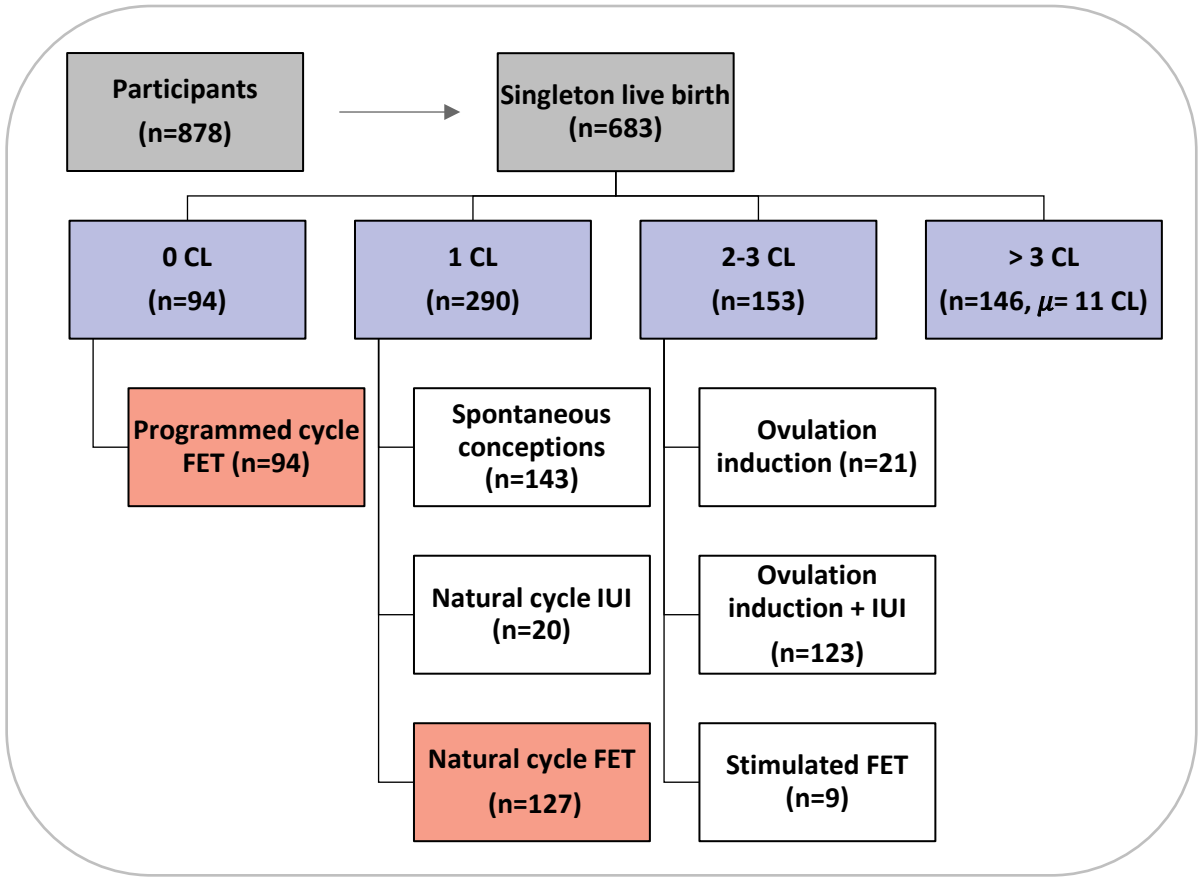
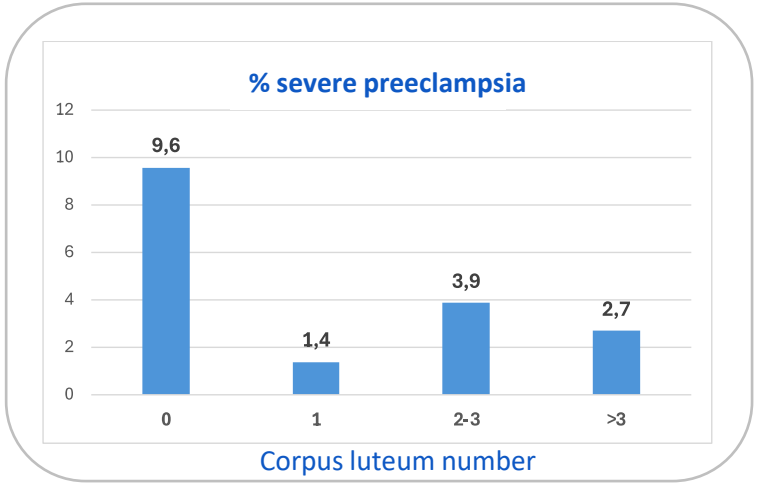
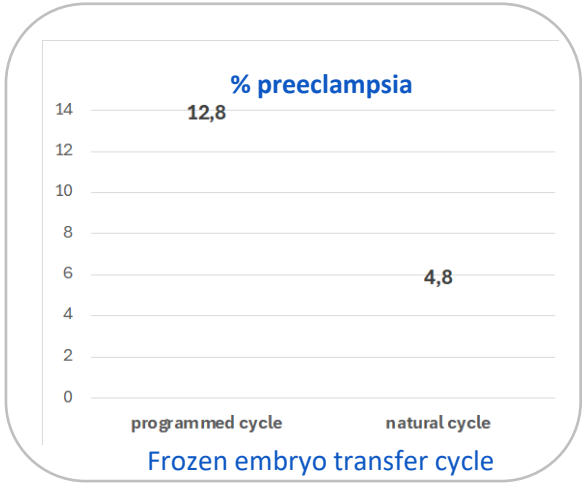
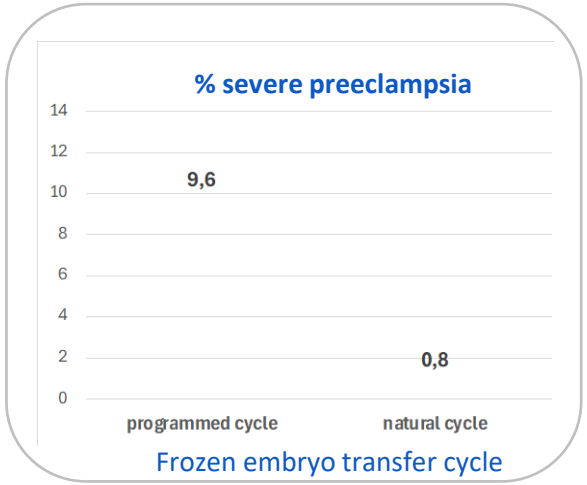








AOR (95% CI)	P-value
3.5 (1.2- 11.9)	0.03

AOR (95% CI)	P-value
15.1 (12.6 – 286.3)	0.01

von Versen-Höynck et al., *Hypertension 2019*

CL; corpus luteum, FET; Frozen embryo transfer, IUI; intrauterine insemination

Confirmation of Findings Through Observational Studies

	Hypertensive disease of pregnancy	Preeclampsia	Gestational hypertension
natural vs. programmed*	OR 0.61 (0.50; 0.73); N=10	OR 0.47 (0.42; 0.53); N=4	OR 0.72 (0.51; 1.02); N=3
programmed vs. natural**	OR 1.90 (1.64; 2.20); N=12	OR 2.11 (1.87; 2.39); N=7	OR 1.45 (1.03;2.07); N=4
programmed vs. true natural**	OR 1.96 (1.53; 2.51); N=4	OR 1.98 (1.56; 2.53); N=2	OR 1.05 (0.75; 1.46); N=2
programmed vs. modified natural**	OR 2.19 (1.36; 3.52); N=2	OR 2.91 (1.67; 5.08); N=2	OR 4.16 (0.79; 22.01); N=1
programmed vs. stimulated**	OR 1.60 (1.43; 1.78); N=5	OR 1.34 (0.60; 2.96); N=2	OR 1.05 (0.75; 1.46); N=2
modified vs. true natural**	OR 0.73 (0.37; 1.44); N=1	OR 0.50 (0.23; 1.09); N=1	-
stimulated vs. natural**	OR 1.31 (1.00;1.71); N=4	OR 2.24 (1.48-3.33); N=1	OR 1.32 (0.99;1.77); N=2

*Moreno-Sepulveda, *RBMO 2021*, **Busnelli, *Hum Reprod 2022*

Confirmation of Findings Through Observational Studies

	Hypertensive disease of pregnancy	Preeclampsia	Gestational hypertension
natural vs. programmed*	OR 0.61 (0.50; 0.73); N=10	OR 0.47 (0.42; 0.53); N=4	OR 0.72 (0.51; 1.02); N=3
natural**			
programmed vs. modified natural**	OR 2.19 (1.36; 3.52); N=2	OR 2.91 (1.67; 5.08); N=2	OR 4.16 (0.79; 22.01); N=1
programmed vs. stimulated**	OR 1.60 (1.43; 1.78); N=5	OR 1.34 (0.60; 2.96); N=2	OR 1.05 (0.75; 1.46); N=2
modified vs. true natural**	OR 0.73 (0.37; 1.44); N=1	OR 0.50 (0.23; 1.09); N=1	-
stimulated vs. natural**	OR 1.31 (1.00;1.71); N=4	OR 2.24 (1.48-3.33); N=1	OR 1.32 (0.99;1.77); N=2

Higher risk for hypertensive disease and preeclampsia in programmed FET cycles

Results from RCTs awaited

*Moreno-Sepulveda, *RBMO 2021*, **Busnelli, *Hum Reprod 2022*

Early vs. late onset preeclampsia

Increased Preeclampsia Risk and Reduced Aortic Compliance With In Vitro Fertilization Cycles in the Absence of a Corpus Luteum

Frauke von Versen-Höynck,* Amelia M. Schaub,* Yueh-Yun Chi, Kuei-Hsun Chiu, Jing Liu, Melissa Lingis, R. Stan Williams, Alice Rhoton-Vlasak, Wilmer W. Nichols, Raquel R. Fleischmann, Wendy Zhang, Virginia D. Winn, Mark S. Segal, Kirk P. Conrad,† Valerie L. Baker†

Table 3. Hypertensive Disorders of Pregnancy as a Function of CL Category for the Prospective Cohort Study of Obstetric Outcomes

	CL Category				
Hypertensive Disorder of Pregnancy	0 CL (n=94)	1 CL (n=290)	>1 CL (n=153)	Fresh IVF (n=146)	*P* Value
Gestational hypertension	3 (3.2)	8 (2.8)	3 (2.0)	0	0.14
Preeclampsia	12 (12.8)	14 (4.8)	9 (5.9)	7 (4.7)	0.06
sPE	9 (9.6)	4 (1.4)	6 (3.9)	4 (2.7)	0.004
Early-onset preeclampsia	0	1 (0.3)	1 (0.7)	1 (0.7)	1
HELLP syndrome	0	0	0	2 (1.4)	0.06
Chronic hypertension with superimposed preeclampsia	1 (1.1)	5 (1.7)	0	1 (0.7)	0.41
Eclampsia	0	0	0	0	

von Versen-Höynck et al., *Hypertension 2019*

Early vs. late onset preeclampsia

Journal of Assisted Reproduction and Genetics
https://doi.org/10.1007/s10815-023-02785-0

ASSISTED REPRODUCTION TECHNOLOGIES

Is artificial endometrial preparation more associated with early-onset or late-onset preeclampsia after frozen embryo transfer?

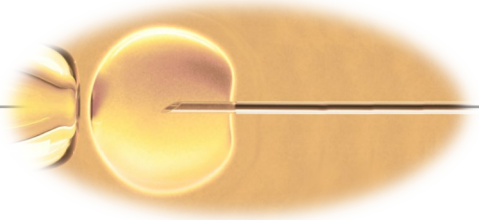
Yue Niu[1,2,3] · Lu Suo[1,2,3] · Dingying Zhao[1,2,3] · Yuhuan Wang[1,2,3] · Ruolan Miao[1,2,3] · Jialin Zou[1,2,3] · Xinwei Han[1,2,3] · Zi-Jiang Chen[1,2,3] · Yan Li[1,2,3] · Daimin Wei[1,2,3]

Table 2 Obstetric and perinatal outcomes by the different protocols

	FreET group $N=11178$	FET-NC group $N=8691$	FET-AC group $N=4260$	P-value
Obstetric outcomes				
Preeclampsia[b,c]	96/11178 (0.9%)	74/8691(0.9%)	93/4260 (2.2%)	<0.001
Early-onset preeclampsia	26/11178 (0.2%)	20/8691 (0.2%)	17/4260 (0.4%)	0.151
Late-onset preeclampsia[b,c]	70/11178 (0.6%)	54/8691(0.6%)	76/4260 (1.8%)	<0.001
Preeclampsia with preterm delivery[b,c]	82/11178 (0.7%)	61/8691 (0.7%)	67/4260 (1.6%)	<0.001
Preeclampsia without preterm delivery [b,c]	14/11178 (0.1%)	13/8691 (0.1%)	26/4260 (0.6%)	<0.001
Gestational hypertension[b,c]	262/11178 (2.3%)	202/8691 (2.3%)	217/4260 (5.1%)	<0.001
Preterm delivery[b,c]	640/11178 (5.7%)	485/8691 (5.6%)	316/4260 (7.4%)	<0.001
Post-term delivery[b,c]	24 /11178 (0.2%)	17/8691 (0.2%)	21/4260 (0.5%)	0.003

Niu, *JARG* 2023

Research question



Assisted Reproduction

Fresh embryo transfer

Adverse obstetrical outcomes; e.g. preeclampsia

Frozen embryo transfer ↑ ↑

Effect of Mode of Conception on Maternal Serum Relaxin, Creatinine, and Sodium Concentrations in an Infertile Population

Reproductive Sciences
2019, Vol. 26(3) 412-419

DOI: 10.1177/1933719118776792
journals.sagepub.com/home/rsx
SAGE

Frauke von Versen-Höynck, MD, MS[1,2], Nairi K. Strauch, MS[1], Jing Liu, PhD[3], Yueh-Yun Chi, PhD[3], Maureen Keller-Woods, PhD[4], Kirk P. Conrad, MD[5,6], and Valerie L. Baker, MD[1]

Am J Physiol Regul Integr Comp Physiol 321: R454–R468, 2021.
First published August 4, 2021; doi:10.1152/ajpregu.00174.2020

american physiological society
AMERICAN JOURNAL OF PHYSIOLOGY
REGULATORY, INTEGRATIVE AND COMPARATIVE PHYSIOLOGY

RESEARCH ARTICLE

Hormones, Reproduction and Development

Relationships between reproductive hormones and maternal pregnancy physiology in women conceiving with or without in vitro fertilization

Kirk P. Conrad,[1,2*] Shèdy Taher,[1*] Yueh-Yun Chi,[3,4] Yingjie Qiu,[4] Mingyue Li,[4] Melissa Lingis,[5] R. Stan Williams,[2] Alice Rhoton-Vlasak,[2] Maureen Keller-Wood,[6] and Mark S. Segal[5,7]

Am J Physiol Regul Integr Comp Physiol 318: R1091–R1102, 2020.
First published April 29, 2020; doi:10.1152/ajpregu.00015.2020.

RESEARCH ARTICLE | *Hormones, Reproduction and Development*

Maternal endothelial function, circulating endothelial cells, and endothelial progenitor cells in pregnancies conceived with or without in vitro fertilization

Kirk P. Conrad,[1,2,3*] Melissa Lingis,[4*] Larysa Sautina,[4] Shiyu Li,[4] Yueh-Yun Chi,[5] Yingjie Qiu,[5] Mingyue Li,[5] R. Stan Williams,[2] Alice Rhoton-Vlasak,[2] and Mark S. Segal[4,6]

Wiegel *et al. Reprod Biol Endocrinol* (2021) 19:164
https://doi.org/10.1186/s12958-021-00843-9

Reproductive Biology and Endocrinology

RESEARCH Open Access

Corpus luteum number and the maternal renin-angiotensin-aldosterone system as determinants of utero-placental (vascular) development: the Rotterdam Periconceptional Cohort

Rosalieke E. Wiegel[1], Maud J. H. Karsten[1], Igna F. Reijnders[1], Lenie van Rossem[1], Sten P. Willemsen[1,2], Annemarie G. M. G. J. Mulders[1], Anton H. J. Koning[3], Eric A. P. Steegers[1], A. H. Jan Danser[4†] and Régine P. M. Steegers-Theunissen[1*†]

Hypertension
Volume 74, Issue 3, September 2019; Pages 705-715
https://doi.org/10.1161/HYPERTENSIONAHA.119.13015

American Heart Association.

PREGNANCY

Maternal Cardiovascular Dysregulation During Early Pregnancy After In Vitro Fertilization Cycles in the Absence of a Corpus Luteum

RBMO

ELSEVIER

ARTICLE

First-trimester maternal renin–angiotensin–aldosterone system activation and fetal growth and birthweight: the Rotterdam Periconceptional Cohort

BIOGRAPHY

Rosalieke Wiegel is a PhD candidate of the Periconception Epidemiology Group as part of the Department of Obstetrics and Gynecology at the Erasmus University Medical Center in Rotterdam, the Netherlands. Her research focuses mainly on the role of the periconceptional renin–angiotensin–aldosterone system in early pregnancy adaptation, fetal growth and pregnancy outcomes.

Rosalieke E. Wiegel[1], Damiat Aoulad Fares[1], Sten P. Willemsen[1,2], Eric A.P. Steegers[1], A.H. Jan Danser[3,4], Régine P.M. Steegers-Theunissen[1,4,*]

The Journal of Clinical Endocrinology & Metabolism, 2020, Vol. 105, No. 11, 1–13
doi:10.1210/clinem/dgaa582
Clinical Research Article

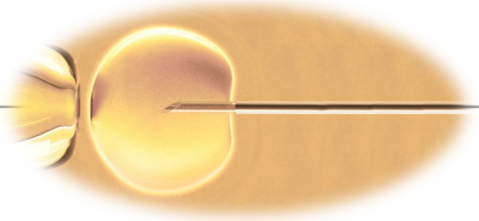
ENDOCRINE SOCIETY

Clinical Research Article

Determinants of Maternal Renin-Angiotensin-Aldosterone-System Activation in Early Pregnancy: Insights From 2 Cohorts

Rosalieke E. Wiegel,[1] A.H. Jan Danser,[2] Régine P.M. Steegers-Theunissen,[1] Joop S.E. Laven,[1] Sten P. Willemsen,[1,3] Valerie L. Baker,[4] Eric A.P. Steegers,[1] and Frauke von Versen-Höynck[5]

Research question



Assisted Reproduction

Fresh embryo transfer

→

Adverse obstetrical outcomes;
e.g. preeclampsia

Frozen embryo transfer ↑ ↑

<u>Hypotheses:</u>

The presence/absence of corpora lutea at conception impacts:

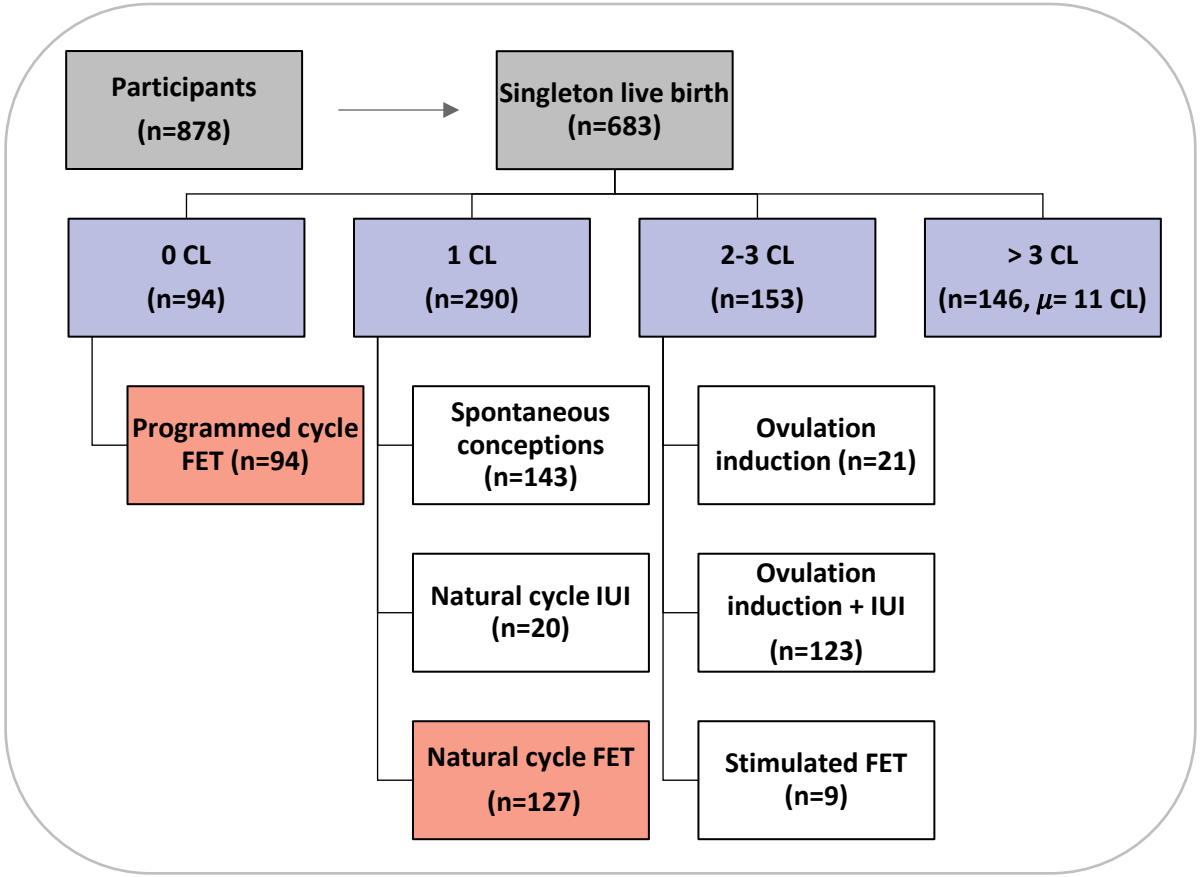
1. **Preeclampsia risk**
2. **Maternal vascular adaptation in pregnancy**

Study design

Recruitment

6-8 wks

Delivery



Recruitment

1 — 6-8 wks

2 — **11-14 wks**

3 — **35-37 wks**

Delivery

6-12 wks postpartum

- **Blood pressure & endothelial function**
- **Corpus luteum hormones**
- **Endothelial progenitor cells**

von Versen-Höynck et al., *Hypertension 2019*

CL; corpus luteum, FET; Frozen embryo transfer, IUI; intrauterine insemination

Study results

Ovary

no corpus luteum

Lack of relaxin and other corpus luteum products

Hormone	programmed cycle FET (n=17)	natural cycle FET (n=12)	p-value
Relaxin (pg/ml)	**13.0 (12.0 - 15.5)**	**489.7 (251.5 to 864.2)**	**<0.0001**
Estradiol (pg/ml)	2416 (1665.5 to 3126.5)	2571.5 (2200.3 to 2938)	0.45
Progesterone (ng/ml)	34.1 (29.7 to 42.4)	35.62 (26.9 to 35.6)	0.76

von Versen-Höynck et al. *Hypertension 2019 & 2020*; Conrad et al. *Hypertension 2020;*
von Versen-Höynck et al. *Reprod Sciences 2019;* Wiegel et al. *J Clin Endocrinol Metab 2020*

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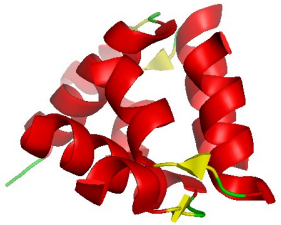
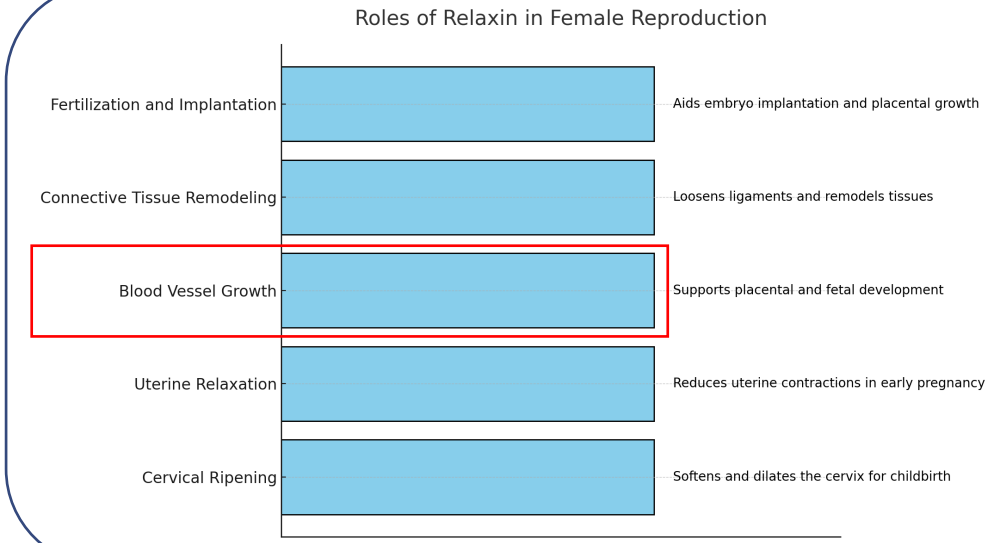


Relaxin –

- peptide hormone
- insulin-like structure
- two chains connected via disulfide bonds



von Versen-Höynck et al. *Hypertension 2019 & 2020*; Conrad et al. *Hypertension 2020;*
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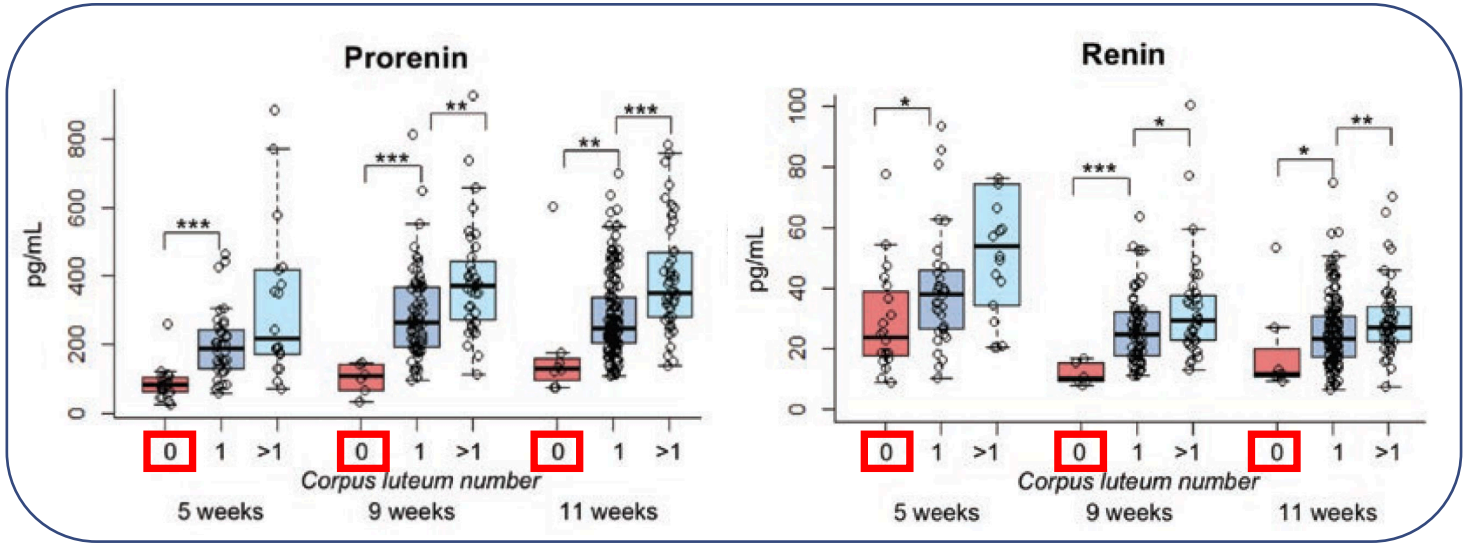

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von Versen-Höynck et al. *Reprod Sciences 2019;* Wiegel et al. *J Clin Endocrinol Metab 2020*

Study results

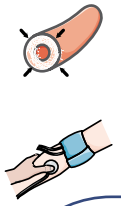
Ovary

no corpus luteum

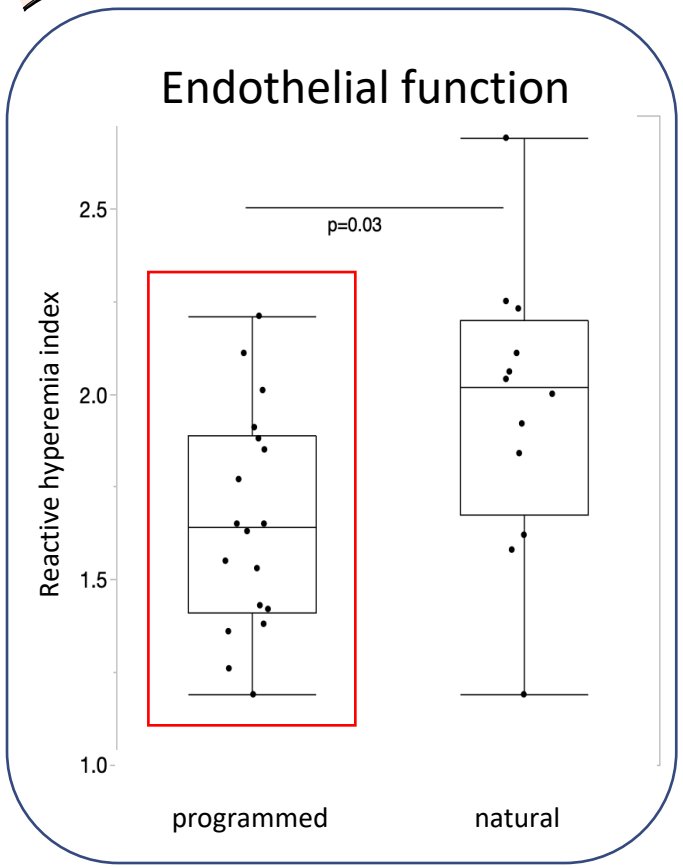
Lack of relaxin and other corpus luteum products

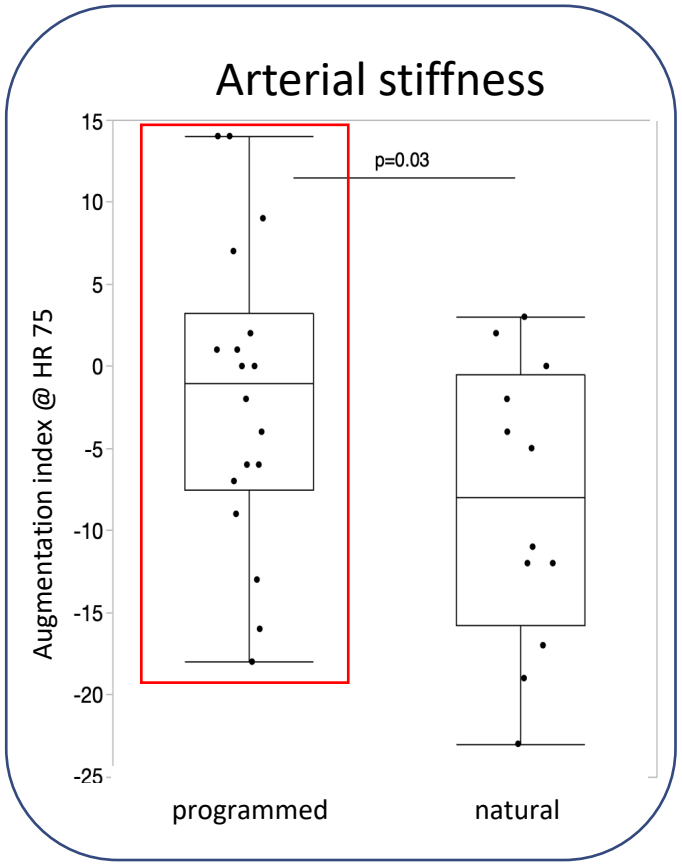
peripheral vasodilation ↓

arterial stiffness ↑



blood pressure ↑





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von Versen-Höynck et al. *Reprod Sciences 2019;* Wiegel et al. *J Clin Endocrinol Metab 2020*

Study results

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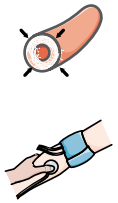
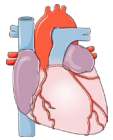


blood pressure ↑

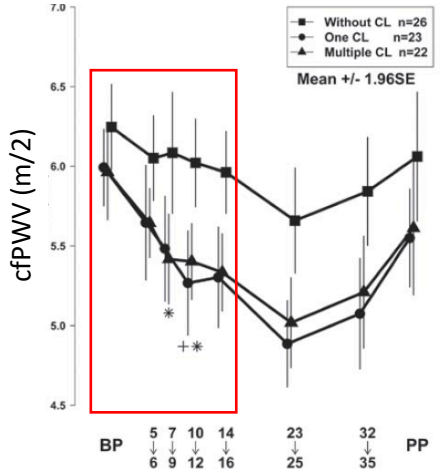
pulse wave velocity ↑

pulse wave transit time ↓

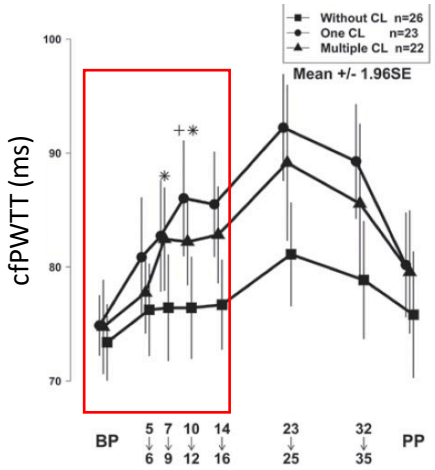


cardiac output ↓

Pulse wave velocity



Pulse wave transit time



von Versen-Höynck et al. *Hypertension 2019 & 2020*; Conrad et al. *Hypertension 2020;*
von Versen-Höynck et al. *Reprod Sciences 2019;* Wiegel et al. *J Clin Endocrinol Metab 2020*

Study results

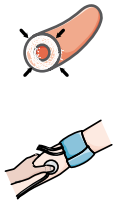
Ovary

no corpus luteum

Lack of relaxin and other corpus luteum products

peripheral vasodilation ↓

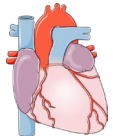
arterial stiffness ↑



blood pressure ↑

pulse wave velocity ↑

pulse wave transit time ↓



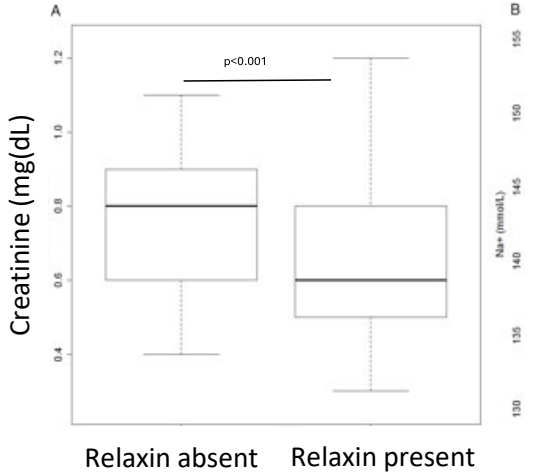
cardiac output ↓

creatinine ↑

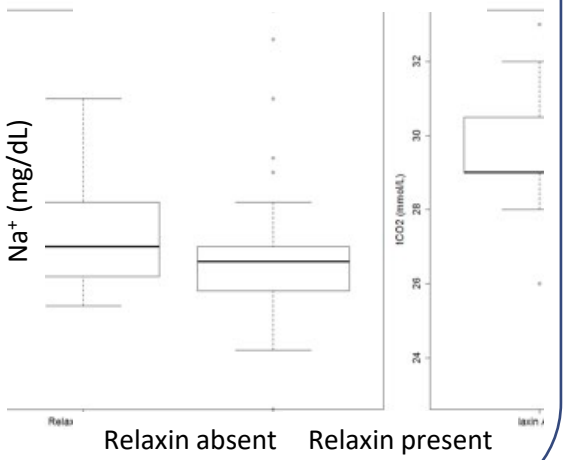
sodium ↑

renal adaptation ↓

Creatinine



Sodium



von Versen-Höynck et al. *Hypertension 2019 & 2020*; Conrad et al. *Hypertension 2020;*
von Versen-Höynck et al. *Reprod Sciences 2019;* Wiegel et al. *J Clin Endocrinol Metab 2020*

Impaired cardiovascular and renal adaptation as a precursor for preeclampsia

Ovary

no corpus luteum

Lack of relaxin and other corpus luteum products

peripheral vasodilation ↓

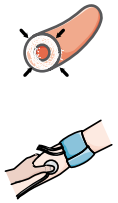
arterial stiffness ↑

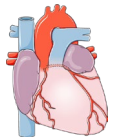
pulse wave velocity ↑

pulse wave transit time ↓

creatinine ↑

sodium ↑



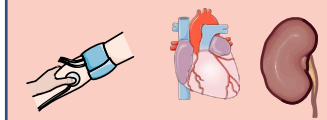


blood pressure ↑

cardiac output ↓

renal adaptation ↓

Impaired adaptation



↓

Preeclampsia

von Versen-Höynck et al. *Hypertension 2019 & 2020*; Conrad et al. *Hypertension 2020;*
von Versen-Höynck et al. *Reprod Sciences 2019;* Wiegel et al. *J Clin Endocrinol Metab 2020*

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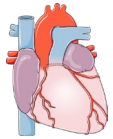


creatinine ↑

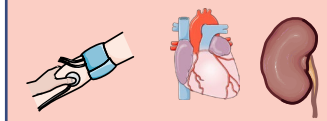
sodium ↑

blood pressure ↑

cardiac output ↓

renal adaptation ↓

Impaired adaptation



↓

Preeclampsia

↓

Long-term morbidity

von Versen-Höynck et al. *Hypertension 2019 & 2020*; Conrad et al. *Hypertension 2020;*
von Versen-Höynck et al. *Reprod Sciences 2019;* Wiegel et al. *J Clin Endocrinol Metab 2020*

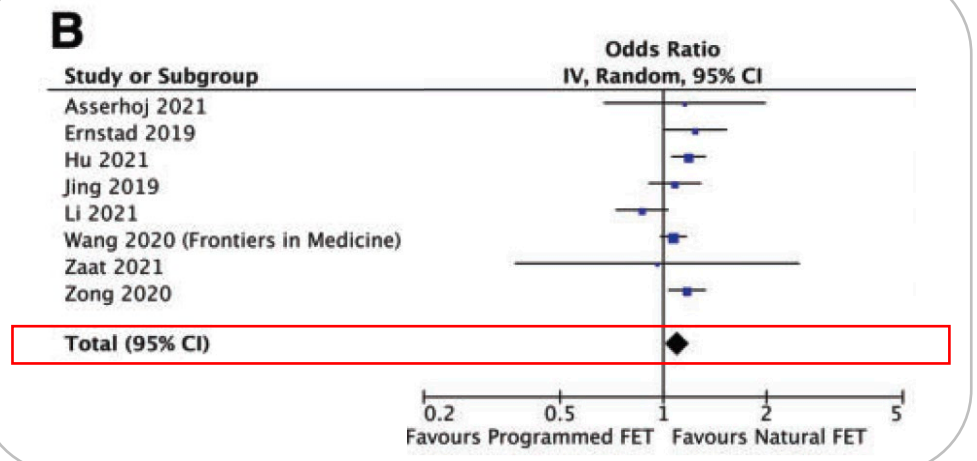
Additional outcomes

Programmed FET cycle

Natural FET cycle

Large for gestational age infants

Odds ratio: 0.88 (0.83; 0.94)



Rosalik et al. *Human Reprod* 2021; Zaat et al. *Human Reprod Update* 2023; Yang et al. *BMC Pregnancy and Childbirth 2020*

Additional outcomes

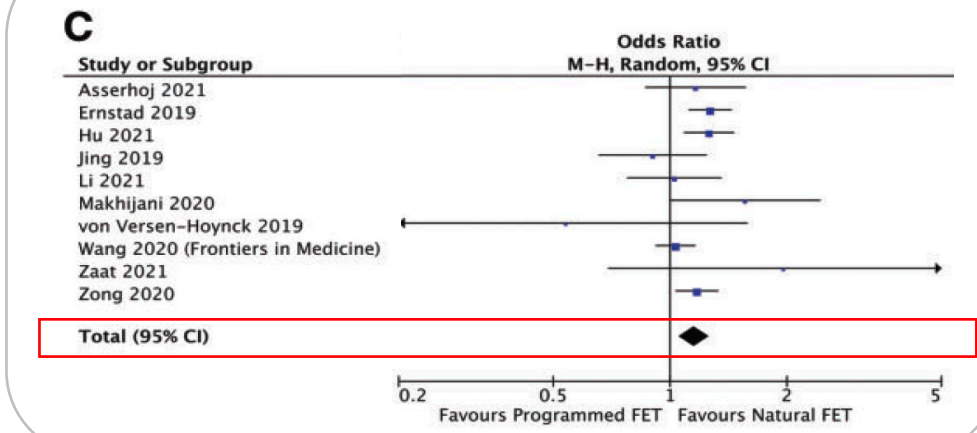
Programmed FET cycle

Natural FET cycle

Large for gestational age infants

Macrosomia

Odds ratio: 0.81 (0.71; 0.93)



Rosalik et al. *Human Reprod* 2021; Zaat et al. *Human Reprod Update* 2023; Yang et al. *BMC Pregnancy and Childbirth 2020*

Additional outcomes

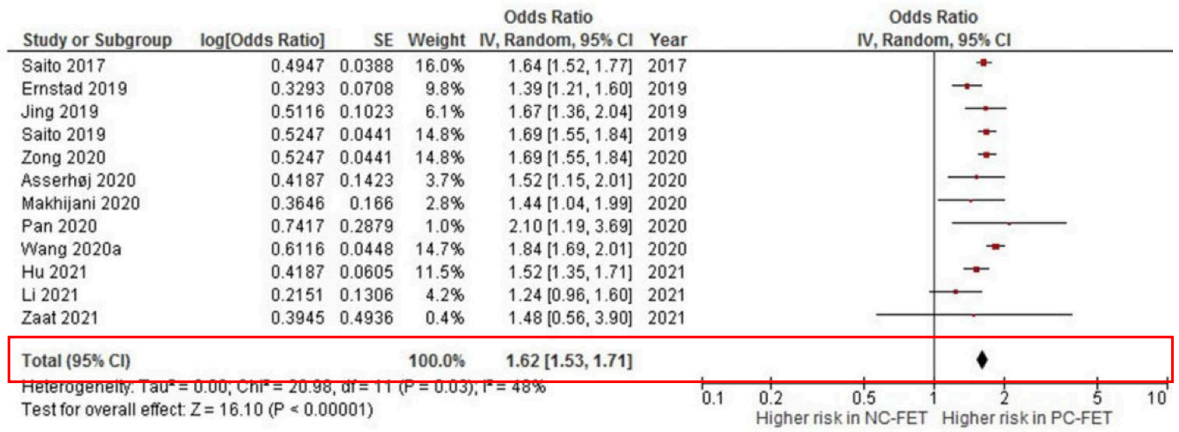
Programmed FET cycle

↑ Caesarean section

Odds ratio: 1.62 (1.53; 1.71)

Natural FET cycle

↓ Large for gestational age infants
Macrosomia



Rosalik et al. *Human Reprod* 2021; Zaat et al. *Human Reprod Update* 2023; Yang et al. *BMC Pregnancy and Childbirth 2020*

Additional adverse outcomes and impact of findings

Programmed FET cycle

↑ Caesarean section

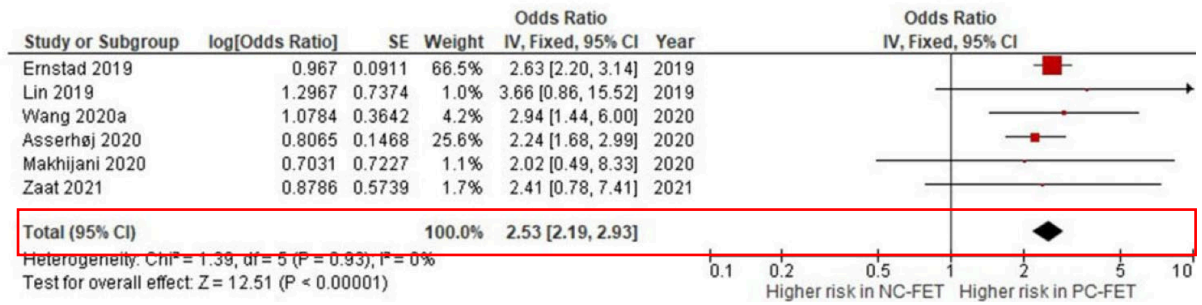
↑ Postpartum hemorrhage

Odds ratio: 2.53 (2.19; 2.93)

Natural FET cycle

↓ Large for gestational age infants

↓ Macrosomia



Rosalik et al. *Human Reprod* 2021; Zaat et al. *Human Reprod Update* 2023; Yang et al. *BMC Pregnancy and Childbirth 2020*

Additional adverse outcomes and impact of findings

Programmed FET cycle

↑ Caesarean section
Postpartum hemorrhage

Natural FET cycle

↓ Large for gestational age infants
Macrosomia

↓ Preterm birth (< 37 weeks)*
Very preterm birth (< 32 weeks)**

↓

Odds ratio: 0.80 (0.75; 0.85) - 21 studies*
Odds ratio: 0.66 (0.53; 0.84) - 11 studies**

Rosalik et al. *Human Reprod* 2021; Zaat et al. *Human Reprod Update* 2023; Yang et al. *BMC Pregnancy and Childbirth 2020*

Additional outcomes and impact of findings

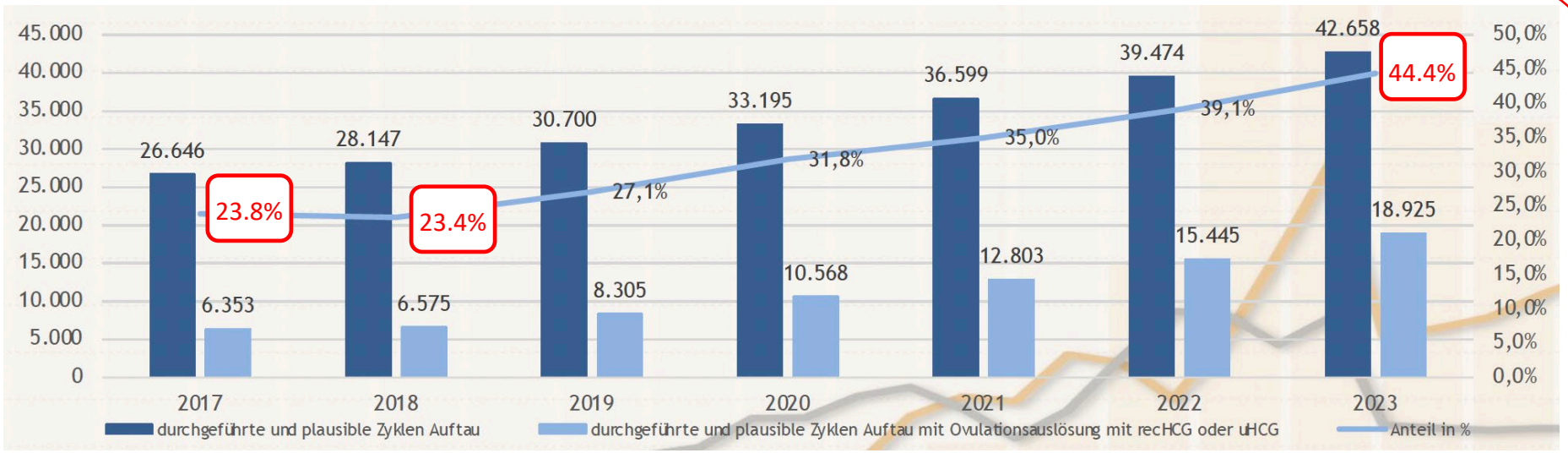
Programmed FET cycle

↑ Caesarean section
Postpartum hemorrhage

Natural FET cycle

↓ Large for gestational age infants
Macrosomia

Preterm birth (< 37 weeks)
Very preterm birth (< 32 weeks)



Special evaluation of the German IVF Registry (D.I.R.), November 2024

21% increase in ovulatory FET cycles in Germany (2018-2023)

Rosalik et al. *Human Reprod* 2021; Zaat et al. *Human Reprod Update* 2023; Yang et al. *BMC Pregnancy and Childbirth 2020*

Presentation outline

Physiological and clinical background

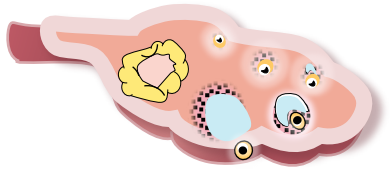
Corpus luteum, ART and pregnancy outcomes

FET – The dilemma of choice

Research perspectives and open questions

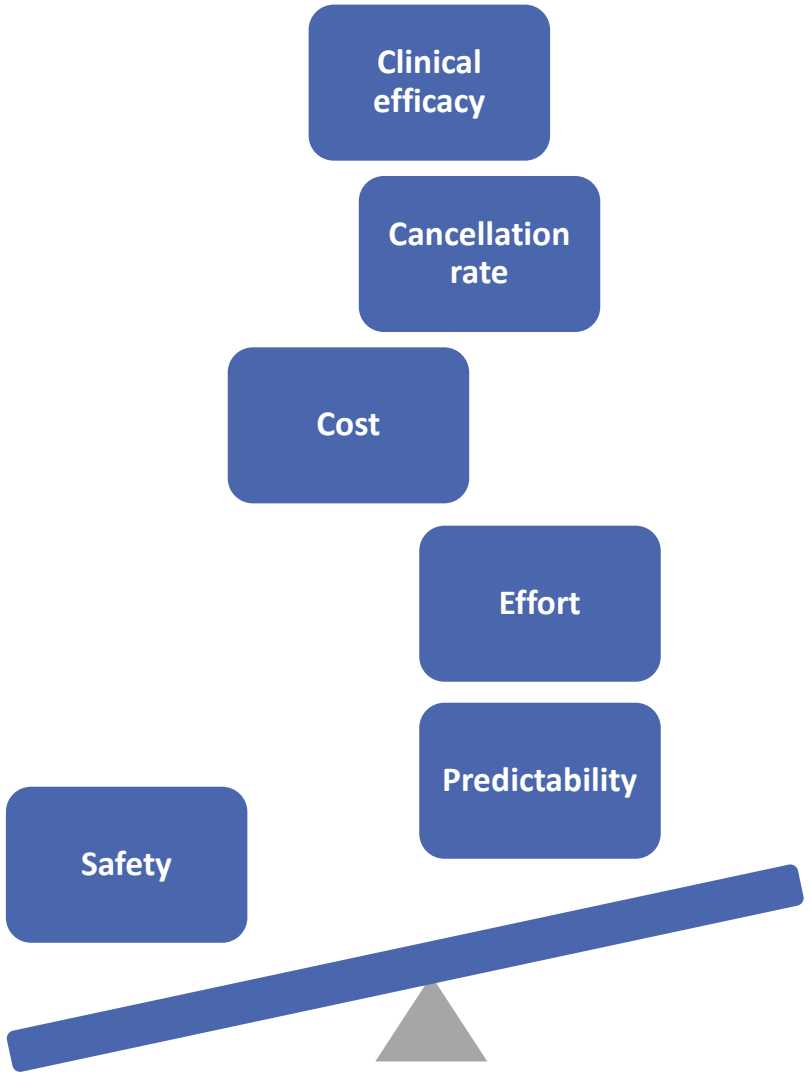
Frozen embryo transfer - The dilemma of choice

Ovulatory

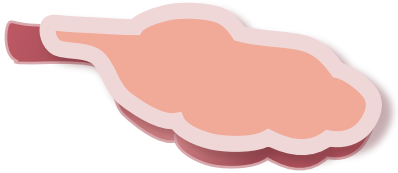


(modified) natural cycle

ovulation induction/ stimulated cycle



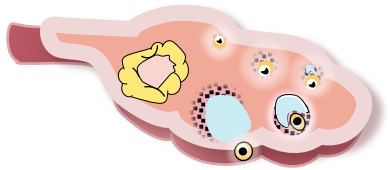
Anovulatory



HRT/ programmed/ artificial cycle

Ovulatory cycles – Is there a more flexible approach?

Ovulatory



(modified) natural cycle

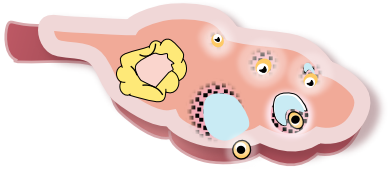
ovulation induction/ stimulated cycle

New Kids on the Block

Predictability

Effort

Ovulatory



Natural proliferative phase (NPP)

Programmed ovulatory (PO)

Mendes Godinho et al, *Hum Reprod 2024;* Eggersmann, *Hum Reprod 2024*, ESHRE oral presentation

Ovulatory cycles – Is there a more flexible approach?

1 RBMO VOLUME 49 ISSUE 1 2024 103775

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VIEWPOINT

Avoiding weekend frozen embryo transfer in modified natural cycles: is it possible?

Barbara Lawrenz[1,2], Christophe Blockeel[3,4,*]

European Journal of Obstetrics & Gynecology and Reproductive Biol

Contents lists availabl

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Full length article

Should the modified natural cycle pr
be modified? A prospective case serie

Amir Weiss[a,b,*], S. Baram[a], Y. Geslevich[a], S. Goldma
eck-Fruchter[a]

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[b] Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, 3525433, Isr

Abstract citation ID: deae108.241
O-208 The Programmed Ovulatory Frozen-Thawed Embryo Transfer Cycle (PO-FET): a suggested FET protocol integrating aspects of embryo transfer scheduling, efficacy optimization and maternal/fetal safety

T. K. Eggersmann[1], N. Hamala[1], R. A. F. Hiller[1], M. Depenbusch[1], A. Schultze-Mosgau[1], P. Edimiris[2], D. Baston-Buest[2], A. Bielfeld[2], J. S. Krüssel[2], S. Von Otte[3], W. Junkers[3], S. Tauchert[4], R. Vonthein[5], G. Griesinger[1]

OXFORD human reproduction

Human Reproduction, 2024, **00(0)**, 1–9
https://doi.org/10.1093/humrep/deae061
Original Article

Reproductive endocrinology

Natural proliferative phase frozen embryo transfer—a
w approach which may facilitate scheduling
hout hindering pregnancy outcomes

ndes Godinho[1,*], Sérgio Reis Soares[1], Sofia Gouveia Nunes[1], Juan M Mascarós Martínez[2], and
os-Ribeiro[1,3]

RBMO VOLUME 49 ISSUE 1 2024 103774

RBMO

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TICLE

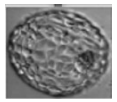
dified natural cycle allows a window of
days for frozen embryo transfer planning

BIOGRAPHY
Carlos Alonso is a Reproductive Medicine Specialist at IVIRMA, Spain. He obtained his medical degree from the University of Barcelona, completed his obstetrics and gynaecology residency at Hospital General Universitario Gregorio Marañón and pursued a Master's Degree in Reproductive Medicine at Complutense University. His primary areas of interest encompass gynaecological endocrinology and reproductive surgery.

Carlos Alonso-Mayo[1,*], Graciela Kohls[1], Samuel Santos-Ribeiro[2], Sergio Reis Soares[2], Juan A. Garcia-Velasco[1,3,4]

KEY MESSAGE
Comparable clinical outcomes are achieved when frozen embryo transfer (FET) is planned with rHCG when the dominant follicle size ranges from 13 to 22 mm in a modified natural cycle. This allows a flexibility that may help both patients and fertility units when monitoring and scheduling for FET.

Ovulatory cycles – Is there a more flexible approach?



Fresh ET	Ovarian stimulation	hCG		**OP**			**3**		**5**	**6**
	day 2/3									
„True“ natural	Follicular growth	LH↑	LH+1	LH+2	LH+3	LH+4	LH+5	LH+6	LH+7	
plus P			P Day 1	P Day 2	P Day 3	P Day 4	P Day 5	P Day 6	P Day 7	
Modified natural	Follicular growth	hCG	hCG+1	hCG+2	hCG+3	hCG+4	hCG+5	hCG+6	hCG+7	hCG+8
plus P			P Day 1	P Day 2	P Day 3	P Day 4	P Day 5	P Day 6	P Day 7	
Natural prolifer-ative phase*	Endometrium ≥ 7mm, follicle ≥ 14 mm, progesterone ≤ 1,5 ng/ml		P Day 1	P Day 2	P Day 3	P Day 4	P Day 5	P Day 6	P Day 7	

micronised vaginal progesterone 400 mg BID till 11th week gestation

Modified after Mumusoglu Front Endocrinol 2021; Mackens, Hum Reprod 2017,
*Mendes Godhino et al, Hum Reprod 2024; **Eggersmann, Hum Reprod 2024, ESHRE oral presentation

Ovulatory cycles – Is there a more flexible approach?

Start Monitoring (Endometrium) day 8

Natural proliferative phase*

Endometrium ≥ 7mm, follicle ≥ 14 mm, progesterone ≤ 1,5 ng/ml

P Day 1 | P Day 2 | P Day 3 | P Day 4 | P Day 5 | P Day 6 | P Day 7

micronised vaginal progesterone 400 mg BID till 11th week gestation

Table 2. Comparison of pregnancy outcomes after frozen embryo transfer considering each subgroup with confounder adjustment.

	AC (n = 2226)	NPP (n = 349)	NC (n = 3216)	P-value
hCG-positive pregnancy	1343 (60.4%) **0.96 (0.93–0.99)**	219 (62.8%) 1.01 (0.96–1.07)	1978 (61.6%) Reference	0.56
Clinical pregnancy	1122 (50.5%) **0.94 (0.91–0.96)**	199 (57.0%) 1.01 (0.95–1.07)	1748 (54.4%) Reference	<0.01†
Miscarriage	466/1335 (34.9%) **1.11 (1.07–1.15)**	43/218 (19.7%) 0.98 (0.92–1.04)	491/1962 (25.0%) Reference	<0.01*,†
Live birth	848/2206 (38.4%) **0.91 (0.88–0.94)**	168/342 (49.1%) 1.02 (0.96–1.09)	1437/3182 (45.2%) Reference	<0.01*,†

Pairwise $P < 0.05$ for the following comparisons:
* AC versus NPP.
† AC versus NC.
PGT-A, preimplantation genetic testing for aneupoidies, AC, artificial cycle; NPP, natural proliferative phase; NC, natural cycle. Confounder-adjustment was performed using multivariable GEE regression analysis, adjusting for the potentially relevant confounding variables: female age at oocyte retrieval, oocyte source (autologous without PGT-A versus autologous with PGT-A versus donated), number of oocytes retrieved/donated, embryo developmental stage (Day 5 versus Day 6), number of embryos transferred, quality of best embryo transferred (A versus B versus C) and year of treatment. Confounder-adjusted data are presented with odds-ratios (95% CIs), in which results with $P < 0.05$ from the reference group are highlighted in bold.

*Mendes Godinho et al, Hum Reprod 2024

Ovulatory cycles – Is there a more flexible approach?

Start Monitoring (Endometrium) day 8

Natural proliferative phase*

Endometrium ≥ 7mm, follicle ≥ 14 mm, progesterone ≤ 1,5 ng/ml

P Day 3 | P Day 4 | P Day 5 | P Day 6 | P Day 7

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Comparable live birth and miscarriage rates after NPP in comparison to natural cycles, poorer outcomes in programmed cycles.

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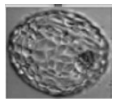
Ovulatory cycles – Is there a more flexible approach?



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			micronised vaginal progesterone 400 mg BID till 11th week gestation							
Programmed ovulatory**	Endometrium ≥ 6mm, follicle ≥ 16 mm, estradiol ≥ 180 pg/ml		Dyd Day 1	Dyd Day 2	Dyd Day 3	Dyd Day 4	Dyd Day 5	Dyd Day 6	Dyd Day 7	
			Dydrogesterone 10 mg/die till 7/8 week gestation							

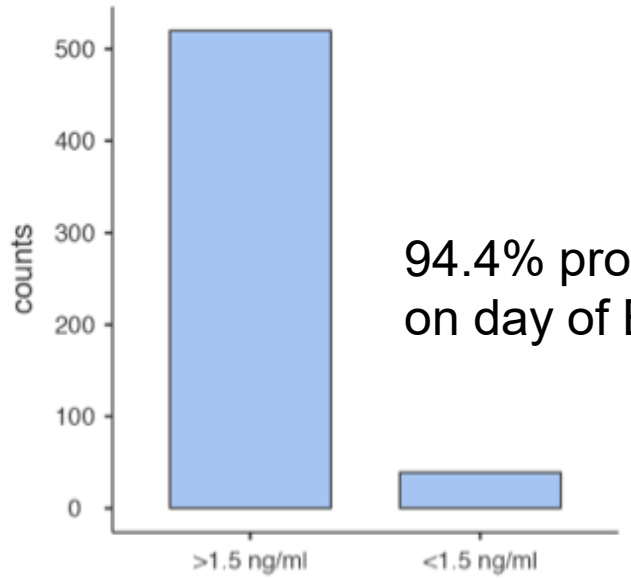
Modified after Mumusoglu Front Endocrinol 2021; Mackens, Hum Reprod 2017,
*Mendes Godhino et al, Hum Reprod 2024; **Eggersmann, Hum Reprod 2024, ESHRE oral presentation

Ovulatory cycles – Is there a more flexible approach?

Start Monitoring (Endometrium) day 10-12 → **ET**

Programmed ovulatory**	Endometrium ≥ 6mm, follicle ≥ 16 mm, estradiol ≥ 180 pg/ml	Dyd Day 1	Dyd Day 2	Dyd Day 3	Dyd Day 4	Dyd Day 5	Dyd Day 6	Dyd Day 7

Dydrogesterone 10 mg/die till 7/8 week gestation



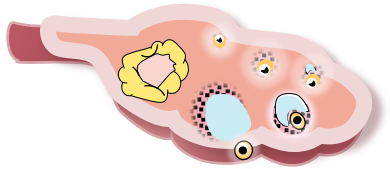
94.4% progesterone > 1.5 ng/ml on day of ET

- Assessment of corpus luteum activity possible

**Eggersmann, Hum Reprod 2024, ESHRE oral presentation

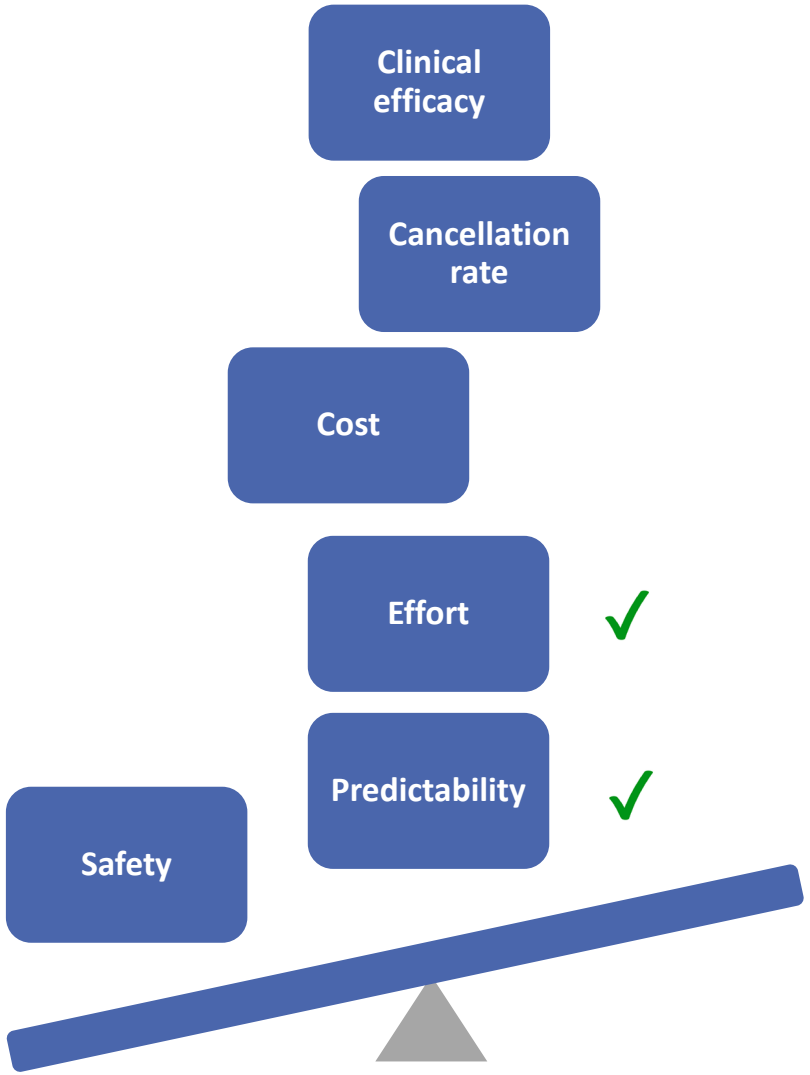
Frozen embryo transfer - The dilemma of choice

Ovulatory

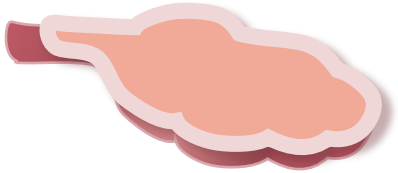


(modified) natural cycle
Ovulation induction/ stimulated cycle

Natural proliferative phase (NPP)
Programmed ovulatory (PO)



Anovulatory



HRT/ programmed/ artificial cycle

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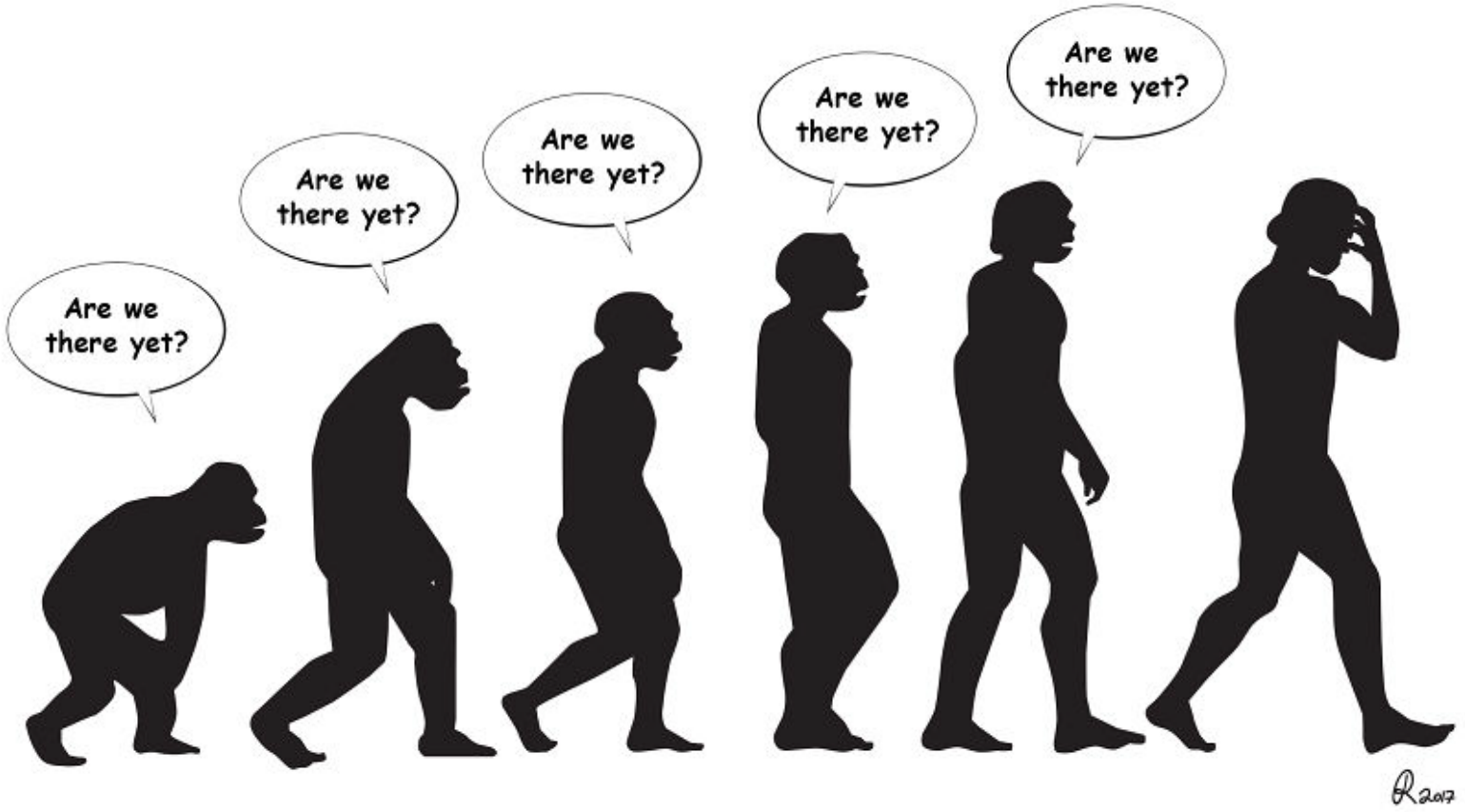
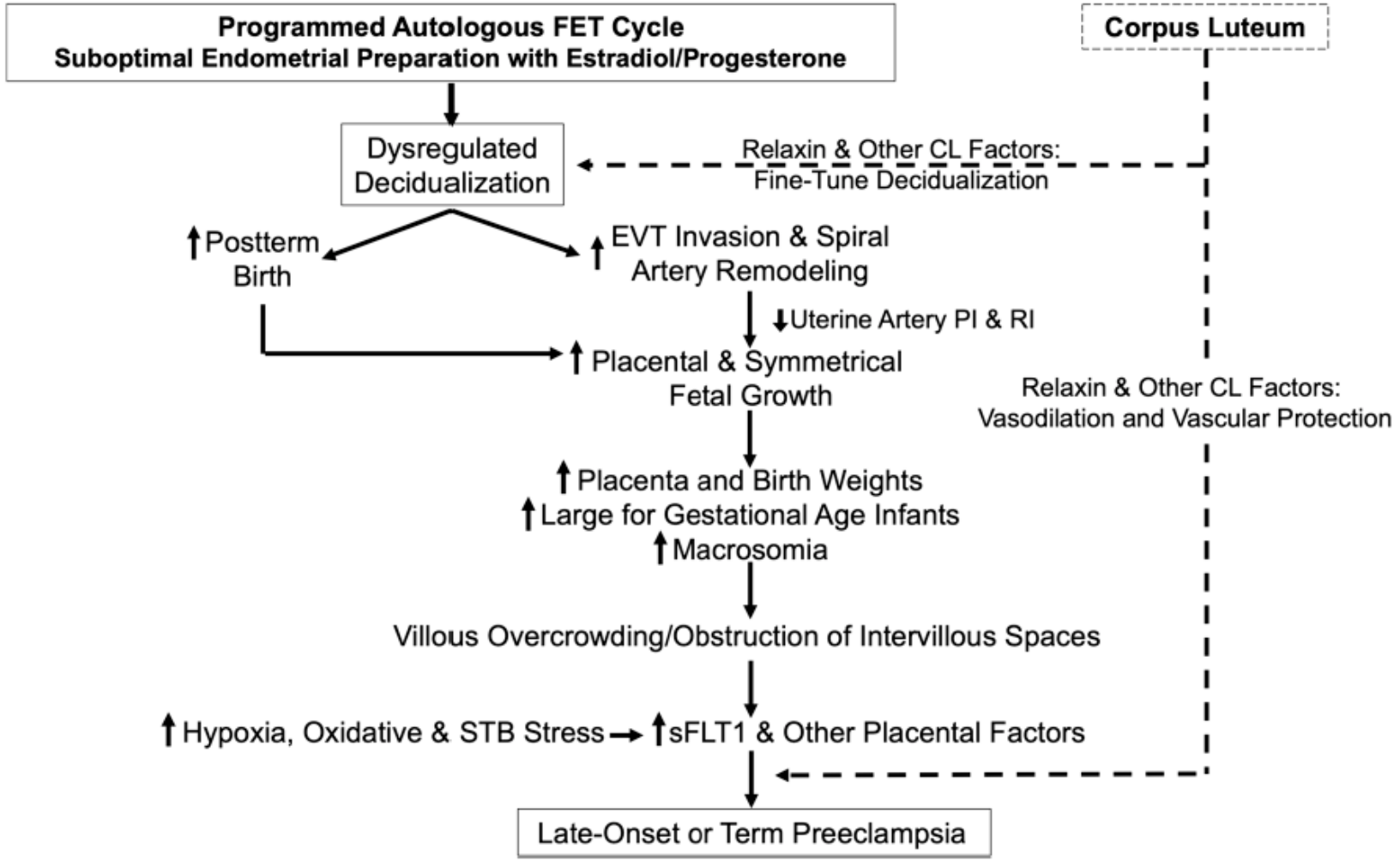
Research perspectives and open questions

Research perspectives and open questions in FET

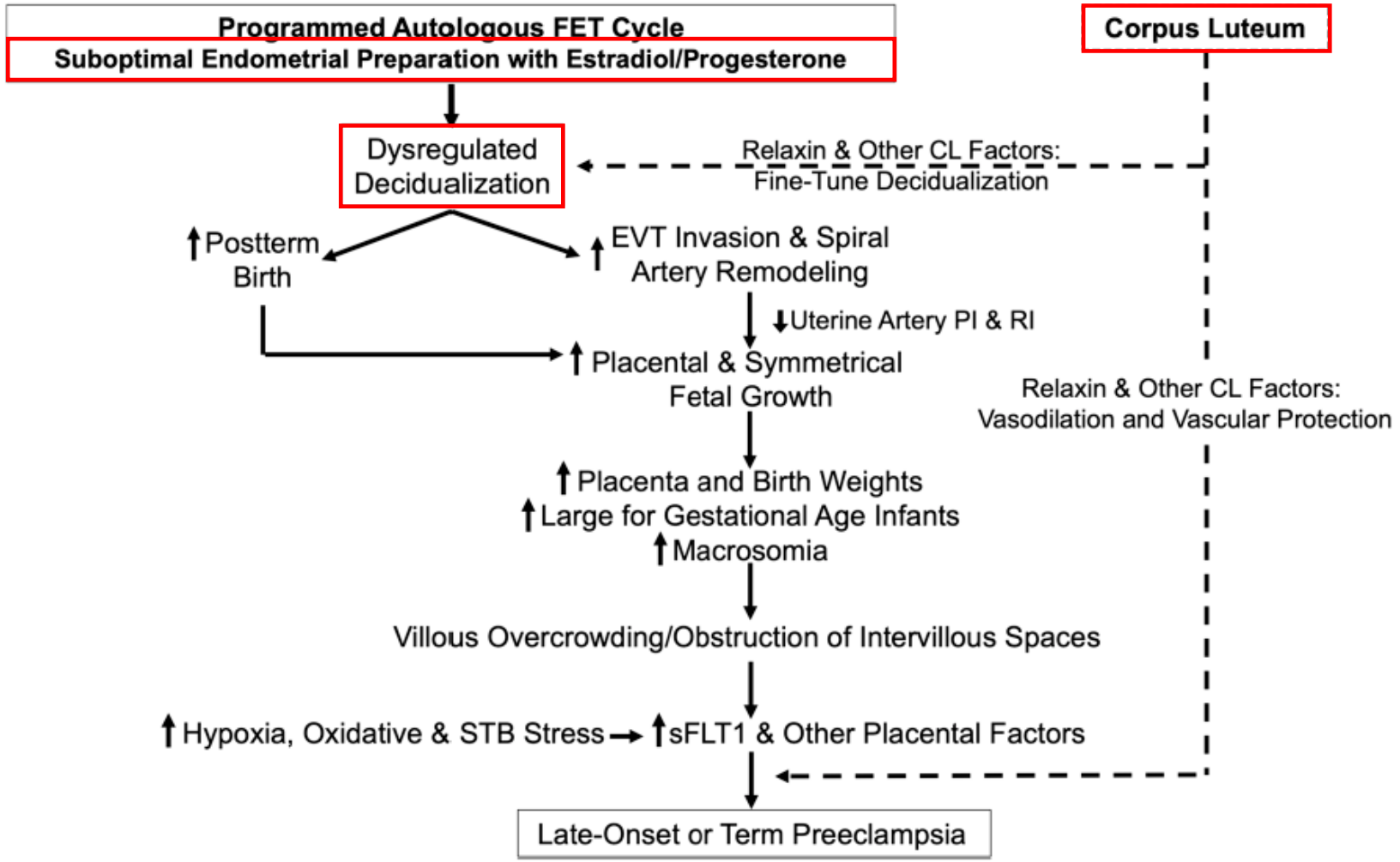


Research perspectives and open questions in FET



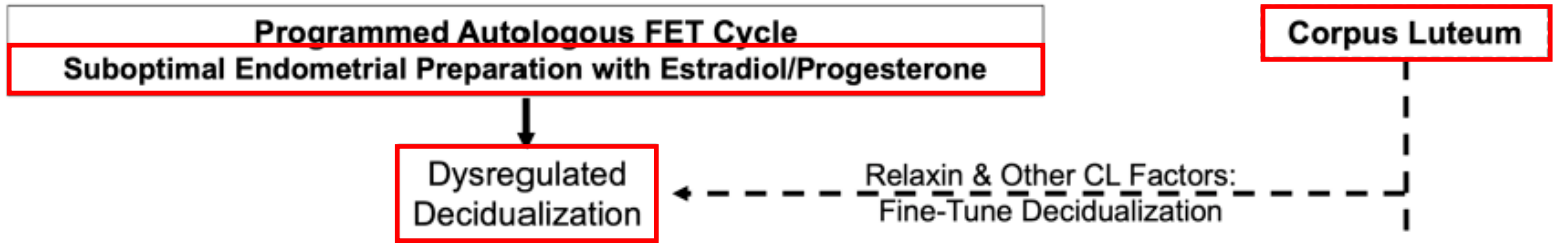
Conrad et al *JARG* 2024

Research perspectives and open questions in FET



Conrad et al *JARG* 2024

Research perspectives and open questions in FET



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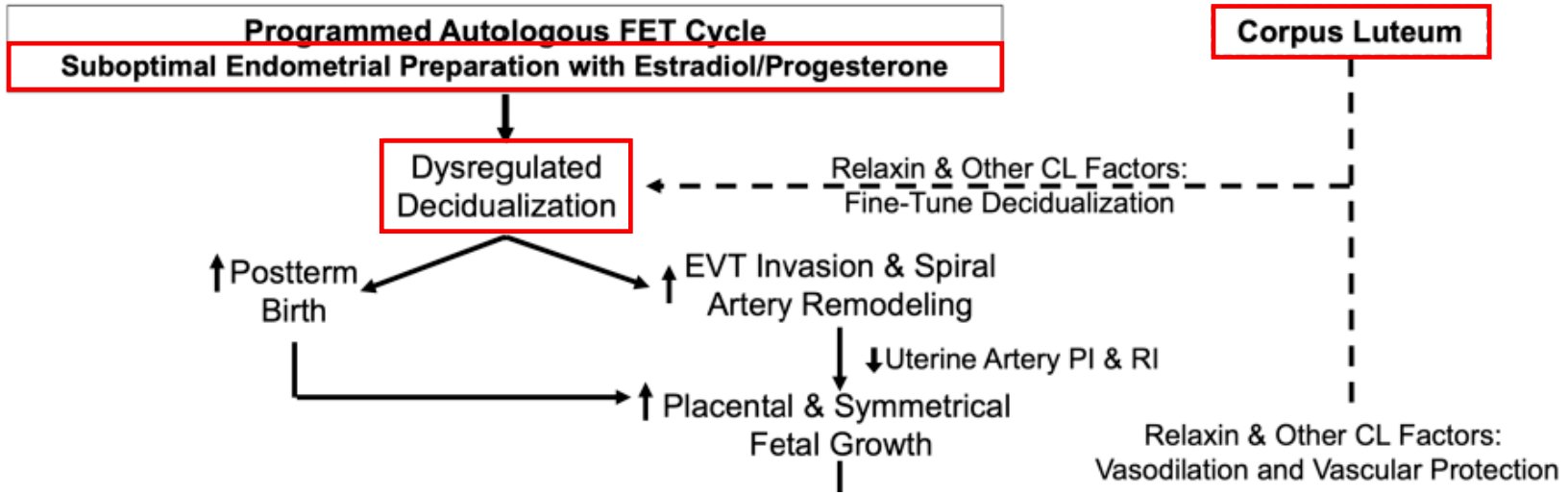
Research perspectives and open questions in FET



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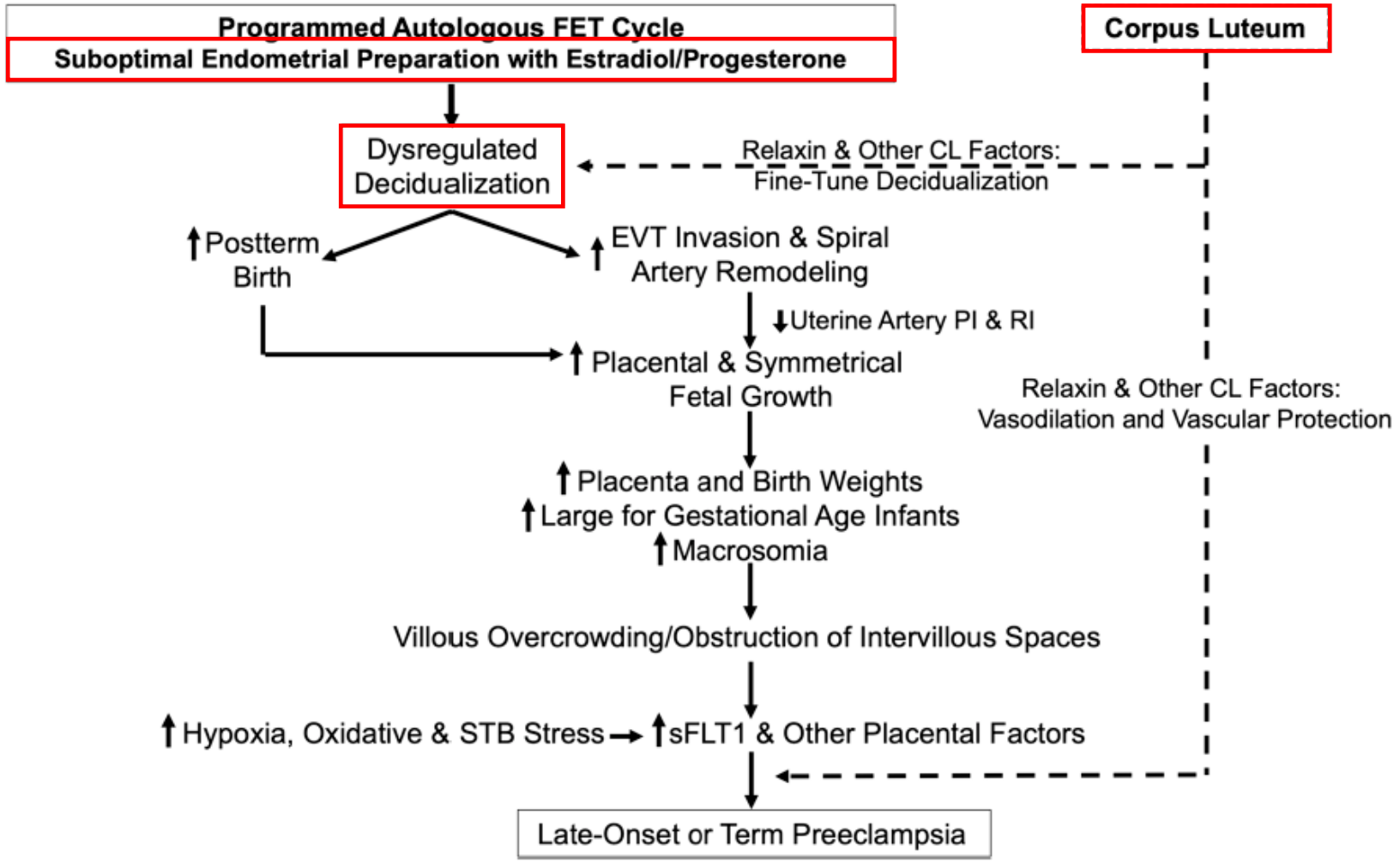
Research perspectives and open questions in FET



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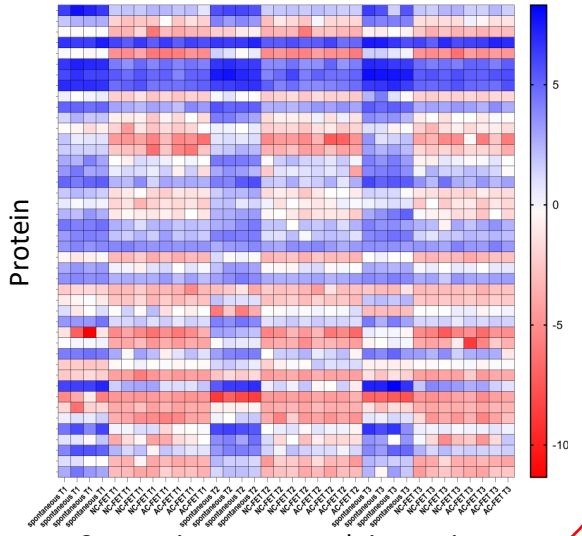
Research perspectives and open questions in FET

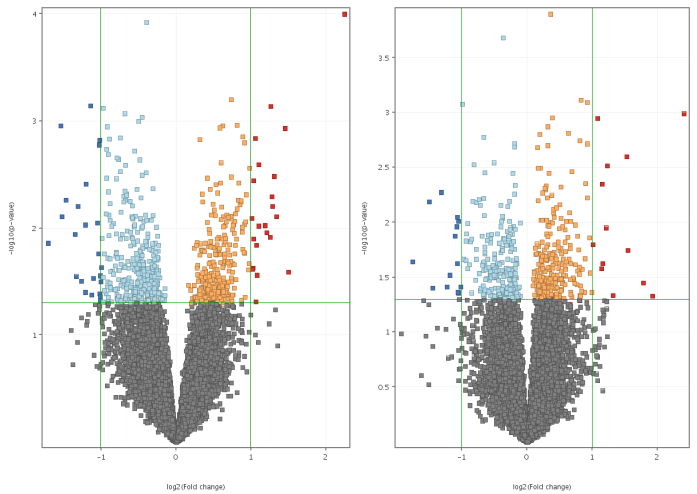
1) Identification of corpus luteum products

Heatmap of LFQ intensities

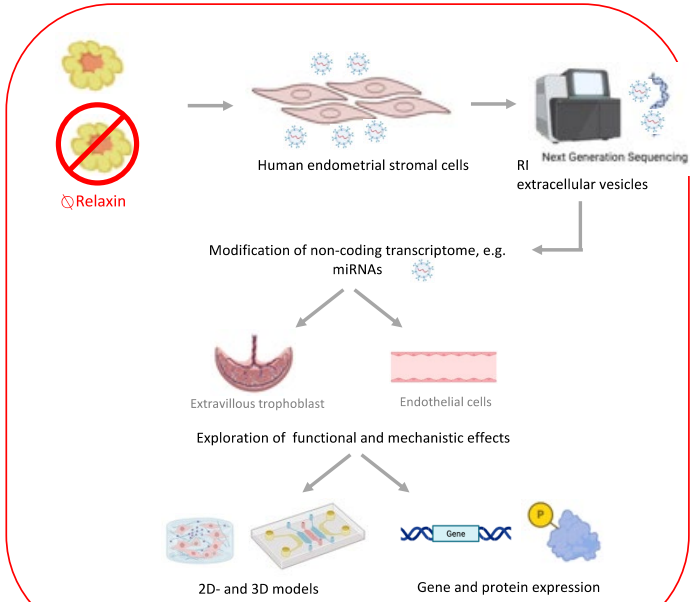


2) Exploration of decidual gene expression

Volcano plots



3) Investigation of intercellular communication



Many open questions, such as:

Artificial FET cycles:

- Impact of dose, route and timing of estradiol and progesterone in artificial FET cycles
- Should aspirin be given to prevent hypertensive disease?

Ovulatory cycles:

- Who benefits from hCG trigger?
- Is luteal phase support necessary in ovulatory cycles? For how long?
- What could personalized luteal phase support look like?

Summary

Outcomes:

- fewer pregnancy complications in ovulatory FET cycles, e.g. preeclampsia

Physiology:

- programmed FET cycles lack the corpus luteum's secretion of vasoactive substances, such as relaxin → these are critical for vascular adaptation during pregnancy

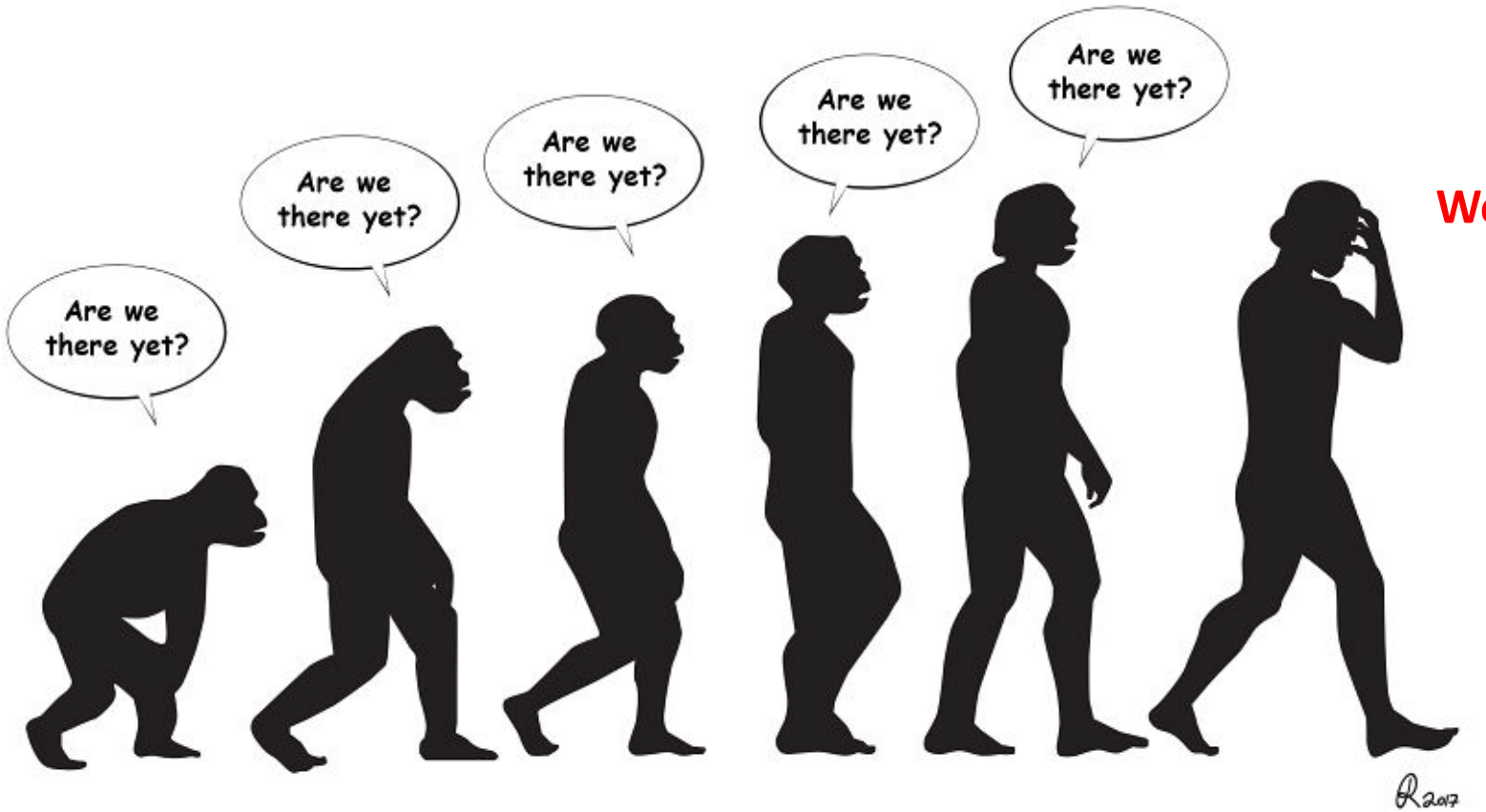
→ **target pregnancy in an ovulatory FET cycle**

- (modified) natural, ovulation (stimulated) induction

- new (ovulatory) protocols:
  - less monitoring and easier planning
  - clinical outcomes and safety must now be further investigated

Perspectives:

- personalized luteal phase support
- development of supplementation strategies for anovulatory women in programmed cycles (e.g. corpus luteum products)



We are not there yet!

Q&A

Question 1

Which of the following best describes the hormonal differences between natural and programmed frozen embryo transfer (FET) cycle protocols?

A. Natural FET cycles rely on the body's endogenous hormone production, primarily estradiol and progesterone, while programmed cycles use exogenous hormones to mimic the natural cycle.
B. Programmed FET cycles completely suppress endogenous hormone production and rely solely on exogenous estradiol and progesterone to prepare the endometrium.
C. Natural FET cycles require exogenous hormone supplementation to initiate ovulation, whereas programmed cycles do not involve hormone administration.
D. Programmed FET cycles involve higher doses of gonadotropins compared to natural cycles to stimulate follicular development.

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C. Natural FET cycles require exogenous hormone supplementation to initiate ovulation, whereas programmed cycles do not involve hormone administration.
D. Programmed FET cycles involve higher doses of gonadotropins compared to natural cycles to stimulate follicular development.

Correct Answer: A

Question 2

Which of the following adverse obstetrical outcomes has been reported to differ significantly between programmed and natural frozen embryo transfer (FET) protocols?

A. Increased risk of preterm birth in natural FET cycles.
B. Higher incidence of preeclampsia in programmed FET cycles.
C. Increased likelihood of fetal growth restriction in programmed FET cycles.
D. Elevated risk of placental abruption in natural FET cycles.

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C. Increased likelihood of fetal growth restriction in programmed FET cycles.
D. Elevated risk of placental abruption in natural FET cycles.

Correct Answer: B

Question 3

What recent evidence links the absence of the corpus luteum in programmed frozen embryo transfer (FET) cycles to an increased risk of complications such as preeclampsia?

A. The absence of the corpus luteum leads to reduced progesterone levels, which impairs endometrial receptivity and early placentation.
B. Programmed FET cycles lack the corpus luteum's secretion of vasoactive substances, such as relaxin, which are critical for vascular adaptation during pregnancy.
C. Without a corpus luteum, estrogen levels are excessively high in programmed FET cycles, leading to abnormal placental development.
D. Natural FET cycles with a corpus luteum demonstrate a significantly higher rate of placental insufficiency compared to programmed cycles.

Question 3

What recent evidence links the absence of the corpus luteum in programmed frozen embryo transfer (FET) cycles to an increased risk of complications such as preeclampsia?

A. The absence of the corpus luteum leads to reduced progesterone levels, which impairs endometrial receptivity and early placentation.
B. Programmed FET cycles lack the corpus luteum's secretion of vasoactive substances, such as relaxin, which are critical for vascular adaptation during pregnancy.
C. Without a corpus luteum, estrogen levels are excessively high in programmed FET cycles, leading to abnormal placental development.
D. Natural FET cycles with a corpus luteum demonstrate a significantly higher rate of placental insufficiency compared to programmed cycles.

Correct Answer: B