Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 36 (2024) 101123

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Full Length Article

Clinical features of preeclampsia and hypertensive disorders in pregnancies after different frozen embryo transfer regimens

Eeva-Maria Pohjonen [a,b,*], Katja Ahinko [a], Heini Huhtala [c], Tarja Erkinaro [d], Johanna Lehto [e], Elena Pellas [f], Tiina Vilmi-Kerälä [g], Hannele Laivuori [a,b,h]

[a] Department of Obstetrics and Gynecology, Tampere University Hospital, Wellbeing Services County of Pirkanmaa. Elämänaukio 2, 33521 Tampere, Finland
[b] Tampere University, Faculty of Medicine and Health Technology. Center for Child, Adolescent, and Maternal Health Research, Tampereen yliopisto, Arvo Ylpön katu 34, 33520 Tampere, Finland
[c] Faculty of Social Sciences, Tampere University, Tampere, Finland
[d] Department of Obstetrics and Gynecology, Satasairaala Central Hospital, Pori, Finland
[e] Department of Obstetrics and Gynecology, Seinäjoki Central Hospital, Seinäjoki, Finland
[f] Department of Obstetrics and Gynecology, Vaasa Central Hospital, Vaasa, Finland
[g] Department of Obstetrics and Gynecology, Kanta-Häme Central Hospital, Hämeenlinna, Finland
[h] Institute for Molecular Medicine Finland (FIMM), Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland

ARTICLE INFO

Keywords:
Preeclampsia
Gestational hypertension
Frozen embryo transfer
Corpus luteum
Clinical features
postpartum hemorrhage

ABSTRACT

Objectives: To compare whether the clinical features of preeclampsia (PE) or gestational hypertension (GH) were different in pregnancies after a frozen embryo transfer (FET), depending on the FET regimen used.
Study design: A retrospective study including 58 pregnancies with PE and 64 pregnancies with GH, all with singleton live births. Pregnancies were stratified according to the presence or absence of a corpus luteum (CL).
Main outcome measures: Clinical characteristics of PE and GH, maternal background factors, postpartum hemorrhage (PPH), key perinatal outcomes.
Results: Among PE patients, no difference was found in the clinical characteristics and in the maternal background factors, when comparing women with a CL to women without a CL. PE patients in the group without a CL had a hemorrhage of > 500 mL or > 1000 mL significantly more often than patients with a CL. Multivariable analyses confirmed this risk. Perinatal outcomes were similar.
Among GH patients, there was no difference in the clinical features and maternal background factors, when comparing CL cycles to cycles without a CL. The amount of PPH was higher among the patients without a CL, but the frequency of a > 500 mL or > 1000 mL hemorrhage was similar between groups. No risk increase was seen in multivariable analyses.
Conclusions: Among FET patients with PE, the risk of PPH was increased in pregnancies after cycles without a CL, compared to cycles with a CL. The presence or absence of a CL did not effect the severity of PE and GH, the duration of pregnancy or blood pressure levels.

1. Introduction

Preeclampsia (PE) is a disease with varying manifestations and severity. The incidence varies in different populations between 2 and 8 % [1]. Depending greatly on the severity of the disease, it adds a substantial morbidity and mortality burden to the mother and the newborn. The greatest risks are associated with early onset PE, often associated with intrauterine growth restriction, and more frequently followed by a preterm birth of a small for gestational age infant. The risks affect not only the pregnant woman and the child during the pregnancy and the peripartum period, but also her health and the health of her offspring in later life [2–4]. Gestational hypertension (GH) and hypertensive

Abbreviations: PE, preeclampsia; GH, gestational hypertension; CL, corpus luteum; PPH, postpartum hemorrhage; AC-FET, frozen embryo transfer in an artificial cycle; HDP, hypertensive disorders of pregnancy; ART, assisted reproductive technology; IVF, in vitro fertilization; OD, ovum donation; RAAS, renin-angiotensin-aldosterone system; HELLP, elevated liver enzymes and low platelets.

* Corresponding author at: Department of Obstetrics and Gynecology, Tampere University Hospital, Elämänaukio 2, 33521 Tampere, Finland.
E-mail address: eeva-maria.pohjonen@tuni.fi (E.-M. Pohjonen).

https://doi.org/10.1016/j.preghy.2024.101123
Received 9 January 2024; Received in revised form 29 March 2024; Accepted 5 April 2024
Available online 17 April 2024

disorders of pregnancy (HDP) are also risk factors for later cardiovascular disease [5,6]. Many risk factors have been identified and some prophylactic measures, e.g. low dose aspirin, can be offered to specific risk groups.

PE is defined as de novo hypertension after 20 weeks of gestation, accompanying either proteinuria or signs of organ dysfunction or fetal growth restriction. The HDPs include gestational hypertension, preeclampsia and also chronic hypertension diagnosed before pregnancy or in early pregnancy [7]. The etiology of PE is still not fully understood. It is a cascade of events, starting from impaired placentation and ending in endothelial dysfunction sometimes concerning multiple organ systems [1,8,9]. Chronic hypertension is a strong risk factor for PE [8].

The increased risk of hypertensive disorders after frozen embryo transfer (FET) has experienced a detangling process during the past decade. Earlier studies showed that there was an increased risk for HDP after assisted reproductive technology (ART) procedures in general, compared to spontaneous pregnancies [10,11]. Later, it was shown that the increased risk is mainly associated with FET compared to fresh embryo transfer after in vitro fertilization (IVF-ET) [12–14]. Only during the past few years there has been increasing evidence that the risk, in fact, seems to be associated with mainly artificial cycle FETs (AC-FET), that is, cycles without a CL.

So far numerous observational studies have compared different FET regiments (natural cycle, stimulated cycle and artificial cycle) and their hypertensive outcomes [15–23]. In an AC-FET, there is no corpus luteum (CL) present. Most studies report an increased risk of PE and HDPs in pregnancies with AC-FET cycles, compared with natural cycle FETs. Data from meta-analyses confirm this [24,25]. Another meta-analysis comparing the risk of PE and HDP as a function of corpus luteal status in singletons, reported an OR of 2.23 (95 %CI 1.99–2.50) and 2.11 (95 % CI 1.90–2.36), respectively [26]. According to some studies, AC-FET seems to be associated with late-onset rather than early-onset PE [27].

The role of relaxin in early pregnancy renal response was recognized almost two decades ago [28]. The CL as a link between maternal cardiovascular adaptations and maternal outcomes was further evolved, based on observations in a rat model and a cohort with ovum donation (OD) pregnancies [29]. A prospective study showed that the risk of PE was associated with the presence or absence of a CL [15]. In addition to progesterone and estradiol, secretory products of the CL include vasoactive and angiogenic substances such as relaxin and prorenin, a precursor of renin. Relaxin levels correlate with the number of corpora lutea and women lacking a CL had altered cardiovascular changes compared to women with a CL [26,29,30]. The renin-angiotensin-aldosterone system (RAAS) has a role in maternal vascular adaptation during early pregnancy and the levels of prorenin are shown to be lower in cycles without a CL [31].

Relaxin-2 is proposed to have an effect on placental vascular remodelling and endometrial immune tolerance, and also a hemodynamic effect on the maternal circulation, reducing arterial stiffness and enhancing endothelial function [32]. In animal models, relaxin deficiency causes arterial stiffness and reduced fetal weight, but the alterations could be reversed by relaxin treatment [33].

Our aim was to compare whether the clinical features or morbidity were different in pregnancies after a FET among women who all had a diagnosis of PE or GH, depending on the frozen embryo transfer regimen used.

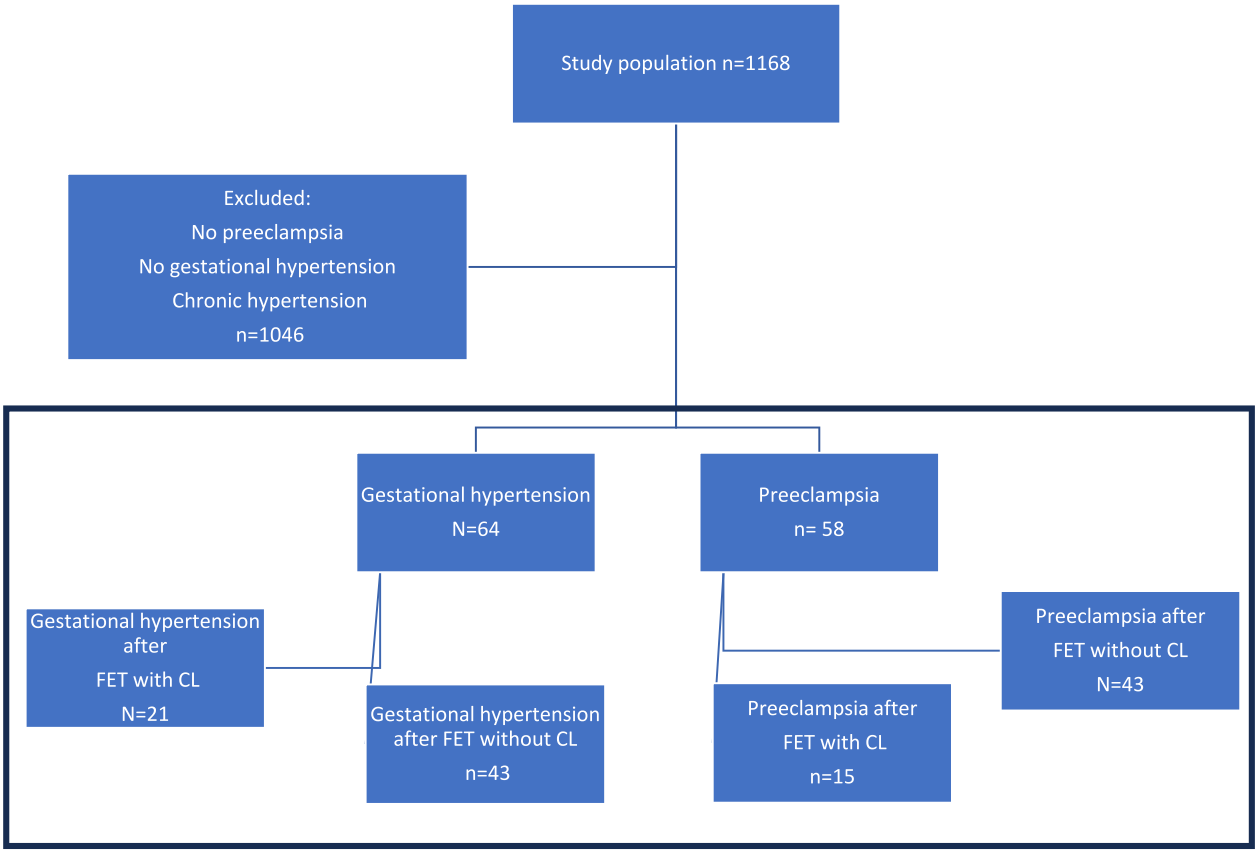

Fig. 1. Flow chart.

2. Methods

This study includes 58 pregnancies with PE and 64 pregnancies with GH. It is a subcohort of a larger retrospective study on maternal and perinatal complications after 1168 singleton live births resulting from frozen embryo transfer (Fig. 1). Women with chronic hypertension diagnosed before pregnancy, or in the first trimester, were not included in the analyses.

In the larger study, we identified the 1168 singleton live births after FET by searching the local in vitro fertilisation (IVF) treatment database (Babe). All transfers took place at the infertility clinic in Tampere University Hospital between 1.1.2012 and 31.12.2020. Excluded were multiple pregnancies, pregnancies with donated gametes, pregnancies from preimplantation genetic testing (PGT) cycles, and pregnancies that were lost to follow-up after FET.

We stratified patients according to the presence or absence of a CL. Most patients (83.3 %) in the CL group were non-stimulated cycles with or without a human chorionic gonadotropin (hCG) trigger (Supplementary table 1). Standard luteal phase support in the CL group was micronized progesterone vaginally from the day of the embryo transfer, continued until the pregnancy test day. This was used in all cycles with a CL. Cycles without a CL were artificial cycles with high-dose estrogen (oral or transdermal), and vaginal progesterone, without GnRH agonist suppression. Estrogen and progesterone treatments were continued until 10–12 weeks of gestation in the artificial cycles.

Background data for all patients were collected from patient records. Data were collected on maternal age, body mass index, parity, use of aspirin.

Delivery was defined as pregnancy duration $22^{0/7}$weeks of gestation or over, or birth weight over 500 g. Pregnancy monitoring and deliveries took place in five different hospitals in the region: Tampere University Hospital, Vaasa Central Hospital, Seinäjoki Central Hospital, Kanta-Häme Central Hospital and Satasairaala Central Hospital. Most (52 %) of the deliveries took place at Tampere University Hospital. Clinicians from these five different centers collected data on the pregnancy from hospital records and varying databases collecting routine delivery data. PE was defined according to ISSHP criteria [34]. The following pregnancy complications were actively searched for in the patient records: PE, GH, gestational diabetes, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, proteinuria, thrombocytopenia, postpartum hemorrhage (PPH). Early onset preeclampsia was defined as both diagnosis and delivery before $34^{0/7}$ weeks of gestation. All clinicians who collected patient data are experienced specialists in obstetrics and gynecology. They all gathered, classified and reported the data according to the same definitions, criteria and instructions. If there was a discrepancy in the used International Classification of Diseases, version 10 (ICD-10) codes and the described clinical status in patient records, they were instructed to re-classify the diagnosis of PE, according to the International Society for the Study of Hypertension of Pregnancy (ISSHP) criteria [34]. In the original study with 1168 patients, there were some patients who had a diagnosis of both chronic hypertension and GH simultaneously. After going through all patient records in this subcohort, we excluded the patients with chronic hypertension or elevated blood pressure before week 20. We have included severe features that warrant a closer attention in PE as follows: SBP $>$ 160 mmHg, or DBP $>$ 110 mmHg, and/or/coinciding with symptoms that were interpreted as worsening clinical condition (e.g. headaches, visual disturbances), proteinuria $>$ 5 g/24 h, dipstick 3 + or oliguria $<$ 500 mL /24 h.

Outcomes included placental retention defined here as either diagnosis of placenta accreta, need for manual displacement of placenta postpartum, or postpartum abrasion for retained placental tissue.

Perinatal outcomes included birth weight, preterm birth, 5 min APGAR score and pH and infant sex.

The data were analysed using IBM SPSS version 28. Descriptive statistics were reported as mean with standard deviation (SD) or median and interquartile range (Q_1-Q_3) or frequency (n) and percentage (%). The Independent Samples *t* Test, Chi-square test and Mann-Whitney *U* test were applied to compare the groups. The significance level was set at p value less than 0.05.

To predict factors associated with PPH over 500 mL and 1000 mL, Firths logistic regression analysis was used. This approach was chosen to address convergence issues that may arise from sparse data. Adjustments used in multivariable analyses were maternal age (</> 35 years), BMI, delivery mode, birth weight, placental retention and aspirin use.

The original retrospective cohort study was approved by the ethics committee of Tampere University Hospital (R20033R). No informed consent was obtained, as this was a retrospective register study.

3. Results

Among the patients with PE, no difference was found in maternal background factors, when comparing women with a CL cycle to women without a CL. Between the groups, there was no difference in the clinical manifestations of PE: incidence of HELLP, proteinuria, PE with severe features, maximum systolic or diastolic blood pressure. Perinatal outcomes were also comparable (Table 1). PE patients in the group without a CL more frequently had a PPH over 500 mL or 1000 mL, and higher absolute amounts of blood loss in mL:s. In multivariable analysis, a FET without a CL significantly increased the risk of having a PPH over 500 mL or 1000 mL (Table 3).

Among the patients with GH, there was no difference in any of the background factors or clinical features, when comparing cycles with a CL to cycles without a CL (Table 2). Among GH patients, the amount of blood loss in mL:s was higher in the FET group without a CL, but the frequency of a PPH over 500 mL or 1000 mL was no different. In multivariable analysis, no increased risk was seen for PPH over 500 mL or 1000 mL, after adjustments (Table 3).

4. Discussion

Among the patients with PE, there was no difference in any of the background factors or the clinical features between patients with, or without a CL. The presence or lack of a CL did not have any effect on the severity of PE, the duration of pregnancy or blood pressure levels. Hence, lacking a CL does not seem to make the symptoms worse in a PE pregnancy. The risk of a PPH was greater among women without a CL, compared to women with a CL.

The higher risk of PPH in pregnancies without a CL has been reported in studies comparing pregnancy outcomes with or without a CL, though not specifically in an isolated group of only PE pregnancies. In our study, the risk is highlighted even inside this PE population. The risk for $>$ 500 mL/$>$1000 mL PPH among the preeclamptic patients was increased even after adjusting for age, birth weight, delivery mode, BMI, placental retention, and aspirin use (Table 3). No increased risk was found in multivariable analyses for PPH $>$ 500 mL/1000 mL, among GH patients, with or without a CL. Nevertheless, the amount of blood loss (in mL:s) was significantly greater even among GH patients. It is known that the CL secretes several angiogenic metabolites that regulate implantation and placentation. Relaxin stimulates uterine growth, vascularization, and vascular endothelial growth factor in early pregnancy. There are differences in maternal hemodynamics (in early pregnancy) between patients with or without a CL, but there is no known mechanism how a CL could modify the risk of PPH in late pregnancy. The PPH risk seems to be an independent risk, but much larger studies are needed to elucidate this risk. The statistical power of the study was limited due to the number of women with preeclampsia and pregnancy hypertension in the subcohort.

A vast majority of patients were diagnosed having PE with severe features. However, no difference was found between the study groups. It is debatable, whether symptoms like headache always are a sign of acutely worsening PE. Nevertheless, we categorized all patients who

Table 1
Background factors and outcomes in patients with preeclampsia.

Preeclampsia n = 58	Cycle with CL		Cycle without CL		
	n = 15		n = 43		
	n/mean/median	%/sd/Q_1-Q_3	n/mean/median	%/sd/Q_1-Q_3	p-value
Age of woman	33.8	3.8	32.2	3.8	0.173
Body mass index	26.4	4.0	25.2	3.9	0.324
Diabetes					1.000
No diabetes	9	64.3	28	65.1	
Gestational diabetes	4	28.6	13	30.2	
Diabetes type 1 or 2	1	7.1	2	4.7	
Parity					1.000
Primipara	10	66.7	28	65.1	
Non-primipara, same partner	4	26.7	12	27.9	
Non-primipara, new partner	1	6.7	3	7.0	
Use of aspirin	1	6.7	4	9.5	1.000
Duration of pregnancy (days)	268.0	254.0–276.0	277.0	258.5–285.3	0.201
Duration of pregnancy					0.172
< 34 weeks	0	0	4	9.5	
34 + 0 – 36 + 6	5	33.3	6	14.3	
> 37 weeks	10	66.7	32	76.2	
Preterm birth	5	33.3	10	23.8	0.507
Mode of delivery					0.503
Vaginal	6	40.0	21	48.8	
Vacuum	1	6.7	6	14.0	
C-section	8	53.3	16	37.2	
Birth weight (g)	3152.0	645.8	3181.2	831.4	0.902
Large for gestational age (LGA)	1	6.7	1	2.4	0.461
Postpartum hemorrhage (PPH) (mL)	450.0	300.0–1000.0	1075	550.0–1887.5	**0.001**
PPH > 500 mL	5	33.3	31	77.5	**0.002**
PPH > 1000 mL	0	0	21	52.5	**< 0.001**
pH	7.26	0.074	7.28	0.066	0.276
Placental weight (g)	585.4	140.8	596.3	156.1	0.836
APGAŔ5 < 7	1	6.7	1	2.4	0.461
Sex of baby					0.885
Girls	7	46.7	21	48.8	
Boys	8	53.3	22	51.2	
Placental retention	0	0	4	9.3	0.564
HELLP syndrome	1	6.7	3	7.0	1.000
Preeclampsia with severe features	12	80.0	29	72.5	0.734
Early onset preeclampsia	0	0	4	9.3	0.564
Proteinuria	14	93.3	41	95.3	1.000
Thrombocytopenia	6	46.2	17	40.5	0.717
ALAT > 40 U/l	2	14.3	8	19.5	1.000
Creatinine elevation	1	16.7	3	20.0	1.000
Antihypertensive medication during pregnancy	12	80.0	27	62.8	0.340
Max systolic BP (mmHg)	167.5	161.5–172.0	162.5	153.5–180.0	0.541
Max diastolic BP (mmHg)	105.0	100.8–107.8	109.0	97.0–113.8	0.429
Max ALAT level (U/L)	28.0	14.5–37.0	23.5	14.3–38.0	0.791
Max creatinine level (μmol/L) *					
Minimum thrombocyte count (E9/L)	139.0	116.0–176.0	147.0	125.3–186.5	0.625

APGAŔ5 = 5 min APGAR score, BP = blood pressure, HELLP = hemolysis, elevated liver enzymes, low platelets -syndrome, ALAT = alanine aminotransferase.
*) The proportion of missing data for creatinine levels was too large for reliable analyses.

reported such symptoms after being diagnosed with PE, as severe feature PE, as these symptoms usually have a real impact on interventions and patient care. In contrast to our study, in some studies, the lack of a CL has been especially predictive of severe forms of preeclampsia, compared to pregnancies without a CL [15]. Incidence of early-onset PE, defined as both diagnosis and birth before $34^{0/7}$ weeks of gestation, was the same within the two groups.

Early-onset and late-onset PE seem to be two different diseases with different pathogenic mechanisms and risk factors. Investigations on the circulatory changes and vasoactive agents during pregnancy show differences between women with or without a CL. Relaxin is produced by the CL, and Placental growth factor (PlGF) is produced by the placenta after the CL-placental shift in early pregnancy. There are also several vasoconstrictory agents, such as Soluble fms-like tyrosine kinase1 (sFLT1). Several substances produced by the ovaries and the endometrium are known to date, although the exact mechanisms of involvement are not all clear [32]. In a study on the relationship between hormonal changes and vascular adaptations during pregnancy, relaxin levels correlated inversely with cardiac output and positively with sFLT1 and vasoconstriction, in early spontaneous pregnancies. It was suspected that relaxin has a biphasic effect, as relaxin later became positively correlated with cardiac output when estrogen levels increased. In the same study, among a cohort of pregnant patients without a CL, PlGF levels had no correlation with cardiac output in the first trimester, but did so later in pregnancy. This correlation was stronger compared to the cohort group with a CL. The authors suggested that PlGF acts as a rescue mechanism, possibly limiting vasoconstriction and the risk of preeclampsia. The authors also speculate, that there might be previously unrecognised vasoactive agents involved [35].

In the end, the fate of an individual parturient is the sum of all risk factors and possible protectant factors arising from the woman herself, her genes, the environment, and factors associated with the ongoing pregnancy. In a clinical setting, an individual risk assessment is needed since the magnitude of different risk factors varies. Women receiving donor eggs because of ovarian insufficiency fall in a greater risk category, as the fetal genome is totally allogeneic to the mother. Using an

Table 2
Background factors and outcomes in patients with gestational hypertension.

Gestational hypertension n = 64	CL		AC (no CL)		
	n = 21		n = 43		
	n/mean/median	%/sd/Q_1-Q_3	n/mean/median	%/sd/Q_1-Q_3	p-value
Age of woman	32.8	3.9	33.1	4.9	0.787
Body mass index	26.9	3.9	26.3	4.5	0.619
Parity					0.686
Primipara	13	61.9	31	72.1	
Non-primipara, same partner	7	33.3	10	23.3	
Non primipara, new partner	1	4.8	2	4.7	
Gestational diabetes	8	38.1	15	34.9	0.801
Duration of pregnancy (days)	278.0	269.0–284.5	282.2	274.0–289.0	0.150
Duration of pregnancy					0.500
< 34 weeks	1	4.8	0	0	
34 + 0 – 36 + 6 weeks	1	4.8	2	4.7	
>37 weeks	19	90.5	41	95.3	
Mode of delivery					0.591
Vaginal	10	47.6	21	48.8	
Vacuum	2	9.5	8	18.6	
C-section	9	42.9	14	32.6	
Birth weight (g)	3500.5	761.2	3651.3	530.0	0.360
Large for gestational age (LGA)	2	9.5	2	4.7	0.592
Postpartum hemorrhage (PPH) (ml)	450	300.0–600.0	675.0	412.5–1250.0	**0.013**
PPH > 500 mL	8	42.1	25	62.5	0.140
PPH > 1000 mL	1	5.3	11	27.5	0.081
pH	7.24	0.071	7.26	0.091	0.444
Placental weight (g)	674.7	188.7	641.0	142.4	0.475
APGAŔ5 < 7	1	4.8	0	0	0.328
Sex of baby					0.934
Girls	11	52.4	23	53.5	
Boys	10	47.6	20	46.5	
Placental retention	0	0.0	4	9.3	0.294
Use of aspirin	1	4.8	0	0	0.328
Max systolic BP (mmHg)	158.0	147.5–168.0	154.0	148.5–169.3	0.875
Max diastolic BP (mmHg)	100.0	95.0–107.0	98.5	95.0–107.5	0.799
Antihypertensive medication during pregnancy	5	23.8	16	37.2	0.284

APGAŔ5 = 5 min APGAR score, BP = blood pressure.

Table 3
Risk of PPH among patients with preeclampsia or gestational hypertension. Adjusted OŔs in pregnancies after FET without a corpus luteum (compared with FET with corpus luteum).

	outcome	Adjusted OR (95 % CI)	p-value
Preeclampsia	PPH > 500 mL	6.21 (1.40—-27.64)	0.016
	PPH > 1000 mL	83.76 (2.80—-2508.64)	0.011
Gestational hypertension	PPH > 500 mL	1.90 (0.51—-7.01)	0.337
	PPH > 1000 mL	1.63 (0.22—12.34)	0.637

Adjustments: Age </>35 years, delivery mode, birth weight, BMI, placental retention and aspirin use.
FET = frozen embryo transfer, PPH = postpartum hemorrhage.

artificial cycle is often obligatory in their transfers. Still, it is often also used for non-medical reasons, such as the ease of scheduling the transfer, something that benefits both patient and clinic for obvious, but non-medical reasons.

Another option is secondary prevention, which would mean special surveillance and possible preventive measures e.g. aspirin. Whether relaxin, or another substance yet to be recognized, can be administered as a replacement therapy in the future, remains to be seen.

5. Conclusions

Among FET patients without a CL, the risk of a severe PPH is significantly increased in PE pregnancies. Other maternal or perinatal outcomes seem to be comparable between patients with or without a CL. The increased risk of PPH is usually a treatable complication in high income countries with good capacity to react to obstetric emergencies. Still, PPH remains a significant and life-threatening risk for mothers on a global scale. All the data from this study - and numerous other studies concerning increased risks after various infertility treatments - emphasizes the need of communication between the infertility units and maternity units. Choices made in the very beginning of the process of starting a pregnancy, modify the risk of adverse events in later pregnancy and delivery.

Funding

This study was financially supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital (project number 9AB034) and by Tampere University Hospital Support Foundation, Tampere University Hospital (project number MK292). The funding sources had no role in writing or editing the manuscript.

CRediT authorship contribution statement

Eeva-Maria Pohjonen: Conceptualization, Funding acquisition, Data curation, Writing – original draft, Writing – review & editing, Visualization, Formal analysis, Methodology. **Katja Ahinko**: Conceptualization, Data curation, Writing – review & editing, Visualization, Methodology, Supervision. **Heini Huhtala:** Formal analysis, Methodology, Writing – review & editing, Software. **Tarja Erkinaro:** Data curation, Writing – review & editing, Investigation. **Johanna Lehto:** Data curation, Writing – review & editing, Investigation. **Elena Pellas:** Data curation, Writing – review & editing, Investigation. **Tiina Vilmi-Kerälä:** Data curation, Writing – review & editing, Investigation. **Hannele Laivuori:** Conceptualization, Funding acquisition, Data curation, Writing – review & editing, Visualization, Methodology, Supervision, Resources, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors wish to thank MD Noora Kaartinen for her valuable comments while designing the study, and docent Pekka Karhunen for valuable comments on the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2024.101123.

References

[1] C.W. Ives, R. Sinkey, I. Rajapreyar, A.T.N. Tita, S. Oparil, Preeclampsia-pathophysiology and clinical presentations: JACC state-of-the-art review, J. Am. Coll. Cardiol. 76 (2020) 1690–1702.
[2] L. Bellamy, J.-P. Casas, A.D. Hingorani, D.J. Williams, Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis, BMJ 335 (2007) 974.
[3] J.G. Ray, P.C. Austin, A.L. Park, E. Cohen, J. Fang, A. Chu, Severity of obstructive coronary artery stenosis after pre-eclampsia, Heart Br. Card. Soc. 109 (2023) 449–456.
[4] M. Acevedo, P. Varleta, R. Tagle, Long-term maternal cardiovascular risk after preeclampsia: a latent vascular enemy, Heart Br. Card. Soc. 109 (2023) 422–424.
[5] L. Benschop, J.J. Duvekot, J.E. Roeters van Lennep, Future risk of cardiovascular disease risk factors and events in women after a hypertensive disorder of pregnancy, Heart Br. Card. Soc. 105 (2019) 1273–1278.
[6] C.C.W. Lo, A.C.Q. Lo, S.H. Leow, G. Fisher, B. Corker, O. Batho, et al., Future cardiovascular disease risk for women with gestational hypertension: a systematic review and meta-analysis, J. Am. Heart Assoc. 9 (2020) e013991.
[7] L.A. Magee, M.A. Brown, D.R. Hall, S. Gupte, A. Hennessy, S.A. Karumanchi et al. et al., The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice, Pregnancy Hypertens., 27 (2022)148–169.
[8] L.C. Chappell, C.A. Cluver, J. Kingdom, S. Tong, Pre-eclampsia, Lancet Lond. Engl. 398 (2021) 341–354.
[9] E. Dimitriadis, D.L. Rolnik, W. Zhou, G. Estrada-Gutierrez, K. Koga, R.P. V. Francisco, et al., Pre-eclampsia, Nat. Rev. Dis. Primers 9 (2023) 8.
[10] C. Thomopoulos, C. Tsioufis, H. Michalopoulou, T. Makris, V. Papademetriou, C. Stefanadis, Assisted reproductive technology and pregnancy-related hypertensive complications: a systematic review, J. Hum. Hypertens. 27 (2013) 148–157.
[11] S. Pandey, A. Shetty, M. Hamilton, S. Bhattacharya, A. Maheshwari, Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis, Hum. Reprod. Update 18 (2012) 485–503.
[12] S. Opdahl, A.A. Henningsen, A. Tiitinen, C. Bergh, A. Pinborg, P.R. Romundstad, et al., Risk of hypertensive disorders in pregnancies following assisted reproductive technology: a cohort study from the CoNARTaS group, Hum. Reprod. 7 (2015) 1724–1731.
[13] A. Maheshwari, S. Pandey, E. Amalraj Raja, A. Shetty, M. Hamilton, S. Bhattacharya, Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? Hum. Reprod. Update 24 (2018) 35–58.
[14] T. Zaat, M. Zagers, F. Mol, M. Goddijn, M. van Wely, S. Mastenbroek, Fresh versus frozen embryo transfers in assisted reproduction, Cochrane Database Syst. Rev. 2 (2021) CD011184.
[15] F. Von Versen-Höynck, A.M. Schaub, Y.Y. Chi, K.H. Chiu, J. Liu, M. Lingis, et al., Increased preeclampsia risk and reduced aortic compliance with in vitro fertilization cycles in the absence of a corpus luteum, Hypertension 73 (2019) 640–649.
[16] R. Makhijani, C. Bartels, P. Godiwala, A. Bartolucci, J. Nulsen, D. Grow, et al., Maternal and perinatal outcomes in programmed versus natural vitrified-warmed blastocyst transfer cycles, Reprod. Biomed. Online 41 (2020) 300–308.
[17] L. Zong, P. Liu, L. Zhou, D. Wei, L. Ding, Y. Qin, Increased risk of maternal and neonatal complications in hormone replacement therapy cycles in frozen embryo transfer, Reprod. Biol. Endocrinol. 18 (2020) 36.
[18] S. Jing, X.F. Li, S. Zhang, F. Gong, G. Lu, G. Lin, Increased pregnancy complications following frozen-thawed embryo transfer during an artificial cycle, J. Assist. Reprod. Genet. 36 (2019) 925–933.
[19] J. Lin, J. Zhao, G. Hao, J. Tan, Y. Pan, Z. Wang, et al., Maternal and neonatal complications after natural vs. hormone replacement therapy cycle regimen for frozen single blastocyst transfer, Front. Med. 7 (2020) 338.
[20] Z. Wang, H. Liu, H. Song, X. Li, J. Jiang, Y. Sheng, et al., Increased risk of pre-eclampsia after frozen-thawed embryo transfer in programming cycles, Front. Med. 7 (2020) 104.
[21] Y. Pan, B. Li, Z. Wang, Y. Wang, X. Gong, W. Zhou, et al., Hormone replacement versus natural cycle protocols of endometrial preparation for frozen embryo transfer, Front. Endocrinol. 11 (2020) 546532.
[22] K. Saito, A. Kuwahara, T. Ishikawa, N. Morisaki, M. Miyado, K. Miyado, et al., Endometrial preparation methods for frozen-thawed embryo transfer are associated with altered risks of hypertensive disorders of pregnancy, placenta accreta, and gestational diabetes mellitus, Hum. Reprod. 34 (2019) 1567–1575.
[23] K.-L. Hu, D. Zhang, R. Li, Endometrium preparation and perinatal outcomes in women undergoing single-blastocyst transfer in frozen cycles, Fertil. Steril. 115 (2021) 1487–1494.
[24] A. Busnelli, I. Schirripa, F. Fedele, A. Bulfoni, P.E. Levi-Setti, Obstetric and perinatal outcomes following programmed compared to natural frozen-thawed embryo transfer cycles: a systematic review and meta-analysis, Hum. Reprod. 37 (2022) 1619–1641.
[25] J. Moreno-Sepulveda, J.J. Espinós, M.A. Checa, Lower risk of adverse perinatal outcomes in natural versus artificial frozen-thawed embryo transfer cycles: a systematic review and meta-analysis, Reprod. Biomed. Online 42 (2021) 1131–1145.
[26] K.P. Conrad, F. von Versen-Höynck, V.L. Baker, Potential role of the corpus luteum in maternal cardiovascular adaptation to pregnancy and preeclampsia risk, Am. J. Obstet. Gynecol. 226 (2022) 683–699.
[27] Y. Niu, L. Suo, D. Zhao, Y. Wang, R. Miao, J. Zou, et al., Is artificial endometrial preparation more associated with early-onset or late-onset preeclampsia after frozen embryo transfer? J. Assist. Reprod. Genet. 40 (2023) 1045–1054.
[28] M.C. Smith, A.P. Murdoch, L.A. Danielson, K.P. Conrad, J.M. Davison, Relaxin has a role in establishing a renal response in pregnancy, Fertil. Steril. 86 (2006) (Jul. 2006) 253–255.
[29] K.P. Conrad, V.L. Baker, Corpus luteal contribution to maternal pregnancy physiology and outcomes in assisted reproductive technologies, Am. J. Physiol. Regul. Integr. Comp. Physiol. 304 (2013) 69–72.
[30] F. von Versen-Höynck, P. Narasimhan, E.S. Selamet Tierney, N. Martinez, K. P. Conrad, V.L. Baker, et al., Absent or excessive corpus luteum number is associated with altered maternal vascular health in early pregnancy, Hypertension 73 (2019) 680–690.
[31] R.E. Wiegel, A.H. Jan Danser, R.P.M. Steegers-Theunissen, J.S.E. Laven, S. P. Willemsen, V.L. Baker, et al., Determinants of maternal renin-angiotensin-aldosterone-system activation in early pregnancy: insights from 2 cohorts, J. Clin. Endocrinol. Metab. 105 (2020) 3505–3517.
[32] M.M. Pereira, M. Mainigi, J.F. Strauss, Secretory products of the corpus luteum and preeclampsia, Hum. Reprod. Update 27 (2021) 651–672.
[33] J.H. Gooi, M.L. Richardson, M. Jelinic, J.E. Girling, M.E. Wlodek, Enhanced uterine artery stiffness in aged pregnant relaxin mutant mice is reversed with exogenous relaxin treatment, Biol. Reprod. 89 (2013) 18.
[34] M.A. Brown, L.A. Magee, L.C. Kenny, S.A. Karumanchi, F.P. McCarthy, S. Saito, et al., Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice, Hypertension 72 (2018) 24–43.
[35] K.P. Conrad, S. Taher, Y.-Y. Chi, Y. Qiu, M. Li, M. Lingis, R.S. Williams, et al., Relationships between reproductive hormones and maternal pregnancy physiology in women conceiving with or without in vitro fertilization, Am. J. Physiol. Regul. Integr. Comp. Physiol. 321 (2021) 454–468.