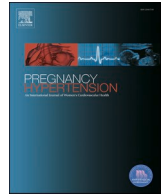




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Full Length Article

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

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### 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.

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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.

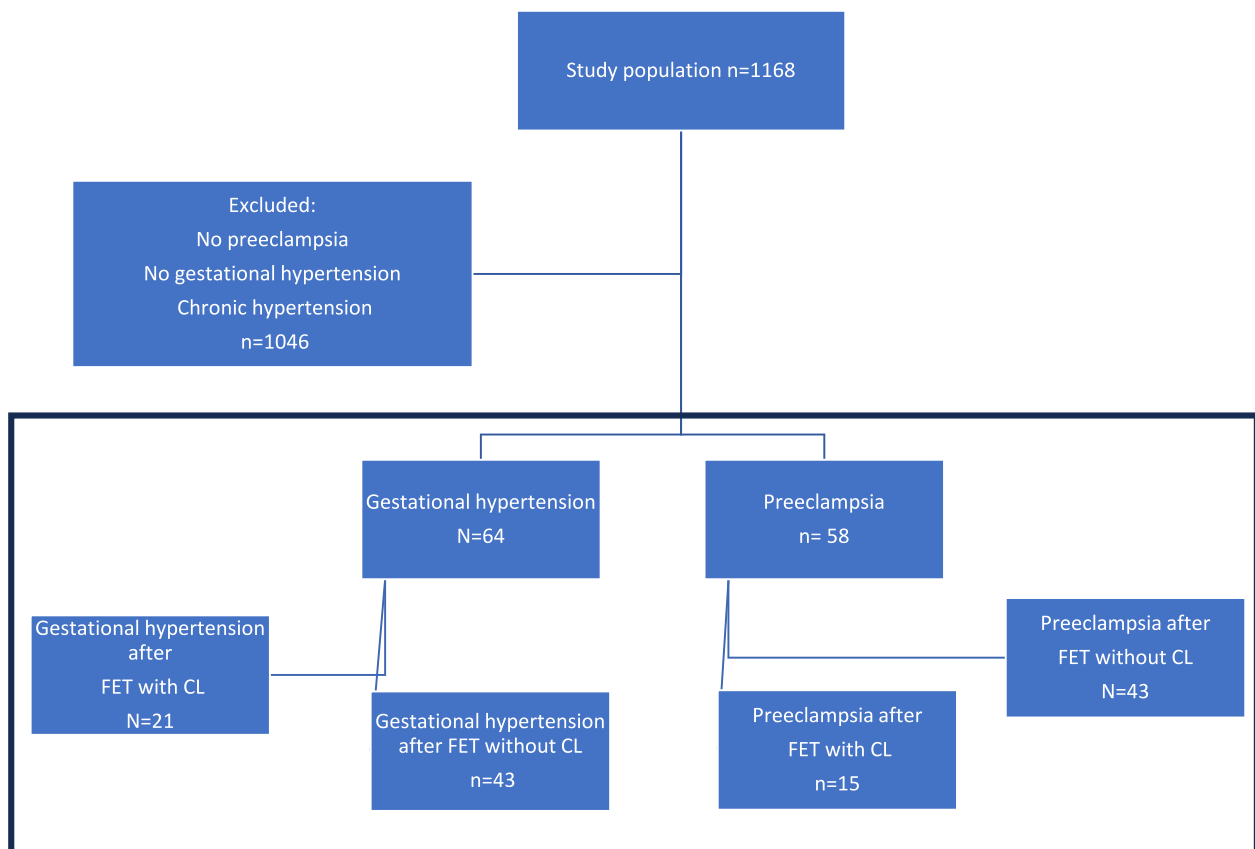
So far numerous observational studies have compared different FET regimens (natural cycle, stimulated cycle and artificial cycle) and their hypertensive outcomes [15–23]. In an AC-FET, there is no corpus luteum (CL) present. Most studies report an increased risk of PE and HDPs in pregnancies with AC-FET 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.



FET = frozen embryo transfer, CL= corpus luteum

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/occurring 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<sub>1</sub>-Q<sub>3</sub>) 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, Firth's 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		p-value
	n = 15 n/mean/median	%/sd/Q <sub>1</sub> -Q <sub>3</sub>	n = 43 n/mean/median	%/sd/Q <sub>1</sub> -Q <sub>3</sub>	
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
APGAR <sub>5</sub> < 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

APGAR<sub>5</sub> = 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<sup>0/7</sup> 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)		p-value
	n = 21	%/sd/Q <sub>1</sub> -Q <sub>3</sub>	n = 43	%/sd/Q <sub>1</sub> -Q <sub>3</sub>	
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	<b>0.013</b>
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
APGAR <sub>5</sub> < 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

APGAR<sub>5</sub> = 5 min APGAR score, BP = blood pressure.

**Table 3**  
Risk of PPH among patients with preeclampsia or gestational hypertension. Adjusted ORs 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.

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## 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.

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## Appendix A. Supplementary data

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

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