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Obstetric and perinatal outcomes following programmed compared to natural frozen-thawed embryo transfer cycles: a systematic review and meta-analysis

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STUDY QUESTION: Is there an association between the different endometrial preparation protocols for frozen embryo transfer (FET) and obstetric and perinatal outcomes?

SUMMARY ANSWER: Programmed FET protocols were associated with a significantly higher risk of hypertensive disorders of pregnancy (HDP), pre-eclampsia (PE), post-partum hemorrhage (PPH) and cesarean section (CS) when compared with natural FET protocols.

WHAT IS KNOWN ALREADY: An important and growing source of concern regarding the use of FET on a wide spectrum of women, is represented by its association with obstetric and perinatal complications. However, reasons behind these increased risks are still unknown and understudied.

STUDY DESIGN, SIZE, DURATION: Systematic review with meta-analysis. We systematically searched PubMed, MEDLINE, Embase and Scopus, from database inception to 1 November 2021. Published randomized controlled trials, cohort and case control studies were all eligible for inclusion. The risk of bias was assessed using the Newcastle–Ottawa Quality Assessment Scale. The quality of evidence was also evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Studies were included only if investigators reported obstetric and/or perinatal outcomes for at least two of the following endometrial preparation protocols: programmed FET cycle (PC-FET) (i.e. treatment with hormone replacement therapy (HRT)); total natural FET cycle (tNC-FET); modified natural FET cycle (mNC-FET); stimulated FET cycle (SC-FET).

MAIN RESULTS AND THE ROLE OF CHANCE: Pooled results showed a higher risk of HDP (12 studies, odds ratio (OR) 1.90; 95% CI 1.64–2.20; $P < 0.00001$; $I^2 = 50\%$) (very low quality), pregnancy-induced hypertension (5 studies, OR 1.46; 95% CI 1.03–2.07; $P = 0.03$; $I^2 = 0\%$) (very low quality), PE (8 studies, OR 2.11; 95% CI 1.87–2.39; $P < 0.00001$; $I^2 = 29\%$) (low quality), placenta previa (10 studies, OR 1.27; 95% CI 1.05–1.54; $P = 0.01$; $I^2 = 8\%$) (very low quality), PPH (6 studies, OR 2.53; 95% CI 2.19–2.93; $P < 0.00001$; $I^2 = 0\%$) (low quality), CS (12 studies, OR 1.62; 95% CI 1.53–1.71; $P < 0.00001$; $I^2 = 48\%$) (very low quality), preterm birth (15 studies, OR 1.19; 95% CI 1.09–1.29; $P < 0.0001$; $I^2 = 47\%$) (very low quality), very preterm birth (7 studies, OR 1.63; 95% CI 1.23–2.15; $P = 0.0006$; $I^2 = 21\%$) (very low quality), placenta accreta (2 studies, OR 6.29; 95% CI 2.75–14.40; $P < 0.0001$; $I^2 = 0\%$) (very low quality), preterm premature rupture of membranes (3 studies, OR 1.84; 95% CI 0.82–4.11; $P = 0.14$; $I^2 = 61\%$) (very low quality), post-term birth (OR 1.90; 95% CI 1.25–2.90; $P = 0.003$; $I^2 = 73\%$) (very low quality), macrosomia (10 studies, OR 1.18; 95% CI 1.05–1.32; $P = 0.007$; $I^2 = 45\%$) (very low

quality) and large for gestational age (LGA) (14 studies, OR 1.08; 95% CI 1.01–1.16; $P=0.02$; $I^2=50\%$) (very low quality), in PC-FET pregnancies when compared with NC (tNC + mNC)-FET pregnancies. However, after pooling of ORs adjusted for the possible confounding variables, the endometrial preparation by HRT maintained a significant association in all sub-analyses exclusively with HDP, PE, PPH (low quality) and CS (very low quality).

LIMITATIONS, REASONS FOR CAUTION: The principal limitation concerns the heterogeneity across studies in: (i) timing and dosage of HRT; (ii) embryo stage at transfer; and (iii) inclusion of preimplantation genetic testing cycles. To address it, we undertook subgroup analyses by pooling only ORs adjusted for a specific possible confounding factor.

WIDER IMPLICATIONS OF THE FINDINGS: Endometrial preparation protocols with HRT were associated with worse obstetric and perinatal outcomes. However, because of the methodological weaknesses, recommendations for clinical practice cannot be made. Well conducted prospective studies are thus warranted to establish a safe endometrial preparation strategy for FET cycles aimed at limiting superimposed risks in women with an '*a priori*' high-risk profile for obstetric and perinatal complications.

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Key words: frozen embryo transfer / endometrial preparation protocol / hormone replacement therapy / programmed cycles / obstetric outcomes / perinatal outcomes

Introduction

Cryopreservation in ART makes it possible to conserve surplus gametes and embryos for further use (Shi *et al.*, 2018). Improvements in embryo freezing protocols and the introduction of vitrification led to the widespread use of strategies involving deferred embryo transfer (ET) (Shi *et al.*, 2018; Coutifaris, 2019). Since, in most cases, this is an optional procedure, the decision to adopt it should be taken after a careful analysis of benefits and harms (Morgan *et al.*, 2020). Patients' safety is undoubtedly one of the elements that most strongly supports this practice. Indeed, even if available evidence is of low quality, theoretical considerations suggest that embryo freezing is probably effective in the prevention of ovarian hyperstimulation syndrome after IVF (Mourad *et al.*, 2017). Some authors also speculated a beneficial effect of the so-called 'freeze-all' strategy on the IVF success rates (Stormlund *et al.*, 2020; Wei *et al.*, 2019).

Focusing on harms, an important and growing source of concern regarding the use of frozen embryo transfer (FET) on a wide spectrum of women is represented by its association with obstetric and perinatal complications. In a well-conducted meta-analysis of randomized controlled trials (RCTs), Roque *et al.* (2019) reported a higher risk of pre-eclampsia (PE) in pregnancies resulting from elective FET than from fresh ET. A pivotal multicenter RCT comparing frozen versus fresh single blastocyst transfer in ovulatory women, confirmed this finding (relative risk (RR) 3.13; 95% CI 1.06–9.30; $P=0.029$) (Wei *et al.*, 2019). Maheshwari *et al.* (2018) pooled results of observational studies and showed that babies conceived from frozen thawed embryos were at lower risk of small for gestational age (SGA) and low birth weight (LBW) but at higher risk of large for gestational age (LGA) and high birth weight (Maheshwari *et al.*, 2018; Somigliana *et al.*, 2018). In a more recent meta-analysis, Conforti *et al.* (2021) not only confirmed the increased risk of LGA and PE but also observed a higher rate of cesarean section (CS) after the intrauterine transfer of a frozen-thawed blastocyst.

Mechanisms behind the observed maternal and perinatal risks in FET cycles are still unknown and understudied. In this regard, von Versen-Höynck *et al.* (2019) speculated that the considerable higher PE risk may be in part due to the impact of the IVF protocols on the maternal hormonal milieu in the first trimester of pregnancy. In programmed FET cycles (PC-FET), the agenesis of the corpus luteum (CL) inevitably determines the absence of circulating vasoactive factors such as relaxin, a potent vasodilator able to promote the maternal cardiovascular adaptation during the first months of pregnancy (von Versen-Höynck *et al.*, 2019). Starting from its role, von Versen-Höynck *et al.* (2019) theorized that the lack of relaxin may determine a higher susceptibility to PE development.

In the last 2 years, the von Versen-Höynck's hypothesis attracted the attention of many investigators (von Versen-Höynck *et al.*, 2019; Asserhøj *et al.*, 2021; Levi-Setti *et al.*, 2020; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Zong *et al.*, 2020; Wang *et al.*, 2020a,b; Hu *et al.*, 2021; Li *et al.*, 2021). However, extrapolating the independent influence of the endometrial preparation protocol on the most important obstetric and perinatal outcomes is a difficult task. In fact, both preconception (i.e. history of chronic hypertension, maternal age and maternal BMI) and IVF related (i.e. indication to IVF/ICSI, fertilization method, embryo stage at transfer or embryo culture duration) variables may confound the observed associations (von Versen-Höynck *et al.*, 2021). Furthermore, the heterogeneity between studies both in terms of comparisons carried out and of outcomes analyzed makes the general picture complex and confusing.

Against that background, the objective of the present systematic review and meta-analysis is to synthesize the available evidence regarding the association between the different endometrial preparation protocols for FET cycles and both maternal and perinatal risks. Our efforts also focused on controlling, as much as possible, the effect of confounding factors in order to determine the impact of the endometrial preparation protocol *per sè* on maternal and neonatal health.

Materials and methods

This literature overview was reported according to the PRISMA guidelines for systematic reviews (Moher *et al.*, 2009; Deeks *et al.*, 2018) and the meta-analysis was conducted according to the MOOSE guidelines (Brooke *et al.*, 2021). Since published de-identified data were used, this study was exempt from institutional review board approval.

A protocol for this systematic review and meta-analysis has been registered at PROSPERO (ID number: CRD42021249927).

Sources and study selection

The present systematic review and meta-analysis was restricted to published research articles that reported data relevant to the association between different protocols for endometrial preparation in FET cycles and risk of obstetric and perinatal complications. We systematically searched PubMed, MEDLINE, Embase and Scopus, from database inception to 1 November 2021. Searches were limited to studies in humans and were conducted using the following terms: 'frozen embryo transfer' OR 'FET' OR 'frozen blastocyst transfer' OR 'programmed frozen embryo transfer cycle' OR 'natural frozen embryo transfer cycle' OR 'stimulated frozen embryo transfer cycle' AND 'obstetric complication' OR 'pregnancy complication' OR 'perinatal complication' OR 'neonatal complication' OR 'preterm birth' OR 'gestational hypertension' OR 'pre-eclampsia' OR 'post-partum hemorrhage' OR 'placenta previa' OR 'cesarean section' OR 'post-term birth' OR 'gestational diabetes' OR 'placental abruption' OR 'premature rupture of membranes' OR 'low birth weight' OR 'macrosomia' OR 'large for gestational age' OR 'small for gestational age' OR 'neonatal mortality' OR 'stillbirth' OR 'birth defect'.

Studies were included only if: (i) investigators reported obstetric and/or perinatal outcomes for one of the following endometrial preparation protocol: PC-FET (i.e. treatment with estrogen and progesterone with or without prior downregulation with GnRH agonist or antagonist (no CL)); total natural FET cycle (tNC-FET) (i.e. without any exogenous hormone and based on the endogenous LH surge (1 CL)); modified natural FET cycle (mNC-FET) (i.e. administration of hCG trigger after a natural cycle monitoring (1 CL)); stimulated FET cycle (SC-FET) (i.e. a mix of cycles using different ovulatory agents (e.g. clomiphene citrate or letrozole with or without hCG, gonadotropin stimulation including FSH or hMG with or without GnRH agonist/antagonist, or luteal support including progesterone with or without hCG (at least 1 CL) (Ginström Ernstad *et al.*, 2019)); (ii) investigators included at least 50 cases per analyzed endometrial preparation protocol. The embryo stage at the time of transfer (i.e. cleavage stage or blastocyst stage) was not considered either as an inclusion or an exclusion criterion.

Published RCTs, cohort and case control studies were all eligible for inclusion. Both manuscripts and conference abstracts were screened. All pertinent articles were retrieved, and their reference lists were systematically reviewed to identify additional reports for inclusion in the meta-analysis. Moreover, review articles and meta-analyses that focused on the association between FET and pregnancy and/or perinatal complications were consulted, and their reference lists searched for potential additional studies. No attempt was made to identify unpublished studies.

Two authors (A.Bus. and I.S.) independently performed an initial screening of every article's title and abstract. Studies were excluded if they were deemed irrelevant by both the observers. If there was ambiguity or uncertainty for inclusion, studies were discussed at group meetings with the other authors. Reports were classified according to the study design into RCTs, case-control studies, prospective and retrospective cohort studies.

Investigated outcomes

Primary outcomes were: hypertensive disorders of pregnancy (HDP); pregnancy-induced hypertension (PIH) and PE. Secondary outcomes were: placenta previa (PP); placenta accreta; CS; post-partum hemorrhage (PPH); very preterm birth (VPTB); pre-term birth (PTB); post-term birth, macrosomia and LGA. We also investigated the association between endometrial preparation protocol and gestational diabetes mellitus (GDM); placental abruption; preterm premature rupture of membranes (PPROM); LBW; very low birth weight; SGA; stillbirth and congenital malformations. Their definitions in individual studies are reported in Supplementary Table SI.

Risk of bias and quality assessment

Two authors (A.Bus. and A.Bul.) independently assessed the included studies for risks of bias using the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies (Wells *et al.*, 2009) and the Cochrane 'Risk of bias' assessment tool for randomized clinical trials (RCTs) (Higgins *et al.*, 2019). They also graded the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Atkins *et al.*, 2004). Quality of evidence was downgraded by one level for serious concerns and by two levels for very serious concerns for risk of bias, inconsistency, indirectness, imprecision and publication bias.

Data extraction and analysis

Two authors (A.Bus. and F.F.) independently evaluated all articles and extrapolated the data on standardized forms. A final abstraction form was compiled from the two evaluation forms after a discussion with the remaining authors. For every study, the year of publication; location; study design; data source; study period; characteristics of the included subjects; included endometrial preparation protocols (i.e. tNC-FET, mNC-FET, PC-FET and SC-FET); investigated obstetric and perinatal outcomes were recorded.

For every obstetric and perinatal outcome, the risk estimate was calculated for the following comparisons (if enough data were available): (i) PC-FET versus NC-FET (tNC-FET + mNC-FET); (ii) PC-FET versus tNC-FET; (iii) PC-FET versus mNC-FET; (iv) PC-FET versus SC-FET; (v) SC-FET versus tNC-FET; (vi) SC-FET versus mNC-FET; (vii) tNC-FET versus mNC-FET.

In order to account for possible confounders, sub-analyses were conducted by pooling only risk estimates adjusted for covariates. In particular, we considered both preconception (i.e. history of chronic hypertension, history of pregestational diabetes, maternal age and maternal BMI) and IVF related (i.e. cause of infertility/indication to IVF/ICSI, fertilization method (classical IVF versus ICSI), embryo stage at transfer or embryo culture duration, embryo biopsy for preimplantation genetic testing (PGT)) confounding variables (Nouri *et al.*, 2013; Horton *et al.*, 2019; Kobayashi *et al.*, 2020; Spangmose *et al.*, 2020).

The risk estimate was expressed using an odds ratio (OR) with 95% CI. The inconsistency of the studies' results was measured using Cochrane Q and the I^2 statistic (Higgins *et al.*, 2019). Risk estimates were combined in a meta-analysis using a fixed effects model when the heterogeneity found among the studies was absent to moderate ($0\% \leq I^2 < 30\%$). When heterogeneity was moderate, substantial or considerable ($I^2 \geq 30\%$), the DerSimonian and Laird method was used

(DerSimonian and Laird 1986, DerSimonian and Kacker, 2007) for a random-effects model (Egger et al., 2001). All analyses were performed using Review Manager version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration).

Results

Results of search and description of studies

Figure 1 summarizes the process of literature identification and selection of studies (Moher et al., 2009). Our literature searches yielded 315 studies, of which 18 duplicates were removed. After a full review of titles and abstract, 28 studies were identified as potentially eligible for inclusion. After a full review, we excluded five systematic reviews and meta-analyses (Maheshwari et al., 2012, 2018; Roque et al., 2019; Moreno-Sepulveda et al., 2021; Zaat et al., 2021a), two reviews (Singh et al., 2020; Pereira et al., 2021), one study because obstetric and perinatal outcomes of NC-FET cycles and of spontaneous conception were not reported separately (Wiegel et al., 2020) and one study because obstetric and perinatal outcomes of NC-FET and SC-FET cycles were not reported separately (Waschkies et al., 2021).

Data relevant to the association between the protocol adopted for endometrial preparation in FET cycles and risk of obstetrics and perinatal complications were extracted from the remaining 19 studies (Guan et al., 2016; Saito et al., 2017; Alur-Gupta et al., 2018; Ginström Ernstad et al., 2019; Jing et al., 2019; Saito et al., 2019; von Versen-Höynck et al., 2019; Asserhøj et al., 2021; Levi-Setti et al., 2020; Lin et al., 2020; Makhijani et al., 2020; Pan et al., 2020; Zong et al., 2020; Wang et al., 2020a,b; Hu et al., 2021; Li et al.,

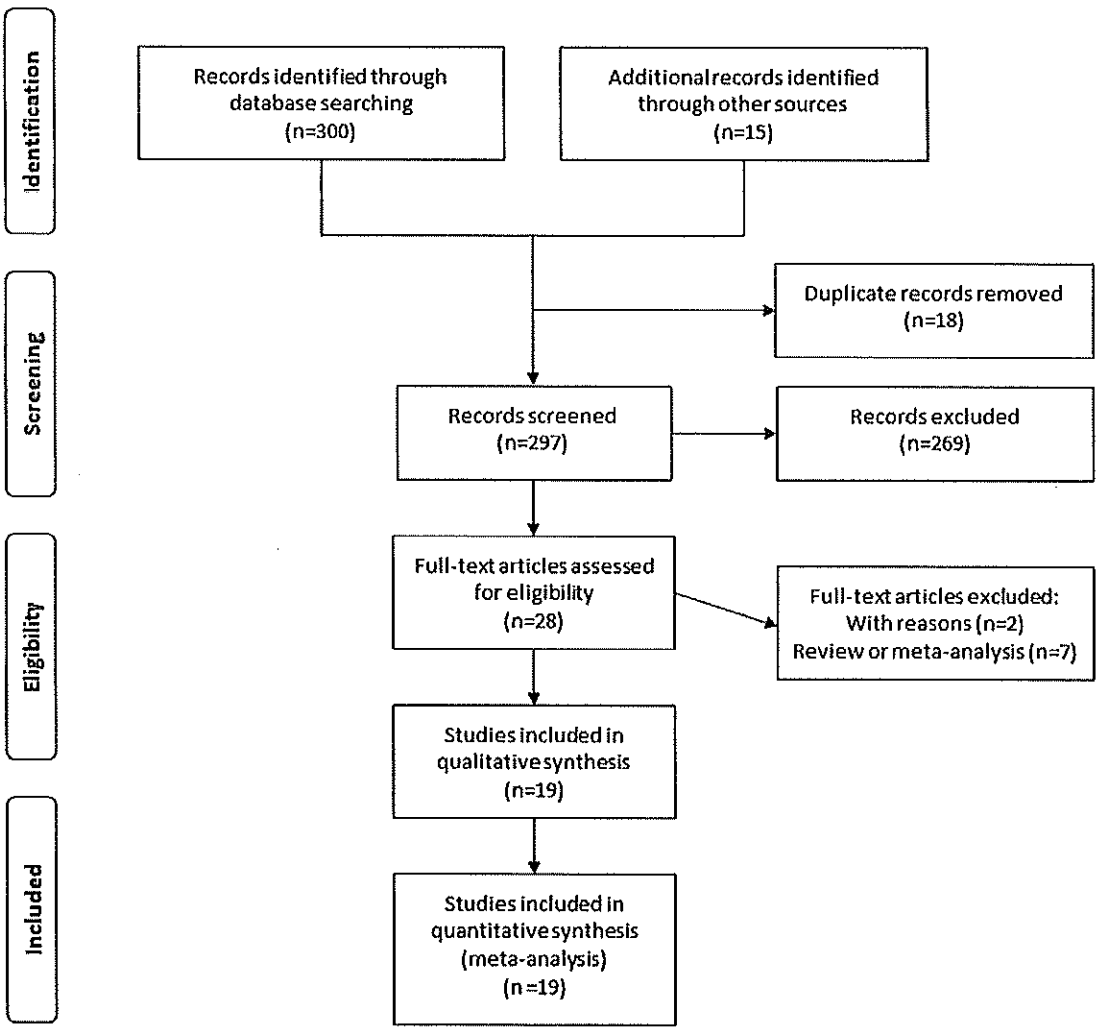

Figure 1. Study flow chart.

2021; Tao et al., 2021; Zaat et al., 2021b). Of these, 18 were retrospective cohort studies and 1 was a prospective cohort study (von Versen-Höynck et al., 2019). As regards the origin of data, the included studies can be divided into two groups: (i) studies based on the analysis of data extracted from national registries or obtained by combining those of multiple IVF centers (Saito et al., 2017; Ginström Ernstad et al., 2019; Saito et al., 2019; Asserhøj et al., 2021; Pan et al., 2020); (ii) studies based on data extracted from a single IVF center registry (Alur-Gupta et al., 2018; Jing et al., 2019; von Versen-Höynck et al., 2019; Levi-Setti et al., 2020; Makhijani et al., 2020; Zong et al., 2020; Wang et al., 2020a,b; Hu et al., 2021; Li et al., 2021; Tao et al., 2021; Zaat et al., 2021b). Characteristics of all included studies are reported in Table I.

Primary outcomes

Hypertensive disorders of pregnancy

Twelve studies were meta-analyzed. We observed a higher risk of HDP in PC-FET pregnancies (random effects model, OR 1.90; 95% CI 1.64–2.20; $P<0.00001$; $I^2=50\%$) (very low quality) (Ginström Ernstad et al., 2019; Jing et al., 2019; Saito et al., 2019; von Versen-Höynck et al., 2019; Asserhøj et al., 2021; Makhijani et al., 2020; Pan et al., 2020; Zong et al., 2020; Wang et al., 2020b; Hu et al., 2021; Li et al., 2021; Zaat et al., 2021b) (Supplementary Fig. S1A).

Two studies reported OR adjusted for a positive history of chronic hypertension (Ginström Ernstad et al., 2019; Makhijani et al., 2020). Pooling of their adjusted ORs (aORs) confirmed the association (fixed effects model, OR 1.85; 95% CI 1.51–2.27; $P<0.00001$; $I^2=0\%$). Six studies reported OR adjusted for maternal age (Ginström Ernstad et al., 2019; Saito et al., 2019; Asserhøj et al., 2021; Makhijani et al., 2020; Zong et al., 2020; Hu et al., 2021) (random effects model, OR 1.95; 95% CI 1.58–2.41; $P<0.00001$; $I^2=65\%$). Four studies reported OR adjusted for embryo stage at transfer or embryo culture duration (Ginström Ernstad et al., 2019; Jing et al., 2019; Saito et al., 2019; Asserhøj et al., 2021) (fixed effects model, OR 1.67; 95% CI 1.46–1.91; $P<0.00001$; $I^2=0\%$) (Table II). Five studies reported OR adjusted for BMI (Ginström Ernstad et al., 2019; Jing et al., 2019; Makhijani et al., 2020; Zong et al., 2020; Hu et al., 2021) (random effects model, OR 2.08; 95% CI 1.74–2.48; $P<0.00001$; $I^2=43\%$). Two studies reported OR adjusted for the adopted fertilization method (Ginström Ernstad et al., 2019; Asserhøj et al., 2021) (fixed effects model, OR 1.80; 95% CI 1.47–2.19; $P<0.00001$; $I^2=0\%$). Seven studies reported OR adjusted for embryo biopsy (PGT) (random effects model, OR 2.02; 95% CI 1.62, 2.52; $P<0.00001$; $I^2=58\%$) (Asserhøj et al., 2021; Makhijani et al., 2020; Pan et al., 2020; Zong et al., 2020; Wang et al., 2020b; Hu et al., 2021; Li et al., 2021). Four studies reported OR adjusted for the indication to IVF/ICSI (Ginström Ernstad et al., 2019; Saito et al., 2019; Makhijani et al., 2020; Hu et al., 2021) (random effects model, OR 1.98; 95% CI 1.45–2.71; $P<0.00001$; $I^2=78\%$) (Table II).

Pregnancy-induced hypertension

Results from five studies were pooled. A significantly higher risk of PIH was observed in PC-FET pregnancies (fixed effects model, OR 1.46; 95% CI 1.03–2.07; $P=0.03$; $I^2=0\%$) (very low quality) (Ginström Ernstad et al., 2019; von Versen-Höynck et al., 2019; Lin et al., 2020; Li et al., 2021; Zaat et al., 2021b) (Table II). One study reported OR adjusted for maternal age, BMI, embryo biopsy (PGT) and for indication to IVF/ICSI and failed to confirm this association (Li et al., 2021) (Table II).

Pre-eclampsia

Eight studies were meta-analyzed. We observed a higher risk of PE in PC-FET pregnancies (fixed effects model, OR 2.11; 95% CI 1.87–2.39; $P<0.00001$; $I^2=29\%$) (low quality) (Ginström Ernstad et al., 2019; von Versen-Höynck et al., 2019; Asserhøj et al., 2021; Lin et al., 2020; Wang et al., 2020a,b; Li et al., 2021; Zaat et al., 2021b) (Supplementary Fig. S1B).

Two studies reported OR adjusted for a positive history of chronic hypertension (Ginström Ernstad et al., 2019; von Versen-Höynck et al., 2019). Pooling of their adjusted ORs (aORs) confirmed the association (fixed effects model, OR 2.00; 95% CI 1.61–2.49; $P<0.00001$; $I^2=11\%$) (Table II).

One study focused only on blastocyst stage ET (Lin et al., 2020) and two studies reported OR adjusted for embryo culture duration (Ginström Ernstad et al., 2019; Asserhøj et al., 2021). Pooling of their results confirmed the association (fixed effects model, OR 1.99; 95% CI 1.63–2.43; $P<0.00001$; $I^2=0\%$). Six studies reported OR adjusted for maternal age (Ginström Ernstad et al., 2019; von Versen-Höynck et al., 2019; Asserhøj et al., 2021; Lin et al., 2020; Wang et al., 2020a; Li et al., 2021) (fixed effects model, OR 2.17; 95% CI 1.91–2.46; $P<0.00001$; $I^2=13\%$). Four studies reported OR adjusted for BMI (Ginström Ernstad et al., 2019; von Versen-Höynck et al., 2019; Wang et al., 2020a; Li et al., 2021) (random effects model, OR 2.28; 95% CI 1.80–2.89; $P<0.00001$; $I^2=43\%$). Three studies reported OR adjusted the adopted fertilization method (Ginström Ernstad et al., 2019; Asserhøj et al., 2021; Wang et al., 2020a) (random effects model, OR 2.26; 95% CI 1.87–2.73; $P<0.00001$; $I^2=31\%$). Three studies reported OR adjusted for embryo biopsy (fixed effects model, OR 1.92; 95% CI 1.56, 2.37; $P<0.00001$; $I^2=0\%$) (Asserhøj et al., 2021; Wang et al., 2020b; Li et al., 2021). Three studies reported an OR adjusted for the indication to IVF/ICSI (Ginström Ernstad et al., 2019; Wang et al., 2020a; Li et al., 2021) (random effects model, OR 2.13; 95% CI 1.75–2.59; $P<0.00001$; $I^2=51\%$) (Table II).

Secondary outcomes

Placenta previa

Results from 10 studies were pooled. We observed a higher risk of PP in PC-FET pregnancies (fixed effects model, OR 1.27; 95% CI 1.05–1.54; $P=0.01$; $I^2=8\%$) (very low quality) (Ginström Ernstad et al., 2019; Saito et al., 2019; Asserhøj et al., 2021; Lin et al., 2020; Makhijani et al., 2020; Zong et al., 2020; Wang et al., 2020a,b; Hu et al., 2021; Zaat et al., 2021b) (Table II).

Six studies reported OR adjusted for maternal age. Pooling of their aORs showed the absence of an association (fixed effects model, OR 1.16; 95% CI 0.89–1.50; $P=0.27$; $I^2=0\%$) (Ginström Ernstad et al., 2019; Saito et al., 2019; Asserhøj et al., 2021; Makhijani et al., 2020; Zong et al., 2020; Hu et al., 2021). Four studies reported OR adjusted for maternal BMI (fixed effects model, OR 1.28; 95% CI 0.90–1.80; $P=0.17$; $I^2=24\%$) (Ginström Ernstad et al., 2019; Makhijani et al., 2020; Zong et al., 2020; Hu et al., 2021). Two studies reported OR adjusted for the fertilization method (fixed effects model, OR 0.84; 95% CI 0.49–1.43; $P=0.52$; $I^2=0\%$) (Ginström Ernstad et al., 2019;

Table I Characteristics of included studies.

Study	Country	Design	Data origin	Study period	Included population	Embryo stage at transfer	Nr. of included pregnancies for each endometrial protocol	HRT scheme	PGT	Investigated outcomes
Guan *et al.*, 2016	Japan	Register-based cohort study	Japanese ART registry for 2016	2016	Women with regular menstrual intervals. Patients with a history of RIF or abortion were excluded.	Cleavage	mNC-FET (n = 184); PC-FET (n = 271)	4–6 mg/day of oral estradiol (estradiol valerate, Progynova, Bayer HealthCare, Germany) starting on Days 2–4 of the natural menstrual cycle. The estradiol dosage was adjusted based on the endometrial thickness and level of serum E2. After adequate endometrial proliferation (diameter ≥8 mm) and serum E2 concentration (200–300 ng/l) were documented, intramuscular progesterone administration was commenced. Both estradiol and progesterone were administered until 10 weeks of gestation.	NR	HDP, GDM, PTB, IUGR, macrosomia, stillbirth, congenital malformations
Saito *et al.*, 2017	Japan	Retrospective cohort study	Japanese ART registry for 2013	2013	Women who underwent autologous FET at 557 Japanese ART facilities in 2013 and achieved a live birth after 22 weeks of gestation.	Both cleavage and blastocyst	NC-FET (n = 6287); PC-FET (n = 10235)	Oral and transdermal estrogen preparations and oral, injectable and transvaginal progesterone are used. The exact HRT protocol adopted is not specified by authors because it differs among participating clinics and are not precisely reported in the Japanese ART registry.	NR	CS, PTB, PostTB, LBW, macrosomia, SGA, LGA, stillbirth
Afur-Gupta *et al.*, 2018	USA	Retrospective cohort study	Pen Fertility Care center	2013–2017	Women of all ages and fertility diagnoses undergoing autologous blastocyst transfers.	Blastocyst	NC-FET (n = 105); PC-FET (n = 923)	Luteal phase GnRH analog suppression. Oral estradiol was then initiated at a dose of 2 mg daily and titrated to 6 mg daily over 12 days. In cases of inadequate endometrial thickness or morphology or inadequate E2 level, vaginal E2 or higher doses of oral E2 were administered. Intramuscular progesterone was initiated at 50 mg when appropriate parameters were met, and blastocyst transfer was scheduled to occur on the 6th day of progesterone supplementation.	Analyses were adjusted also for the adoption of PGT	Stillbirth
Ginström Ernstad *et al.*, 2019	Sweden	Register-based cohort study	National ART registry cross-linked with	2005–2015	All singleton deliveries achieved in Sweden through homologous IVF between 2005 and 2015.	Both cleavage and blastocyst	PC-FET (n = 1446); NC-FET (n = 6297); SC-FET (n = 1983)	Estrogen and progesterone with or without suppression with a GnRHa/antagonist	NR	PP, PAbr, HDP, PE, PIH, PPH, CS, congenital malformations, PTB, VPTB, stillbirth, LGA, SGA, macrosomia, LBW, VLBW, PostTB

(continued)

Table I Continued

Study	Country	Design	Data origin	Study period	Included population	Embryo stage at transfer	Nr. of included pregnancies for each endometrial protocol	HRT scheme	PGT	Investigated outcomes
Jing et al., 2019	China	Retrospective cohort study	Citic-Xiangya Hospital fertility center registry	2013–2016	The included women had at least one blastocyst or two cleavage-stage embryos in storage, regular ovulatory cycles, and at most two previous ET cycles.	Both cleavage and blastocyst	PC-FET (n = 1025); NC-FET (n = 3872)	Estrogen (Progynova, DELPHARM Lille S.A.S., France) (2 mg estradiol valerate) was administered orally: one pill on Days 1, 2, 3 and 4; two pills on Days 5, 6 and 7; three pills on Days 8, 9, 10 and 11; four pills on Days 12, 13, 14, 15 and 16; and two pills on Days 17 to 31. When the endometrial thickness reached at least 8 mm, dydrogesterone was administered orally (10 mg per 12 h; Duphaston, Abbott Biologicals B.V.) and progesterone vaginally (200 mg, three times a day; Utrogestan, Capsugel).	NR	SGA, LGA, GDM, HDP, CS
Lin et al., 2020	China	Multicenter retrospective cohort study	Registries of 21 academic fertility centers	2016–2017	Women with regular menstrual cycles undergoing their first cycle of IVF.	Blastocyst	PC-FET (n = 144); mNC-FET (n = 305);	Oral estradiol valerate (Progynova, Delpharm Lille, Lys-Lez- Lannoy, France) at a dose of 4–8 mg daily was started on Days 1–3 of the menstrual cycle. Vaginal progesterone gel (Crinone, Merck Serono) 90 mg/day and oral dydrogesterone 10 mg twice daily were added when the endometrial thickness reached 7 mm or more.	NR	GDM, HDP, PE, PIH, PP, PTB, PPH, SGA, LGA, congenital malformations
Saito et al., 2019	Japan	Retrospective cohort study	Japanese ART registry for 2014	2014	Women who underwent autologous FET at 574 ART Japanese facilities in 2014.	Both cleavage and blastocyst	NC-FET (n = 29 760); PC-FET (n = 75 474)	Oral and trasdermal estrogen preperations and oral, injectable and trasvaginal progesterone are used. The exact HRT protocol adopted is not specified by authors because it differs among participating clinics and are not precisely reported in the Japanese ART registry.	NR	PTB, PostTB, CS, PP, PAbr, HDP, PAccr, GDM, PPROM, LBW, macrosomia, SGA, LGA
von Versen-Höynck et al., 2019	USA	Prospective cohort study	Reproductive Endocrinology and Infertility clinic, University of Florida	2011–2017	Three cohorts of pregnant women conceiving: (i) spontaneously; (ii) by autologous or donor FET (iii) after ovarian stimulation, IVF and fresh embryo transfer.	NR	PC-FET (n = 94); NC-FET (n = 127)	OCPs on Day 3 of the menstrual cycle for 14–40 days. 3 days prior to discontinuation of OCPs, 81 mg of ASA and 1 mg of Lupron SC were started. Once adequate suppression was achieved, 0.1 mg estradiol patch was placed and changed every other day. On Days 7–8 of estrogen therapy, dosing was increased to 2 patches every other day, on Days 9–12 dosing was increased to 3 patches and on Days 13–14 to 4 patches. Pending adequate response, Prometrium 200 mg vaginally twice a day and Progesterone 1 ml/50 mg IM nightly were started.	NR	HDP, PIH, PE

(continued)

Table I Continued

Study	Country	Design	Data origin	Study period	Included population	Embryo stage at transfer	Nr. of included pregnancies for each endometrial protocol	HRT scheme	PGT	Investigated outcomes
Asserhøj et al., 2021	Denmark	Register-based cohort study	National ART registry cross linked with national Patient Register	2006–2014	Data from 1136 deliveries after autologous FET.	Both cleavage and blastocyst	PC-FET (n = 357); mNC-FET (n = 611); tNC-FET (n = 168)	Progesterone and/or estradiol with or without prior downregulation with GnRH agonist/antagonist. No hCG was administered during the FET cycle.	Authors excluded pregnancies achieved after PGT	HDP, PE, PPROM, PP, Pabr, PPH, CS, PostTB, PTB, VPTB, macrosomia, SGA, LGA
Levi-Setti et al., 2020	Italy	Retrospective cohort study	Humanitas Fertility center registry	2011–2017	Women who underwent single blastocyst transfers with vitrified/rewarmed Day 5 or Day 6 blastocysts.	Blastocyst	NC-FET (n = 561); mNC-FET (n = 1749); PC-FET (n = 585)	Estradiol valerate (Progynova, Bayer, 2 mg) from the second day of the menstrual cycle until the endometrial thickness reached at least 7 mm. If endometrial thickness was less than 7 mm, after 12 days of E2V, the dose was increased to 8 mg/day. Endometrial preparation for transfer consisted of continued estradiol (6–8 mg, a day E2V) combined with 600 mg of vaginal micronized progesterone tablets (Prometrium, Rottapharm S.p.a., 200 mg every 8 h).	NR	LGA
Mishani et al., 2020	USA	Retrospective cohort study	University-affiliated fertility center	2013–2018	Women who underwent ET of previously vitrified blastocysts derived from autologous oocytes between March 2013 and October 2018 and achieved a singleton live birth.	Blastocyst	PC-FET (n = 391); NC-FET (n = 384)	Programmed cycles consisted of downregulation with a GnRH agonist in the luteal phase of the preceding cycle followed by increasing doses of oral or transdermal estradiol after menses. Intramuscular progesterone was started when endometrial thickness measured about 8 mm.	Analyses performed using logistic regression were adjusted also for the adoption of PGT	GDM, HDP, PPROM, Pabr, PAccr, PP, PPH, CS, PTB, VPTB, LBW, macrosomia, congenital malformations
Pan et al., 2020	China	Retrospective cohort study	Registers of 20 fertility centers	2015–2017	Women aged between 20 and 35 years who achieved pregnancy after FET between 2015 and 2017.	Cleavage	NC-FET (n = 683); PC-FET (n = 225)	Oral estradiol valerate was given daily at a dose of 4–8 mg started on the 1–3 day of the period. When the endometrial thickness reached 7 mm or more, twice daily oral dydrogesterone (10 mg) and vaginal progesterone gel (90 mg/day) were added.	Authors excluded pregnancies achieved after PGT	GDM, HDP, CS, PTB, PostTB, LBW, macrosomia, SGA, LGA, congenital malformations
Wang et al., 2020a	China	Retrospective cohort study	Registry of the center for Reproductive Medicine Affiliated to Shandong University	2013–2018	Singleton deliveries after frozen blastocyst transfer. Exclusion criteria: (i) age > 40 years; (ii) BMI ≥ 35 kg/m^2; (iii) PCOS; (iv) self or family history of PE; (v) general health problems; (vi) RIF	Blastocyst	NC-FET (n = 10211); PC-FET (n = 4162)	Estrogen, at a dose of 4–6 mg daily, was initiated on the second or third day of the menstrual cycle and lasted for 10–14 days commonly, with the purpose of promoting endometrial proliferation and inhibiting follicular growth. The dosage and duration of estrogen were raised until the endometrial thickness reached a proper state for embryo transfer (commonly at least 8 mm), at which time luteum support was added.	NR	PE, GDM, PP, PAbr, PPH, LBW, macrosomia, LGA, SGA

(continued)

Table I Continued

Study	Country	Design	Data origin	Study period	Included population	Embryo stage at transfer	Nr. of included pregnancies for each endometrial protocol	HRT scheme	PGT	Investigated outcomes
Wang *et al.*, 2020b	China	Retrospective cohort study	Shanghai Ninth People's Hospital IVF center registry	2014–2017	Women who underwent autologous FET cycles. All singleton live births with gestational age no <28 weeks, were identified.	Both cleavage and blastocyst	PC-FET (n = 2744); mNC-FET (n = 2224); SC-FET (n = 4299)	Oral 17b-estradiol (Fematon 2 mg, three times daily; Abbott Healthcare Products B.V.) was commenced on the 2nd or 3rd day of a natural or progesterone-induced menstrual cycle. When the endometrial thickness was 8 mm, vaginal progesterone suppositories (400 mg/day; Utrogestan; Besins Healthcare, Brussels, Belgium) and yellow oral Fematon tablets (consisting of 2 mg 17b-estradiol and 10 mg dydrogesterone per tablet, 6 mg/day) were initiated.	Authors excluded pregnancies achieved after PGT	PP, GDM, HDP, PTB, LBW, VLBW, SGA, LGA, macrosomia
Zong *et al.*, 2020	China	Retrospective cohort study	Registry of the center for Reproductive Medicine, Shandong University	2015–2018	Women aged 20–40, who received FET treatment after IVF/ICSI cycles from January 2015 to July 2018 and delivered singleton live birth baby after 28 weeks of pregnancy.	Blastocyst	NC-FET (n = 4727); PC-FET (n = 1642); mNC-FET (n = 517)	4 mg oral estradiol valerate (Progynova, Delpharm Lille) since Days 2–4 of menstruation for 5–6 days, and then 6 mg for the following 5–6 days. Thereafter the dose of estradiol valerate, which was 8 mg/day maximally, was modulated according to the endometrium thickness and the E2 levels. When the endometrium thickness reached at least 7 mm, FET was scheduled in 5 days. Dydrogesterone 40 mg/day and progesterone capsules (Utrogestan, Capsugel) 200 mg/day were given as luteal phase support until the 12th week of pregnancy.	Authors excluded pregnancies achieved after PGT	HDP, GDM, PP, PTB, LBW, SGA, LGA
Li *et al.*, 2021	China	Retrospective cohort study	International Peace Maternity and Child Health Hospital	2010–2017	Deliveries after FET.	NR	NC-FET (n = 1491); PC-FET (n = 1234); SC-FET (n = 272)	Valerate estrogen was administered orally until the endometrial thickness reached up to 7 mm, dydrogesterone was administered orally, together with progesterone was administered vaginally for luteal phase support.	Authors excluded pregnancies achieved after PGT	HDP, PE, PIH, GDM, PTB, CS, LBW, macrosomia, SGA, LGA
Tao *et al.*, 2021	China	Retrospective cohort study	Reproductive Medicine Centre of the Shanghai Ninth People's Hospital	2003–2019	Pregnancies achieved after autologous FET.	Both cleavage and blastocyst	PC-FET (n = 26776); SC-FET (n = 29121)	From cycle Day 3 onwards, oral ethinylestradiol (Shanghai Xinyi Pharma, China) 75 μg/day was administered. When the endometrial thickness was >8 mm, four yellow Femoston tablets (Solvay Pharmaceuticals B.V., USA) (total of 8 mg estradiol and 40 mg dydrogesterone) per day were started. The progestin supplement was continued until 8 weeks of gestation if pregnancy was achieved.	NR	CS, PTB, PostTB, PP, Pabr, HDP, Pacer, GDM, PPROM, stillbirth

(continued)

Table I Continued

Study	Country	Design	Data origin	Study period	Included population	Embryo stage at transfer	Nr. of included pregnancies for each endometrial protocol	HRT scheme	PGT	Investigated outcomes
Hu *et al.*, 2021	China	Retrospective cohort study	University-affiliated fertility center registry	2013–2019	Women who underwent FET. Exclusion criteria: FET protocol not recorded, women lost to follow-up and women who had failed cycles, twin deliveries, or neonatal death.	Blastocyst	NC-FET (n = 3790); PC-FET (n = 2561); SC-FET (n = 670)	Oral estradiol (3 mg, Progynova; Bayer) was used twice a day on cycle Day 2. This dose was adjusted based on endometrial thickness every 7 days. After 10 to 14 days, a transvaginal ultrasound was performed, and the serum progesterone level was measured. If no dominant follicle was found, oral dydrogesterone (10 mg, with dose changed to 20 mg 2 days later) was added to the regimen.	Authors excluded pregnancies achieved after PGT	CS, PTB, VPTB, PostTB, LBW, macrosomia, SGA, LGA, HDP, GDM, PP, congenital malformations
Zaat *et al.*, 2021b	Netherlands	Retrospective analysis of a RCT	University of Amsterdam, Center for Reproductive Medicine	2009–2014	Women who underwent FET. Inclusion criteria: (i) age between 18 and 40 years; (ii) first, second or third IVF/ICSI cycle; (iii) regular menstrual cycle.	Both cleavage and blastocyst	PC-FET (n = 37); mNC-FET (n = 45)	Oral estrogen (progynovaw 2 mg, three times daily; Bayer) was commenced on the first or second day of the cycle with the aim of supporting endometrial proliferation and suppressing follicle growth. After 12–14 days, vaginal ultrasound examination was performed to confirm that no dominant follicle had emerged and to measure endometrial thickness. When the endometrial thickness reached ≥8 mm, vaginal micronized progesterone 200 mg three times daily was administered and embryo thawing and transfer was planned.	NR	LBW, macrosomia, LGA, SGA, HDP, PE, PIH, GDM, Pacc, Pabr, PTB, VPTB, CS, PPH, congenital malformations

CS, cesarean section; GDM, gestational diabetes mellitus; HDP, hypertensive disorder of pregnancy; HRT, hormone replacement therapy; LBW, low birth weight; LGA, large for gestational age; mNC-FET, modified natural cycle for frozen embryo transfer; NC-FET, natural cycle for frozen embryo transfer; NR, not reported; OCP, oral contraceptive pill; PAbr, placental abruption; PAccr, placenta accreta; PC-FET, programmed cycle for frozen embryo transfer; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; PostTB, post-term birth; PP, placenta previa; PPROM, preterm premature rupture of membranes; PTB, preterm birth; RIF, recurrent implantation failure; SC-FET, stimulated FET cycle; SGA, small for gestational age; tNC-FET, total natural cycle for frozen embryo transfer; VLBW, very low birth weight; VPTB, very preterm birth.

Table II Obstetric and perinatal outcomes in pregnancies following frozen embryo transfer using a programmed (PC-FET) versus natural (including modified natural; NC-FET = tNC-FET + mNC-FET) protocol.

Outcome	Included studies	Odds ratio (95% CI)	Possible confounding variable	Studies reporting odds ratio adjusted for the confounding variable	Pooling of adjusted odds ratio results
HDP	Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Saito *et al.*, 2019; von Versen-Höynck *et al.*, 2019; Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Wang *et al.*, 2020b; Zong *et al.*, 2020; Hu *et al.*, 2021; Li *et al.*, 2021; Zaat *et al.*, 2021b	Random effects model, OR 1.90; 95% CI 1.64–2.20; $P < 0.00001$; $I^2 = 50\%$	History of chronic hypertension	Ginström Ernstad *et al.*, 2019; Makhijani *et al.*, 2020	Fixed effects model, OR 1.85; 95% CI 1.51–2.27; $P < 0.00001$; $I^2 = 0\%$
			Maternal age	Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Zong *et al.*, 2020; Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Hu *et al.*, 2021	Random effects model, OR 1.95; 95% CI 1.58–2.41; $P < 0.00001$; $I^2 = 65\%$
			Embryo stage at transfer or embryo culture duration	Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021	Fixed effects model, OR 1.67; 95% CI 1.46–1.91; $P < 0.00001$; $I^2 = 0\%$
			Maternal BMI	Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Zong *et al.*, 2020; Makhijani *et al.*, 2020; Hu *et al.*, 2021	Random effects model, OR 2.08; 95% CI 1.74–2.48; $P < 0.00001$; $I^2 = 43\%$
			Fertilization method (classical IVF vs ICSI)	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021	Fixed effects model, OR 1.80; 95% CI 1.47–2.19; $P < 0.00001$; $I^2 = 0\%$
			Embryo biopsy (PGT)	Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Wang *et al.*, 2020b; Zong *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 2.02; 95% CI 1.62–2.52; $P < 0.00001$; $I^2 = 58\%$
			Indication to IVF/ICSI	Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Makhijani *et al.*, 2020; Hu *et al.*, 2021	Random effects model, OR 1.98; 95% CI 1.45–2.71; $P < 0.0001$; $I^2 = 78\%$
PIH	Lin *et al.*, 2020; Ginström Ernstad *et al.*, 2019; von Versen-Höynck *et al.*, 2019; Li *et al.*, 2021; Zaat *et al.*, 2021b	Fixed effects model, OR 1.46; 95% CI 1.03–2.07; $P = 0.03$; $I^2 = 0\%$	Maternal age	Li *et al.*, 2021	OR 1.31; 95% CI 0.96–1.79
			Maternal BMI	Li *et al.*, 2021	OR 1.31; 95% CI 0.96–1.79
			Embryo biopsy (PGT)	Li *et al.*, 2021	OR 1.31; 95% CI 0.96–1.79
			Fertilization method (classical IVF vs ICSI)	Li *et al.*, 2021	OR 1.31; 95% CI 0.96–1.79
PE	Ginström Ernstad *et al.*, 2019; von Versen-Höynck *et al.*, 2019; Asserhøj *et al.*, 2021; Lin *et al.*, 2020; Wang *et al.*, 2020a,b; Li *et al.*, 2021; Zaat *et al.*, 2021b	Fixed effects model, OR 2.11; 95% CI 1.87–2.39; $P < 0.00001$; $I^2 = 29\%$)	History of chronic hypertension	Ginström Ernstad *et al.*, 2019; von Versen-Höynck *et al.*, 2019	Fixed effects model, OR 2.00; 95% CI 1.61–2.49; $P < 0.00001$; $I^2 = 11\%$
			Embryo stage at transfer or embryo culture duration	Lin *et al.*, 2020; Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021	Fixed effects model, OR 1.99; 95% CI 1.63–2.43; $P < 0.00001$; $I^2 = 0\%$
			Maternal age	Ginström Ernstad *et al.*, 2019; von Versen-Höynck *et al.*, 2019; Asserhøj *et al.*, 2021; Lin *et al.*, 2020; Wang *et al.*, 2020a; Li *et al.*, 2021	Fixed effects model, OR 2.17; 95% CI 1.91–2.46; $P < 0.00001$; $I^2 = 13\%$
			Maternal BMI	Ginström Ernstad *et al.*, 2019; von Versen-Höynck *et al.*, 2019; Wang *et al.*, 2020a; Li *et al.*, 2021	Random effects model, OR 2.28; 95% CI 1.80–2.89; $P < 0.00001$; $I^2 = 43\%$
			Fertilization method (classical IVF vs ICSI)	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021; Wang *et al.*, 2020a	Random effects model, OR 2.26; 95% CI 1.87–2.73; $P < 0.00001$; $I^2 = 31\%$
			Embryo biopsy (PGT)	Asserhøj *et al.*, 2021; Wang *et al.*, 2020b; Li *et al.*, 2021	Fixed effects model, OR 1.92; 95% CI 1.56–2.37; $P < 0.00001$; $I^2 = 0\%$
			Indication to IVF/ICSI	Ginström Ernstad *et al.*, 2019; Wang *et al.*, 2020a; Li *et al.*, 2021	Random effects model, OR 2.13; 95% CI 1.75–2.59; $P < 0.00001$; $I^2 = 51\%$

(continued)

Table II Continued

Outcome	Included studies	Odds ratio (95% CI)	Possible confounding variable	Studies reporting odds ratio adjusted for the confounding variable	Pooling of adjusted odds ratio results
PP	Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhoj *et al.*, 2021; Lin *et al.*, 2020; Makhijani *et al.*, 2020; Wang *et al.*, 2020a,b; Zong *et al.*, 2020; Zaat *et al.*, 2021b; Hu *et al.*, 2021	Fixed effects model, OR 1.27; 95% CI 1.05–1.54; $P = 0.01$; $I^2 = 8\%$	Maternal age	Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhoj *et al.*, 2021; Makhijani *et al.*, 2020; Zong *et al.*, 2020; Hu *et al.*, 2021	Fixed effects model, OR 1.16; 95% CI 0.89–1.50; $P = 0.27$; $I^2 = 0\%$
			Maternal BMI	Ginström Ernstad *et al.*, 2019; Makhijani *et al.*, 2020; Zong *et al.*, 2020; Hu *et al.*, 2021	Fixed effects model, OR 1.28; 95% CI 0.90–1.80; $P = 0.17$; $I^2 = 24\%$
			Fertilization method (classical IVF vs ICSI)	Ginström Ernstad *et al.*, 2019; Asserhoj *et al.*, 2021	Fixed effects model, OR 0.84; 95% CI 0.49–1.43; $P = 0.52$; $I^2 = 0\%$
			Embryo stage at transfer or embryo culture duration	Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhoj *et al.*, 2021	Fixed effects model, OR 0.93; 95% CI 0.66–1.31; $P = 0.68$; $I^2 = 0\%$
			Embryo biopsy (PGT)	Asserhoj *et al.*, 2021; Makhijani *et al.*, 2020; Wang *et al.*, 2020b; Zong *et al.*, 2020; Hu *et al.*, 2021	Fixed effects model, OR 1.58; 95% CI 1.21–2.07; $P = 0.0009$; $I^2 = 0\%$
			Indication to IVF/ICSI	Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Makhijani *et al.*, 2020; Hu *et al.*, 2021	Fixed effects model, OR 1.06; 95% CI 0.78–1.46; $P = 0.70$; $I^2 = 12\%$
PPH	Ginström Ernstad *et al.*, 2019; Asserhoj *et al.*, 2021; Lin *et al.*, 2020; Makhijani *et al.*, 2020; Wang *et al.*, 2020a; Zaat *et al.*, 2021b	Fixed effects model, OR 2.53; 95% CI 2.19–2.93; $P < 0.00001$; $I^2 = 0\%$	Maternal age	Ginström Ernstad *et al.*, 2019; Lin *et al.*, 2020; Makhijani *et al.*, 2020; Wang *et al.*, 2020a; Asserhoj *et al.*, 2021	Fixed effects model, OR 2.54; 95% CI 2.19–2.94; $P < 0.00001$; $I^2 = 0\%$
			Maternal BMI	Ginström Ernstad *et al.*, 2019; Makhijani *et al.*, 2020; Wang *et al.*, 2020a	Fixed effects model, OR 2.64; 95% CI 2.22–3.13; $P < 0.00001$; $I^2 = 0\%$
			Fertilization method (classical IVF vs ICSI)	Ginström Ernstad *et al.*, 2019; Asserhoj *et al.*, 2021; Wang *et al.*, 2020a	Fixed effects model, OR 2.53; 95% CI 2.18–2.94; $P < 0.00001$; $I^2 = 0\%$
			Embryo stage at transfer or embryo culture duration	Ginström Ernstad *et al.*, 2019; Asserhoj *et al.*, 2021	Fixed effects model, OR 2.52; 95% CI 2.16–2.93; $P < 0.00001$; $I^2 = 0\%$
			Embryo biopsy (PGT)	Asserhoj *et al.*, 2021; Lin *et al.*, 2020; Makhijani *et al.*, 2020	Fixed effects model, OR 2.27; 95% CI 1.72–3.00; $P < 0.00001$; $I^2 = 0\%$
			Indication to IVF/ICSI	Ginström Ernstad *et al.*, 2019; Makhijani *et al.*, 2020; Wang *et al.*, 2020a	Fixed effects model, OR 2.64; 95% CI 2.22–3.13; $P < 0.00001$; $I^2 = 0\%$
CS	Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Saito *et al.*, 2019; Asserhoj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Wang *et al.*, 2020a; Zong *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021; Zaat *et al.*, 2021b	Random effects model, OR 1.62; 95% CI 1.53–1.71; $P < 0.00001$; $I^2 = 48\%$	Maternal age	Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhoj *et al.*, 2021; Makhijani *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021	fixed effects model, OR 1.54; 95% CI 1.44–1.66; $P < 0.00001$; $I^2 = 44\%$
			Maternal BMI	Jing *et al.*, 2019; Ginström Ernstad *et al.*, 2019; Makhijani *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021	Fixed effects model, OR 1.47; 95% CI 1.36–1.58; $P < 0.00001$; $I^2 = 4\%$
			Fertilization method (classical IVF vs ICSI)	Ginström Ernstad *et al.*, 2019; Asserhoj *et al.*, 2021	Fixed effects model, OR 1.41; 95% CI 1.25–1.60; $P < 0.00001$; $I^2 = 0\%$
			Embryo stage at transfer or embryo culture duration	Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhoj *et al.*, 2021	Random effects model, OR 1.54; 95% CI 1.34–1.78; $P < 0.00001$; $I^2 = 64\%$
			Embryo biopsy (PGT)	Asserhoj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Zong *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 1.55; 95% CI 1.41–1.71; $P < 0.00001$; $I^2 = 33\%$
			Indication to IVF/ICSI	Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Makhijani *et al.*; Li *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 1.54; 95% CI 1.43–1.67; $P < 0.0001$; $I^2 = 43\%$

(continued)

Table II Continued

Outcome	Included studies	Odds ratio (95% CI)	Possible confounding variable	Studies reporting odds ratio adjusted for the confounding variable	Pooling of adjusted odds ratio results
PTB	Guan *et al.*, 2016; Saito *et al.*, 2017; Saito *et al.*, 2019; Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Lin *et al.*, 2020; Wang *et al.*, 2020a,b; Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Zong *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021; Zaat *et al.*, 2021b	Random effects model, OR 1.19; 95% CI 1.09–1.29; $P < 0.0001$; $I^2 = 47\%$)	Maternal age	Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019 Asserhøj *et al.*, 2021; Lin *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 1.19; 95% CI 1.05–1.36; $P = 0.007$; $I^2 = 46\%$
			Maternal BMI	Jing *et al.*, 2019; Ginström Ernstad *et al.*, 2019; Li *et al.*, 2021	Fixed effects model, OR 1.11; 95% CI 1.00–1.24; $P = 0.05$; $I^2 = 0\%$
			Fertilization method (classical IVF vs ICSI)	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021	Fixed effects model, OR 1.10; 95% CI 0.89–1.35; $P = 0.39$; $I^2 = 0\%$
			Embryo stage at transfer or embryo culture duration	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021	Fixed effects model, OR 1.10; 95% CI 0.89–1.35; $P = 0.39$; $I^2 = 0\%$
			Embryo biopsy (PGT)	Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Wang *et al.*, 2020b; Zong *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 1.29; 95% CI 1.10–1.53; $P = 0.002$; $I^2 = 50\%$
			Indication to IVF/ICSI	Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Li *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 1.22; 95% CI 1.06–1.41; $P = 0.006$; $I^2 = 67\%$
VPTB	Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Wang *et al.*, 2020b; Hu *et al.*, 2021; Zaat *et al.*, 2021b	Fixed effects model, OR 1.63; 95% CI 1.23–2.15; $P = 0.0006$; $I^2 = 21\%$	Maternal age	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 1.71; 95% CI 0.92–3.19; $P = 0.09$; $I^2 = 68\%$
			Maternal BMI	Ginström Ernstad *et al.*, 2019; Hu *et al.*, 2021	Random effects model, OR 1.64; 95% CI 0.66–4.05; $P = 0.29$; $I^2 = 84\%$
			Fertilization method (classical IVF vs ICSI)	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021	Random effects model, OR 1.29; 95% CI 0.71–2.33; $P = 0.41$; $I^2 = 34\%$
			Embryo stage at transfer or embryo culture duration	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021	Random effects model, OR 1.29; 95% CI 0.71–2.33; $P = 0.41$; $I^2 = 34\%$
			Embryo biopsy (PGT)	Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Wang *et al.*, 2020b; Hu *et al.*, 2021	Fixed effects model, OR 2.00; 95% CI 1.40–2.85; $P = 0.0001$; $I^2 = 0\%$
			Indication to IVF/ICSI	Ginström Ernstad *et al.*, 2019; Hu *et al.*, 2021	Random effects model, OR 1.64; 95% CI 0.66–4.05; $P = 0.29$; $I^2 = 84\%$
Paccr	Saito *et al.*, 2019; Makhijani *et al.*, 2020	Fixed effects model, OR 6.29; 95% CI 2.75–14.40; $P < 0.0001$; $I^2 = 0\%$	Maternal age	Saito *et al.*, 2019; Makhijani *et al.*, 2020	Fixed effects model, OR 6.29; 95% CI 2.75–14.40; $P < 0.0001$; $I^2 = 0\%$
			Maternal BMI	Makhijani *et al.*, 2020	OR 2.98, 95% CI 0.25–35.52
			Indications to IVF/ICSI/Cause of infertility	Saito *et al.*, 2019	OR 6.91, 95% CI 2.87–16.64
			Embryo biopsy (PGT)	Makhijani *et al.*, 2020	OR 2.98, 95% CI 0.25–35.52
			Embryo stage at transfer or embryo culture duration	Saito *et al.*, 2019	OR 6.91, 95% CI 2.87–16.64

(continued)

Table II Continued

Outcome	Included studies	Odds ratio (95% CI)	Possible confounding variable	Studies reporting odds ratio adjusted for the confounding variable	Pooling of adjusted odds ratio results
PostTB	Guan *et al.*, 2016; Saito *et al.*, 2017; Saito *et al.*, 2019; Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021; Pan *et al.*, 2020; Wang *et al.*, 2020a; Hu *et al.*, 2021	Random effects model, OR 1.90; 95% CI 1.25–2.90; $P = 0.003$; $I^2 = 73\%$	Maternal age	Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 2.13; 95% CI 1.18–3.84; $P = 0.01$; $I^2 = 84\%$
			Maternal BMI	Ginström Ernstad *et al.*, 2019; Hu *et al.*, 2021	Fixed effects model, OR 1.55; 95% CI 1.26–1.89; $P < 0.0001$; $I^2 = 6\%$
			Fertilization method (classical IVF vs ICSI)	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021	Fixed effects model, OR 1.56; 95% CI 1.28–1.91; $P < 0.0001$; $I^2 = 0\%$
			Embryo stage at transfer or embryo culture duration	Ginström Ernstad *et al.*, 2019	OR 1.59; 95% CI 1.29–1.96
			Embryo biopsy (PGT)	Asserhøj *et al.*, 2021; Pan *et al.*, 2020; Hu *et al.*, 2021	Fixed effects model, OR 1.32; 95% CI 0.84–2.09; $P = 0.23$; $I^2 = 0\%$
			Indication to IVF/ICSI	Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Hu *et al.*, 2021	Random effects model, OR 2.38; 95% CI 1.17–4.84; $P = 0.02$; $I^2 = 87\%$
Macrosomia	Guan *et al.*, 2016; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Wang *et al.*, 2020a,b; Li *et al.*, 2021; Hu *et al.*, 2021; Zaat *et al.*, 2021b	Random effects model, OR 1.18; 95% CI 1.05–1.32; $P = 0.007$; $I^2 = 45\%$)	Maternal age	Asserhøj *et al.*, 2021; Li *et al.*, 2021; Hu *et al.*, 2021	Fixed effects model, OR 1.12; 95% CI 1.00–1.25; $P = 0.05$; $I^2 = 0\%$
			Maternal BMI	Li *et al.*, 2021; Hu *et al.*, 2021	OR 1.10; 95% CI 0.94–1.29
			Fertilization method (classical IVF vs ICSI)	Asserhøj *et al.*, 2021	OR 1.20; 95% CI 0.88–1.64
			Embryo stage at transfer or embryo culture duration	Asserhøj *et al.*, 2021	OR 1.20; 95% CI 0.88–1.64
			Embryo biopsy (PGT)	Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Wang *et al.*, 2020b; Li *et al.*, 2021; Hu *et al.*, 2021	Fixed effects model, OR 1.16; 95% CI 1.05–1.28; $P = 0.004$; $I^2 = 0\%$
			Indication to IVF/ICSI	Li *et al.*, 2021; Hu *et al.*, 2021	OR 1.10; 95% CI 0.94–1.29
LGA	Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Levi-Setti *et al.*, 2020; Lin *et al.*, 2020; Pan *et al.*, 2020; Wang *et al.*, 2020a, b; Zong *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021; Zaat *et al.*, 2021b	Random effects model, OR 1.08; 95% CI 1.01–1.16; $P = 0.02$; $I^2 = 50\%$	Maternal age	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021; Lin *et al.*, 2020; Zong *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021	Fixed effects model, OR 1.08; 95% CI 0.95–1.24; $P = 0.23$; $I^2 = 53\%$
			Maternal BMI	Ginström Ernstad *et al.*, 2019; Zong *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 1.08; 95% CI 0.93–1.27; $P = 0.32$; $I^2 = 71\%$
			Fertilization method (classical IVF vs ICSI)	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021	Fixed effects model, OR 1.27; 95% CI 1.04–1.56; $P = 0.02$; $I^2 = 0\%$
			Embryo stage at transfer or embryo culture duration	Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021	Fixed effects model, OR 1.27; 95% CI 1.04–1.56; $P = 0.02$; $I^2 = 0\%$
			Embryo biopsy (PGT)	Asserhøj *et al.*, 2021; Pan *et al.*, 2020; Wang *et al.*, 2020b; Zong *et al.*, 2020; Li *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 1.09; 95% CI 0.96–1.24; $P = 0.32$; $I^2 = 71\%$
			Indication to IVF/ICSI	Ginström Ernstad *et al.*, 2019; Li *et al.*, 2021; Hu *et al.*, 2021	Random effects model, OR 1.06; 95% CI 0.84–1.33; $P = 0.63$; $I^2 = 80\%$

CS, cesarean section; HDP, hypertensive disorder of pregnancy; LGA, large for gestational age (birthweight > 90° pct for gestational age); Macrosomia (i.e., birthweight > 4000 g); mNC, FET, modified natural cycle for frozen embryo transfer; NC, FET, natural cycle for frozen embryo transfer; OR, odds ratio; Pacer, placenta accreta; PC, FET, programmed cycle for frozen embryo transfer; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; PostTB, post-term birth (i.e. birth after 42 weeks of gestation); PP, placenta previa; PTB, preterm birth (i.e. birth before 37 weeks of gestation); tNC, FET, total natural cycle for frozen embryo transfer; VPTB, very preterm birth (i.e. birth before 34 weeks of gestation).

Asserhøj *et al.*, 2021). Three studies reported OR adjusted for embryo culture duration (fixed effects model, OR 0.93; 95% CI 0.66–1.31; $P=0.68$; $I^2=0\%$) (Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021). Five studies reported OR adjusted for embryo biopsy (PGT) (fixed effects model, OR 1.58; 95% CI 1.21, 2.07; $P=0.0009$; $I^2=0\%$) (Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Zong *et al.*, 2020; Wang *et al.*, 2020b; Hu *et al.*, 2021). Four studies reported OR adjusted for the indication to IVF/ICS (Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Makhijani *et al.*, 2020; Hu *et al.*, 2021) (fixed effects model, OR 1.06; 95% CI 0.78–1.46; $P=0.70$; $I^2=12\%$) (Table II).

Placenta accreta

Results from two studies were meta-analyzed. A higher risk of placenta accreta was observed in PC-FET pregnancies (fixed effects model, OR 6.29; 95% CI 2.75–14.40; $P<0.0001$; $I^2=0\%$) (very low quality) (Saito *et al.*, 2019; Makhijani *et al.*, 2020) (Table II).

Both studies calculated OR adjusted for maternal age. Saito *et al.* (2019) adjusted the calculated OR also for embryo stage/culture duration and indication to IVF/cause of infertility (OR 6.91, 95% CI 2.87–16.64). Makhijani *et al.* (2020) adjusted the calculated OR also for maternal BMI and embryo biopsy (PGT) (OR 2.98, 95% CI 0.25–35.52) (Table II).

Cesarean section

Results from 12 studies were meta-analyzed. We observed a significantly higher CS rate in PC-FET (random effects model, OR 1.62; 95% CI 1.53–1.71; $P<0.0000$1; $I^2=48\%$) (very low quality) (Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Zong *et al.*, 2020; Wang *et al.*, 2020a; Hu *et al.*, 2021; Li *et al.*, 2021; Zaat *et al.*, 2021b) (Supplementary Fig. S1D).

Seven studies reported OR adjusted for maternal age (fixed effects model, OR 1.54; 95% CI 1.44–1.66; $P<0.0000$1; $I^2=44\%$) (Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Hu *et al.*, 2021; Li *et al.*, 2021). Five studies reported OR adjusted for maternal BMI (fixed effects model, OR 1.47; 95% CI 1.36–1.58; $P<0.0000$1; $I^2=4\%$) (Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Makhijani *et al.*, 2020; Hu *et al.*, 2021; Li *et al.*, 2021). Two studies reported OR adjusted for fertilization method (fixed effects model, OR 1.41; 95% CI 1.25–1.60; $P<0.0000$1; $I^2=0\%$) (Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021). Three studies reported OR adjusted for embryo cuclture duration or embryo stage at transfer (random effects model, OR 1.54; 95% CI 1.34–1.78; $P<0.0000$1; $I^2=64\%$) (Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021). Six studies reported OR adjusted for embryo biopsy (P'GT) (random effects model, OR 1.55; 95% CI 1.41, 1.71; $P<0.0000$1; $I^2=33\%$) (Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Zong *et al.*, 2020; Hu *et al.*, 2021; Li *et al.*, 2021). Six studies reported OR adjusted for the indication to IVF/ICSI (Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Makhijani *et al.*, 2020; Hu *et al.*, 2021; Li *et al.*, 2021) (random effects model, OR 1.54; 95% CI 1.43–1.67; $P<0.0001$; $I^2=43\%$) (Table II).

Post-partum hemorrhage

Six studies were meta-analyzed. A significantly higher risk of PPH was observed in PC-FET pregnancies (fixed effects model, OR 2.53; 95% CI 2.19–2.93; $P<0.0000$1; $I^2=0\%$) (low quality) (Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021; Lin *et al.*, 2020; Makhijani *et al.*, 2020; Wang *et al.*, 2020a; Zaat *et al.*, 2021b). All ORs included in the present meta-analysis were adjusted for maternal age (Supplementary Fig. S1C).

Three studies reported OR adjusted for maternal BMI (fixed effects model, OR 2.64; 95% CI 2.22–3.13; $P<0.0000$1; $I^2=0\%$) (Ginström Ernstad *et al.*, 2019; Makhijani *et al.*, 2020; Wang *et al.*, 2020a). Three studies reported OR adjusted for the fertilization method (fixed effects model, OR 2.53; 95% CI 2.18–2.94; $P<0.0000$1; $I^2=0\%$) (Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021; Wang *et al.*, 2020a). Two studies reported OR adjusted for embryo culture duration (fixed effects model, OR 2.52; 95% CI 2.16–2.93; $P<0.0000$1; $I^2=0\%$) (Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021). Three studies reported OR adjusted for embryo biopsy (PGT) (fixed effects model, OR 2.27; 95% CI 1.72, 3.00; $P<0.0000$1; $I^2=0\%$) (Lin *et al.*, 2020; Makhijani *et al.*, 2020; Asserhøj *et al.*, 2021). Three studies reported OR adjusted for the indication to IVF/ICS (Ginström Ernstad *et al.*, 2019; Makhijani *et al.*, 2020; Wang *et al.*, 2020a) (fixed effects model, OR 2.64; 95% CI 2.22–3.13; $P<0.0000$1; $I^2=0\%$) (Table II).

Preterm birth

Fifteen studies were meta-analyzed. A higher risk of PTB was observed in PC-FET pregnancies (random effects model, OR 1.19; 95% CI 1.09–1.29; $P<0.0001$; $I^2=47\%$) (very low quality) (Guan *et al.*, 2016; Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Lin *et al.*, 2020; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Zong *et al.*, 2020; Wang *et al.*, 2020a,b; Hu *et al.*, 2021; Li *et al.*, 2021; Zaat *et al.*, 2021b) (Table II).

Seven studies reported OR adjusted for maternal age (random effects model, OR 1.19; 95% CI 1.05–1.36; $P=0.007$; $I^2=46\%$) (Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Lin *et al.*, 2020; Hu *et al.*, 2021; Li *et al.*, 2021). Three studies reported OR adjusted for maternal BMI (fixed effects model, OR 1.11; 95% CI 1.00–1.24; $P=0.05$; $I^2=0\%$) (Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Li *et al.*, 2021). Two studies reported OR adjusted for fertilization method and for embryo culture duration (fixed effects model, OR 1.10; 95% CI 0.89–1.35; $P=0.39$; $I^2=0\%$) (Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021). Seven studies reported OR adjusted for embryo biopsy (PGT) (random effects model, OR 1.29; 95% CI 1.10, 1.53; $P=0.002$; $I^2=50\%$) (Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Zong *et al.*, 2020; Wang *et al.*, 2020b; Hu *et al.*, 2021; Li *et al.*, 2021). Three studies reported OR adjusted for the indication to IVF/ICSI (Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Hu *et al.*, 2021; Li *et al.*, 2021) (random effects model, OR 1.22; 95% CI 1.06–1.41; $P=0.006$; $I^2=67\%$) (Table II).

Very preterm birth

Results from seven studies were pooled. A higher risk of VPTB was observed in PC-FET pregnancies (fixed effects model, OR 1.63; 95% CI 1.23–2.15; $P=0.0006$; $I^2=21\%$) (very low quality) (Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Wang *et al.*, 2020b; Hu *et al.*, 2021; Zaat *et al.*, 2021b) (Table II).

Three studies reported OR adjusted for maternal age (random effects model, OR 1.71; 95% CI 0.92–3.19; $P=0.09$; $I^2=68\%$) (Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021; Hu *et al.*, 2021). Two studies reported OR adjusted for maternal BMI (random effects model, OR 1.64; 95% CI 0.66–4.05; $P=0.29$; $I^2=84\%$) (Ginström Ernstad *et al.*, 2019; Hu *et al.*, 2021). Two studies reported OR adjusted for fertilization method and for embryo culture duration (random effects model, OR 1.29; 95% CI 0.71–2.33; $P=0.41$; $I^2=34\%$) (Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021). Four studies reported OR adjusted for embryo biopsy (PGT) (fixed effects model, OR 2.00; 95% CI 1.40, 2.85; $P=0.0001$; $I^2=0\%$) (Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Wang *et al.*, 2020b; Hu *et al.*, 2021). Two studies reported OR adjusted for the indication to IVF/ICSI (Ginström Ernstad *et al.*, 2019; Hu *et al.*, 2021) (random effects model, OR 1.64; 95% CI 0.66–4.05; $P=0.29$; $I^2=84\%$) (Table II).

Post-term birth

Results from eight studies were meta-analyzed. A higher risk of post-term birth was observed in PC-FET pregnancies (random effects model, OR 1.90; 95% CI 1.25–2.90; $P=0.003$; $I^2=73\%$) (very low quality) (Guan *et al.*, 2016; Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Pan *et al.*, 2020; Wang *et al.*, 2020a; Hu *et al.*, 2021) (Supplementary Fig. S1E).

Five studies reported OR adjusted for maternal age (random effects model, OR 2.13; 95% CI 1.18–3.84; $P=0.01$; $I^2=84\%$) (Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Hu *et al.*, 2021). Two studies reported OR adjusted for maternal BMI (fixed effects model, OR 1.55; 95% CI 1.26–1.89; $P<0.0001$; $I^2=6\%$) (Ginström Ernstad *et al.*, 2019; Hu *et al.*, 2021). Two studies reported OR adjusted for fertilization method (fixed effects model, OR 1.56; 95% CI 1.28–1.91; $P<0.0001$; $I^2=0\%$) (Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021). Ginström Ernstad *et al.* (2019) reported OR adjusted for embryo culture duration and confirmed the association (OR 1.59; 95% CI 1.29–1.96). Three studies reported OR adjusted for embryo biopsy (PGT) (fixed effects model, OR 1.32; 95% CI 0.84, 2.09; $P=0.23$; $I^2=0\%$) (Asserhøj *et al.*, 2021; Pan *et al.*, 2020; Hu *et al.*, 2021). Four studies reported OR adjusted for the indication to IVF/ICS (Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Saito *et al.*, 2019; Hu *et al.*, 2021) (random effects model, OR 2.38; 95% CI 1.17–4.84; $P=0.02$; $I^2=87\%$) (Table II).

Macrosomia

Results from 10 studies were meta-analyzed. A higher risk of macrosomia was observed in PC-FET pregnancies (random effects model, OR 1.18; 95% CI 1.05–1.32; $P=0.007$; $I^2=45\%$) (very low quality) (Guan *et al.*, 2016; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Wang *et al.*, 2020a,b; Hu *et al.*, 2021; Li *et al.*, 2021; Zaat *et al.*, 2021b) (Table II).

Three studies reported OR adjusted for maternal age (fixed effects model, OR 1.12; 95% CI 1.00–1.25; $P=0.05$; $I^2=0\%$) (Asserhøj *et al.*, 2021; Hu *et al.*, 2021; Li *et al.*, 2021) and two for maternal BMI and indication to IVF/ICSI (random effects model, OR 1.10; 95% CI 0.94–1.29; $P=0.23$; $I^2=41\%$) (Hu *et al.*, 2021; Li *et al.*, 2021). Six studies reported OR adjusted for embryo biopsy (PGT) (fixed effects model, OR 1.16; 95% CI 1.05, 1.28; $P=0.004$; $I^2=0\%$) (Asserhøj *et al.*, 2021; Makhijani *et al.*, 2020; Pan *et al.*, 2020; Wang *et al.*, 2020b; Hu *et al.*, 2021; Li *et al.*, 2021). Asserhøj *et al.* (2021) reported OR adjusted for fertilization method and embryo culture duration (OR 1.20; 95% CI 0.88–1.64).

Large for gestational age (LGA)

Fourteen studies were meta-analyzed. A higher risk of LGA was observed in PC-FET pregnancies (random effects model, OR 1.08; 95% CI 1.01–1.16; $P=0.02$; $I^2=50\%$) (very low quality) (Saito *et al.*, 2017; Ginström Ernstad *et al.*, 2019; Jing *et al.*, 2019; Saito *et al.*, 2019; Asserhøj *et al.*, 2021; Levi-Setti *et al.*, 2020; Lin *et al.*, 2020; Pan *et al.*, 2020; Zong *et al.*, 2020; Wang *et al.*, 2020a,b; Hu *et al.*, 2021; Li *et al.*, 2021; Zaat *et al.*, 2021b) (Table II).

Six studies reported OR adjusted for maternal age (fixed effects model, OR 1.08; 95% CI 0.95–1.24; $P=0.23$; $I^2=53\%$) (Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021; Lin *et al.*, 2020; Zong *et al.*, 2020; Hu *et al.*, 2021; Li *et al.*, 2021). Four studies reported OR adjusted for maternal BMI (random effects model, OR 1.08; 95% CI 0.93–1.27; $P=0.32$; $I^2=71\%$) (Ginström Ernstad *et al.*, 2019; Zong *et al.*, 2020; Hu *et al.*, 2021; Li *et al.*, 2021). Two studies reported OR adjusted for fertilization method and for embryo culture duration (fixed effects model, OR 1.27; 95% CI 1.04–1.56; $P=0.02$; $I^2=0\%$) (Ginström Ernstad *et al.*, 2019; Asserhøj *et al.*, 2021). Five studies reported OR adjusted for embryo biopsy (PGT) (random effects model, OR 1.09; 95% CI 0.96, 1.24; $P=0.32$; $I^2=71\%$) (Asserhøj *et al.*, 2021; Pan *et al.*, 2020; Zong *et al.*, 2020; Hu *et al.*, 2021; Li *et al.*, 2021). Three studies reported OR adjusted for the indication to IVF/ICS (Ginström Ernstad *et al.*, 2019; Hu *et al.*, 2021; Li *et al.*, 2021) (random effects model, OR 1.06; 95% CI 0.84–1.33; $P=0.63$; $I^2=80\%$) (Table II).

Additional material

Results about remaining outcomes obtained from the main comparison PC-FET versus NC-FET (tNC-FET + mNC-FET) are available as Supplementary data and reported in Supplementary Table SII. Results of other comparisons (i.e. PC-FET versus tNC-FET; PC-FET versus mNC-FET; SC-FET versus NC-FET (tNC + mNC); PC-FET versus SC-FET pregnancies; mNC-FET versus tNC-FET pregnancies) are reported in Supplementary Tables SIII, SIV, SV, SVI, and SVII.

Risk of bias and quality assessment results

Results obtained from our risk of bias assessment for observational studies are summarized in Table III. Overall, the quality assessment of these eligible studies showed a low or moderate risk of bias. Among the nine applicable stars assessing the three main categories of selection, comparability and outcomes, the eligible studies received between 6 and 9 stars. Funnel plots were generated (Supplementary Fig. S2). Visual inspection of funnel plot asymmetry for the meta-analysis comparing the risk of CS in PC-FET versus NC-FET suggest the presence of publication bias (Supplementary Fig. S2D). A summary of results and quality of evidence according to the GRADE system is reported in Table IV. The quality of the evidence significantly suffers from the retrospective design of the vast majority of included studies. Evidence showing an increased risk of PE, and PPH after PC-FET when compared with NC-FET (tNC-FET + mNC-FET) and an increased risk of HDP and PPH after PC-FET when compared with tNC-FET was deemed of low quality. All remaining evidence was judged of very low quality.

Discussion

Main findings

In the present study, the principal analysis showed a significantly higher incidence of HDP, PIH, PE, PP, PPH, CS, PTB, VPTB, placenta accreta, post-term birth, macrosomia and LGA in PC-FET pregnancies when compared with NC-FET (tNC-FET + mNC-FET) pregnancies. After pooling of ORs adjusted for the possible confounding variables PC-FET maintained a significant association in all sub-analyses with HDP, PE, PPH and CS.

When the comparator was restricted to tNC-FET pregnancies, we observed a significantly higher RR of HDP, PE, placental abruption, CS, PTB, VPTB, post-term birth, macrosomia and LGA in PC-FET pregnancies. Also in this case, sub-analyses confirmed an association only with HDP, PE, PPH and CS. Studies comparing SC-FET with NC-FET (tNC-FET + mNC-FET) and tNC-FET with mNC-FET failed to show an association between the endometrial preparation protocol and the obstetric and perinatal outcomes. Five studies compared PC-FET and SC-FET. Pooling of their results showed a significantly higher risk of HDP, CS, PP, LGA, PTB, macrosomia and LBW and a lower risk of SGA after PC-FET but only the association with HDP and CS was confirmed in all sub-analyses. Only one study provided enough data to compare PC-FET pregnancies with mNC-FET pregnancies. Authors adjusted effect estimates for maternal age, embryo stage at transfer and fertilization method and reported a significantly higher risk of HDP, PE PPH, CS and VPTB in patients who underwent PC-FET (Asserhøj *et al.*, 2021).

The increased risk of HDP in women treated with hormone replacement therapy (HRT) endometrial preparation protocols indirectly supports the pivotal etiopathogenic role of the CL (von Versen-Höynck *et al.*, 2019). This theory has been also recently strengthened by the prospective study of two periconception cohorts demonstrating that, during the first trimester, pregnancies conceived in the absence of a CL are characterized by lower circulating renin and prorenin concentrations compared with those conceived naturally (Wiegel *et al.*, 2020). Interestingly, Li *et al.* (2021) showed that the higher risk of PIH in pregnancies resulting from PC-FET than from NC-FET vanishes after adjusting the effect estimate for maternal age, BMI and for the indication to IVF/ICSI. This finding, although still need to be confirmed in larger studies, suggests that HRT might not be responsible for a generalized increased risk of all forms of HDP but play a role exclusively in the pathophysiology of PE (Li *et al.*, 2021).

Our results mean that women exposed to HRT have approximately a 100% increase in the odds of developing PE during pregnancy. The absence of modifications in the effect estimates after the adjustment for all the confounding variables as well as the low level of heterogeneity between studies and the narrow width of CIs make this association particularly reliable. Unfortunately, the included studies do not report information about the clinical phenotype of PE. However, the lack of CL vasoactive products may alter the early placentation process thus probably determining a form of PE characterized by increased free radical formation, major hemodynamic abnormalities and fetal growth restriction (Busnelli *et al.*, 2019). The marked association between PC-FET and severe features of PE reported by von Versen-Höynck *et al.*E (2019) reinforces this hypothesis.

Our meta-analysis provided contrasting results regarding the association between endometrial preparation protocols and placenta accreta and placental abruption. We observed a substantially higher risk of placenta accreta in PC-FET pregnancies when compared with NC-FET (tNC-FET + mNC-FET) pregnancies. After considering the possible confounding variables, the association was confirmed in all sub-analyses except when adjusted for maternal BMI (Makhijani *et al.*, 2020). On the other hand, the association between placental abruption and PC-FET is less convincing. Indeed, it was observed only in the sub-analysis comparing PC-FET with tNC-FET pregnancies. Taken together, these findings suggest a possible effect of HRT on the placentation process. Previous studies found that the high estradiol levels achieved during controlled ovarian hyperstimulation (COH) may determine an alteration in endometrial gene expression affecting remodeling and angiogenesis and leading to an abnormal trophoblast invasion (Senapati *et al.*, 2018; Sacha *et al.*, 2020). Nevertheless, it is unlikely that this hypothesis could fully explain our findings. In fact, notwithstanding the supraphysiologic serum estrogen levels to which women undergoing HRT are exposed to, the serum concentration reached by this hormone is not comparable to the one reached in women undergoing COH. Yet again, the absence of the CL is more likely to play a central role. Indeed, an unbalanced early hormonal milieu would also impair placental angiogenesis and development (Pereira *et al.*, 2021). At this stage, more research is needed in order to evaluate the effect embryo freezing and HRT on placental pathologies in programmed-FET pregnancies (Sacha *et al.*, 2020). The increased risk of PPH in PC-FET pregnancies could be part of this same process being a secondary outcome of the abnormal placenta invasion. As an alternative, it could be another effect of the progesterone-induced myometrial physiological modification and result from a decreased uterine contractility in the third stage of labor.

The significantly higher incidence of CS in PC-FET pregnancies can be addressed by different theories. However, the most likely hypothesis is that this association might actually be a consequence of the increased occurrence of some of the above-mentioned obstetric complications. In fact, among the indications for CS there are: (i) first stage dystocia, which could be due to the hypothesized reduced uterine contractility; (ii) second stage dystocia, which might be the result of a cephalopelvic disproportion secondary to the abnormal fetal growth; (iii) severe forms of HDP; (iv) placentation defects such as placenta accreta; and (v) labor conditions requiring an urgent intervention such as placental abruption. The reliability of the association between PC-FET and CS is undermined by publication bias. For this reason, although all effect estimates agree in suggesting an increased risk of CS in women treated with HRT protocols, the quality of this evidence (assessed using GRADE) was judged very low.

Limitations

The principal limitation of the present systematic review and meta-analysis concerns the heterogeneity across studies. The reasons that might explain it are manifold. First of all, due to the retrospective design of included studies, it cannot be excluded that compared populations differ in baseline characteristics (e.g. parity, ethnicity, socioeconomic status, pregnancy interval, adverse obstetric and perinatal outcomes in previous pregnancies, previous medical conditions, etc.). A negative influence on the between-study homogeneity is also

Table III Risk of bias and quality assessment.

Cohort studies	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at the start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	
Guan *et al.*, 2016	*	*	*	*			*	*	6
Saito *et al.*, 2017	*	*		*	*		*	*	6
Alur-Gupta *et al.*, 2018	*	*	*	*	*		*	*	7
Ginström Ernstad *et al.*, 2019	*	*		*	*	*	*	*	7
Jing *et al.*, 2019	*	*	*	*	*	*	*	*	8
Lin *et al.*, 2020	*	*	*	*	*	*	*	*	8
Saito *et al.*, 2019	*	*		*	*	*	*	*	7
von Versen-Höynck *et al.*, 2019	*	*	*	*	**	*	*	*	9
Asserhøj *et al.*, 2021	*	*		*	*	*	*	*	7
Levi-Setti *et al.*, 2020	*	*	*	*	*		*	*	7
Makhijani *et al.*, 2020	*	*		*	*	*	*	*	7
Pan *et al.*, 2020	*	*	*	*	*		*	*	7
Wang *et al.*, 2020a	*	*	*	*	*	*	*	*	8
Wang *et al.*, 2020b	*	*	*	*	*	*	*	*	8
Zong *et al.*, 2020	*	*	*	*	*	*	*	*	8
Li *et al.*, 2021	*		*	*	*		*	*	6
Tao *et al.*, 2021	*	*	*	*	*	*	*	*	8
Zaat *et al.*, 2021b	*	*	*	*	*		*	*	7
Hu *et al.*, 2021	*	*	*	*	*	*	*	*	8

Newcastle–Ottawa Quality Assessment Scale: this scale has a scoring system using asterisks based on three domains, including selection of study groups, comparability of groups and ascertainment of exposure. A maximum of four asterisks could be given to the selection domain, two asterisks to the comparability domain and three asterisks to the exposure domain. A greater number of asterisks indicates greater quality. Selection (1) Representativeness of the exposed cohort: (a) Truly representative (one star), (b) Somewhat representative (one star), (c) Selected group (no star), (d) No description of the derivation of the cohort (no star); (2) Selection of the non-exposed cohort: (a) Drawn from the same community as the exposed cohort (one star), (b) Drawn from a different source (no star), (c) No description of the derivation of the non-exposed cohort (no star); (3) Ascertainment of exposure: (a) Secure record (e.g. surgical record) (one star), (b) Structured interview (one star), (c) Written self-report (no star), (d) No description (no star), (e) Other (no star); (4) Demonstration that outcome of interest was not present at start of study: (a) Yes (one star), (b) No (no star); Comparability (1) Comparability of cohorts on the basis of the design or analysis controlled for confounders: (a) The study controls for age, sex and marital status (one star), (b) Study controls for other factors (one star), (c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders (no star); Outcome (1) Assessment of outcome: (a) Independent blind assessment (one star), (b) Record linkage (one star), (c) Self report (no star), (d) No description (no star), (e) Other (no star); (2) Was follow-up long enough for outcomes to occur (a) Yes (one star), (b) No (no star). Indicate the median duration of follow-up and a brief rationale for the assessment above : _____; (3) Adequacy of follow-up of cohorts: (a) Complete follow up—all subject accounted for (one star), (b) Subjects lost to follow up unlikely to introduce bias—number lost ≤20% or description of those lost suggested no different from those followed (one star), (c) Follow-up rate <80% and no description of those lost (no star), (d) No statement (no star). Thresholds for converting the Newcastle–Ottawa scales to AHRQ standards (good, fair and poor): Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Table IV Summary of results and quality of evidence.

Outcome	PC-FET vs NC-FET			PC-FET vs tNC-FET			PC-FET vs mNC-FET		
	Nr of studies	OR [95% CI]	Quality of evidence (GRADE)	Nr of studies	OR [95% CI]	Quality of evidence (GRADE)	Nr of studies	OR [95% CI]	Quality of evidence (GRADE)
HDP	12	1.90 [1.64–2.20	Very low	4	1.96 [1.53–2.51]	Low	2	2.19 [1.36–3.52]	Very low
PIH	4	1.45 [1.03–2.07]	Very low	2	1.05 [0.75–1.46]	Very low	1	4.16 [0.79–22.01]	Very low
PE	7	2.11 [1.87–2.39	Low	2	1.98 [1.56–2.53]	Very low	2	2.91 [1.67–5.08;]	Very low
GDM	10	1.00 [0.82–1.21]	Very low	1	1.07 [0.87–1.40]	Very low	1	1.22 [0.07–21.23]	Very low
PP	10	1.27 [1.05–1.54]	Very low	//	//	//	2	1.12 [0.46–2.76]	Very low
PPH	6	2.53 [2.19–2.93]	Low	2	2.52 [2.16–2.93]	Low	2	2.23 [1.67–2.99]	Very low
Pabr	6	1.38 [0.83–2.17]	Very low	2	1.05 [0.54–2.04]	Very low	2	1.26 [0.41–3.86]	Very low
CS	12	1.62 [1.53–1.71]	Very low	4	1.44 [1.33–1.56]	Very low	2	1.56 [1.18–2.07]	Very low
PTB	15	1.19 [1.09–1.29]	Very low	4	1.28 [1.06–1.55]	Very low	2	0.93 [0.57–1.52]	Very low
VPTB	7	1.63 [1.23–2.15]	Very low	3	1.89 [1.04–3.41]	Very low	2	2.36 [0.94–5.91]	Very low
Paccr	2	6.29 [2.75–14.40]	Very low	//	//	//	//	//	//
PPROM	3	1.84 [0.82–4.11]	Very low	1	1.19 [0.81–1.75]	Very low	1	1.27 [0.84–1.92]	Very low
PostTB	8	1.90 [1.25–2.90]	Very low	3	1.52 [1.23–1.87]	Very low	1	2.34 [0.98–5.59]	Very low
Macros.	10	1.18 [1.05–1.32]	Very low	4	1.19 [0.99–1.44]	Very low	2	1.13 [0.85–1.51]	Very low
LBW	11	0.94 [0.60–1.47]	Very low	3	1.45 [0.92–2.28]	Very low	1	0.23 [0.01–4.99]	Very low
VLBW	5	1.19 [0.81–1.75]	Very low	1	1.01 [0.46–2.22]	Very low	//	//	//
LGA	14	1.08 [1.01–1.16]	Very low	4	1.06 [0.87–1.30]	Very low	2	1.11 [0.68–1.80]	Very low
SGA	13	1.04 [0.98–1.10]	Very low	4	1.11 [0.91–1.35]	Very low	2	1.37 [0.65–2.87]	Very low
Stillbirth	5	1.50 [0.47–4.79]	Very low	1	1.55 [0.43–5.59]	Very low	//	//	//
Cong. m.	8	0.98 [0.76–1.26]	Very low	2	1.03 [0.78–1.37]	Very low	1	0.71 [0.16–3.17]	Very low

Outcome	SC-FET vs NC-FET			PC-FET vs SC-FET			mNC-FET vs tNC-FET		
	Nr of studies	OR [95% CI]	Quality of evidence (GRADE)	Nr of studies	OR [95% CI]	Quality of evidence (GRADE)	Nr of studies	OR [95% CI]	Quality of evidence (GRADE)
HDP	4	1.31 [1.00–1.71]	Very low	5	1.60 [1.43–1.78]	Very low	1	0.73 [0.37–1.44]	Very low
PIH	2	1.32 [0.99–1.77]	Very low	2	1.05 [0.75–1.46]	Very low	//	//	//
PE	1	2.24 [1.48–3.33]	Very low	2	1.34 [0.60–2.96]	Very low	1	0.50 [0.23–1.09]	Very low
GDM	1	1.44 [0.97–2.16]	Very low	4	0.91 [0.84–1.00]	Very low	//	//	//
PP	3	0.90 [0.59–1.35]	Very low	4	1.80 [1.38–2.35]	Very low	1	0.55 [0.19–1.59]	Very low
PPH	//	//	//	//	//	//	1	1.42 [0.92–2.19]	Very low
Pabr	//	//	//	2	0.70 [0.38–1.28]	Very low	1	1.65 [0.20–13.61]	Very low
CS	3	1.07 [0.93–1.23]	Very low	3	1.33 [1.03–1.74]	Very low	1	0.92 [0.64–1.32]	Very low
PTB	4	0.98 [0.71–1.36]	Very low	4	1.30 [0.97–1.73]	Very low	1	0.65 [0.17–2.49]	Very low
VPTB	//	//	//	//	//	//	1	0.27 [0.10–0.73]	Very low
Paccr	//	//	//	//	//	//	//	//	//
PPROM	//	//	//	//	//	//	1	0.73 [0.45–1.18]	Very low
PostTB	2	1.42 [0.47–4.29]	Very low	//	//	//	1	0.22 [0.09–0.54]	Very low
Macros.	3	1.15 [0.97–1.36]	Very low	3	1.29 [1.06–1.58]	Very low	1	0.68 [0.48–0.96]	Very low
LBW	4	1.15 [0.93–1.42]	Very low	5	1.18 [0.88–1.58]	Very low	//	//	//
VLBW	//	//	//	//	//	//	//	//	//

(continued)

Table IV Continued

Outcome	SC-FET vs NC-FET			PC-FET vs SC-FET			mNC-FET vs tNC-FET		
	Nr of studies	OR [95% CI]	Quality of evidence (GRADE)	Nr of studies	OR [95% CI]	Quality of evidence (GRADE)	Nr of studies	OR [95% CI]	Quality of evidence (GRADE)
LGA	4	0.99 [0.86–1.14]	Very low	4	1.18 [1.09–1.27]	Very low	1	0.82 [0.40–1.68]	Very low
SGA	4	1.21 [0.99–1.48]	Very low	5	0.82 [0.75–0.90]	Very low	1	0.64 [0.24–1.71]	Very low
Stillbirth	//	//	//	//	//	//	//	//	//
Cong. m.	2	1.02 [0.79–1.32]	Very low	//	//	//	//	//	//

Cong. m., congenital malformations; CS, cesarean section; GDM, gestational diabetes mellitus; HDP, hypertensive disorder of pregnancy; LBW, low birth weight (i.e. birthweight < 2500 g); LGA, large for gestational age (birthweight > 90° pct for gestational age); Macros., macrosomia; Macrosomi (i.e. birthweight > 4000 g); mNC-FET, modified natural cycle for frozen embryo transfer; NC-FET, natural cycle for frozen embryo transfer (tNC-FET + mNC-FET cycles); OR, odds ratio; PAbr, placental abruption; PC-FET, programmed cycle for frozen embryo transfer; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; PostTB, Post term birth (i.e. birth after 42 weeks of gestation); PP, placenta previa; PPROM, preterm premature rupture of membranes; PTB, preterm birth (i.e. birth before 37 weeks of gestation); SC-FET, stimulated cycle for frozen embryo transfer; SGA, small for gestational age (birthweight > 10° pct for gestational age); tNC-FET, total natural cycle for frozen embryo transfer; VLBW, very low birth weight (i.e. birthweight < 1500 g); VPTB, very preter birth (i.e. birth before 34 weeks of gestation).

determined by the differences in the HRT protocols. Thirteen studies accurately reported timing and doses of administered drugs. Although the routes of administration differ, the prescribed doses of estrogen and progesterone are similar. On the contrary, the pretreatment strategy varies from one study to another: in some studies, an oral contraceptive pill (OCP) was administered, whereas in others a suppression with a GnRH agonist or antagonist was performed. In the remaining six studies, the exact HRT protocol is not specified since, in the majority of cases, it differs between participating clinics. Other methodological aspects may have contributed negatively. For example, some studies included only patients who underwent blastocyst stage ET, while others did not adopt limitations and included IVF cycles in which cleavage stage embryos were also transferred. Similarly, in some studies, authors did not specify whether or not they included FET cycles that involved transfer of blastocyst(s) that had undergone trophectoderm biopsy which recently was demonstrated to be associated with an increased risk of HDP (Feldman *et al.*, 2020; Makhijani *et al.*, 2021). In order to control the heterogeneity across studies, we undertook subgroup analyses by pooling only ORs adjusted for a specific possible confounding factor. However, many of this effect estimates have also been adjusted for other covariates and this may create interpretational issues. On the other hand, to date, this seems to be the only possible approach. In fact, the low incidence of the analyzed outcomes makes it very difficult to conduct RCTs with an adequate sample size.

Wider implications

Endometrial preparation protocols with HRT are associated with worse obstetric and perinatal outcomes. The absence of a CL almost certainly plays a role. However, the pathophysiology underlying some of the observed associations could also be more complex. In particular, a HRT directly mediated effect at uterine level cannot be excluded (von Versen-Höynck *et al.*, 2021).

Given the effect estimates and the described limitations, we are not able to make inferences regarding a causal relationship between endometrial preparation with HRT and obstetric and perinatal complications. Therefore, our results should not prompt clinicians to change their treatment attitudes.

Noteworthy, they open to a new and fruitful avenue for future research. Overall, we suggest focusing on three main areas. First, we encourage efforts toward testing the association between the different endometrial preparation protocols and the most dangerous obstetric and perinatal complications. Particularly, attention should be paid to the selection of an adequate population and to the homogeneity of both the adopted HRT protocol and the diagnostic criteria for the considered outcomes. Second, we encourage prospective studies aimed at determining a proper therapeutic strategy in women presenting with an '*a priori*' high-risk profile. Indeed, it is well established that a number of preconception maternal risk factors are associated with the development of adverse obstetric outcomes, particularly PE (e.g. history of PE, chronic hypertension, nulliparity, maternal age >35 years, chronic kidney disease, pre-pregnancy BMI and pre-GDM) (Chaemsaithong *et al.*, 2020). Likewise, some quite frequent pathologies of infertile women have been shown to be associated with an unfavorable obstetric profile. For instance, endometriosis seems to be responsible for an increased risk of a variety of complications, including PTB, PP, PE, PPH and SGA (Kobayashi *et al.*, 2020). Pregnant women with polycystic ovary syndromes have increased risks for adverse pregnancy outcomes (i.e. GDM, HDP, PE, PTB, CS, SGA and LGA) independently of subfertility and use of ART (Valent and Barbour, 2021). Based on the available data, one cannot state with certainty that the risk associated with the administration of HRT is additive to the baseline one. However, until proven otherwise in future prospective studies, a conservative attitude should be adopted. In the IVF context, therapeutic personalization has always been investigated in order to increase the chances of success. Our results shift the focus and suggest implementing personalization protocols in order to protect mother and fetus safety. In light of this, the assessment of the preconception risk profile of infertile women is of fundamental importance and should be routinely performed in all IVF clinics.

Third, robust evidence suggests that the administration of low-dose aspirin initiated before 16 weeks' gestation significantly reduces the rate of preterm preeclampsia, (Chaemsaithong *et al.*, 2020). In future contributions, authors should thus differentiate the PE phenotypes. In fact, if the association with preventable forms of PE was confirmed, HRT endometrial preparation protocols for FET could be introduced

as a new maternal factor in the screening algorithms for the early detection of pregnant women at high risk for PE (Chaemsaithong *et al.*, 2020).

Conclusion

Consistently with the recent literature, our study demonstrates an increased risk of adverse obstetric and perinatal outcomes in women conceiving via PC-FET. Our results indirectly support the pivotal role of CL in the processes of vascular remodeling and placentation. However, because of the above-mentioned methodological weaknesses, recommendations for clinical practice cannot be made. Well conducted prospective studies are thus warranted to establish a safe endometrial preparation strategy for FET cycles aimed at limiting superimposed risks particularly in women with an '*a priori*' high-risk profile for obstetric and perinatal complications.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article have been extracted from already published articles. All the new generated data are reported in the present version of the manuscript.

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None.

Authors' roles

A.Bus. conceived the study. A.Bus., I.S. and P.E.L.-S. designed the study protocol. All authors participated in study selection. A.Bus. and A.Bul. were involved in quality assessment. A.Bus. and F.F. extrapolated data. All authors analyzed and interpreted data. A.Bus. drafted the first version of the manuscript. A.Bul. and P.E.L.-S. revised the first version of the manuscript. All authors approved the final version to be published.

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Conflict of interest

All authors have no financial and non-financial competing interest to declare.

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