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Fresh versus elective frozen embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis of reproductive outcomes

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BACKGROUND: Elective freezing of all good quality embryos and transfer in subsequent cycles, i.e. elective frozen embryo transfer (eFET), has recently increased significantly with the introduction of the GnRH agonist trigger protocol and improvements in cryotechniques. The ongoing discussion focuses on whether eFET should be offered to the overall IVF population or only to specific subsets of patients. Until recently, the clinical usage of eFET was supported by only a few randomized controlled trials (RCT) and meta-analyses, suggesting that the eFET not only reduced ovarian hyperstimulation syndrome (OHSS), but also improved reproductive outcomes. However, the evidence is not unequivocal, and recent RCTs challenge the use of eFET for the general IVF population.

OBJECTIVE AND RATIONALE: This systematic review and meta-analysis aimed at evaluating whether eFET is advantageous for reproductive, obstetric and perinatal outcomes compared with fresh embryo transfer in IVF/ICSI cycles. Additionally, we evaluated the effectiveness of eFET in comparison to fresh embryo transfer in different subgroups of patients undergoing IVF/ICSI cycles.

SEARCH METHODS: We conducted a systematic review, using PubMed/Medline and EMBASE to identify all relevant RCTs published until March 2018. The participants included infertile couples undergoing IVF/ICSI with or without preimplantation genetic testing for aneuploidy (PGT-A). The primary outcome was the live birth rate (LBR), whereas secondary outcomes were cumulative LBR, implantation rate, miscarriage, OHSS, ectopic pregnancy, preterm birth, pregnancy-induced hypertension, pre-eclampsia, mean birthweight and congenital anomalies. Subgroup analyses included normal and hyper-responder patients, embryo developmental stage on the day of embryo transfer, freezing method and the route of progesterone administration for luteal phase support in eFET cycles.

OUTCOMES: Eleven studies, including 5379 patients, fulfilling the inclusion criteria were subjected to qualitative and quantitative analysis. A significant increase in LBR was noted with eFET compared with fresh embryo transfer in the overall IVF/ICSI population [risk ratio (RR) = 1.12; 95% CI: 1.01–1.24]. Subgroup analyses indicated higher LBRs by eFET than by fresh embryo transfer in hyper-responders (RR = 1.16; 95% CI: 1.05–1.28) and in PGT-A cycles (RR = 1.55; 95% CI: 1.14–2.10). However, no differences were observed for LBR in normo-responders (RR = 1.03; 95% CI: 0.91–1.17); moreover, the cumulative LBR was not significantly different in the overall population (RR = 1.04; 95% CI: 0.97–1.11). Regarding safety, the risk of moderate/severe OHSS was significantly lower with eFET than with fresh embryo transfer (RR = 0.42; 95% CI: 0.19–0.96). In contrast, the risk of pre-eclampsia increased with eFET (RR = 1.79; 95% CI: 1.03–3.09). No statistical differences were noted in the remaining secondary outcomes.

WIDER IMPLICATIONS: Although the use of eFET has steadily increased in recent years, a significant increase in LBR with eFET was solely noted in hyper-responders and in patients undergoing PGT-A. Concerning safety, eFET significantly decreases the risk of moderate and severe OHSS, albeit at the expense of an increased risk of pre-eclampsia.

Key words: freeze-all / elective frozen embryo transfer / fresh transfer / IVF/ICSI / live birth / ovarian hyperstimulation syndrome / pre-eclampsia / obstetric outcomes / perinatal outcomes, preimplantation genetic testing for aneuploidy

Introduction

Improvements in vitrification protocols have enabled elective freezing of all embryos, followed by transfer in a subsequent cycle, also known as elective frozen embryo transfer (eFET), 'freeze-all', deferred ET or cycle segmentation. Initially, this strategy was indicated for hyper-responders, as these individuals are at a high risk of developing ovarian hyperstimulation syndrome (OHSS) (Devroey *et al.*, 2011; Griesinger et al., 2011). The first randomized controlled trial (RCT) comparing frozen and fresh ET was published in 1999 to evaluate the safety and efficacy of eFET in patients at risk of OHSS (Ferraretti *et al.*, 1999). The results concerning the clinical outcomes should be carefully evaluated, as this study was published in 1999 (Ferraretti *et al.*, 1999), and the outcomes of FET cycles have improved tremendously during the past few years (Wong *et al.*, 2014).

Later, it was hypothesized that controlled ovarian stimulation (COS) would lead to adverse effects in the endometrium, disrupting successful embryo–endometrium interaction. Hence, it was suggested that performing eFET would not only decrease the risk of OHSS, but also improve the reproductive outcomes of IVF treatment (Shapiro *et al.*, 2008). In this way, based on the initial trials the use of eFET was suggested for the general IVF/ICSI population, as this strategy—according to the first meta-analysis (Roque *et al.*, 2013)—was superior to fresh ET, both in terms of reducing the incidence of OHSS, and in improving the reproductive outcomes. While the aforementioned meta-analysis reported higher clinical [risk ratio (RR) = 1.31; $P = 0.002$] and ongoing (RR = 1.32; $P = 0.003$) pregnancy rates in favor of eFET (Roque *et al.*, 2013), none of the included studies reported live birth rates (LBR) (Shapiro *et al.*, 2011a,b). Importantly, the meta-analysis included only three RCTs (Aflatoonian *et al.*, 2010; Shapiro *et al.*, 2011a, b) evaluating 633 patients, and one of the included studies (Aflatoonian *et al.*, 2010) was retracted from the literature due to methodological flaws after the publication of the meta-analysis (Aflatoonian *et al.*, 2013).

The biologically plausible hypothesis for the aforementioned findings is related to the supraphysiological hormonal levels achieved at the end of COS, which induce an endometrial advancement, resulting in an 'out of phase' endometrium at the time of implantation (Ubaldi *et al.*, 1997; Kolibianakis *et al.*, 2002). Moreover, even in the 'in phase' endometrium, the increase in steroid levels achieved with COS may negatively affect the endometrial receptivity (Marchini *et al.*, 1991; Bourgain and Devroey, 2003; Fauser and Devroey, 2003; Horcajadas *et al.*, 2005; Labarta *et al.*, 2011) when performing a fresh ET, thereby reducing implantation rates (Shapiro *et al.*, 2014a; Roque, 2015a; Roque *et al.*, 2017a). Specifically, the rise in late follicular progesterone level is thought to be negative for successful implantation(Bosch *et al.*, 2010; Labarta *et al.*, 2011; Al-Azemi et al., 2012; Xu *et al.*, 2012; Venetis et al., 2013; Hamdine et al., 2014; Bosch, 2015; Fatemi and Van Vaerenbergh, 2015; Venetis et al.,

2015; Lawrenz and Fatemi, 2017; Wang et al., 2017; Lawrenz et al., 2018a,b). However, the possible adverse effect of the supraphysiological steroid levels induced by COS disappears in the cycle following COS, whereby transfer of frozen–thawed embryos can be successfully performed (Santos-Ribeiro et al., 2016; Lattes et al., 2017; Ozgur et al., 2018).

Despite the limited evidence mentioned above, several fertility clinics have adopted a liberal approach towards eFET (Zhu et al., 2018), increasing its overall use (Wong et al., 2014; Shapiro et al., 2014a,b; Dyer et al. 2016; Shapiro & Garner, 2017). Meanwhile, new RCTs have reported mixed results in terms of the reproductive outcomes when comparing fresh ET to eFET in specific IVF/ICSI populations, such as in patients with polycystic ovary syndrome (PCOS) (Chen et al., 2016), in normo-ovulatory women (Shi et al., 2018), in women without PCOS (Vuong et al., 2018), and in patients undergoing preimplantation genetic testing for aneuploidy (PGT-A) (Coates et al., 2017). In a recent Cochrane meta-analysis including four RCTs and 1892 patients (Wong et al., 2017), moderate quality evidence suggested no significant difference in the cumulative LBR with an odds ratio (OR) of 1.09 [95% CI: 0.91–1.31; I^2 = 0%] when comparing eFET to fresh ET. However, at the time of this meta-analysis, only two trials reported OHSS rates and pregnancy complications, resulting in equivocal results, as eFET was associated with reduced OHSS rates, but an increase in the composite outcome designated 'pregnancy complications'. Since the publication of the Cochrane review, a total of five additional RCTs have been published (Aghahosseini et al., 2017; Coates et al., 2017; Aflatoonian et al., 2018; Shi et al., 2018; Vuong et al., 2018). Moreover, additional data concerning obstetric and perinatal outcomes from previous trials have been published (Shapiro et al., 2016a; Zhang et al., 2018), which taken together support the potential for better-quality evidence from meta-analyses. Notably, previous meta-analyses comparing the obstetric and perinatal outcomes between fresh ET and eFET were based on observational studies (Maheshwari et al., 2012, 2018; Pinborg et al., 2013), rendering them subject to bias. The present systematic review and meta-analysis was based on RCTs, aiming to provide an update on the impact of eFET on the reproductive outcomes in IVF/ICSI cycles.

Methods

Protocol and registration

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Shamseer et al., 2015). The study protocol is accessible at http://www.crd.york.ac.uk/PROSPERO/ (registration number CRD42018087454). This study was exempted from the institutional review board approval, as it was a meta-analysis.

Eligibility criteria

The selection criteria were described according to **P**atients, **I**ntervention, **C**omparison and **O**utcomes (PICO) statements. We included only studies that compared the reproductive outcomes between fresh ET and eFET in IVF/ICSI cycles (Tables I and II).

Search strategy

With the support of a research librarian, a systematic literature search using PubMed/MEDLINE and EMBASE was performed to identify all relevant RCTs on the eFET strategy published from 1 January 2016 to 22 March 2018, that is, an update of the literature search from the latest Cochrane review from which we included all RCTs (Wong et al., 2017). Moreover, the reference lists of relevant studies were scrutinized for any additional studies not covered by the literature search, and the authors were contacted in order to obtain unpublished data. The literature search combined the terms and descriptors related to eFET concerning literature published in English (see Supplementary Data for full literature search). Conference abstracts were not considered.

Selection of studies and validity assessment

Citations were managed in Covidence© (Veritas Health Innovation Ltd., Melbourne, Australia). Duplicates were removed, and all citations were subsequently screened by the title and abstract by two of the authors (MR and TH). Any discrepancies were solved by discussion and, if needed, a consensus was reached with the help of senior authors (S.C.E., S.G. and P.H.). Trials published only as abstracts, quasi-randomized trials, and studies retracted from the literature after their publication were excluded upfront. Next, the full texts of eligible RCTs were obtained to evaluate the eligibility of the studies and, subsequently, to extract data following the risk of bias assessment as per the instructions specified in the Cochrane handbook version 5.1 (http://handbook-5-1.cochrane.org/, accessed 9 June 2018).

Data extraction

Data extracted from all studies was summarized for each outcome listed below (Tables I and II). The primary outcome measure was the LBR per woman randomized. The secondary outcome measures were the cumulative LBR (per women randomized) and the rates of implantation, miscarriage, OHSS, ectopic pregnancy, preterm birth, pregnancy-induced hypertension, pre-eclampsia, birthweight and congenital anomalies. With only minor changes, the outcome definitions adhered to The International Committee Monitoring Assisted Reproductive Technologies/World Health Organization glossary (Zegers-Hochschild et al., 2017). LBR was defined as the ratio between the number of deliveries resulting in at least one live birth per woman randomized (i.e. intention-to-treat). Two independent reviewers (T.H. and M.R.) referred to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to evaluate the quality of evidence for each outcome (Schünemann et al., 2018).

Quantitative analysis

All analyses were performed based on intention-to-treat and defined as the inclusion of all randomized participants in the denominator, except for the missing patients. The cumulative LBR was calculated by computing the rate of live births following the transfers of all (fresh or frozen–thawed) embryos available from the stimulated cycle per randomized patient.

Data related to the dichotomous outcomes were pooled to determine the RR with corresponding 95% CIs. Data from the continuous outcomes were pooled using the inverse variance model, and the mean difference (MD) was calculated between the groups to determine the effect size (Higgins et al., 2003). We combined the outcome data from the included studies using a Mantel–Haenszel model and applied the random effects models. Heterogeneity was evaluated using the *I*-squared statistic (I^2), and publication bias was evaluated in funnel plots (Supplementary Data). Sensitivity analysis was performed for the outcomes with funnel plot asymmetry to assess the leverage of the studies on the results (Higgins et al., 2003).

Finally, sub-analyses were made to assess the effect of eFET on LBRs in different patient subgroups: ovarian response, stratifying PCOS patients

and hyper-responder patients with ≥15 retrieved oocytes to be compared with non-PCOS/normo-responders, i.e. <15 retrieved oocytes; method of cryopreservation (vitrification and slow freezing); embryo selection (PGT-A and no PGT-A); embryo developmental stage (cleavage and blastocyst), and different interventions for luteal phase support in FET cycles, i.e. vaginal/oral progesterone, i.m. progesterone, and natural cycle FET protocol. Statistical significance was set at $P < 0.05$. We used the Review Manager (RevMan Version 5.3 Software, Copenhagen, Denmark) for statistical analysis.

Results

Study selection

The literature search retrieved 502 citations, of which 19 were eligible for further consideration after screening of titles and abstracts (Fig. 1). Among these, seven citations were excluded because they were only available as abstracts; two citations were duplicates; and one study was not a valid RCT, as patients were submitted to fresh ET or eFET based on the number of mature follicles achieved during COS (Chandel *et al.*, 2016). One study investigated PGT-A without randomization (Ma *et al.*, 2016), and one study was not a true RCT, as also confirmed by the authors through correspondence (Magdi *et al.*, 2017). Three RCTs not present in the updated literature search were added from the Cochrane review (Wong *et al.*, 2017) and, finally, one study was added after completing the systematic literature search due to a final screening of new studies on June 2018 (Aflatoonian *et al.*, 2018).

Description of included studies

Overall, 11 studies fulfilled our inclusion criteria, and these included data on 5379 women randomized to eFET or fresh ET (Ferraretti *et al.*, 1999; Shapiro *et al.*, 2011a,b, 2016a; Chen *et al.*, 2016; Aghahosseini *et al.*, 2017; Coates *et al.*, 2017; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018; Zhang *et al.*, 2018). Among these, nine studies reported LBRs, whereas two studies were post-hoc analyses of three previously published RCTs (Shapiro *et al.*, 2011a,b; Chen *et al.*, 2016) reporting obstetric outcomes in subsequent publications after evaluating the initial reproductive data. The

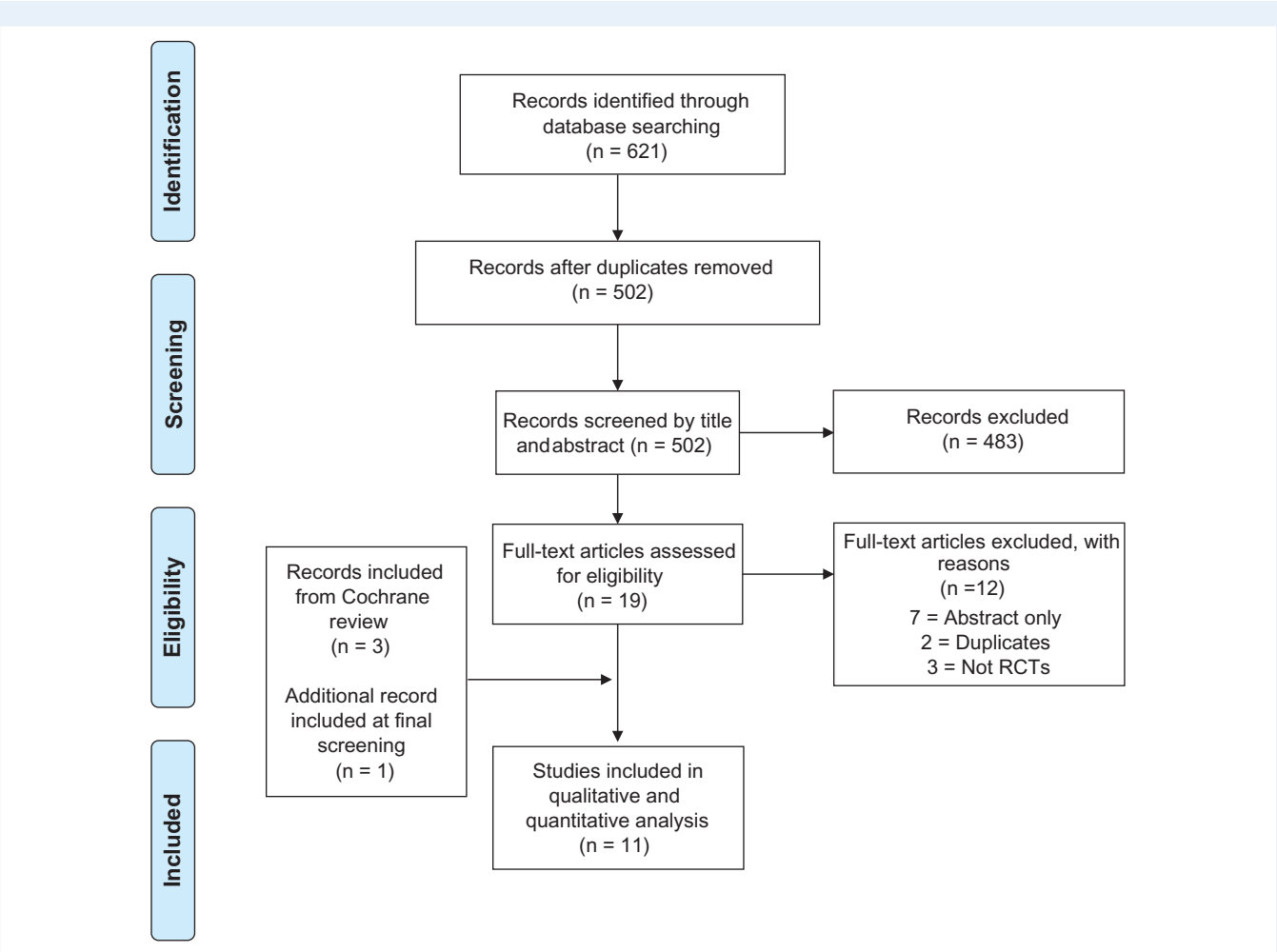

Figure 1 Flowchart for the study identification and selection process according to preferred reporting items for systematic reviews and meta-analyses guidelines. RCT = randomized controlled trial.

risk of bias assessment in the included RCTs has been presented in the Supplementary Data.

Outcomes

Live births

Nine studies reported LBR including 2676 patients randomized in the eFET group and 2703 patients in the fresh ET group. The overall RR for LBR was 1.12 (95% CI: 1.01–1.24; I^2 = 46%; P = 0.04; Fig. 2a), favoring the eFET group. The quality of evidence was low according to GRADE (Table I).

A subgroup analysis concerning the ovarian response in PCOS/hyper-responder patients (four studies; n = 2035 patients) indicated that the eFET increased the LBR with an RR of 1.16 (95% CI: 1.05–1.28; I^2 = 0%; P = 0.004; low quality of evidence; Supplementary Fig. S1a). However, in non-PCOS/normo-responders (three studies; n = 3076 patients) there was no significant difference between groups considering LBR (RR = 1.03; 95% CI: 0.91–1.17; I^2 = 34%; low quality of evidence; Supplementary Fig. S1a). In cleavage-stage ET (six studies; n = 4941 patients), there were no differences in LBRs (RR = 1.06; 95% CI: 0.96–1.16; I^2 = 31%; low quality of evidence; Supplementary Fig. S1b). In contrast, eFET was associated with an increased LBR compared with fresh ET when blastocysts (three studies; n = 438 patients) were transferred (RR = 1.33; 95% CI: 1.11–1.61; I^2 = 0%; P = 0.002; very low quality of evidence; Supplementary Fig. S1b).

We also performed sub-analysis considering the different routes of progesterone administration in eFET cycles (i.e. vaginal, IM or oral). An increase in LBR favoring the eFET group was observed for patients who received IM progesterone (six studies; n = 2160 patients) as luteal phase support in eFET cycles (RR = 1.20; 95% CI: 1.09–1.31; I^2 = 0%; P = 0.0001; low quality of evidence; Supplementary Fig. S1c). No differences were noted between the eFET and fresh ET groups when vaginal progesterone (two studies; n = 1062 patients; RR = 1.07; 95% CI: 0.89–1.28; I^2 = 0%, low quality of evidence; Supplementary Fig. S1c) and oral progesterone (one study included; n = 2157 patients; RR = 0.97; 95% CI: 0.89–1.06) were administered in eFET cycles.

The method of embryo cryopreservation did not affect the LBR among patients undergoing eFET (slow freezing: RR = 1.17; 95% CI: 0.95–1.44, I^2 = 0%; vitrification: RR = 1.11; 95% CI: 0.98–1.27, I^2 = 62%, very low quality of evidence; Supplementary Fig. S1d). Three studies used slow freezing method (n = 384 patients) and six studies used vitrification (n = 4995 patients).

The subgroup analysis in patients without PGT-A (eight studies; n = 5200 patients) revealed no significant differences between the groups as regards to LBR (RR = 1.07; 95% CI: 0.99–1.17; I^2 = 22%; low quality of evidence; Supplementary Fig. S1e). In patients with

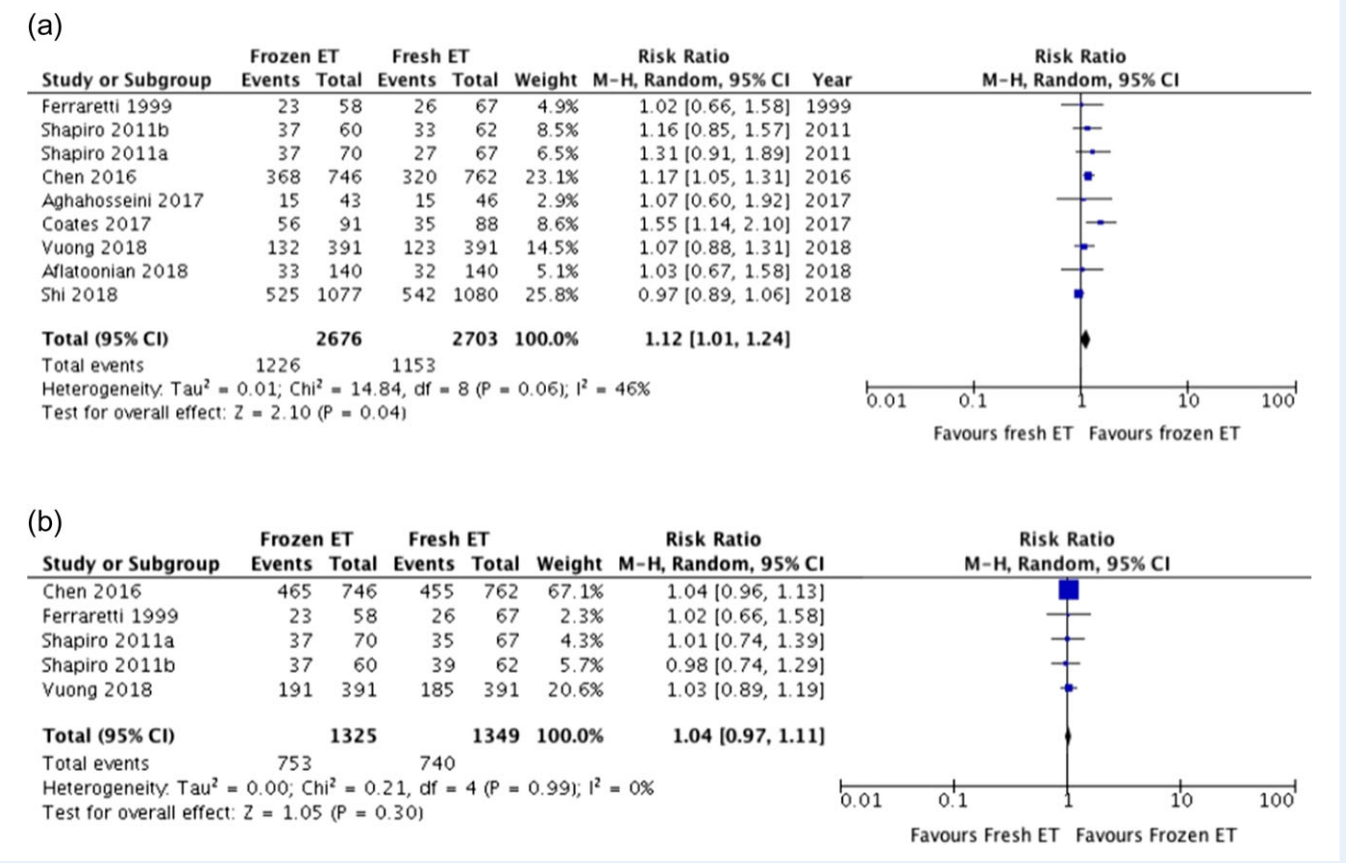

Figure 2 Forest-plots comparing live birth rates after fresh and elective frozen embryo transfer. Intention-to-treat analysis for (**a**) live birth rates and (**b**) cumulative live birth rates after 12 months. ET = embryo transfer.

Table I Summary of findings table displaying the overall PICO question, results of primary outcome and sub-analysis comparing elective frozen embryo transfer with fresh embryo transfer.

Study question: Should elective frozen embryo transfer versus fresh embryo transfer be used for IVF/ICSI treatment?

Population: IVF/ ICSI patients
Intervention: Elective frozen embryo transfer (eFET)
Comparator: Fresh embryo transfer (ET)
Studies: Randomized controlled trials

Outcome	Absolute effect Risk difference per 1000 eFET versus fresh ET (95% CI)	Risk ratio (95% CI)	Total patients (studies)	Quality of evidence (GRADE)
Primary outcomes				
Live birth rate per randomized patient	51 more per 1000 (4 more to 102 more)	1.12 (1.01–1.24)	5379 patients (9 studies)	⊕⊕⊖⊖ low
Live birth rate—PCOS/Hyper-responder	64 more per 1000 (20 more to 112 more)	1.16 (1.05–1.28)	2035 patients (4 studies)	⊕⊕⊖⊖ low
Live birth rate—non-PCOS/Normo-responder	13 more per 1000 (40 fewer to 76 more)	1.03 (0.91–1.17)	3076 patients (3 studies)	⊕⊕⊖⊖ low
Live birth rate—I.M. progesterone (in luteal phase support in FET cycle)	100 more per 1000 (45 more to 156 more)	1.20 (1.09–1.31)	2160 patients (6 studies)	⊕⊕⊖⊖ low
Live birth rate—vaginal progesterone (in luteal phase support in FET cycle)	20 more per 1000 (32 fewer to 82 more)	1.07 (0.89–1.28)	1062 patients (2 studies)	⊕⊕⊖⊖ low
Live birth rate—cleavage state	26 more per 1000 (17 fewer to 68 more)	1.06 (0.96–1.16)	2486 patients (6 studies)	⊕⊕⊖⊖ low
Live birth rate—blastocyst	144 more per 1000 (48 more to 267 more)	1.33 (1.11–1.61)	438 patients (3 studies)	⊕⊖⊖⊖ very low
Live birth rate—slow freezing	75 more per 1000 (22 fewer to 193 more)	1.17 (0.95–1.44)	384 patients (3 studies)	⊕⊖⊖⊖ very low
Live birth rate—vitrification	47 more per 1000 (9 fewer to 115 more)	1.11 (0.98–1.27)	4995 patients (6 studies)	⊕⊖⊖⊖ very low
Live birth rate—no-PGT-A	30 more per 1000 (4 fewer to 73 more)	1.07 (0.99–1.17)	5200 patients (8 studies)	⊕⊕⊖⊖ low

PICO = **P**atients, **I**ntervention, **C**omparison and **O**utcomes; GRADE = Grading of Recommendations Assessment, Development and Evaluation; PCOS = polycystic ovary syndrome; PGT-A = preimplantation genetic testing for aneuploidy.

PGT-A (1 study; $n = 179$ patients), the eFET increased LBR with an RR of 1.55 (95% CI: 1.14–2.10; $P = 0.005$; Supplementary Fig. S1e).

Cumulative LBR (per woman randomized) within 12 months

Five studies, including 2674 randomized patients, provided information on the cumulative LBR after 12 months of follow-up; these studies either directly reported the cumulative LBR or additional information was achieved through correspondence with the author. There was no significant difference between the eFET and fresh ET groups (RR = 1.04; 95% CI: 0.97–1.11; $I^2 = 0\%$; low quality of evidence; Fig. 2b) in cumulative LBR based on the number of women randomized (Table II).

Implantation

Five studies, which included 3377 patients, provided data on the implantation rate (Table II). No differences were observed in the implantation rates between the eFET group and the fresh ET group (RR = 1.16; 95% CI: 0.98–1.36; $I^2 = 80\%$; very low quality of evidence; Fig. 3a); however, heterogeneity was substantial.

Miscarriage

Eight studies, including 5183 patients, evaluated the miscarriage rates. No difference was noted in the miscarriage rates between eFET and fresh ET cycles among the biochemical pregnancies (RR = 1.08; 95% CI: 0.72–1.61; $I^2 = 62\%$; very low quality of evidence; Fig. 3b), but heterogeneity was substantial.

OHSS

Seven studies, which included 5111 patients, were part of this analysis. The overall risk of moderate/severe OHSS was significantly lower in the eFET group than in the fresh ET group (RR = 0.42; 95% CI: 0.19–0.96; $I^2 = 76\%$; $P = 0.04$; low quality of evidence; Fig. 3c), albeit heterogeneity was substantial.

Ectopic pregnancy

Four studies that included 4572 patients were pooled in this meta-analysis. Overall, no difference was noted in the ectopic pregnancy rates between the eFET and fresh ET cycles (RR = 0.88; 95% CI: 0.45–1.71; $I^2 = 41\%$; very low quality of evidence; Supplementary Fig. S2a).

Preterm birth

Four studies, including 4727 patients, were analyzed. The overall risk of preterm birth was not significantly different among the pregnancies resulting from the eFET and fresh ET cycles (RR = 1.13; 95% CI: 0.93–1.36; $I^2 = 0\%$; low quality of evidence; Supplementary Fig. S2b).

Pregnancy-induced hypertension

Three studies, including 4447 patients, were used in this analysis. Overall, no difference in the risk of developing pregnancy-induced hypertension was noted among the pregnancies resulting from eFET and fresh ET cycles (RR = 1.03; 95% CI: 0.48–2.18; $I^2 = 17\%$; low quality of evidence; Supplementary Fig. S2c).

Table II Summary of findings for the secondary outcomes.

Study question: Should elective frozen embryo transfer versus fresh embryo transfer be used for IVF/ICSI treatment?

Population: IVF/ ICSI patients
Intervention: Elective frozen embryo transfer (eFET)
Comparator: Fresh embryo transfer (ET)
Studies: Randomized controlled trials

Outcome	Absolute effect Risk difference per 1000 eFET versus fresh ET (95% CI)	Risk ratio (95% CI)	Total patients or other denominator (studies)	Quality of evidence (GRADE)
Secondary Outcomes				
Cumulative live birth rate (12 months follow-up)	22 more per 1000 (16 fewer to 60 more)	1.04 (0.97–1.11)	2674 patients (5 studies)	⊕⊕⊖⊖ low
OHSS	31 fewer per 1000 (43 fewer to 2 fewer)	0.42 (0.19–0.96)	5111 patients (7 studies)	⊕⊕⊖⊖ low
Implantation rate	63 more per 1000 (8 fewer to 142 more)	1.16 (0.98–1.36)	6122 embryos transferred (5 studies)	⊕⊖⊖⊖ very low
Miscarriage rate	8 more per 1000 (28 fewer to 142 more)	1.08 (0.72–1.61)	5183 hCG pregnancies (8 studies)	⊕⊖⊖⊖ very low
Ectopic pregnancy	3 fewer per 1000 (15 fewer to 19 more)	0.88 (0.45–1.71)	2765 patients (4 studies)	⊕⊖⊖⊖ very low
Preterm birth	19 more per 1000 (10 fewer to 53 more)	1.13 (0.93–1.36)	2382 live births (4 studies)	⊕⊕⊖⊖ low
Pregnancy-induced hypertension	0 fewer per 1000 (7 fewer to 17 more)	1.03 (0.48–2.18)	2398 clinical pregnancies (3 studies)	⊕⊕⊖⊖ low
Pre-eclampsia	18 more per 1000 (1 more to 47 more)	1.79 (1.03–3.09)	2388 patients (3 studies)	⊕⊕⊕⊖ moderate
Birthweight (mean difference)	127 grams higher (3 lower to 257 higher)	*	1489 patients (4 studies)	⊕⊖⊖⊖ very low
Congenital anomalies	5 fewer per 1000 (22 fewer to 28 more)	0.88 (0.46–1.69)	2363 patients (2 studies)	⊕⊖⊖⊖ very low

OHSS = ovarian hyperstimulation syndrome. *Mean Difference = 127.06 (95% CI:–2.99–257.11).

Pre-eclampsia

Three studies, including 4447 patients, were pooled in this analysis. The risk of pre-eclampsia was higher in pregnancies resulting from the eFET than from fresh ET (RR = 1.79; 95% CI: 1.03–3.09; I^2 = 13%; P = 0.04; moderate quality of evidence; Supplementary Fig. S2d).

Mean birthweight

Four studies, including 4706 patients, were analyzed. Overall, no difference was noted in the mean birthweight of newborns resulting from deliveries involving eFET and fresh ET cycles (MD = 127.06; 95% CI:–2.99–257.11; I^2 = 79%; very low quality of evidence; Supplementary Fig. S2e).

Congenital anomalies

Only two studies, including 3665 patients, were pooled in this analysis. Overall, there was no difference in the rates of congenital anomalies among the offspring resulting from the eFET and fresh ET strategies (RR = 0.88; 95% CI: 0.46–1.69; I^2 = 59%; very low quality of evidence; Supplementary Fig. S2f).

Sensitivity analysis

Sensitivity analysis only had a significant impact on the pooled effect size concerning mean birthweight (Supplementary Data).

Discussion

Principal findings

Low quality evidence indicated that LBRs are increased with the use of eFET in preference to fresh ET in the overall population undergoing IVF/ICSI (Fig. 2). However, after exclusion of the PGT-A study by Coates *et al.* (2017), which compared eFET PGT-A cycles at the blastocyst stage to fresh ET at Day 6, low quality evidence indicated that there are no differences in LBR by the use of eFET in preference to fresh ET in the overall (non-PGT-A) population undergoing IVF/ICSI. The GRADE quality of evidence was low, mainly due to the substantial inter-study heterogeneity, which was presumed to be caused by differences in the study populations and the use of different types of luteal phase support in the FET cycles. Similarly, subgroup analyses from studies investigating PCOS/hyper-responders and normo-responders indicated that eFET is associated with a

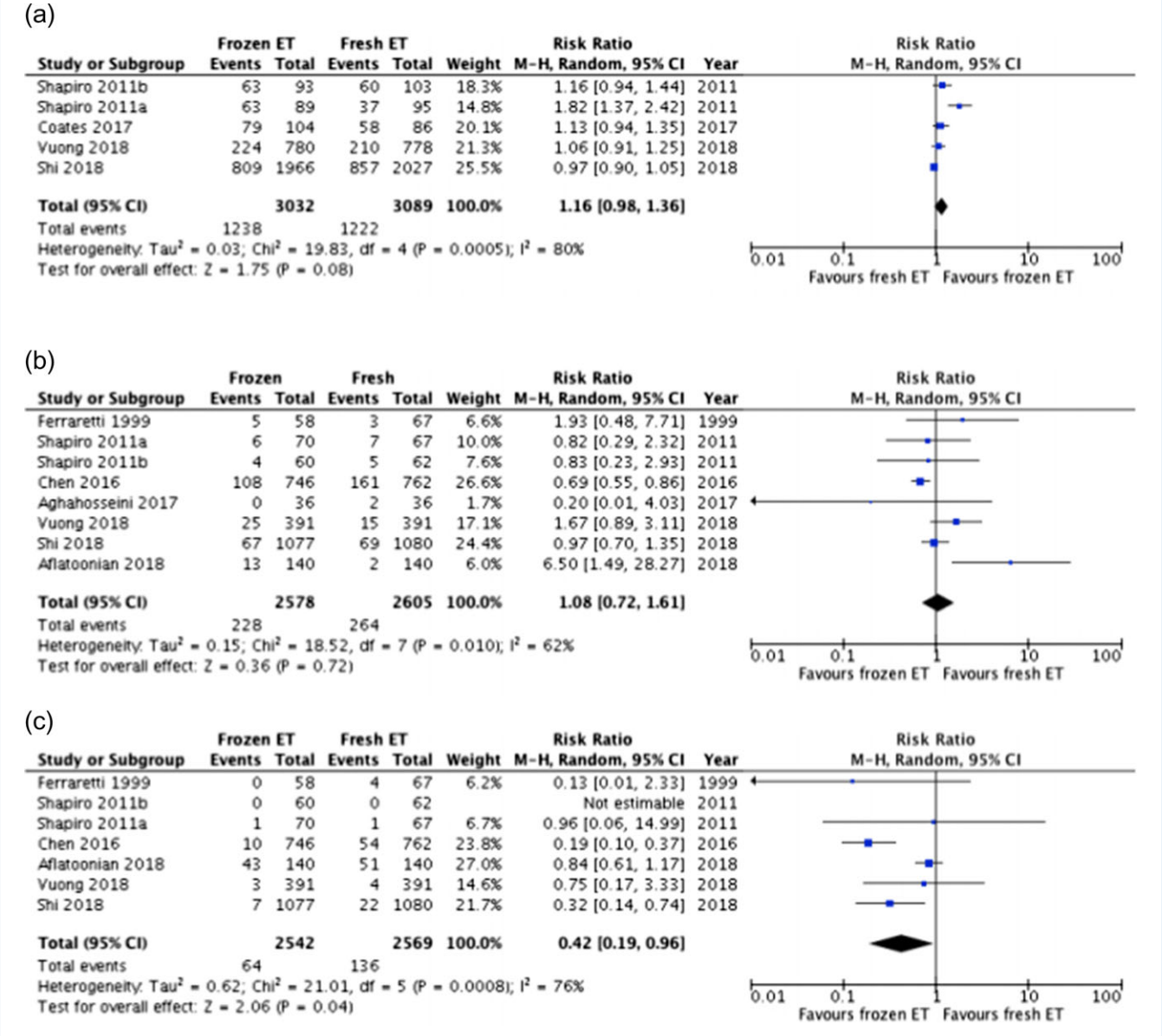

Figure 3 Forest-plots comparing outcomes after fresh and elective frozen embryo transfer. (**a**) Overall implantation rate, (**b**) miscarriage rate and (**c**) moderate/severe ovarian hyperstimulation syndrome.

significantly higher LBR than fresh ET in the PCOS/hyper-responder group, only. In contrast, no effect was noted in the normo-responder group. However, superiority of eFET concerning LBRs among the former patients was only observed when progesterone was administered i.m. in the frozen–thawed ET cycle. Lastly, no significant difference in the cumulative LBR was observed between the eFET and fresh ET groups in the overall IVF/ICSI population.

Our findings corroborate, in part, the results of a recent Cochrane review (Wong *et al.*, 2017), which concluded that the cumulative LBR does not differ between eFET and fresh ET. While our study indicated superiority of eFET concerning LBR in the overall IVF/ICSI population (including the PGT-A study), subgroup analyses revealed that this effect was only maintained in hyper-responders, in those patients in whom i.m. progesterone was used in FET cycles, and in couples undergoing PGT-A. The aforementioned pooled effect size favoring eFET was not evident in normo-responders and even in hyper-responders in whom oral or vaginal progesterone was used for luteal phase support in FET cycles. Moreover, among couples undergoing IVF/ICSI without the use of PGT-A, eFET was equally effective as fresh ET. Taken together, the present study included nearly three times as many patients (5379 versus 1892) compared to the aforementioned Cochrane review, which adds more confidence to the pooled effect estimates.

Another important outcome to be considered when comparing cumulative outcomes among two different strategies in ART is the time to pregnancy (TTP) and/or the time to live birth (Maheshwari *et al.*, 2015). However, only one of the studies (Vuong *et al.*, 2018) included in the present systematic review and meta-analysis

addressed the TTP. In their study, a post-hoc analysis of clinical outcomes after 12 months of randomization demonstrated an increase in the median TTP in patients undergoing eFET when compared to fresh ET (absolute difference, 1.4 months; 95% CI: 0.95–1.84; $P < 0.001$; Vuong *et al.*, 2018).

Biological plausibility

The earlier IVF/ICSI studies suggested that COS with exogenous gonadotrophins may negatively affect endometrial receptivity. Thus, ETs performed in women with endometrial advancement of >3 days resulted in virtually no pregnancies (Ubaldi *et al.*, 1997; Kolibianakis *et al.*, 2002). Previously, the overexpression of late follicular stromal and glandular progesterone receptors as well as downregulation of estrogen receptors have been observed in stimulated cycles (Papanikolaou *et al.*, 2005). Overall, >200 genes related to implantation were over- or under-expressed in the stimulated cycle compared to the natural cycle (Horcajadas *et al.*, 2005). These observations derive mostly from studies involving either hyper-responder patients (Horcajadas *et al.*, 2005; Labarta *et al.*, 2011) or patients with supraphysiological progesterone levels on the day of ovulation trigger (Labarta *et al.*, 2011). However, generalizability of these findings to the overall population of women undergoing IVF/ICSI needs to be confirmed.

In fact, only one RCT compared eFET versus fresh ET in patients with elevated progesterone levels on the trigger day (Aghahosseini *et al.*, 2017; $n = 72$ patients). In this study, the progesterone cutoff level was 1.8 ng/mL, and LBRs were not statistically different between the eFET and fresh ET group. These findings are consistent with those of a recently published review (Esteves *et al.*, 2018) and a large prospective observational study (Martinez *et al.*, 2016), concluding that there is insufficient evidence to recommend eFET based on the rise in the progesterone level during late follicular phase. Moreover, presently, there are no RCTs comparing fresh ET and FET in poor ovarian responders (POR). The results of the few existing observational studies are equivocal. While some reports indicate that the POR patient does not benefit from the eFET in terms of ongoing pregnancy rates (Roque *et al.*, 2017b) and LBRs (Çelik *et al.*, 2015; Xue *et al.*, 2018), other publications suggest that increased implantation and pregnancy rates were achieved using eFET in POR (Berkkanoglu *et al.*, 2017).

Clinical considerations

An interesting finding of the present meta-analysis is that the difference in LBR favoring eFET was only observed when i.m. progesterone was used for support of the FET cycle. In contrast, LBRs were not different when vaginal progesterone was used for luteal phase support in FET cycles. This novel finding could be explained by insufficient circulating serum progesterone levels achieved in FET cycles using vaginal progesterone only (Labarta *et al.*, 2017). However, differences in results could be related to bias, since the studies using i.m. progesterone were predominantly conducted in patients with hyper-response to ovarian stimulation or in patients undergoing PGT-A. Undoubtedly, the route of administration of progesterone for luteal phase support in FET cycles deserves further investigation.

Regarding the use of eFET in PGT-A cycles, only one RCT (Coates *et al.*, 2017) evaluated this issue in a total of 179 women randomized to eFET or fresh ET after trophectoderm biopsy for genetic screening. The authors found that LBRs were higher in the eFET group than in the fresh ET group (61.5 versus 39.8%, respectively; $P < 0.01$). However, LBRs were not significantly different after adjusting for female age and the number of metaphase-two oocytes (OR = 2.1; 95% CI: 0.95–4.68) (Coates *et al.*, 2017). Notably, embryo biopsies were performed on Day 5, and ETs were performed on Day 6 in patients in the fresh ET group. It remains equivocal whether the poorer reproductive outcomes with fresh ET in that study were caused by embryo–endometrium asynchrony as suggested by previous studies (Shapiro *et al.*, 2008, 2016b; Sunkara *et al.*, 2010; El-Toukhy *et al.*, 2011; Poulsen *et al.*, 2017; Shapiro et al., 2013).

OHSS

Low quality evidence favors eFET compared to fresh ET for OHSS reduction (RR = 0.42, 95% CI 0.19–0.96; $I^2 = 76\%$; $P = 0.04$). Although heterogeneity was substantial, the pooled effect size was not affected when performing sensitivity analysis (Supplementary Data). In all but one study, hCG was used for trigger in both arms. Among the normo-responder patients, the OHSS rates were not different between women subjected to eFET or fresh ET in the studies by Shapiro *et al.* (2011b) and Vuong *et al.* (2018), whereas the results favored the eFET group in the study by Shi *et al.* (2018). Despite unusually high OHSS rates, it was interesting that OHSS rates were not statistically different between eFET and fresh ET in the only RCT that used GnRH agonist for triggering final follicular maturation, followed by modified luteal phase support (1500 hCG at the oocyte retrieval) (Aflatoonian *et al.*, 2018). Moreover, in a per-protocol analysis of the largest RCT published until date (Shi *et al.*, 2018), the risk of OHSS was not significantly higher between the fresh ET group and the eFET group since the patients considered to be at high risk of OHSS were rescheduled to the eFET strategy for safety reasons, regardless of randomization.

Collectively, current evidence suggests that the eFET approach is superior to fresh ET in terms of reducing the risk of OHSS in both normo-responder and hyper-responder patients subjected to hCG trigger. However, it remains unclear whether OHSS is reduced in patients triggered with a GnRH agonist followed by modified luteal phase support and fresh ET.

Obstetric and perinatal outcomes

Moderate quality evidence suggests that the risk of pre-eclampsia is higher with eFET than with fresh ET. Our findings are in accordance with those of observational studies (Sazonova *et al.*, 2012; Ishihara *et al.*, 2014; Opdahl *et al.*, 2015) and recent meta-analyses (Maheshwari *et al.*, 2018; Roque *et al.*, 2018a). A possible explanation for the increased risk of pre-eclampsia relates to endometrial priming with estrogens performed during artificial FET cycles. Notably, Shi *et al.* (2018) found no differences in pre-eclampsia or hypertensive disorders between fresh ET and eFET when eFET was performed in the natural cycle (Shi *et al.*, 2018). Contrasting results were found in the study by Chen *et al.* (2016), wherein most FET cycles were performed after estradiol valerate priming. In this study, the authors also reported that the mean birthweight was higher among infants born from eFET cycles than from fresh ET cycles (Chen *et al.*, 2016), corroborating previous epidemiological studies

(Pinborg *et al.*, 2013). Interestingly, Shi *et al.* (2018) performed most of the FET cycles in the natural cycle and did not find any significant differences in the mean birthweight in singleton pregnancies. No significant difference was noted in the mean birthweight between eFET and fresh cycle groups in the present analyses. The use of endometrial priming in preparation for FET seems to be a critical issue when analyzing the outcomes between FET and fresh ET. In fact, our sensitivity analysis revealed that the pooled effect size of the mean birthweight was influenced by the removal of the Shi *et al.* (2018) study, which was responsible for asymmetry in the funnel plot concerning this outcome measure (Supplementary Data).

Regarding the rates of ectopic pregnancy, preterm birth, and congenital anomalies, our study revealed no difference between fresh ET and eFET. In this regard, our results differ from those of previous meta-analyses (Maheshwari *et al.*, 2012, 2018), which reported a significantly higher risk of preterm birth, low birthweight and smaller gestational age in fresh ET compared to eFET, as well as a higher risk of greater gestational age and a higher birthweight in FET compared to fresh ET. Although an extensive literature review and adjusted analysis was performed by the authors (Maheshwari *et al.*, 2018), an apparent bias cannot be ruled out since most of the studies included were observational. Moreover, the design of the studies made it difficult to perform group comparison in terms of the cryopreservation method applied, the embryo development, the endometrial priming for FET and the route of progesterone administration.

Strengths and limitations

This systematic review and meta-analysis was performed according to the PRISMA statement, thereby securing a high methodological quality. The total number of patients was more than 5000, which alongside predefined sub-analyses enabled the appraisal of statistical heterogeneity. However, we cannot exclude that the pooled effect estimates in the subgroup analyses were confounded by the nature of subgroups (e.g. ovarian response/PCOS) and different progesterone regimens. These factors could co-exist or be mutually exclusive as the studies included in some of the subgroup analyses were very similar to each other. In addition, bias may have been introduced as data not published as full-text articles and in languages other than English were excluded from the meta-analysis. Importantly, the present study obtained previously unpublished cumulative live birth data. In addition, we rated the strength of evidence with reference to GRADE.

Future research

Presently, the number of available studies on the eFET strategy concerning reproductive, obstetric, and perinatal outcomes is limited. Future studies and meta-analyses assessing the eFET strategy should further explore its causal relationship with ovarian response, hormonal levels during COS, type of freezing and embryo developmental stage in pre-specified subgroups, including patients of advanced reproductive age and endometriosis. Moreover, studies should report follow-up data on relatively rare neonatal and childhood outcomes to be aggregated in future meta-analyses, aiming at providing more reliable and useful answers on the effects of the FET (Pogue and Yusuf, 1998). Along the same lines, trial sequential analysis might provide more precise estimates, thus enhancing the generalizability (external validity) of the results and establishing when firm evidence is reached in cumulative meta-analysis (Wetterslev *et al.*, 2008, 2017). Furthermore, the effects observed consistently in trials conducted in a range of centers involving many embryologists, obstetricians and gynecologists should infer greater confidence in implementing the optimal intervention strategy based on best quality evidence.

The cost-effectiveness of the eFET strategy also needs to be clarified (Papaleo et al., 2017; Roque et al., 2015b). This approach is believed to help improve the precision of the estimated effect sizes, allowing for better clinical decision-making. Although some centers used the eFET strategy for all IVF/ICSI patients in the past decade (Zhu *et al.*, 2018), with reported LBRs of 51% in more than 20 000 patients, it is important to consider that these findings lack a control group for comparison. Thus, Zhu *et al.* (2018) reported that their study population consisted of a total of 68% patients with tubal factor infertility, indicating a selection bias that questions the generalizability of the findings (Roque *et al.*, 2018b). The eFET strategy seems to be an example of a new treatment modality that may have been pretermly introduced based on the results of an early meta-analysis (Roque *et al.*, 2013). Although the eFET indication for hyper-responders seems to be a closed chapter, only one RCT compared GnRH agonist trigger in fresh ET cycles to eFET, reporting no increase in OHSS and no difference in reproductive outcomes (Aflatoonian *et al.*, 2018). Hence, even in the hyper-responder subgroup, more RCTs are warranted and, especially, the association between eFET and pre-eclampsia warrants further investigation and a conservative attitude as regards the use of eFET.

Conclusions

There are currently no clinical data supporting the indiscriminate use of eFET for all patients submitted to IVF/ICSI. Based on the available RCTs, it seems appropriate to implement this strategy in patients at risk of OHSS, in hyper-responders, and in those undergoing PGT-A at the blastocyst stage. In contrast, the use of eFET for other clinical scenarios is unlikely to offer any improvement in neither clinical, obstetric nor perinatal outcomes. In contrast, eFET may increase the cost of treatment and workload, requiring additional embryo manipulation and, ultimately, an increase in the time to live birth. Taken together, the present data suggest that the eFET policy should be individualized in line with modern patient handling approaches.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

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Authors' roles

M.R. and T.H. worked on study concept and design, acquisition of data, analysis and interpretation of data and drafting the article. P.H.

and S.C.E. worked on study concept, interpretation of data and critical revision of the article and final draft. S.G. participated in interpretation of data, critical revision of the article and the final draft.

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