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META-ANALYSIS ***Infertility***

Higher probability of live-birth in high, but not normal, responders after first frozen-embryo transfer in a freeze-only cycle strategy compared to fresh-embryo transfer: a meta-analysis

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STUDY QUESTION: Does the outcome of the comparison of live birth rates between the first frozen embryo transfer (ET) (in a freeze-only cycles strategy, i.e. frozen ET group) and a fresh embryo transfer (fresh ET group) differ considering the type of ovarian response?

SUMMARY ANSWER: A significantly higher probability of live birth is present in high, but not normal, responders, after the first frozen ET in a freeze-only cycle strategy as compared to a fresh ET.

WHAT IS KNOWN ALREADY: It has been hypothesised that freezing all good embryos in a fresh *in-vitro* fertilisation (IVF) cycle and deferring embryo transfer in subsequent cycles may provide a more physiological endometrial environment for embryo implantation when compared to a fresh ET. However, currently, three relevant meta-analyses have been published with conflicting results, while none of them has taken into consideration the type of ovarian response. Recently, the publication of additional, large relevant randomised controlled trials (RCTs) in patients with different types of ovarian response makes possible the comparative evaluation of the first frozen ET (in a freeze-only cycle strategy) versus fresh ET, considering the type of ovarian response.

STUDY DESIGN, SIZE, DURATION: A systematic review and meta-analysis was performed aiming to identify RCTs comparing the first frozen ET (in a freeze-only cycle strategy) to a fresh ET. The main outcome was live birth, while secondary outcomes included ongoing pregnancy, clinical pregnancy, moderate/severe ovarian hyperstimulation syndrome (OHSS) and miscarriage.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We identified eight eligible RCTs, including 5265 patients, which evaluated the first frozen ET in a freeze-only cycle strategy versus a fresh ET either in high responders ($n = 4$) or in normal responders ($n = 4$). No relevant RCTs were present in poor responders. Meta-analysis of weighted data using fixed and random effects model was performed. Results are reported as relative risk (RR) with 95% confidence interval (CI).

MAIN RESULTS AND THE ROLE OF CHANCE: Eligible RCTs were published between 2011 and 2018. Four RCTs ($n = 3255$ patients) compared the first frozen ET (in a freeze-only cycle strategy) to a fresh ET in normal responders and four RCTs ($n = 2010$ patients) did the comparison in high responders. In high responders, a significantly higher probability of live birth was observed in the frozen ET group when compared with the fresh ET group (RR: 1.18, 95% CI: 1.06–1.31; fixed effects model; heterogeneity: $I^2 = 0\%$; three studies; $n = 3398$ patients). However the probability of live birth was not significantly different between the frozen ET group and the fresh ET group in normal responders (RR: 1.13, 95% CI: 0.90–1.41; random effects model; heterogeneity: $I^2 = 77\%$; three studies; $n = 1608$ patients). The risk of moderate/severe OHSS was significantly lower in the frozen ET group when compared with the fresh ET group both in high (RR: 0.19, 95% CI:

0.10–0.37; fixed effects model; heterogeneity: not applicable; a single study; $n = 1508$ patients) and normal responders (RR: 0.39, 95% CI: 0.19–0.80; fixed effects model; heterogeneity: $I^2 = 0\%$; two studies; $n = 2939$ patients).

LIMITATIONS, REASONS FOR CAUTION: Considerable heterogeneity was present among the studies, regarding ovarian stimulation protocols and the triggering signal used for inducing final oocyte maturation as well as the cryopreservation methods, while the quality of evidence was poor for the live birth rate in high responders. Moreover, the analysis did not apply a standard for determining 'high' or 'normal' responders since the type of ovarian response followed the characterisation of populations as reported by the authors of the eligible studies.

WIDER IMPLICATIONS OF THE FINDINGS: A freeze-only cycle strategy should be the preferred option in high responders since it enhances the probability of live birth, while reducing the chance of moderate/severe OHSS. In normal responders, the same strategy could be applied, in the interest of patient safety or clinic convenience, without compromising the chances of live birth.

STUDY FUNDING/COMPETING INTEREST(S): No external funding was used and there were no competing interests.

PROSPERO REGISTRATION NUMBER: PROSPERO registration number: CRD42018099389.

Key words: frozen embryo transfer / fresh embryo transfer / freeze-only cycles / normal responders / high responders / live birth / OHSS

Introduction

During ovarian stimulation for IVF, the development of multiple follicles leads to elevated estradiol (E2) (Kosmas *et al.*, 2004) and progesterone (P) levels (Venetis *et al.*, 2013, 2015). This periconceptional endocrine milieu may adversely affect the probability of embryo implantation (Simon *et al.*, 1995; Venetis *et al.*, 2016). However, no convincing evidence exists to suggest that the quality of oocytes or embryos is negatively associated with the intensity of ovarian stimulation (Santos *et al.*, 2010; Venetis *et al.*, 2013).

Suboptimal development of the endometrium in the early luteal phase has been demonstrated in cycles stimulated with gonadotrophins in conjunction with either gonadotrophin releasing hormone (GnRH) agonists or antagonists (Ubaldi *et al.*, 1997; Kolibianakis *et al.*, 2002). In addition, studies at the molecular level have shown diverse endometrial gene expression in stimulated as compared with unstimulated cycles (Haouzi *et al.*, 2009; Van Vaerenbergh *et al.*, 2009). Thus, the decreased probability of implantation associated with abnormal steroid levels is likely to be attributed to decreased endometrial receptivity, rather than decreased embryo quality.

In this respect, milder stimulation protocols or natural cycles have been proposed as an alternative to conventional ovarian stimulation, with the aim to avoid the adverse effects of ovarian stimulation on the endometrium. Widespread acceptance of these methods, however, has been impeded due to doubts regarding their clinical effectiveness (Fauser *et al.*, 2010; Ho and Paulson, 2017).

An alternative strategy aiming to bypass the adverse effects of ovarian stimulation on endometrial receptivity has been evaluated in clinical practice (Griesinger *et al.*, 2007). According to this strategy, which was originally developed in order to eliminate the risk of severe OHSS (Devroey and Adriaensen, 2011), all good quality embryos produced in a fresh cycle are frozen and transferred in subsequent natural or artificially prepared cycles (Griesinger *et al.*, 2011; Roque, 2015). In this way, embryos are replaced in a more receptive endometrium, not exposed to abnormal steroid levels. Apparently, relevant laboratory protocols should provide a clear definition of what a good quality embryo is.

Recently, two meta-analyses (Roque *et al.*, 2013; Zhang *et al.*, 2018b) have compared frozen embryo transfer (ET), in a freeze-only cycle strategy, versus fresh ET, and suggested that there is a higher probability of pregnancy after frozen ET compared with fresh ET. However, in these meta-analyses, the type of ovarian response was not taken into consideration.

In theory, if the decision to freeze all embryos is taken in the presence of an excess number of follicles, and thus of many embryos, then it might be feasible to more easily select an optimal embryo to be transferred in a normal endometrium in a subsequent frozen–thawed cycle. At the same time, a more deteriorated endometrium might be expected in the fresh cycle, when multiple follicles have been developed, due to the presence of higher steroid levels produced by these follicles (Venetis *et al.*, 2007). In such a scenario, superiority of the freeze-only cycles approach, considering the first frozen ET compared to a conventional fresh ET, might be expected. However, such a benefit might not be present when a small numbers of follicles, and thus oocytes and embryos, are available. Despite the presence of a less deteriorated endometrium due to the absence of grossly elevated steroid levels produced by fewer follicles, it might also be more difficult to select an optimal embryo for transfer in a normal endometrium of a subsequent frozen–thawed cycle, due to decreased embryo availability. In such a scenario, the freeze only cycle approach might not be superior in all patients. Thus, it is not clear whether the conclusions drawn so far from the above meta-analyses (Roque *et al.*, 2013; Zhang *et al.*, 2018b) are applicable to all patients or vary according to the type of ovarian response.

In contrast to the meta-analyses by Roque *et al.* (2013) and Zhang *et al.* (2018b), the meta-analysis by Wong *et al.* (2017), including four RCTs, suggested that no difference exists between the two strategies regarding cumulative live birth rate. This is not surprising, since a theoretical superiority of the freeze-only cycles over the fresh transfer strategy, regarding the probability of pregnancy, is likely to be apparent only in the comparison between the first frozen ET and the fresh ET. The probability of pregnancy in subsequent frozen–thawed cycles, in either the freeze-only cycles or the fresh transfer strategy would not be expected to differ since endometrial receptivity would be similar in both strategies. Thus, the use of cumulative live birth rate as primary outcome measure in the comparison between the freeze-only cycles versus the fresh transfer strategy would not be expected to show a superiority of the freeze-only cycles approach.

The research question of the current systematic review and meta-analysis was whether the outcomes of the comparison of live birth rates between the first frozen ET (in a freeze-only cycles strategy, i.e. frozen ET group) and a fresh ET (fresh ET group) differ considering the type of ovarian response.

Materials and Methods

Identification of literature

A computerised literature search in MEDLINE, CENTRAL and randomised controlled trials (RCT) registries covering the period until July 2018 was performed independently by two reviewers (J.K.B and E.M.K), aiming to identify all available studies evaluating the research question of interest (PROSPERO registration number: CRD42018099389).

A search strategy with keywords aiming to identify three different terms: 'Intervention', 'Study type' and 'Setting' was used. Various synonyms describing each term were entered as free-text terms in the electronic databases in an attempt to maximise the sensitivity of the search strategy (Table I). Additionally, the citation lists of all relevant publications and review articles were hand-searched. Meeting proceedings of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine were also hand-searched for the identification of relevant studies. No language limitations were applied. Institutional Board Review was not obtained as previously published data were used.

Selection of studies

Criteria for inclusion/exclusion of studies were established prior to the literature search. Studies had to fulfil the following criteria for eligibility: (a) studies comparing the first frozen ET, in a freeze-only cycle strategy, to fresh ET, (b) women being subjected to IVF/ICSI using gonadotrophins and GnRH analogues for ovarian stimulation, (c) use of a parallel comparative design with random allocation of patients in the compared groups. Studies that included asymmetric interventions (co-interventions) were excluded. Selection of the studies was performed independently by two of the reviewers (J.K.B and E.M.K). Any disagreement was resolved by discussion.

Data extraction

Data extraction was performed independently by two of the reviewers (J.K.B and E.M.K). The following data types were recorded from each of the eligible studies: demographic (year of publication, country, study period, number of patients included), methodological (method of randomisation, allocation concealment) and procedural (whether financial support was declared, type of GnRH analogue and protocol used for LH surge inhibition, dose and protocol of the intervention proposed, type and starting dose of gonadotrophin administered for ovarian stimulation, type and dose of medication used for triggering final oocyte maturation, criteria used for triggering final oocyte maturation, type of fertilisation, day of ET, cryopreservation protocol, type of luteal support, endometrial preparation). The study was categorised as having been performed in normal, high or poor responders based on the definition given by the authors of each eligible RCT. Any disagreement between the two reviewers responsible for data extraction was resolved by discussion. In case of missing data or ambiguities in study design or trial conduct, the study authors were contacted by e-mail to request additional information.

Outcomes

The main outcome of the current meta-analysis was live birth per intention to treat (ITT). Secondary outcomes included ongoing pregnancy (a pregnancy with positive heartbeat beyond 12 weeks of gestation), clinical pregnancy (detection of a gestational sac at 6–8 weeks), moderate/severe OHSS and miscarriage.

Quantitative data synthesis

The dichotomous data results for each of the studies eligible for meta-analysis were expressed as risk ratio (RR) with 95% confidence intervals (CI). These results were combined for meta-analysis using the Mantel/Haenszel model (Mantel and Haenszel, 1959), when using the fixed effects method, and the DerSimonian and Laird model (DerSimonian and Laird, 1986), when using the random effects method. When the outcome of interest was of a continuous nature, the differences were pooled across the studies, which provided information on this outcome, resulting in a weighted mean difference (WMD) with 95% CI. The inverse variance method (Hedges and Olkin, 1985) and the DerSimonian and Laird method (DerSimonian and Laird, 1986) were used when the fixed or random effects method were applied, respectively. Study-to-study variation was assessed by using the Chi^2 statistic (the hypothesis tested was that the studies are all drawn from the same population, i.e. from a population with the same effect size). In addition, the use of the I^2 index was employed in order to indicate the proportion of inconsistency between studies that could not be attributed to chance, with $I^2 \geq 40\%$ (Higgins and Green, 2011) indicating significant heterogeneity. A fixed effects model was used where no statistically significant heterogeneity was present, whereas in the presence of statistically significant heterogeneity, a random effects model was applied. The presence of publication bias was tested by using the Harbord-Egger's test (Harbord *et al.*, 2006). Statistical significance was set at a *P*-level of 0.05. Meta-analysis of weighted data was performed using STATA v14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

The transformation of the pooled RRs (and their 95% CIs) to absolute live birth rate reduction and subsequently to number-needed-to-treat

Table I Search strategy used for the identification of eligible studies (These terms were search as 'Free-text' terms).

Terms						
Intervention				*Study type*		*Setting*
[(embryo transfer) OR ET]	AND	((freeze-all) OR (freeze all) OR freezing OR frozen OR fresh OR cryopreservation OR vitrification OR cryopreserv* OR thaw*)]	AND	[(randomi?ed clinical trial) OR RCT OR (clinical trial) OR random*)]	AND	[(in-vitro fertili?ation) OR (in vitro fertili?ation) OR (IVF) OR (intracytoplasmic sperm injection) OR (intracytoplasmic sperm injection) OR microinjection OR (ICSI)]

*,?: Wildcards have been used where available to increase the sensitivity of the search. The asterisk (*) stands for any one or more characters. The question mark (?) stands for any single character.

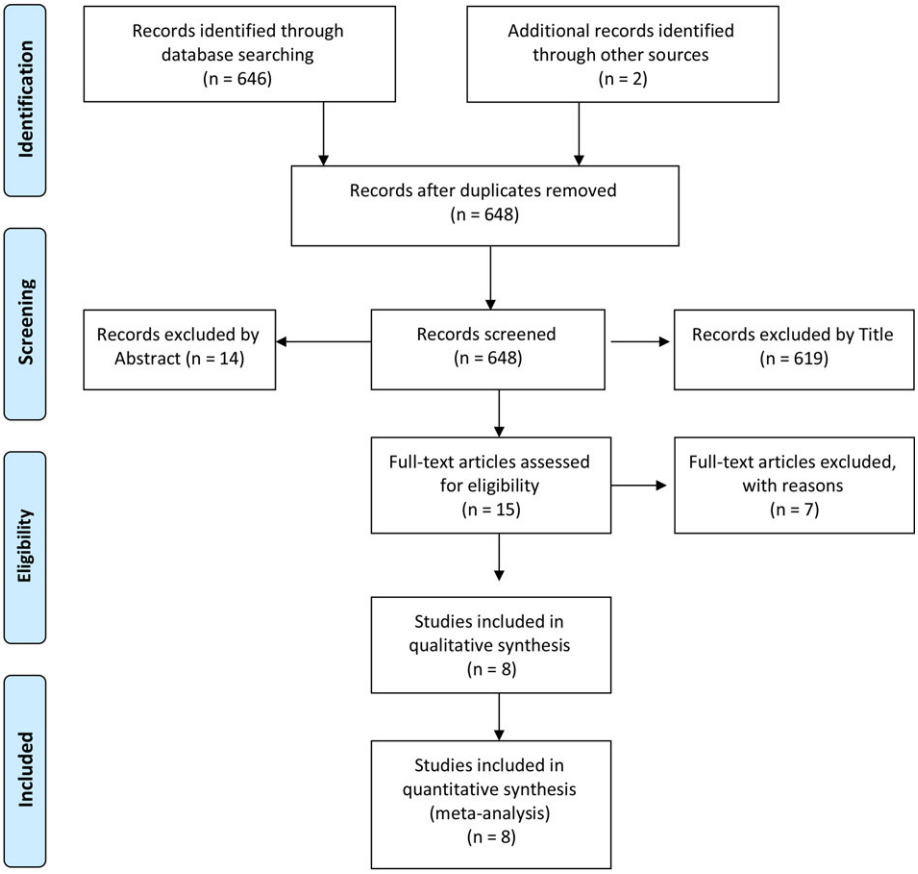

Figure 1 Flow diagram.

(NNT) was considered necessary in order to provide a clinically meaningful measure. This transformation was performed by using a standard methodology proposed by the Cochrane Collaboration (Schunemann *et al.*, 2011). This methodology assumes that the RR remains relatively constant across a range of live birth rates drawn from the studies included in the meta-analysis (Cates, 2002; Furukawa *et al.*, 2002).

Overall quality of the body of evidence

A 'summary of findings' table using GRADEpro software and Cochrane methods (GRADEpro GDT 2014) is provided. This table evaluates the overall quality of the body of evidence for the main review outcomes. Two of the authors (J.K.B and E.M.K) independently evaluated the overall quality of the evidence for the outcomes (live birth, ongoing pregnancy, clinical pregnancy, OHSS and miscarriage) using GRADE criteria (study limitations such as risk of bias, consistency of effect, imprecision, indirectness and publication bias).

Results

Identification of literature

The literature search yielded 648 studies, which resulted in 29 potentially eligible publications after screening of the titles. After reading the abstracts of these studies, 14 were excluded and the full text of the remaining 15 studies was further evaluated. Eventually, eight RCTs (Shapiro *et al.*, 2011a,b; Absalan *et al.*, 2013; Chen *et al.*, 2016; Coates *et al.*, 2017; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018) were included in the present systematic review and meta-analysis. A detailed flow chart of the process is presented in Fig. 1.

From the seven excluded studies, the study by Zhang *et al.* (2018a) analysed the obstetric complications after the first frozen versus fresh ET of a previously published study (Chen *et al.*, 2016) and the study by Chandel *et al.* (2016) was characterised by unclear methodology and poor presentation of the results for which no further information could be retrieved after contacting the authors. In the study by Shaker *et al.* (1996), an asymmetric co-intervention was present, since intravenous albumin was administered in the fresh but not in the frozen ET group. Finally, the studies by Ferraretti *et al.* (1999), Shapiro *et al.* (2016), Yang *et al.* (2015) and Aghahosseini *et al.* (2017) were excluded since they did not answer the research question.

Systematic review

Overall quality of the body of evidence

The summary of findings for the outcome measures evaluated is shown in Supplementary Table SI. The summary and graph of risk of bias for the included studies are presented in Supplementary Fig. S1 and in Supplementary Fig. S2, respectively.

Characteristics of eligible studies

The eight eligible RCTs, including 5265 patients, were published between 2011 and 2018. The number of patients included in the studies ranged from 100 to 2157 patients (median 179). Five studies (Absalan *et al.*, 2013; Chen *et al.*, 2016; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018) were conducted in Asia (4827 patients) and three studies (Shapiro *et al.*, 2011a,b; Coates *et al.*, 2017) were from the USA (438 patients). Four RCTs (Shapiro *et al.*, 2011a; Coates *et al.*, 2017; Shi *et al.*, 2018; Vuong *et al.*, 2018) (n = 3255 patients) evaluated the first frozen ET in a freeze-only cycles protocol versus fresh ET in normal responders, while four RCTs (Shapiro *et al.*, 2011b; Absalan *et al.*, 2013; Chen *et al.*, 2016; Aflatoonian *et al.*, 2018) (n = 2010 patients) did the same evaluation in high responders, and no RCTs were present in poor responders.

Tables II–IV present the characteristics of the studies included in the systematic review. Randomisation method and allocation concealment were reported in seven (Shapiro *et al.*, 2011a,b; Chen *et al.*, 2016; Coates *et al.*, 2017; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018) out of the eight individual studies. In six (Absalan *et al.*, 2013; Chen *et al.*, 2016; Coates *et al.*, 2017; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018) out of the eight studies, data for live birth was available, while in the remaining two studies (Shapiro *et al.*, 2011a,b), data was available for ongoing pregnancy (Table II). Power analysis was peformed in six studies (Shapiro *et al.*, 2011a; Chen *et al.*, 2016; Coates *et al.*, 2017; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018). Financial support was also declared in six (Shapiro *et al.*, 2011a,b; Chen *et al.*, 2016; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018) out of the eight individual studies (Table II). To inhibit premature LH surge, GnRH antagonists were used in seven studies (Shapiro *et al.*, 2011a,b; Chen *et al.*, 2016; Coates *et al.*, 2017; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018), whereas this information was not reported in a single study (Absalan *et al.*, 2013) (Table III). Ovarian stimulation was performed with the use of recombinant follicle stimulating hormone (FSH) in four studies (Chen *et al.*, 2016; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018), with urinary FSH in one study (Absalan *et al.*, 2013), with a combination of recombinant FSH and recombinant LH in two studies (Shapiro *et al.*, 2011a,b), and with a combination of recombinant FSH and human menopausal gonadotrophin (hMG) in a single study (Coates *et al.*, 2017) (Table III). Human chorionic gonadotrophin (hCG) was used to trigger final oocyte maturation in five studies (Absalan *et al.*, 2013; Chen *et al.*, 2016; Coates *et al.*, 2017; Shi *et al.*, 2018; Vuong *et al.*, 2018), leuprolide acetate was used in a single study (Aflatoonian *et al.*, 2018), while a combination of hCG and leuprolide acetate was used in two studies (Shapiro *et al.*, 2011a,b) (Table III). Oocyte retrieval was performed 34–36 h after hCG administration in all studies. Fertilisation methods included IVF in three studies (Shapiro *et al.*, 2011a,b; Absalan *et al.*, 2013), intracytoplasmic sperm injection (ICSI) in a single study (Vuong *et al.*, 2018) and a combination of IVF/ICSI in four studies (Chen *et al.*, 2016; Coates *et al.*, 2017; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018) (Table III). Embryo transfer was performed at the cleavage stage in four studies (Chen *et al.*, 2016; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018) and at the blastocyst stage in three studies (Shapiro *et al.*, 2011a,b; Coates *et al.*, 2017), whereas this information was unclear in a single study (Absalan *et al.*, 2013).

Regarding luteal phase support in the fresh ET group, it involved vaginal (Coates *et al.*, 2017; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018), vaginal and oral (Shi *et al.*, 2018) or intramuscular (Shapiro *et al.*, 2011a,b; Chen *et al.*, 2016) progesterone administration at various dosages, and the addition of estrogens in three studies (Shapiro *et al.*, 2011a,b; Coates *et al.*, 2017), whereas hCG was administered on the day of ET in a single study (Aflatoonian *et al.*, 2018) (Table IV). Cryopreservation of embryos in the frozen ET group was performed by slow freezing method in two studies (Shapiro *et al.*, 2011a,b) and by vitrification in six studies (Absalan *et al.*, 2013; Chen *et al.*, 2016; Coates *et al.*, 2017; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018). Embryos were cryopreserved at the 2PN stage in three studies (Shapiro *et al.*, 2011a,b; Aflatoonian *et al.*, 2018), on Day 3 in two studies (Chen *et al.*, 2016; Vuong *et al.*, 2018), on Day 5 or 6 in a single study (Coates *et al.*, 2017), and at the cleavage or blastocyst stage in a single study (Shi *et al.*, 2018), whereas in one study this information was unclear (Absalan *et al.*, 2013). Endometrial preparation in the frozen ET group involved pretreatment with a GnRH agonist in three studies (Shapiro *et al.*, 2011a,b; Absalan *et al.*, 2013) or a combined oral contraceptive in a single study (Coates *et al.*, 2017), as well as the administration of vaginal (Absalan *et al.*, 2013; Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018), oral (Shi *et al.*, 2018) or intramuscular (Shapiro *et al.*, 2011a,b; Coates *et al.*, 2017) progesterone at various dosages, and oral (Shapiro *et al.*, 2011a,b; Chen *et al.*, 2016; Aflatoonian *et al.*, 2018; Vuong *et al.*, 2018; Shi *et al.*, 2018), transdermal (Shapiro *et al.*, 2011a,b; Absalan *et al.*, 2013) or intramuscular (Coates *et al.*, 2017) estrogens at various dosages (Table IV).

Meta-analysis

Comparability of arms

Number of COCs retrieved. The number of COCs retrieved was not significantly different between the frozen ET group and the fresh ET group in the high responders (WMD: +0.12 COCs, 95% CI: −0.43 to +0.68; fixed effects model; three studies) (Shapiro *et al.*, 2011b; Absalan *et al.*, 2013; Chen *et al.*, 2016) or in the normal responders (WMD: +0.11 COCs, 95% CI: −0.27 to +0.49; fixed effects model; three studies) (Shapiro *et al.*, 2011a; Shi *et al.*, 2018; Vuong *et al.*, 2018).

Number of MII oocytes. No significant difference in the number of MII oocytes was present between the frozen ET group and the fresh ET group in the high responders (WMD: +0.80 MII oocytes, 95% CI: −1.51 to +3.11; fixed effects model; single study) (Shapiro *et al.*, 2011b) or in the normal responders (WMD: −0.15 MII oocytes, 95% CI: −0.75 to +0.45; fixed effects model; two studies) (Shapiro *et al.*, 2011a; Vuong *et al.*, 2018).

Number of fertilised oocytes. No significant difference in the number of fertilised (2PN) oocytes was present between the frozen ET group and the fresh ET group in the high responders (WMD: +2.46 2PN oocytes, 95% CI: −0.05 to +4.96; random effects model; two studies) (Shapiro *et al.*, 2011b; Aflatoonian *et al.*, 2018), whereas a significant difference was observed in the normal responders (WMD: −1.10 2PN

Table II Characteristics of eligible randomised controlled trial.

Study, country of origin, journal or meeting	Study period	Type of study	Number of patients Fresh ET/ Frozen ET	Randomisation method - Time	Allocation concealment	Pregnancy outcomes evaluated	Power analysis	Financial support	Inclusion - Exclusion criteria	Characterisation of population according to the authors	COCs retrieved Fresh ET group Frozen ET group
Normal responders											
Shapiro *et al.* (2011a), USA, Fertil Steril	October 2007–October 2010	RCT, single-centre	**137** 67/70	Random drawing of identical, opaque, unmarked sealed envelopes - After retrieval	Sealed envelopes	Clinical pregnancy Ongoing pregnancy	15% difference in clinical pregnancy rate $a = 0.05$, $b = 0.20$ (group sequential analysis)	Ferring Pharmaceuticals, Parsippany, NJ	First IVF cycle, age <41 years, day 3 FSH <10IU/L, 8–15 AFC - Genetic testing of embryos	Normal responders	**mean** (SD) **14.1** (6.4) **12.9** (4.7)
Coates *et al.* (2017), USA, Fertil Steril	December 2013–August 2015	RCT, single-centre	**179** 88/91	Block randomisation, with stratification according to trial site - At the time of hCG administration	Sealed envelopes	Ongoing pregnancy Live birth	20% difference in absolute increase in pregnancy rate $a = 0.05$, $b = 0.20$	Not reported	Patients undergoing PGS using their own eggs, age 18–42 - use of MESA, TESA, gender selection cycles, decreased ovarian reserve, OHSS	Normal responders	**median** (range) **14** (0–41) **17** (4–44)
Shi *et al.* (2018), China, N Engl J Med	March 2015–March 2017	RCT, Multicentre	**2157** 1080/1077	Block randomisation, with stratification according to trial site - At oocyte retrieval	Randomisation sequence not accessible by investigators enroling patients	Clinical pregnancy Ongoing pregnancy Live birth	10% difference in live birth rate $a = 0.01$, $b = 0.10$	No	First IVF/ICSI cycle, age 20–35, normal menstrual cycle, infertility of >1 year - Unilateral oophorectomy, recurrent spontaneous abortion, PCOS, uterine abnormality, abnormal karyotype, chronic medical condition	Ovulatory women	**mean** (SD) **12.3** (5.2) **12.5** (5.1)
Vuong *et al.* (2018), Vietnam, N Engl J Med	June 2015–April 2016	RCT, single-centre	**782** 391/391	Computer-generated, block randomisation, by an independent study coordinator - On Day 3 after oocyte retrieval	Randomisation by an independent study coordinator	Clinical pregnancy Ongoing pregnancy Live birth	10% difference in ongoing pregnancy rate $a = 0.05$, $b = 0.20$	No	ET on Day 3, at least one grade 1 embryo on Day 3, max 2 embryos for transfer - PCOS, *in vitro* maturation, oocyte donation	Women without PCOS	**mean** (SD) **13.0** (5.0) **13.0** (6.0)

High responders											
Shapiro *et al.* (2011b), USA, Fertil Steril	July 2007–July 2010	RCT, single-centre	**122** 62/60	Random drawing of identical, opaque, unmarked sealed envelopes - After retrieval	Sealed envelopes	Clinical pregnancy Ongoing pregnancy	Not reported	Merck Sharp & Dohme Corporation	First IVF cycle, day 3 FSH <10IU/L, >15 AFC - Genetic testing of embryos	High responders	**mean** (SD) **19.3** (8.6), **20.9** (8.2)
Absalan *et al.* (2013), Iran, J Reprod Infertil	Not reported	RCT, single-centre	**100** 50/50	Not reported	Not reported	Clinical pregnancy Live birth	Not reported	Not reported	E2 ≥3000 pg/ml on the day of hCG and ≥15 follicles of 12–15 mm and ≥16 mm - not reported	High risk for developing OHSS	**mean** (SD) **22.14** (4.3), **21.02** (4.9)
Chen *et al.* (2016), China, N Engl J Med	June 2013–July 2015	RCT, multicentre (14 centres throughout China)	**1508** 762/746	Online central randomisation system - On the day of oocyte retrieval, if >3 and <30 oocytes were retrieved and the patient was at low risk for OHSS (as determined by local investigators)	Not reported	Clinical pregnancy Ongoing pregnancy Live birth	10% difference in live birth rate $a = 0.01$, $b = 0.20$	National Basic Research Programof China, National Natural Science Foundation of China and Thousand Talents Program	PCOS (Rotterdam criteria), first IVF cycle - Unilateral oophorectomy, recurrent spontaneous abortion, congenital or acquired uterine malformations, abnormal karyotyping, chronic medical conditions	Women with PCOS	**mean** (SD) **14.2** (5.8), **14.4** (6.0)
Aflatoonian *et al.* (2018), Iran, Int J Reprod BioMed	January 2014–January 2017	RCT, multicentre (3 centres in Iran)	**280** 140/140	Computer generated random numbers in wrapped, unlabelled envelopes - the day of triggering final oocyte maturation	Sealed envelopes	Clinical pregnancy Ongoing pregnancy Live birth	15% difference in clinical pregnancy rate $a = 0.05$, $b = 0.20$	Yazd Reproductive SciencesInstitute	Age 20–40, 14–25 follicles ≥12 mm on the day of trigger, BMI > 18 and <35 kg/m^2 - <14 and >25 follicles ≥12 mm on the day of trigger, history of OHSS, endocrine disorders, age >40	High responders	**median** (IQR) **12** (10), **19** (11)

RCT, randomised clinical trial; IVF, *in vitro* fertilisation; ICSI intracytoplasmic sperm injection; E2, estradiol; hCG, human chorionic gonadotrophin; FSH, follicle stimulating hormone; ET, embryo transfer; GnRH: gonadotrophin releasing hormone; AFC, antral follicle count; COCs, cumulus oocyte complexes; PCOS, Polycystic ovary syndrome; OHSS, ovarian hyperstimulation syndrome; US, ultrasound scan.

Table III Characteristics of eligible randomised controlled trials.

Study, country of origin, journal or meeting	GnRH-analogue used dose	GnRH analogue protocol	Gonadotrophin type dose	Signal for triggering final oocyte maturation dose	Criteria for triggering final oocyte maturation	OPU	Fertilisation
Normal responders							
Shapiro *et al.* (2011a), USA, Fertil Steril	Ganirelix not reported	Antagonist	rFSH + LH not reported	hCG 5–15IU per pound body weight - leuprolide acetate 4 mg	Not reported	34–36 h after triggering	IVF
Coates *et al.* (2017), USA, Fertil Steril	Not reported	Antagonist fixed (Day 6)	FSH + hMG	hCG 10 000 IU	Leading follicle of ≥18 mm	36 h after triggering	IVF/ICSI
Shi *et al.* (2018), China, N Engl J Med	Ganirelix 0.25 mg/day	Antagonist flexible	rFSH 75–225 IU	hCG not reported	Not reported	34–36 h after triggering	IVF/ICSI
Vuong *et al.* (2018), Vietnam, N Engl J Med	Ganirelix, Cetrorelix not reported	Antagonist fixed (Day 5)	rFSH 150–300 IU	hCG 250 µg	At least 2 follicles of 17 mm	36 h after triggering	ICSI
High responders							
Shapiro *et al.* (2011b), USA, Fertil Steril	Ganirelix not reported	Antagonist	rFSH + LH not reported	hCG 5–15 IU per pound body weight - Leuprolide acetate 4 mg	Not reported	34–36 h after triggering	IVF
Absalan *et al.* (2013), Iran, J Reprod Infertil	Not reported	Not reported	uFSH not reported	hCG 10 000 IU	Not reported	34–36 h after triggering	IVF
Chen *et al.* (2016), China, N Engl J Med	Cetrorelix 0.25 mg/day	Antagonist flexible (as soon as the dominant follicle ≥12 mm)	rFSH 112.5 IU if <60 kg or 150 IU if >60 kg	hCG 4000–8000 IU	At least 2 follicles of ≥18 mm	34–36 h after triggering	IVF/ICSI
Aflatoonian *et al.* (2018), Iran, Int J Reprod BioMed	Cetrorelix 0.25 mg/day	Antagonist flexible (as soon as follicles reached size of ≥14 mm)	rFSH 150–225 IU	Triptorelin acetate 0.2 mg	At least 2 follicles of ≥17 mm	36 h after triggering	IVF/ICSI

GnRH gonadotrophin releasing hormone; hCG, human chorionic gonadotrophin; OPU, oocyte pick up; ET, embryo transfer; rFSH, recombinant follicle stimulating hormone; u-hCG, urinary human chorionic gonadotrophin; h, hours; IVF, *in vitro* fertilisation; ICSI, intracytoplasmic sperm injection; b.i.d, twice daily; r-hFSH, recombinant human follicle stimulating hormone; r-hCG, recombinant human chorionic gonadotrophin; rLH, recombinant luteinizing hormone; E2, estradiol; SC, subcutaneous; P, progesterone; I.M, intramuscular.

oocytes, 95% CI: −1.63 to −0.57; fixed effects model; two studies) (Shapiro *et al.*, 2011a; Vuong *et al.*, 2018).

Number of embryos transferred. The number of embryos transferred was not significantly different between the frozen ET group and the fresh ET group in the high responders (WMD: +0.12 embryos, 95% CI: −0.04 to +0.28; random effects model; four studies) (Shapiro *et al.*, 2011b; Absalan *et al.*, 2013; Chen *et al.*, 2016; Aflatoonian *et al.*, 2018) or in the normal responders (WMD: +0.001 embryos, 95% CI: −0.01 to +0.01; fixed effects model; four studies) (Shapiro *et al.*, 2011a; Coates *et al.*, 2017; Shi *et al.*, 2018; Vuong *et al.*, 2018).

Primary outcome

Live birth. In the high responders, a significantly higher probability of live birth was observed in the frozen ET group when compared with the fresh ET group (RR: 1.18, 95% CI: 1.06–1.31; fixed effects model; heterogeneity: $I^2 = 0\%$; three studies; $n = 3398$ patients; low quality of evidence) (Absalan *et al.*, 2013; Chen *et al.*, 2016; Aflatoonian *et al.*, 2018) (Supplementary Table SI). The probability of live birth was not significantly different between the frozen ET group and the fresh ET group in normal responders (RR: 1.13, 95% CI: 0.90–1.41; random effects model; heterogeneity: $I^2 = 77\%$; three studies; $n = 1608$ patients) (Coates *et al.*, 2017; Shi *et al.*, 2018; Vuong *et al.*, 2018) (Fig. 2). The pooled RRs for the above comparisons, translated in absolute live birth rate reduction and the corresponding NNT (with their 95% CIs), across a range of the reported live birth rates in the eligible studies, are presented in Fig. 3A and B. No significant publication bias was present using the Harbord- Egger's test for the primary outcome.

Sensitivity analyses. A sensitivity analysis was performed by excluding the study by Absalan *et al.* (2013), performed in high responders, due to doubts about the randomisation procedure and the study by

Table IV Type of intervention proposed in the eligible randomised controlled trials.

	Fresh		Freeze-all		
Study, country of origin, journal or meeting	**Fresh ET policy Number of embryos-Stage of development**	**Fresh ET group: Luteal phase support Estrogen-Progesterone**	**Frozen ET group: Cryopreservation protocol-Embryo stage at freezing**	**Frozen ET group: Endometrial preparation Pretreatment-Estrogen-Progesterone**	**Frozen ET policy Number of embryos-Stage of development**
Normal responders					
Shapiro *et al.* (2011a), USA, Fertil Steril	Not reported - Blastocyst	Oral (6 mg/day) and patches of estrogen - I.M. Progesterone (100 mg/day)	Slow freezing - 2pn oocytes	Leuprolide acetate - Oral estrogen (6.0 mg daily) and estrogen patches starting 10–14 days before thaw - I.M. Progesterone (100 mg daily), starting the day before thaw	1 or 2 blastocysts - Blastocyst
Coates *et al.* (2017), USA, Fertil Steril	≤2 embryos - Day 6	Oral estrogen (2 mg b.i.d) - Vaginal progesterone	Vitrification - Day 5 or Day 6	A combined OC (30 mg ethinyl E2/0.15 desogestrel), starting from the third day of the menstrual cycle, for 15–21 days - I.M. Estradiol valerate (4 mg/day) - I.M. Progesterone (50–100 mg/d)	≤2 embryos - Day 6
Shi *et al.* (2018), China, N Engl J Med	≤ 2 embryos - Cleavage	No estrogen - Vaginal progesterone (90 mg/day) and oral dydrogesterone (10 mg b.i.d)	Vitrification - Cleavage or blastocyst	No - Natural cycle - Oral dydrogesterone (10 mg b.i.d) / No - Oral Estradiol valerate (4–8 mg/day) - Vaginal progesterone (90 mg/day) and oral dydrogesterone (10 mg b.i.d)	≤ 2 embryos - Cleavage
Vuong *et al.* (2018), Vietnam, N Engl J Med	1 or 2 embryos - Cleavage	No estrogen - Vaginal progesterone (800 mg/day)	Vitrification - Day 3	No - Oral estrogen valerate (8 mg/day) - Vaginal progesterone (800 mg/day)	≤2 embryos - Cleavage
High responders					
Shapiro *et al.* (2011b), USA, Fertil Steril	Not reported - Blastocyst	Oral (6 mg/day) and patches of estrogen - I.M. Progesterone (100 mg/day)	Slow freezing - 2pn oocytes	Leuprolide acetate - Oral estrogen (6.0 mg daily) and estrogen patches starting 10–14 days before thaw - I.M. Progesterone (100 mg/day), starting the day before thaw	1 or 2 blastocysts - Blastocyst
	Unclear -	Not reported	Vitrification -	GnRH agonist -	Unclear -

Continued

Table IV *Continued*

	Fresh		Freeze-all		
Study, country of origin, journal or meeting	**Fresh ET policy Number of embryos-Stage of development**	**Fresh ET group: Luteal phase support Estrogen-Progesterone**	**Frozen ET group: Cryopreservation protocol-Embryo stage at freezing**	**Frozen ET group: Endometrial preparation Pretreatment-Estrogen-Progesterone**	**Frozen ET policy Number of embryos-Stage of development**
Absalan *et al.* (2013), Iran, J Reprod Infertil	Unclear		Unclear	Estradiol patches (75 mg × 2/2 days) - Vaginal progesterone (200 mg t.i.d)	Unclear
Chen *et al.* (2016), China, N Engl J Med	2 embryos - Day 3	No estrogen - I.M. Progesterone (80 mg/day)	Vitrification - Day 3	No - Oral estrogen valerate (dose not reported) - I.M. Progesterone (80 mg/day)	2 embryos - Day 3
Aflatoonian *et al.* (2018), Iran, Int J Reprod BioMed	2 embryos - Cleavage	Vaginal progesterone (800 mg/day) - hCG 1500 IU on the day of ET	Vitrification - Day 2	No analogue - Oral estradiol valerate (6 mg/day) - Vaginal progesterone (800 mg/day)	Unclear - Day 2

ET, embryo transfer; SC, subcutaneous; I.M, intramuscular.

Aflatoonian *et al.* (2018). In the later study (Aflatoonian *et al.*, 2018), a systematic protocol violation was present (patients with >25 oocytes although randomised in the fresh group had all their embryos frozen due to the risk of OHSS). The exclusion of these two studies did not materially change the direction or the magnitude of the effect observed. In the one remaining paper, a significantly higher probability of live birth was observed in the frozen ET group when compared with the fresh ET group (RR: 1.17, 95% CI: 1.05–1.31; fixed effects model; heterogeneity: not applicable; one study; $n = 1508$ patients).

An additional sensitivity analysis was performed by excluding the study by Coates *et al.* (2017) performed in normal responders, in which patients underwent laser assisted hatching and pre-implantation genetic screening (PGS) before being randomised into the fresh and frozen ET groups. The probability of live birth was then not significantly different between the frozen ET group and the fresh ET group in normal responders (RR: 0.99, 95% CI: 0.92–1.07; fixed effects model; heterogeneity: $I^2 = 0\%$; two studies; $n = 2939$ patients).

Secondary outcomes

Secondary outcomes are presented in Supplementary Table SI.

Ongoing pregnancy. No significant differences in the probability of ongoing pregnancy were observed between the frozen ET group and the fresh ET group in high responders (RR: 1.07, 95% CI: 0.98–1.18; fixed effects model; heterogeneity: $I^2 = 0\%$; three studies; $n = 1910$ patients) (Shapiro *et al.*, 2011b; Chen *et al.*, 2016; Aflatoonian *et al.*, 2018) or in normal responders (RR: 1.15, 95% CI: 0.93–1.43; random effects model; heterogeneity: $I^2 = 77.2\%$; four studies; $n = 3255$ patients) (Shapiro *et al.*, 2011a; Coates *et al.*, 2017; Shi *et al.*, 2018; Vuong *et al.*, 2018).

Clinical pregnancy. No significant differences in the probability of clinical pregnancy were observed between the frozen ET group and the fresh ET group in high responders (RR: 1.06, 95% CI: 0.98–1.15; fixed effects model; heterogeneity: $I^2 = 18.5\%$; four studies; $n = 2010$ patients; low quality of evidence; Supplementary Table SI) (Shapiro *et al.*, 2011b; Absalan *et al.*, 2013; Chen *et al.*, 2016; Aflatoonian *et al.*, 2018), or in normal responders (RR: 1.05, 95% CI: 0.90–1.23; random effects model; heterogeneity: $I^2 = 63.5\%$; three studies; $n = 3076$ patients; low quality of evidence; Supplementary Table SI) (Shapiro *et al.*, 2011a; Shi *et al.*, 2018; Vuong *et al.*, 2018).

OHSS. Two studies offered data for the risk of moderate/severe OHSS in high responders (Chen *et al.*, 2016; Aflatoonian *et al.*, 2018). No pooling of data was performed since a systematic protocol violation was present in the study by Aflatoonian *et al.* (2018) (patients with >25 oocytes although randomised in the fresh group had all their embryos frozen due to the risk of OHSS). In the remaining paper, a lower risk of moderate/severe OHSS was observed in the frozen ET group when compared with the fresh ET group in high responders (RR: 0.19, 95% CI: 0.10–0.37; fixed effects model; heterogeneity: not applicable; a single study; $n = 1508$ patients). Similarly to high responders, a significantly lower risk of moderate/severe OHSS was present in the frozen ET group when compared with the fresh ET group in normal responders (RR: 0.39, 95% CI: 0.19–0.80; fixed effects model;

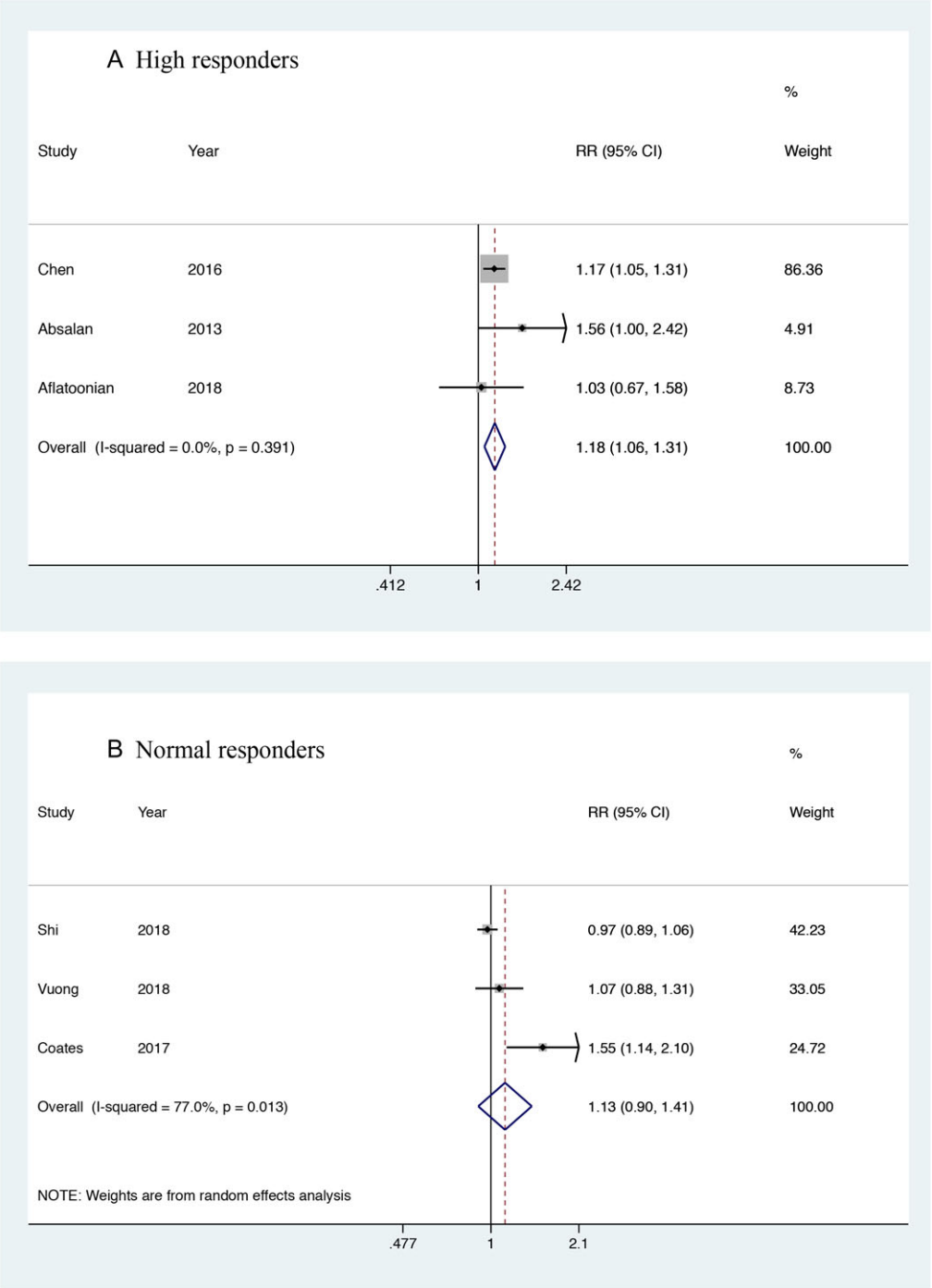

Figure 2 **Live birth in (A) high responders (fixed effects model) and (B) normal responders (random effects model).**

heterogeneity: I^2 = 0%; two studies; *n* = 2939 patients) (Shi *et al.*, 2018; Vuong *et al.*, 2018).

Miscarriage. In high responders, the probability of miscarriage was significantly lower in the frozen ET group when compared with the fresh ET group (RR: 0.69, 95% CI: 0.55–0.86; fixed effects model; heterogeneity: I^2 = 0%; two studies; *n* = 1630 patients) (Shapiro *et al.*, 2011b; Chen *et al.*, 2016). The probability of miscarriage was not significantly different in normal responders (RR: 1.08, 95% CI: 0.82–1.42; fixed effects model; heterogeneity: I^2 = 20.3%; three studies; *n* = 3076 patients) (Shapiro *et al.*, 2011a; Shi *et al.*, 2018; Vuong *et al.*, 2018).

Discussion

The current systematic review and meta-analysis shows that a significantly higher probability of live birth occurs in high, but not normal,

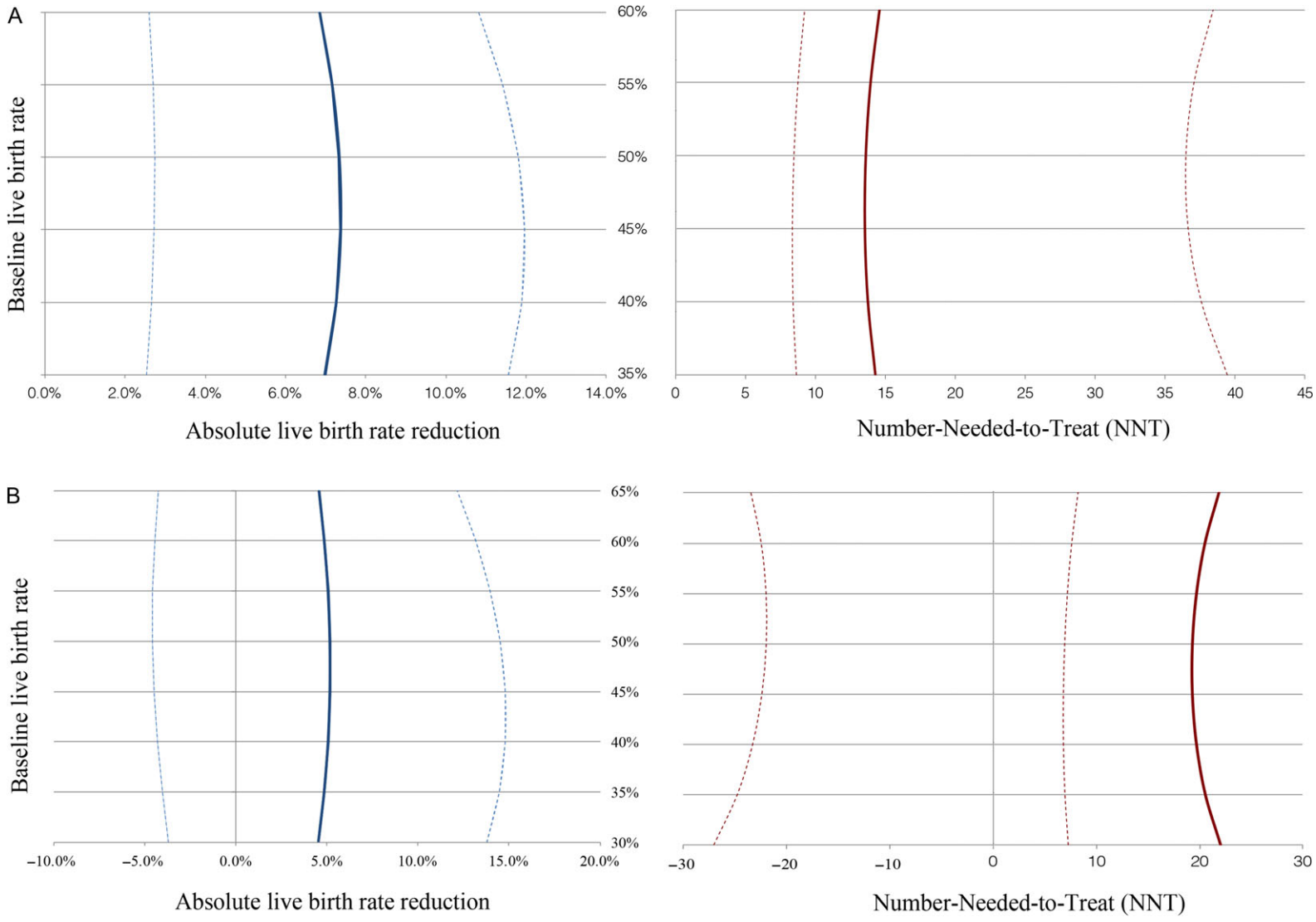

Figure 3 Live birth rate reduction with 95% CIs and NNT with 95% CIs in (**A**) high responders - graphical representation of the transformation of the RR: 1.18, 95% CI: 1.06 to 1.31 to absolute live birth rate reduction with 95% CIs (dotted lines) and to NNT with 95% CIs (dotted lines) and (**B**) normal responders - graphical representation of the transformation of the RR: 1.13, 95% CI: 0.90 to 1.41 to absolute live birth rate with 95% CIs (dotted lines) and to NNT with 95% CIs (dotted lines).

responders after the first frozen ET (in a freeze-only cycle strategy) as compared to a fresh ET. Furthermore, a freeze-only cycle strategy is associated with a lower risk of moderate/severe OHSS in both high and normal responders compared to fresh ET.

The comparison between the first frozen ET, in a freeze-only cycle strategy, and a fresh ET has been the focus of interest recently. The first published meta-analysis (Roque *et al.*, 2013), including three RCTs, suggested an increased ongoing pregnancy rate by performing frozen ET compared with fresh ET. However, after the retraction of one of the included studies (Aflatoonian *et al.*, 2010), this difference was no longer statistically significant (RR: 1.26, 95% CI: 0.99–2.66).

However a subsequent meta-analysis (Zhang *et al.*, 2018b), by analysing seven RCTs, showed an increased probability of live birth after the first frozen ET, in a freeze-only cycles strategy compared with a fresh ET. Yet, that meta-analysis included two RCTs that were excluded from the current meta-analysis, due to the presence of asymmetric co-intervention (Shaker *et al.*, 1996) or improper randomisation (Yang *et al.*, 2015). Thus, the validity of its conclusions is questionable.

The current meta-analysis includes three recent, large RCTs (Aflatoonian *et al.*, 2018; Shi *et al.*, 2018; Vuong *et al.*, 2018), analysing 3219 patients, thus increasing the overall sample size by 131% from the 2220 patients in the meta-analysis by Zhang *et al.* (2018b) to 5265 patients in the present meta-analysis. In this way, besides increasing the confidence in the results obtained, it allows for analysing the comparison of interest in two different patient populations on the basis of their type of ovarian response.

The current meta-analysis suggests that frozen ET in a freeze-only cycles strategy should be the preferred option in high responders, since it enhances the probability of live birth while reducing the chance of OHSS. This increase in the probability of live birth is explained by the lower probability of miscarriage in the high responders in the freeze-only cycles strategy as compared to the fresh ET, suggesting that the biological underpinnings of these findings are likely to be associated with placentation rather than implantation.

It is very important, however, to emphasise that in order for the freeze-only cycles strategy to be the preferred option as compared with a fresh ET in high responders, future studies will need to show that the perinatal outcome of the children born from the two strategies are similar. Currently, such evidence is provided by the study by Zhang *et al.* (2018a), a secondary analysis of a multi-centre, randomised, controlled trial comparing live birth after a freeze-only cycle strategy compared with fresh ET (Chen *et al.*, 2016). In that study, the risks of gestational diabetes mellitus, preterm birth and small for gestational age were not significantly different between the frozen and fresh embryo transfer groups in both singleton and twin births. On the other hand, singleton infants born after frozen embryo transfer were more likely to be large for gestational age (RR: 1.44, 95% CI: 1.01–2.07) than those born after fresh embryo transfer, while the incidence of pre-eclampsia was significantly higher in the frozen than in the fresh embryo transfer group (RR: 4.31, 95% CI: 1.27–14.58) (Zhang *et al.*, 2018a).

Similar findings have been provided by a recent cumulative meta-analysis (Maheshwari *et al.*, 2018) comparing fresh versus frozen ET, not however, in the context of a comparison between a freeze-only cycle and a fresh ET strategy. In addition, in that meta-analysis, decreased risks of small for gestational age, low birth weight and preterm delivery was present in the frozen as compared with the fresh embryo transfer group (Maheshwari *et al.*, 2018).

In normal responders, the freeze-only cycles strategy could be applied, in the interest of patient safety or clinic convenience, without compromising the chances of live birth. It has to be noted that in normal responders, initial pooling of data was performed for three relevant RCTs (n = 1608 patients) with, however, considerable heterogeneity among them (I^2 = 77%). In order to explore the source of this heterogeneity, a sensitivity analysis was performed by excluding the study by Coates *et al.* (2017), in which patients underwent laser assisted hatching and PGS before being randomised into the fresh and frozen ET groups. The exclusion of this study resulted in no heterogeneity (I^2 = 0%) between the remaining two RCTs (n = 2939 patients), allowing the meaningful pooling of their data, which did not materially changed the results observed.

Currently, no relevant RCTs have been performed in low responders, where the risk of OHSS is not present. Such data were recently provided by a retrospective analysis of 82,935 cycles from the Society for Assisted Reproductive Technology (SART) registry. Similarly to the current meta-analysis, the freeze-only cycles strategy was suggested to be beneficial in high responders but not in intermediate or low responders (Acharya *et al.*, 2018).

The present meta-analysis is also characterised by certain limitations that must be taken into consideration when interpreting its results. A considerable heterogeneity was present among studies regarding ovarian stimulation and triggering protocols used for inducing final oocyte maturation as well as the cryopreservation methods used. A subgroup analysis based on the above variables was not possible to be performed due to the limited number of studies available. It should also be noted that the analysis performed did not apply a standard for determining 'high' or 'normal' responders since it was based on the type of ovarian response following the characterisation of populations as reported by the authors of the eligible studies.

Moreover, although in the current meta-analysis, only RCTs were included, a significantly higher number of 2PN oocytes was present in the fresh ET group versus the frozen ET group for normal responders. Despite the fact that this difference was clinically small (WMD: −1.11 2PN oocytes), it might have contributed to the lack of difference between the two groups.

Currently, in the presence of high ovarian response and risk of OHSS, triggering of final oocyte maturation with GnRH agonist, followed by freeze-only cycles protocol, should be considered a standard practice (Tarlatzis *et al.*, 2017), eliminating the probability of OHSS and maintaining high pregnancy rates in subsequent frozen–thawed ET cycles (Vlaisavljevic *et al.*, 2017). However, this approach was not used in the freeze-only cycles arm in the eligible RCTs in the current meta-analysis. This might have further increased the difference in safety, expressed as incidence of moderate/severe OHSS, between the freeze-only cycles and fresh ET policies. Thus, future trials comparing a freeze-only cycles strategy with fresh ET may be more relevant for clinical practice if triggering is performed in the freeze-only cycles arm with a GnRH agonist.

In conclusion, the current systematic review and meta-analysis shows that there is a higher probability of live birth after the first frozen ET, in a freeze-only cycle strategy, compared with the first fresh ET in high responders but not in normal responders.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

J.K.B.: performed the literature search and contributed towards the data extraction, the analyses and interpretation of the data and the drafting of the manuscript. C.A.V.: reviewed the protocol, contributed towards the literature search and the analyses and interpretation of the data, and revised the manuscript for important intellectual content. B.C.T. and G.F.G.: revised the manuscript for important intellectual content. E.M.K.: conceived the idea for the study, constructed the protocol, and contributed towards the data extraction, the analyses and interpretation of the data and the drafting of the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest

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