

# Pregnancy-related complications and perinatal outcomes resulting from transfer of cryopreserved versus fresh embryos in vitro fertilization: a meta-analysis

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**Objective:** To provide an updated comparison of pregnancy-related complications and adverse perinatal outcomes of pregnancies conceived after frozen embryo transfer (FET) versus fresh embryo transfer (fresh ET).

**Design:** Meta-analysis.

**Setting:** University.

**Patient(s):** Pregnancies resulting from FET versus fresh ET.

**Interventions(s):** Pubmed, Embase, Cochrane Library, Google Scholar, and Chinese databases, including the China National Knowledge Infrastructure Database, Wanfang, and Chinese Scientific Journals Full-Text Database were searched by two independent reviewers from January 1980 to September 2017. The results were expressed as risk ratios with 95% confidence intervals.

**Main Outcome Measure(s):** Pregnancy-related complications and perinatal outcomes.

**Result(s):** Our search retrieved 1,397 articles, of which 31 studies were included. Pregnancies resulting from FET were associated with lower relative risks of placenta previa, placental abruption, low birth weight, very low birth weight, very preterm birth, small for gestational age, and perinatal mortality compared with fresh ET. Pregnancies occurring from FET were associated with increased risks of pregnancy-induced hypertension, postpartum hemorrhage, and large for gestational age compared with fresh ET. The risks of gestational diabetes mellitus, preterm premature rupture of the membranes, and preterm birth (PTB) showed no differences between the two groups.

**Conclusion(s):** Our analysis demonstrated that FET results in lower risks of placenta previa, placental abruption, low birth weight, very low birth weight, very preterm birth, small for gestational age, and perinatal mortality than fresh ET, some differences that are attributed to the increased risks of pregnancy-induced hypertension, large for gestational age, and postpartum hemorrhage. Although cryotechnology keeps improving, for comprehensive consideration, individual approaches remain appropriate to balance the options of FET or fresh ET at present. (Fertil Steril® 2017; ■:■-■. ©2017 by American Society for Reproductive Medicine.)

**Key Words:** Embryo transfer, pregnancy complications, perinatal outcome, in vitro fertilization

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In vitro fertilization (IVF), as an infertility treatment, has been spread all over the world and resulted in more than 5 million births

(1). Since the first successful live birth reported through a cryopreserved embryo transfer in 1984 (2), the use of frozen-thawed embryos has been

widely performed (3, 4). The rapid refinement of embryo cryopreservation methods has resulted in better perinatal outcomes of frozen-thawed embryo transfer (FET) and make it a viable alternative to fresh embryo transfer (ET) (5, 6). Considering the growing evidence of improved outcomes with the adoption of FET, routine clinical practice is gradually shifting toward “freeze-all” cycles or preferential FET over fresh ET (1, 7).

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T.S. and X.Y. should be considered similar in author order.

T.S. has nothing to disclose. X.Y. has nothing to disclose. W.C. has nothing to disclose. I.Y.M. has nothing to disclose.

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However, caution should be taken in making such policy, because current evidence that appears to support embryo cryopreservation is based on low-quality randomized controlled trials (RCTs) and individual observational studies (8, 9) lacking the power to demonstrate statistically significant differences in some perinatal outcomes when low background risks of complications exist. Whether FET has better clinical outcomes or not remains controversial and conflicting. A meta-analysis is required to quantify the risks of complications and adverse birth outcomes.

Data available from two meta-analyses suggest that pregnancies arising from the FETs seem to have better clinical outcomes, but both studies have some limitations. The meta-analysis of three RCTs conducted by Roque et al., including 633 women, indicated higher clinical and ongoing pregnancy rates following FETs than after fresh ETs (10). However, the populations studied were generally younger, and were high-responders in two of the studies (7). Limited patient representation made the results remain nongeneralizable beyond women with a poorer prognosis. Furthermore, the review focused only on pregnancy rates and miscarriage rates and not on other perinatal outcomes. A systematic review of 11 observational studies published 5 years ago was the most recent meta-analysis to investigate the association between FET and perinatal outcomes (11). Although the evidence from that meta-analysis appeared to favor FET, there was heterogeneity among the 11 studies at the level of design and population (1). The relatively small number of studies limited the statistical power and the possibility to conduct further subgroup analyses, especially for rare outcomes, such as hypertensive disorders of pregnancy and gestational diabetes. The effect of FET on these outcomes remain uncertain. Considering the limitations of meta-analyses, the association between FET and maternal pregnancy complications needed a further investigation.

It has been 5 years since the latest meta-analysis was published, and many subsequent studies concerning this topic, yielding mixed results, have been published. If the newly published studies could be included in a new meta-analysis, they would increase the statistical power and help to find a meaningful difference for clinical outcomes, especially for rare outcomes. The present study aimed to evaluate the available studies and provide up-to-date and comprehensive evidence to address the question of whether FET reduces the incidence of the pregnancy-related complications and adverse birth outcomes compared with fresh ET.

## MATERIALS AND METHODS

### Data Sources and Search Strategies

An extensive literature search was performed, with an end date of September 2017, on Pubmed, Embase, the Cochrane Library, Google Scholar, and Chinese databases, including those of the China National Knowledge Infrastructure and Wanfang and the Chinese Scientific Journals Full-Text Database, to identify studies that assessed pregnancy-related complications and adverse perinatal outcomes after FET. References from the retrieved studies were searched by hand. The combined search terms were used: (Fresh Embryos),

(Frozen Embryos OR Cryopreserved Embryos OR Cryopreservation of Embryos OR Frozen Thawed Embryos OR Cryopreserved-thawed Embryos), (Embryo Transfer OR Embryo Transfers OR Tubal Embryo Transfer OR Tubal Embryo Stage Transfer), (Vitrification OR Slow Freeze OR Slow Frozen OR Slow Freezing) with (In Vitro Fertilizations/IVF OR Test Tube Babies OR Test Tube Fertilization OR Fertilization in Vitro) OR (ICSI OR Injections, Sperm, Intracytoplasmic OR Injections, Intracytoplasmic Sperm OR Intracytoplasmic Sperm Injection OR Sperm Injection, Intracytoplasmic OR Intracytoplasmic Sperm Injections) with (Pregnancy outcomes OR Pregnancy complications OR Birth outcomes OR Perinatal outcomes OR Obstetric outcomes OR adverse outcomes OR Pregnancy induced hypertension OR Gestational diabetes mellitus OR Placenta previa OR Placenta abruption OR Premature rupture of membranes OR Postpartum hemorrhage OR Perinatal mortality OR small for gestational age OR large for gestational age OR birth weight OR Preterm). The languages were restricted to English and Chinese. Gray literature and conference abstracts were excluded.

We did not contact authors of the primary studies for additional information. We used a Preferred Reporting Items for Systematic Reviews and Meta-analyses statement to report the results of this meta-analysis.

### Selection Criteria

Relevant studies concerning the interesting outcomes after FET or fresh ET were included in the study. Studies were considered to have met eligibility criteria if they: 1) were RCTs or cohort studies; 2) had an exposure of FET; 3) had a control group of fresh ET; and 4) had the outcomes of interest to this study and singleton or twins data could be extracted to a 2×2 table. Poor-quality studies, review articles, government reports, and conference abstracts were excluded.

### Outcome Definitions

The interested pregnancy-related complications involved in this meta-analysis were pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), preterm premature rupture of the membranes (PPROM), placenta previa, placental abruption, and postpartum hemorrhage. The perinatal outcomes included were low birth weight (LBW; <2,500 g), very low birth weight (VLBW; <1,500 g), preterm birth (PTB; <37 weeks of gestation), very preterm birth (VPTB; <32 weeks of gestation), small for gestational age (SGA; birth weight <10th percentile), large for gestational age (LGA; birth weight >90th percentile), and perinatal mortality (stillbirth and early or late neonatal death).

### Data Extraction and Quality Assessment

Two independent reviewers (T.S. and W.C.) conducted the first screening by assessing the titles and abstracts. The second screening was based on full manuscript review. These two authors also assessed and evaluated quality and eligibility and performed the data extraction. When meeting any disagreement or discrepancies, a third reviewer was involved in discussion until agreement was reached. Data extracted from

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