Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis

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CRD summary
The authors concluded that pregnancies through frozen embryo fertilisation treatment may have better obstetric and perinatal outcomes. Low absolute differences and the potential for confounding suggest the authors conclusions may not be reliable.

Authors' objectives
To compare obstetric and perinatal outcomes for frozen thawed and fresh embryos in women undergoing in vitro fertilisation or intracytoplasmic sperm injection.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and DARE were searched up to 2012; no restrictions for languages were applied. References from included studies and relevant journals were also searched (Human Reproduction, Human Reproduction Update, Reproductive BioMedicine Online, Fertility and Sterility).

Study selection
Eligible studies were published observational studies with a control group (no randomised controlled trials were expected) that compared obstetric and perinatal outcomes for fresh and frozen embryos in singleton pregnancies in women undergoing in vitro fertilisation or intracytoplasmic sperm injection. Studies were excluded if it was impossible to differentiate data from singletons and twins, or were based on pregnancies following gamete intrafallopian transfer.

Gestation after being included in the study differed (ranging from all clinical pregnancies up to beyond 28 weeks). Pregnancies from fresh embryos were primarily for the first conception. Embryos were frozen either in cleavage (day two/three) or blastocyst (day five/six) stage using either vitrification or slow freezing. Frozen embryos were transferred using either natural or additional hormone replacement cycles. Most studies were based on registry data, a small proportion directly obtained data by questionnaire or case notes from physicians and parents.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
The Critical Appraisal Skills Programme (CASP) checklist for observational studies was used to assess quality. This includes item such as study recruitment, outcome assessment, confounding, drop-out and generalisability. A CASP score of below 10 was considered low quality.

Two reviewers independently quality assessed included studies.

Data extraction
Outcomes (antepartum haemorrhage, hypertensive disorders of pregnancy, gestational diabetes, delivery before 37 weeks, small for gestational age, low or very low birth weight, induction of labour, caesarean section, congenital anomalies, perinatal mortality, admission to neonatal intensive care) were extracted to calculate risk ratios and risk differences with their 95% confidence intervals.

The authors did not state how many reviewers conducted the data extraction.

Methods of synthesis
Data were pooled primarily using fixed-effect meta-analysis. Authors were contacted when additional data was necessary. Where moderate heterogeneity was identified, sensitivity analyses were conducted using random-effects
meta-analysis. Heterogeneity was assessed using $I^2$ (50% was considered moderate) and $X^2$ statistics.

Subgroup analyses were only conducted on matched cohort studies. Funnel plots were used to assess publication bias.

**Results of the review**

Eleven studies were included in the review: four matched cohort and seven unmatched cohort studies. The total number of participants for all included studies was not reported. All except one study was rated as high quality. There was no evidence of publication bias for any outcome.

**Antepartum haemorrhage**

Two unmatched cohort studies (3,875 frozen versus 7,000 fresh embryo pregnancies) showed a reduced risk associated with the use of frozen thawed embryos (RR 0.67, 95% CI 0.55 to 0.81; $I^2=0\%$), but a relatively small absolute difference (RD 0.02, 95% CI 0.01 to 0.02). Similar relative risk reductions for frozen embryos were found concerning placenta previa and placental abruption.

**Very preterm birth and Preterm delivery**

Four studies of very preterm birth (two case control: 3,050 frozen versus 13,630 fresh) and nine studies of preterm delivery (three matched cohort: 10,017 frozen versus 27,686 fresh) showed a reduced risk associated with frozen embryos for very preterm birth, but this difference wasn't statistically significant.

There was a reduced risk of preterm delivery for frozen embryo treatment but with high heterogeneity (RR 0.84, 95% CI 0.78 to 0.90; $I^2=74\%$). The absolute difference was relatively small (RD 0.02, 95% CI 0.01 to 0.03). This effect remained when conducting a subgroup analysis based on study design, but was not statistically significant when using the random-effects model.

**Small for gestational age**

Two studies (1,933 frozen versus 3,141 fresh) showed a reduced risk of being small for gestational age for frozen embryos (RR 0.45, 95% CI 0.30 to 0.66; $I^2=22\%$). The absolute difference was relatively small (RD 0.02, 95% CI 0.01 to 0.02).

**Low birth weight and Very low birth weight**

Nine studies of low birth weight (three matched cohort: 8,536 frozen versus 25,800 fresh) and four of very low birth weight (3,552 frozen versus 16,469 fresh)

There was a reduced risk of low birth weight for frozen embryos (RR 0.69, 95% CI 0.62 to 0.76; $I^2=28\%$) and a low absolute difference (RD=0.03, 95% CI 0.02 to 0.03).

However, while there was a reduced risk of very low birth weight for frozen embryos this was not statistically significant.

**Caesarean Section**

Five studies (three matched control: 5,435 frozen versus 16,740 fresh) showed an increased risk of caesarean section for frozen embryos (RR 1.10, 95% CI 1.05 to 1.15; $I^2=18\%$) and a low absolute difference (RD=0.03, 95% CI 0.01 to 0.05).

**Perinatal mortality**

Six studies (5,546 frozen versus 17,424 fresh) showed reduced perinatal mortality associated with the use of frozen embryos (RR 0.68, 95% CI 0.48 to 0.96; $I^2=0\%$).

**Congenital anomalies and Admission to intensive care**
Three studies of congenital anomalies (3,152 frozen versus 6,308 fresh) and four of admission to intensive care (one matched cohort: 3,552 frozen versus 16,469 fresh) showed no differences on the risk of admission to intensive care or congenital anomalies.

Authors' conclusions
Pregnancies due to frozen thawed in vitro fertilisation appeared to be associated with better obstetric and perinatal outcomes than fresh embryo transfers.

CRD commentary
The review question and inclusion criteria were clear. The search included a good coverage of electronic databases, but no search terms were reported. No language restrictions were applied. Unpublished studies were not included in the review. There was no evidence of publication bias, but the number of studies in each funnel plot was probably too low to reliably detect this. Appropriate methods to minimise error and bias for study selection and quality assessment were conducted, but this was unclear for data extraction. Meta-analyses included both matched and unmatched cohort studies, but most subgroup analyses did not find large differences between these study designs.

There was consistency in the benefits of frozen embryos across a large number of outcomes, but the absolute differences were relatively small. In addition, there were a range of potential confounding factors that could not be adjusted for which may have impacted on the conclusions.

Low absolute differences and the potential impact of unadjusted confounders suggest the authors conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated when cryopreservation facilities and techniques improve in the future it may be possible to introduce the practice of elective cryopreservation for later use.

Research: The authors stated randomised controlled trials were need to examine the clinical and cost-effectiveness of using frozen compared with fresh embryos. Further research is needed before elective cryopreservation can be recommended as routine practice in preference to fresh embryo transfer.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.