Children born after cryopreservation of embryos or oocytes: a systematic review of outcome data

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CRD summary
This review evaluated outcomes for children conceived through in-vitro fertilisation or intracytoplasmic sperm injection after cryopreservation. Potential for publication and language biases, a lack of information about study quality and a lack of uniform definition of some outcomes made the reliability of the authors’ conclusions unclear.

Authors’ objectives
To evaluate the outcomes for children conceived through in-vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) after cryopreservation, slow freezing and vitrification of early cleavage stage embryos, blastocysts and oocytes.

Searching
MEDLINE, EMBASE and Cochrane Database of Systematic Reviews were searched from 1984 to September 2008 for relevant studies in English; search terms were reported. Reference lists of retrieved articles were searched for additional publications. The reviewers contacted authors where appropriate for further publications.

Study selection
All published controlled studies that reported perinatal or child outcomes for singleton or multiple birth babies after cryopreservation with slow freezing or vitrification were eligible for inclusion. For analysis of early cleavage stage embryos, studies that did not separate the outcomes of singletons from multiple births and studies of cryopreserved embryos after using donor or non-donor oocytes were excluded. Also excluded were studies without a control group (except studies of vitrification). In the analysis of children conceived after thawing of blastocysts or oocytes, all studies (including case reports) were included. Studies of oocytes and blastocysts obtained after in-vitro maturation cycles and studies that reported ongoing pregnancies or deliveries for which neonatal outcome was unknown were excluded.

Included study types were population-based register studies and retrospective hospital-based cohort studies. Methods of cryopreservation varied across studies of early cleavage embryos. Most of the control groups were groups where fresh IVF or ICSI cycles were used; control groups also comprised naturally conceived children. A range of outcome measures that pertained to preterm birth, birth weight, mortality, defects, chromosome abnormalities and childhood growth and development were assessed.

Three reviewers performed study selection. Any disagreements were resolved by discussion and consensus.

Assessment of study quality
The reviewers reported on methodological quality in terms of reporting of methods and the definition of outcome measures.

The authors did not state how the assessment of methodological quality was performed.

Data extraction
Data were collected on outcomes and collated using a predesigned proforma. The results were reported as stated in the included studies. Odds ratios (OR) and 95% confidence intervals (CI) were reported as presented in the original reports.

The reviewers did not state how many reviewers extracted the data.

Methods of synthesis
The results were tabulated and summarised in a narrative review because of heterogeneity and lack of definition of
outcome measures between the included studies.

**Results of the review**

Twenty-one studies of early cleavage stage embryos and 12 studies of blastocysts and oocytes were included in the review. The studies included a total of 11,000 children born after cryopreservation and 3,700 born after fresh IVF/ICSI. Follow-up ranged between 18 months and 25 years for studies of early cleavage embryos.

Mixed results were reported for malformations (17 studies). Three studies reported statistically higher rates of malformation in some groups born after cryopreservation; the other studies found no differences between the groups.

There were inconsistent results across the six trials that compared children born after cryopreservation and children born after fresh conceptions for rates of preterm birth of singletons and twins, rates of low birth weight of singletons and perinatal mortality. In one trial, significantly higher rates of low birth weight were observed for twins conceived from cryopreserved cycles compared to fresh IVF cycles (OR 2.18, 95% CI 1.21 to 3.92).

There were few differences between groups for morbidity, mental development and growth at six months. In one study of 16,280 children three of 1,474 children had a cancer diagnosis when 1.94 was expected. In another study, prevalence of chronic disease was similar across all groups including naturally conceived children. In one study that reported on mental development and neurological assessment, only small differences were found between 91 cryopreserved children and 83 naturally conceived children.

For children born after vitrification of blastocysts (eight studies, n=252), there were no differences in mean gestational age, birth weight, preterm birth rates or congenital birth defects compared with children born after fresh blastocyst transfers.

For children born after slow freezing and vitrification of oocytes (22 studies, n=221; included 11 case reports), 12 studies found that birthweights were within normal ranges. In one study of 200 children mean birth weight was 2.920g for singletons and 2.231g for multiples, low birth weight was 18% among singletons and 80% among multiples and incidence of congenital malformations was 2.5%. There were no control groups.

**Authors' conclusions**

Overall, data on infant outcomes after cryopreservation of embryos was reassuring. There were higher birth weights and lower rates of preterm birth compared to children born after use of freshly implanted embryos conceived using IVF and ICSI. Long-term follow-up of all children conceived using cryopreservation techniques was required.

**CRD commentary**

The review addressed a question that was broad in scope. Criteria for inclusion were clearly specified. Appropriate electronic databases were searched. The extent to which the authors searched for unpublished literature was unclear and they included only published English-language studies, which meant there was a possibility of language and publication biases. Steps were taken to minimise errors and bias during searching and selection of studies; no such measures were reported for quality assessment and data extraction. The reviewers' decision to summarise the results in a narrative appeared justified given differences in definitions of outcomes and cryopreservation protocols used in the included studies. The authors stated limitations in terms of outcome definitions, which were lacking in many studies and included definitions of birth defects. There was insufficient information about the quality of the included studies, so substantial caution was required when interpreting the results of this review. The potential for publication and language biases, the lack of information about study quality and the lack of uniform definition of some outcomes made the reliability of the authors' conclusions unclear.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated a need for properly controlled follow-up studies of neonatal and child outcomes and particularly for children born after cryopreservation of oocytes and blastocysts, for which there was a lack of studies with properly controlled follow-up.
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