Clinical application of oocyte vitrification: a systematic review and meta-analysis of randomized controlled trials
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CRD summary
The review found that vitrification (using specialised freezing techniques) was efficient for preserving oocytes in women undergoing ovum pick-up and subsequent oocyte preservation, but more research was required. The authors' findings require cautious interpretation due to the small amount of evidence available and clinical and methodological differences between the included trials.

Authors' objectives
To evaluate the effects of oocyte vitrification on rates of pregnancy, embryo development, fertilisation and oocyte survival among women undergoing ovum pickup and subsequent cryopreservation.

Searching
MEDLINE, SCOPUS, the Cochrane Central Register of Clinical Trials (CENTRAL) and ClinicalTrials.gov were searched for published and unpublished studies in any language. Some search terms were reported. The meeting abstracts of two professional bodies were searched from 1990.

Study selection
Eligible studies were randomised controlled trials (RCTs) that evaluated the use of human oocytes obtained after vitrification among women undergoing ovum pickup and subsequent cryopreservation for any indication. Eligible comparators involved the use of oocytes obtained after slow freezing or fresh cycles. Studies were required to report one outcome from: ongoing pregnancy per participant (primary outcome); clinical pregnancy per participant; implantation rate per embryo transferred; or oocyte survival, fertilisation rate, or embryo development (rate of top-quality embryos, cleavage rate) per surviving oocyte (secondary outcomes). Outcomes were defined in detail in the review.

Participants in the review were oocyte donors and women undergoing fertility treatment using donor oocytes or their own sibling oocytes (where reported). Participant inclusion criteria varied across trials. In some trials, only women who failed to conceive using fresh cycles underwent embryo transfer. All participants either had at least six metaphase II oocytes after controlled ovarian stimulation or they were oocyte donors. Intracytoplasmic sperm injection was used for fertilisation in all cases. Nearly all cases of embryo transfer involved two or three embryos. All trials used metaphase II oocytes. Trials were set in single centres in China, Brazil, Italy and Spain.

Studies were selected independently by two reviewers, who settled disagreements by consensus.

Assessment of study quality
Study quality was assessed for design, sequence generation, randomisation unit, allocation concealment, blinding, sample size calculation, and potential for conflict of interest. Inclusion in analysis for each outcome was restricted to studies considered by the authors to have lower risk of bias.

Two reviewers assessed and discussed study quality.

Data extraction
Odds ratios (ORs) and 95% confidence intervals (CIs) were extracted or calculated from differences between the two groups in each trial. All primary study authors were contacted for further information.

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

Methods of synthesis
Data were combined using a fixed-effect inverse-variance model to calculate pooled odds ratios and 95% confidence
intervals. Heterogeneity between the trials was assessed using the Q statistic and $I^2$. Where heterogeneity was evident, the effect of using a random-effects model was tested; if this increased the benefit associated with the intervention, it was interpreted as evidence of small study bias.

**Results of the review**

Five RCTs were included in the review. There were 413 women (range 30 to 295) in the four trials that reported sample size. Across the five trials there were 4,282 vitrified oocytes, 3,524 fresh oocytes and 361 slow frozen oocytes. All the trials were of parallel design. The unit of analysis was women in two trials and oocytes in two trials. One trial did not report the unit of randomisation. Four trials reported their method of allocation concealment. Two trials were blinded. Four trials reported sample size calculations. One trial reported a potential conflict of interest in relation to the lead author.

When the vitrification group was compared with the fresh embryo group, there was no significant difference between them in the ongoing pregnancy rate (using intention-to-treat analysis: OR 1.08, 95% CI 0.78 to 1.50; one RCT; 295 women). The trials did not differ significantly in the rate of clinical pregnancy (one RCT), implantation (number of RCTs not stated), fertilisation (three RCTs; $I^2=44\%$), or top-quality embryo and cleavage rates (number of trials not stated). In three RCTs, oocyte survival rates in the vitrification group after warming/thawing ranged from 92.5% to 97%.

When the vitrification group was compared with the slow freeze group, there was no significant difference between them in the clinical pregnancy rate (one RCT). However, when the pregnancy rate was analysed per oocyte, there was a significantly higher rate in the vitrification group (OR 3.18, 95% CI 1.06 to 9.52; one RCT; 78 women). There was a significant benefit in the vitrification group for rates of oocyte survival after warming/thawing (OR 2.46, 95% CI 1.82, 3.32; two RCTs, $I^2=95\%$), fertilisation (OR 1.50, 95% CI 1.07 to 2.11; $I^2=0\%$), top-quality embryos on day three (OR 3.32, 95% CI 1.37 to 8.02), and cleavage on day two (OR 2.00, 95% CI 1.33 to 3.00; one RCT) and day three (OR 2.25, 95% CI 1.32 to 3.85; one RCT). The findings for oocyte survival rate were no longer statistically significant when a random-effects model was used; the high heterogeneity persisted and was attributed by the authors to the use of different methods of vitrification in the two studies.

**Authors' conclusions**

Vitrification was efficient for preserving oocytes in women undergoing ovum pick-up and subsequent oocyte preservation, but more research was required.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies without restriction by language or publication status. Full search terms and dates were not reported, but the authors stated that the search strategy was available as supplementary information. It was unclear whether the authors took adequate steps to minimise the risk of reviewer bias and error in the process of data extraction.

Study design and quality were taken into consideration in the interpretation of review findings, although the authors did not state how they decided which trials were of adequate quality to include in specific analyses. The reliability of the authors' method of assessing the risk of small study bias (by testing the effect of a random-effects model) was unclear. Forest plots were not displayed for all findings; it was not always clear how many trials contributed to an analysis or to what extent findings were homogeneous. Most of the included trials were limited by their failure to report pregnancy rates per woman. As the authors noted, the review was limited by the small number of included trials (most of which had small samples), clinical and statistical differences between the trials, and possible selection bias in some trials (affecting the choice of embryos for transfer and/or which women underwent embryo transfer). The authors suggested that the applicability of the review findings might be limited to good responders. One of the review authors was apparently an author of two of the included trials.

The authors' findings require cautious interpretation due to the small amount of evidence available, along with clinical and methodological differences between the included trials.

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

**Practice:** The authors stated that oocytes from vitrification/warming cycles appear to be associated with similar
outcomes to fresh oocytes and that they may have better survival and fertilisation rates than oocytes from slow-freeze/thawing cycles.

Research: The authors stated that further large controlled trials were needed to support the findings of this review. Such studies should evaluate clinical outcomes after embryo transfer.

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