Increased risk of preterm birth in singleton pregnancies resulting from in vitro fertilization-embryo transfer or gamete intrafallopian transfer: a meta-analysis


CRD summary
This review assessed whether singleton pregnancies resulting from in vitro fertilisation-embryo transfer or gamete intrafallopian transfer (IVF-ET/GIFT) are at higher risk for pre-term birth (less than 37 weeks). The authors concluded that the risk of pre-term birth resulting from IVF-ET/GIFT is twice that of naturally conceived pregnancies. The authors' conclusions are appropriate, but may not be highly reliable since relevant studies might have been missed.

Authors' objectives
To assess whether singleton pregnancies resulting from in vitro fertilisation-embryo transfer (IVF-ET) or gamete intrafallopian transfer (GIFT) are at higher risk for pre-term birth (less than 37 weeks).

Searching
MEDLINE was searched from 1965 to 2000 for studies published in English; the search terms were reported. In addition, the references of identified studies were checked and standard textbooks were searched.

Study selection
Study designs of evaluations included in the review
Controlled studies were eligible for inclusion. The control groups in the included studies were age and parity matched, aged matched alone, or from provincial, hospital or national databases.

Specific interventions included in the review
Studies in which the majority of patients (equal to or greater than 85%) had conceived using IVF-ET or GIFT, compared with naturally conceived singletons or a national reference, were eligible for inclusion. The specific interventions assessed were IVF, IVF or GIFT, IVF or intracytoplasmic sperm injection (ICSI), or ICSI alone.

Participants included in the review
Studies that included patients who had a singleton birth conceived using IVF-ET or GIFT, compared with either naturally conceived singletons from a hospital database or a national reference, were eligible for inclusion.

Outcomes assessed in the review
Studies that reported the incidence of prematurity (clearly defined by the author) in comparison with a control were included. Studies that did not report data from single gestations separately from that of multiple gestations were excluded.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion. This was undertaken blinded to the journal of publication and authors.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two independent reviewers extracted the data. Relative risks (RRs), 95% confidence intervals (CIs) and P-values were extracted where reported. Where these values were not reported, RRs were computed from gonadotropin-stimulated
and control incidence rates, while 95% CIs for the study RRs were estimated using the binomial distribution or asymptotic estimates for the variance of the logarithm of the RR.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a meta-analysis using a fixed-effect model. Where significant statistical heterogeneity was observed, the studies were then combined using a random-effects model. The studies were weighted by the inverse of the variance. Publication bias was assessed but the methods used were unclear.

How were differences between studies investigated?
Differences between the studies were assessed using the chi-squared test. A subgroup analysis was conducted according to the type of control group.

**Results of the review**

Twenty-seven controlled studies (total n greater than 2,440,462) were included. In 12 studies the controls were age and parity matched and in 2 studies they were age matched. The controls were from a provincial database in 1 study, a national database in 8 studies, and a hospital database in 4 studies.

The RRs ranged from 0.67 to 8.00. The pooled RR of 2.13 (95% CI: 2.03, 2.24) from the fixed-effect model indicated that singleton pregnancies resulting from IVF-ET/GIFT were at a significantly greater risk of delivering prematurely compared with spontaneously conceived singletons. There was significant heterogeneity between the studies. The random-effects analysis gave a pooled RR of 1.98 (95% CI: 1.77, 2.22).

Six of the included studies reported data on the incidence of extremely pre-term birth (less than 32 weeks). The RRs ranged from 0.4 to 19.0 across the studies. The random-effects model gave a pooled RR of 2.49 (95% CI: 0.86, 7.21) for extremely pre-term birth after IVF-ET/GIFT.

**Cost information**
The authors stated that of, the US$10.2 billion spent in the USA annually for the initial hospital care of newborns, 57% is spent on the 9% of infants who are delivered before 37 weeks. A 1% increase in prematurity would therefore increase the national health care expenditure by more than US$642 million. The authors also stated that, in terms of initial hospital care, a term infant costs about US$1,197 compared with the US$16,305 for a pre-term infant.

**Authors’ conclusions**
The risk of pre-term birth in singleton pregnancies resulting from IVF-ET/GIFT is twice that of naturally conceived pregnancies.

**CRD commentary**
The review question was clearly defined in terms of the interventions, participants, outcomes and study designs. Only one database was searched for potentially relevant studies, which means that some studies might have been missed. In addition, the studies were limited to those published in English and no efforts were made to identify unpublished studies. Efforts were made to minimise reviewer bias and errors in the inclusion and data extraction processes. However, the quality of the primary studies does not appear to have been assessed. This makes it impossible for the reader to judge how robust the evidence reviewed was. The studies were combined in a meta-analysis and further differences between the studies were examined using a subgroup analysis. Overall, the authors’ conclusions are appropriate but, given the fact that other relevant studies might have been missed, they may not be highly reliable.

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

Practice: The authors stated that the current practice of attempting to make infertility treatments safer by limiting the
occurrence of multiple pregnancies may be expected to have only partial success.

Research: The authors did not state any implications for further research.

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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.