Assisted reproductive technologies and the risk of birth defects: a systematic review

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CRD summary
This review of observational studies explored the risk of birth defects in infants exposed to assisted reproductive technologies. The authors concluded that this risk is increased by 30 to 40% when compared with infants born from spontaneous conceptions. The authors’ conclusions reflect the evidence presented, but certain limitations in the review process may limit their reliability.

Authors’ objectives
To examine the risk of birth defects in infants following assisted reproductive technology (ART).

Searching
MEDLINE (1978 to 2003), EMBASE (1988 to 2003) and Current Contents (1993 to 2003) were searched for relevant studies; the search terms were reported. The reference lists of relevant studies and reviews were screened for additional papers. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
All study designs were eligible for inclusion in the review.

Specific interventions included in the review
Studies of in vitro fertilisation (IVF) and/or intracytoplasmic sperm injection (ICSI) compared with spontaneous conceptions were eligible for inclusion. Most of the studies involved standard IVF or a combination of standard IVF and ICSI or gamete intrafallopian tube transfer.

Participants included in the review
Studies of infants exposed to the interventions of interest were eligible for inclusion. The included studies comprised a mixture of population- and clinic-based samples of singletons alone or singleton and multiples combined.

Outcomes assessed in the review
The primary outcomes of interest were the incidence of major and minor birth defects. The nature of these defects was not defined. Most (64%) of the included studies only assessed the presence of defects at birth; other studies assessed defects at up to 48 months.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The validity of the included studies (for inclusion in a meta-analysis) was assessed according to the following criteria: sample size; whether the same method of assessment had been used in exposed and unexposed infants; whether the investigators were blinded to conception status; whether surveillance intensity differed between the comparison groups; and whether data were matched or adjusted for potential confounders. Seven external reviewers were involved in the validity assessment process. Six reviewers assessed between 3 and 5 papers, and one assessed 12 papers. The reviewers were blinded to the identifying information on each study. These reviewers classified some studies as high quality based on reported validity criteria, but details of this process were not explicitly reported. A sample of 11 randomly selected papers was assessed by two reviewers to ascertain inter-reviewer variation. Disagreements at this stage were resolved by a third reviewer.
Data extraction
The same number of reviewers was involved in the data extraction process as for the validity assessment (see How Were Judgements of Validity Made). Odds ratio (OR) estimates and 95% confidence intervals (CIs) were recorded from the data or (where data not available) calculated by the authors. These results were converted to the number-needed-to-harm (NNTH): the number of infants that needed to be conceived by ART for one additional child to be born with a birth defect.

Methods of synthesis
How were the studies combined?
The studies were combined in meta-analyses. The main meta-analysis was based on data from the 7 studies considered to be good quality. A meta-analysis using data from all 25 studies was also conducted. A fixed-effect model, including precision-based weighting, was used to pool the OR estimates. The results of random-effects models were reported where significant heterogeneity existed between the studies. Several a priori decisions were made regarding the inclusion of adjusted OR estimates and ordering of the analysis; there were reported in the paper. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was tested using the chi-squared test and forest plots were examined. Heterogeneity was explored by reanalysing data after excluding obvious outliers and after excluding studies contributing high weights to the meta-analysis. Differences in study design were explored in a subgroup analysis. Potential causes of heterogeneity were also discussed in the text.

Results of the review
Twenty-five observational studies were included in the analysis. A total of 28,638 ART infants were included.

The majority of the 7 studies deemed to be of good quality had large sample sizes, and outcomes were ascertained without knowledge of conception status. All 7 studies included adjusted data or data matched for maternal age or parity. Methodological limitations were present in the remaining 18 studies, details of which were tabulated. Inter-reviewer agreement on the classification of validity of the 11 selected papers was 73%.

The results of the meta-analysis of the 7 good-quality studies showed a pooled OR of 1.40 (95% CI: 1.28, 1.53), representing a significantly increased risk of birth defects in infants exposed to ART. There was no significant heterogeneity amongst these studies (P=0.12). The pooled OR for all studies combined (n=25) showed a similar trend (OR 1.29, 95% CI: 1.21, 1.37). Statistically significant heterogeneity was observed amongst these studies (P<0.10).

In the subgroup analysis, the trend towards a higher risk of birth defect in ART infants was similar, regardless of how the data were grouped. Pooled OR estimates were high and statistically significant when the analysis was restricted to studies that provided separate data on major birth defects; the OR based on 3 good-quality studies was 2.01 (95% CI: 1.49, 2.69), while the OR based on all 15 studies was 1.32 (95% CI: 1.20, 1.45). No statistically significant heterogeneity was observed. For defects in singleton births, the OR was 1.35 (95% CI: 1.20, 1.51) when based on 6 good-quality studies and 1.31 (95% CI: 1.17, 1.46) when based on all 15 studies. Again, no statistically significant heterogeneity was observed. Similar inferences were evident from the random-effects analysis.

Publication bias was detected and attributed to 3 specific outlying studies. Further analysis that excluded these studies (and those with higher weight) did not substantially alter the pooled estimates.

The pooled ORs from the 7 studies selected for meta-analysis showed a NNTH of between 250 and 62, given a baseline population prevalence of between 1 and 4%.

Authors' conclusions
There is an increased risk (30 to 40%) of birth defects in infants born following ART compared with those from spontaneous conceptions.
CRD commentary
This review was based upon a clear research question and explicit criteria were given for the interventions of interest. However, inclusion criteria for the participants, outcomes and study design were broad and little subsequent detail was given on their characteristics. The search was comprehensive and language bias was addressed. The validity criteria appeared appropriate for the type of study designs included. Bias could not be ruled out in the review process since there was no detail on how the included studies were selected. The data extraction and validity assessment also appeared to have been carried out by a single reviewer for each study, being checked only in the context of a random sample to ascertain inter-reviewer variation. The method of data synthesis seemed appropriate and was thoughtfully executed. Heterogeneity and publication bias were assessed and their implications on the results were discussed. The authors’ conclusions are an accurate reflection of the evidence presented. However, given some methodological weaknesses in the review process, the reliability of these conclusions is unclear.

Implications of the review for practice and research
Practice: The authors stated that practitioners should assess all sources of available data on birth defect risk and should make this information available to prospective ART treatment patients.

Research: The authors stated that larger, population-based studies are needed to explore the aetiology of this potential increase in defects following ART.

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