
Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: a meta-analysis

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CRD summary

The review concluded that children conceived by assisted reproduction technologies were at increased risk of birth defects compared to children conceived spontaneously. There was no risk difference between children conceived by in vitro fertilisation or intracytoplasmic sperm injection. The authors' conclusions reflect the evidence presented, but substantial unexplained heterogeneity limits generalisability of the findings. More long-term research is required.

Authors' objectives

To assess the effect of in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) on birth defects compared with spontaneous conception and compared with each other.

Searching

MEDLINE and EMBASE were searched up to September 2011 for relevant studies published in English or Chinese; limited search terms were reported. Reference lists of retrieved papers were searched.

Study selection

Eligible studies assessed the incidence of birth defects as a result of IVF and/or ICSI compared either with spontaneous conception or comparisons directly between IVF and ICSI. Studies were required to provide relative risks (RRs) with 95% confidence intervals (CIs) or sufficient data to enable their calculation. Studies that were not published as full reports, case reports and studies with inappropriate comparison groups or without control participants were excluded.

About half of the included studies had fewer than 1,000 patients and about half were population based. A few studies matched cases and controls but most adjusted confounding factors such as maternal age, parity, sex, year of birth, social class and smoking. Studies were undertaken in Western countries or China and were published between 1989 and 2011.

Two reviewers independently and blindly selected studies for the review. Disagreements were resolved by other reviewers.

Assessment of study quality

It appeared that study quality was not assessed overall. Two reviewers extracted data on study design and whether studies adjusted for confounders. Discrepancies were resolved by consensus.

Data extraction

Data were extracted on the relative risks of birth defects and 95% confidence intervals. Where adjusted relative risks were not available in the studies the crude relative risk was extracted and used in the overall analyses. Where studies provided data on birth defects separately for IVF and ICSI compared with a spontaneous conception control group, data on IVF and ICSI were pooled and regarded as one comparison group.

Two reviewers independently extracted data. Discrepancies were resolved by consensus.

Methods of synthesis

Pooled summary relative risks and 95% confidence intervals were calculated using a fixed-effect model. Statistical heterogeneity was assessed by the X^2 test and quantified by the I^2 value. A random-effects model was used to calculate the summary effect measure where the p value for the X^2 test was 0.10 or less.

Subgroup analyses investigated use of crude or adjusted relative risks, setting (population or clinic), sample size (>1,000 or <1,000), body system affected (nervous, genitourinary, digestive, circulatory, musculoskeletal systems or eye, ear, face or neck). Sensitivity analysis excluded outlier studies. Publication bias was assessed by inspection of funnel plots and Begg's test.

Results of the review

Fifty-six studies were included in the review. At least 124,468 women underwent IVF or ICSI; the number of control participants was not reported. One study had a case control design; details on the others were not reported.

IVF and/or ICSI versus spontaneous conception: There were 46 studies and 24,468 participants underwent IVF or ICSI. Compared with spontaneous conception, IVF and/or ICSI were associated with a statistically significant increased risk of birth defects (RR 1.37, 95% CI 1.26 to 1.48; $I^2=74.6\%$). In subgroup analyses, the risk of birth defects was significantly larger in clinic-based studies and studies with fewer than 1,000 participants. Sensitivity analysis (exclusion of an outlier study) did not markedly change the estimate and a comparison of analyses using crude or adjusted estimates was not significantly different. Substantial heterogeneity was reported for most subgroup analyses.

IVF versus ICSI: There were 24 studies and 74,644 participants underwent IVF or ICSI. There was no evidence of significant differences in the overall risk of birth defects between IVF and ICSI (RR 1.05, 95% CI 0.91 to 1.20; $I^2=50.6\%$) or in any of the subgroup analyses.

There was no evidence of publication bias from the funnel plots for IVF and/or ICSI compared to spontaneous conception or for IVF compared to ICSI.

Authors' conclusions

Children conceived by IVF and ICSI were at significantly increased risk of birth defects when compared to those conceived by spontaneous conception. There was no risk difference between children conceived by IVF and those conceived by ICSI.

CRD commentary

The review addressed two clear research questions supported by appropriate inclusion criteria. A limited number of sources were searched to identify studies published in English or Chinese so relevant studies may have been missed. The results of formal analysis of publication bias suggested that this was unlikely. Two reviewers selected studies and extracted data which minimised risks of reviewer error and bias. The included studies were not assessed for overall quality which meant that the reliability of the results was unclear. Most of the studies controlled for factors likely to influence the outcome.

Synthesis of the studies and assessment of heterogeneity were appropriate. Substantial heterogeneity was identified for both overall analyses but the authors appropriately undertook subgroup analyses to investigate the influence of other factors on results. The authors noted that any potential causal relationship between assisted reproductive technologies and birth defects could only be assessed adequately by inclusion of studies with infertile comparison groups who conceived spontaneously.

The authors' conclusions reflect the evidence presented but there was substantial unexplained heterogeneity that created uncertainty about the generalisability of the pooled estimates. As highlighted by the authors, large scale research and long-term follow-up of infants is still required.

Implications of the review for practice and research

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

Research: The authors stated that further large scale research should be undertaken with long-term follow-up to assess the prevalence of assisted reproductive technology-associated birth defects. Studies should investigate effects on specific body systems. Studies were needed to compare birth defects in children born to infertile couples conceived with and without assisted reproduction technologies.

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