Perinatal outcomes of singleton pregnancies achieved by in vitro fertilization: a systematic review and meta-analysis

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CRD summary
This well-conducted review concluded that singleton pregnancies conceived through in vitro fertilisation have increased rates of adverse obstetric outcomes compared with spontaneous pregnancies. Overall, the findings of the review appear to be supported by the data presented and are likely to be reliable.

Authors' objectives
To determine the incidence of adverse obstetric events in singleton pregnancies after in vitro fertilisation (IVF).

Searching
MEDLINE (1966 to 28 October 2003) and EMBASE (1980 to 28 October 2003) were searched; the search terms were reported. In addition, the reference lists of retrieved articles were screened. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Case-control and cohort studies were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared IVF or intracytoplasmic sperm injection (ICSI) with fresh or frozen embryos versus spontaneous pregnancies were eligible for inclusion. Studies were excluded if they involved surrogacy, oocyte donation, gamete intrafallopian transfer, zygote intrafallopian transfer or multifetal/selective reduction.

Participants included in the review
Women with singleton pregnancies matched for maternal age were eligible for inclusion. Studies of severe ovarian hyperstimulation syndrome, or where participants were matched for gestational age or birth weight, were excluded from the review. Where reported, women included in the review were mainly selected from hospital departments or private clinics (IVF and ICSI interventions), or from hospital or other registers (spontaneous birth controls). Three studies were from Finland, three from Belgium, two from Israel, and one from each of England, USA, Denmark, Sweden and Hungary.

Outcomes assessed in the review
Eligible studies had to assess perinatal mortality. The main secondary outcomes were the incidence of pre-term birth (delivery before 37 weeks' gestation with subgroups before 32 weeks and 32 to 36 weeks' gestation) and the incidence of low birth weight (less than 1,500 g). Other secondary outcomes of interest included: birth weight; incidence of small for gestational age (SGA; birth weight less than 10% of expected weight); incidence of severe neonatal morbidity (respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, retinopathy or prematurity, transient tachypnoea of the newborn, congenital malformation, low Apgar score at 1, 5 or 10 minutes, or low arterial cord blood pH); incidence of intra-uterine foetal demise (stillbirth); incidence of pre-term premature rupture of membranes (rupture before 37 weeks' gestation in the absence of labour); incidence of antepartum haemorrhage; incidence of placenta previa; incidence of chorioamnionitis (maternal fever greater than 38.0 degrees C, tender abdomen and foetal tachycardia); length of maternal and neonatal postpartum hospitalisation; incidence of Caesarean section; incidence of pre-eclampsia (blood-pressure greater than 140/90 with proteinuria); and incidence of gestational diabetes mellitus.

How were decisions on the relevance of primary studies made?
Two reviewers assessed the relevance of studies; any disagreements were resolved through discussion and consensus, or through the involvement of a third reviewer if necessary.
Assessment of study quality
Two reviewers independently assessed study validity; any disagreements were resolved through discussion and consensus. The studies were assessed using the Cochrane Handbook criteria for observational studies: selection bias, performance bias, attrition bias and detection bias.

Data extraction
Two independent but unmasked reviewers extracted the data using a standardised extraction form. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous data and mean differences for continuous data.

Methods of synthesis
How were the studies combined?
Guidelines for the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) were followed and case-control studies were combined using a random-effects model; pooled ORs or mean differences with 95% CIs were reported. Publication bias was assessed using funnel plots. A descriptive analysis was included for cohort studies.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared and I-squared statistics. Sensitivity analyses were used to investigate the effects of ICSI, freezing embryos, quality and parity.

Results of the review
Fourteen case-control studies (6,728 IVF and 8,454 spontaneous singleton pregnancies) and 4 cohort studies (at least 1,509 IVF and unclear number of spontaneous singleton pregnancies) were included in the review.

Overall, it was difficult to assess performance and attrition bias as relevant information was often missing. Detection bias was reported to have minimal impact and selection bias varied between studies. Overall, the authors reported more concern about poor reporting in cohort studies than in case-control studies. Clinical differences between the case-control studies were considered to be small. No evidence of publication bias was detected.

Cohort studies reported that IVF pregnancies in comparison with spontaneous singleton pregnancies were associated with a statistically significant increased rate of perinatal mortality (OR 2.40, 95% CI: 1.59, 3.63; 6 studies), pre-term birth less than 33 weeks’ gestation (OR 2.99, 95% CI: 1.54, 5.80; 2 studies), pre-term birth 33 to 36 weeks’ gestation (OR 2.30, 95% CI: 1.00, 5.28; 2 studies), pre-term birth less than 37 weeks’ gestation (OR 1.93, 95% CI: 1.36, 2.74; 10 studies), neonatal intensive care unit admission (OR 1.36, 95% CI: 1.20, 1.54; 6 studies), SGA births (OR 1.59, 95% CI: 1.20, 2.11; 9 studies), low birth weight births (OR 1.40, 95% CI: 1.01, 1.95; 8 studies), very low birth weight births (OR 3.78, 95% CI: 2.49, 5.75; 8 studies), congenital malformations (OR 1.41, 95% CI: 1.06, 1.88; 7 studies), Caesarean section (OR 1.81, 95% CI: 1.41, 2.32; 11 studies), electively scheduled Caesarean section (OR 2.21, 95% CI: 1.58, 3.08; 7 studies), spontaneous pre-term birth (OR 1.93, 95% CI: 1.44, 2.60; 3 studies) and antepartum hospitalisation (4.6 (standard deviation, SD=10.2) days in IVF group versus 2.5 (SD=5.4) days in control group; 1 study). No significant differences were reported between IVF and control groups for rates of malpresentation (2 studies), extremely low birth rate (1 study), pre-term premature rupture of the membranes (number of studies not reported), placenta previa (4 studies), antepartum haemorrhage (number of studies not reported), intra-uterine foetal mortality (1 study), pre-eclampsia (7 studies) and gestational diabetes mellitus (2 studies).

Similar results were reported when sensitivity analyses were carried out for study quality and parity, although some effect sizes became non significant analyses comparing frozen and fresh embryos were not possible. The 4 cohort studies also reported increases in adverse outcomes associated with IVF treatment.

Authors’ conclusions
Compared with spontaneous pregnancies matched for maternal age, singleton pregnancies conceived through IVF have increased rates of perinatal mortality, pre-term birth, very low birth weight (less than 1,500 g), low birth weight (less than 2,500 g), SGA births and congenital malformations.

CRD commentary
This review considered a clearly defined research question. Although only two databases were searched for relevant studies, no language restrictions were applied and funnel plots suggested that the risk of publication bias was low. Each stage of the review process was carried out independently by two reviewers, thereby reducing the risk of bias and error. Published guidelines were used to assess the quality of the included studies and to combine the studies in a meta-analysis. Both statistical and clinical differences between the studies were considered in the analysis, and further sensitivity analyses were carried out to investigate any potential sources of heterogeneity. Overall, the findings of the review appear to be supported by the data presented and are likely to be reliable.

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

**Practice:** The authors stated that health care providers should counsel couples considering IVF about the findings of this review. They should also consider more frequent monitoring with regard to 'perinatal mortality and surveillance for possible pre-term birth using transvaginal ultrasound assessment of the cervix and appropriate administration of antenatal corticosteroids for accelerating lung maturity'.

**Research:** The authors stated that future studies should consider whether fresh and frozen-thawed embryos have different outcomes, and whether IVF has a different outcome from ICSI. Studies should assess the long-term effects of IVF and use standardised perinatal outcomes. Validation studies of existing databases are also required.

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