Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies
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CRD summary
This review compared perinatal outcomes for singleton and twin pregnancies after natural versus assisted conception. The authors concluded that singleton pregnancies have significantly worse perinatal outcomes after assisted conception than after natural conception, but that twin pregnancies have about 40% lower mortality. Given that the results were based on potentially biased studies, a more cautious conclusion may be appropriate.

Authors' objectives
To compare perinatal outcomes for singleton and twin pregnancies after natural versus assisted conception

Searching
MEDLINE, EMBASE, LILACS and POPLINE were searched from 1985 to 2002 for publications in any language; the search terms were stated. The reference lists in articles, reviews and dissertations were also checked.

Study selection
Study designs of evaluations included in the review
Controlled studies in which all groups came from the same population were eligible for inclusion. The included studies used matched and non-matched controls. All of the included studies matched for prominent confounders such as age and parity, but studies differed in controls for other known confounders (details of controlled confounders were reported).

Specific interventions included in the review
Studies that compared natural with assisted conception were eligible for inclusion. The types of assisted conception evaluated were in vitro fertilisation, intracytoplasmatic sperm injection, gamete intrafallopian transfer, intra-uterine insemination, ovulation induction and clomiphene.

Participants included in the review
Women with singleton or twin pregnancies were eligible for inclusion. Studies that did not distinguish singleton from multiple pregnancies were excluded.

Outcomes assessed in the review
Studies that reported categorical data for gestational age and weight at birth, Caesarean section, perinatal death, and admission to the neonatal intensive care unit (NICU) were eligible for inclusion. The review used the following international definitions for pre-term (less than 37 weeks), very pre-term (less than 32 weeks), low birth weight (less than 2,500 g), very low birth weight (less than 1,500 g), small for gestational age (birth weight less than the 10th centile for gestation) and perinatal mortality (stillbirths and deaths in first week).

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 authors did not state that they assessed validity.

Data extraction
At least two reviewers independently extracted the data and resolved any disagreements through discussion, if required after contacting the original authors. For each study, data were extracted on the occurrence of each outcome of interest in assisted and natural conceptions and used to calculate a relative risk (RR) with 95% confidence intervals (CIs). For studies that had more than one control group, attempts were made to extract data from the group that was matched for maternal age, infant sex and parity.

Methods of synthesis
How were the studies combined?
The pooled RR and 95% CI were calculated separately for singleton and twin pregnancies using a meta-analysis.

How were differences between studies investigated?
The percentages of event rates among the included studies were reported for assisted and natural conceptions. Differences could be observed in the tables of results for matched and unmatched studies. Data for perinatal mortality in singleton pregnancies were analysed after excluding one study that accounted for 67% of the cases.

Results of the review
Seventeen studies (14 matched and 3 non-matched) assessed singleton pregnancies (n=6,036). Seventeen studies (10 matched and 7 non-matched) assessed twin pregnancies (n=5,485).

Singleton pregnancies.
Studies with matched controls showed that assisted conception was associated with a significant increase in the risk of very pre-term delivery (RR 3.27, 95% CI: 2.03, 5.28), pre-term delivery (RR 2.04, 95% CI: 1.80, 2.32), very low birth weight (RR 3.00, 95% CI: 2.07, 4.36), low birth weight (RR 1.70, 95% CI: 1.50, 1.92), small for gestational age (RR 1.40, 95% CI: 1.15, 1.71), Caesarean section (RR 1.54, 95% CI: 1.44, 1.66), admission to the NICU (RR 1.27, 95% CI: 1.16, 1.40) and perinatal mortality (RR 1.68, 95% CI: 1.11, 2.55), compared with natural conception. The results for perinatal mortality varied widely and were dominated by one large study accounting for 67% of the cases. The removal of this study reduced variation in mortality.

The results were similar for non-matched studies.

Twin pregnancies.
Studies with matched controls showed smaller differences between assisted and natural conceptions for twin compared with singleton pregnancies: the RR was 0.95 (95% CI: 0.78, 1.15) for very pre-term delivery, 1.07 (95% CI: 1.02, 1.13) for pre-term delivery, 0.89 (95% CI: 0.74, 1.07) for very low birth weight, 1.03 (95% CI: 0.99, 1.08) for low birth weight, 1.27 (95% CI: 0.97, 1.65) for small for gestational age, 1.21 (95% CI: 1.11, 1.32) for Caesarean section and 1.05 (95% CI: 1.01, 1.09) for admission to the NICU. Assisted conception was associated with lower perinatal mortality than natural conception (RR 0.58, 95% CI: 0.44, 0.77). The results were dominated by two studies; one accounted for 78% of the cases and the other had high mortality (22%) among controls. Most studies with non-matched controls showed similar results. Overall, the pooled results were dominated by one study which accounted for 54% of singleton pregnancies and 68% of twin cases.

Authors’ conclusions
After assisted conception, singleton pregnancies had significantly worse perinatal outcomes than natural singleton pregnancies, while twin pregnancies had about 40% lower mortality than natural conception.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched and attempts were made to locate unpublished studies, thus reducing the possibility of publication bias. Attempts to minimise language bias were also made. The methods used to select the studies were not described, so it is not known whether any efforts were made to reduce errors and bias. However, methods were used to...
minimise bias in the data extraction process.

Adequate information on the results of the included studies was provided. Details of the study designs were not given, although the authors stated that the matched studies controlled for most potential confounders. This is of particular importance as the reviewers did not perform a quality assessment. The method used to combine the studies was not reported and no formal assessment of heterogeneity was undertaken. Furthermore, differences in the results of the studies were not discussed in depth. This too is of importance as the results were dominated by one study that accounted for more than half of the data, and only perinatal mortality was pooled after excluding this study.

The studies were conducted over a 20-year period (from 1978 to 1999), but the influence of study year on the results was not explored. The authors pointed out that the included studies were conducted at a time when 85% of cycles of in vitro fertilisation involved the transfer of several embryos. Outcomes resulting from the transfer of only one embryo were not considered separately and, therefore, were unknown.

The results were based on observational studies which, as the authors acknowledged, are susceptible to various sources of bias. However, the evidence presented is likely to represent the best quality currently available. Given the concerns highlighted, the results may be susceptible to bias and a more cautious conclusion may have been more appropriate.

Implications of the review for practice and research
Practice: The authors stated that women undergoing assisted conception should be informed of the increased risks of singleton pregnancies.

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

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