Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review

CRD summary
This review investigated the effect of intravenous immunoglobulin (IVIG) for the treatment of recurrent miscarriage. The authors found that IVIG increased the live birth rate of secondary, but not primary, recurrent miscarriage in comparison with placebo. Despite the lack of reporting of some review methodology, the results are likely to be reliable.

Authors' objectives
To evaluate intravenous immunoglobulin (IVIG) for the treatment of spontaneous recurrent miscarriage.

Searching
MEDLINE (1966 to June 2005) and the Cochrane Controlled Trials Register (June 2005) were searched without language restrictions; the search terms were reported. The bibliographies of meta-analyses and trials were manually reviewed to identify relevant reports. Abstracts were excluded from the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of parallel design were eligible for inclusion.

Specific interventions included in the review
Trials comparing any dosage regimen of IVIG with placebo or active control were eligible for inclusion. The included trials involved starting treatment both pre- and post-conception; the various regimens used were described in the review. The control interventions were placebo or aspirin and low molecular weight heparin.

Participants included in the review
Studies of women with primary or secondary spontaneous recurrent miscarriage were eligible for inclusion. Primary recurrent miscarriage was defined as three or more consecutive early miscarriages in women without a successful birth, and secondary recurrent miscarriage as two or more consecutive early miscarriages in women with at least one successful birth. The mean age of the women ranged from 27 to 35 years, and studies included women with between 2 and more than 4 spontaneous miscarriages.

Outcomes assessed in the review
Trials that reported clinically relevant outcomes were eligible for inclusion. The outcomes reported were live birth rate, mean birth weight, gestational age and pregnancy complications.

How were decisions on the relevance of primary studies made?
Two authors independently reviewed the primary studies for relevance. Any disagreements were resolved by consulting a third person.

Assessment of study quality
Validity was assessed using the Jadad scale, based on randomisation, double-blinding and accounting for withdrawals. The authors did not state how many authors performed the validity assessment.

Data extraction
Data on the number of live births and pre-term births, mean birth weight, and gestational age were extracted using standardised abstraction forms. The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**

How were the studies combined?

Live birth rates from the 7 placebo-controlled trials were combined using the DerSimonian and Laird random-effects method to produce a pooled odds ratio (OR) with 95% confidence intervals (CI); the eighth, active comparator study was discussed in the text. The maximum and minimum mean or median (and ranges) were provided for the other outcomes.

How were differences between studies investigated?

Statistical tests for heterogeneity were carried out, although the test used was not reported. Potential reasons for heterogeneity were explored and subgroup analyses were conducted.

**Results of the review**

Eight trials (442 women) were included in the review. Seven trials (400 women) were placebo-controlled, and one (42 women) used aspirin and low molecular weight heparin as the control.

All of the included studies were double-blind and achieved a quality score of 3 or more out of 5, and were therefore considered high quality.

In terms of the live birth rate, there was a non significant benefit of IVIG compared with placebo (OR 1.28, 95% CI: 0.78, 2.10, p=0.33; 7 trials, 400 women), with no significant heterogeneity between the studies (p=0.32). There was no benefit of IVIG compared with placebo in women with primary recurrent miscarriage (5 trials, 183 women), but IVIG was associated with a higher live birth rate than placebo in women with secondary recurrent miscarriage (OR 2.71, 95% CI: 1.09, 6.73, p=0.03; 4 trials, 91 women).

Compared with placebo, IVIG had no effect on the live birth rate when initiated after conception (5 trials, 243 women) but was associated with an increased live birth rate when initiated prior to conception (OR 2.39, 95% CI: 1.08, 5.33, p=0.03; 2 trials, 102 women).

Birthweight (6 trials), gestational age (4 trials) and number of pre-term births (4 trials) did not seem to differ between the IVIG and placebo groups.

There was a greater frequency of minor or moderately severe pregnancy-related complications with IVIG compared to placebo, but this was not statistically significant (OR 3.31, 95% CI: 0.55, 20.01, p=0.19; 7 trials).

**Authors’ conclusions**

IVIG is associated with a higher live birth rate in the treatment of secondary recurrent miscarriage compared with placebo, but there was insufficient evidence for its use in primary recurrent miscarriage.

**CRD commentary**

The authors searched two databases which means some trials could have been missed. This, and the omission of trials published only in abstract form, means that the synthesised results might have been affected by publication bias; this was not assessed in the review. Attempts were made to reduce the potential for language bias. The assessment of relevance was conducted in duplicate, thus reducing the potential for bias, but insufficient description of the data extraction and quality assessment means that it is not possible to exclude the possibility of error or bias during these parts of the review process. A validity assessment was performed and all of the included trials were of a high quality, thereby increasing the reliability of the results. The meta-analytic process was appropriate and adequate. The authors’ conclusions relating to secondary recurrent miscarriage are supported by the evidence presented and are likely to be reliable.
Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that the treatment of primary recurrent miscarriage with IVIG requires further research, and that research relating to the treatment of secondary recurrent miscarriage with IVIG should focus on clarifying the appropriate timing and dosage of treatment.

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