Intravenous immunoglobulin therapy for recurrent spontaneous abortion: a meta-analysis

Daya S, Gunby J, Clark D A

Authors' objectives
To evaluate the effectiveness of intravenous immunoglobulin therapy for recurrent spontaneous abortion.

Searching
MEDLINE (1988 to 1997) was searched using the medical subject headings: habitual abortion, random allocation, randomised controlled trial, and intravenous immunoglobulin. The MEDLINE search was performed on titles, abstracts, and keywords of the listed articles. The Excerpta Medica CD: Fertility database and EMBASE were searched from 1985 to April 1997. The search was performed on titles and abstracts using recurrent abortion and intravenous immunoglobulin as keywords. The bibliographies of relevant publications and review articles were scanned, and abstracts of major scientific meetings from 1983 to 1997 were handsearched. Authors of relevant abstracts and articles were contacted to obtain further details on their studies. Peer consultation was sought for any remaining articles.

Study selection
Study designs of evaluations included in the review
Trials reporting random allocation to either IVIG or placebo were included. Treatment doses varied for different treatments. Treatment usually started in follicular phase pre-pregnancy and length of treatment ranged from up to week 24 to week 32. Trials were included whether treatment was commenced preconceptually or after pregnancy was confirmed.

Specific interventions included in the review
Intravenous Immunoglobulin (IVIG) treatment, including: verum (5% IVIG), Nordimmun (IVIG), and Gamimune N (5% IVIG). Dosages in two studies ranged from 20g every 3 weeks to 35g weekly, depending on stage of pregnancy. In the two remaining studies, the dose was 500mg/kg.

Placebo condition included 5% human albumin, 0.5% albumin and saline.

Participants included in the review
Women with recurrent spontaneous abortion (i.e. two or more losses) which include primary (i.e. no pregnancy beyond 20 weeks of gestation) and secondary abortion (i.e. at least one pregnancy that progressed beyond 20 weeks of gestation). The age of participants ranged from 18 to 45 in those studies which stated the participant age range.

Two studies included only women who were pregnant, and two studies included both pregnant and non-pregnant women.

Outcomes assessed in the review
The primary outcome of interest was the live birth rate. Ectopic pregnancies and therapeutic abortions were classified as failures for the purpose of this review. The frequency of karyotic abnormalities in the abortus material from failed pregnancies was assessed as a secondary outcome.

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

Assessment of study quality
The methodological quality of each trial was assessed using a predetermined scoring system consisting of six criteria. The evaluation included the type of randomisation procedure, and whether it was concealed, the use of blinding, the presence of cointervention, the completeness of follow-up and whether a sample size calculation had been performed.
The minimum possible score was 3, and the maximum was 16. Each study was assessed independently by two reviewers and was ranked for its methodological vigour and its potential to introduce bias. The level of agreement estimated by the kappa statistic was greater than 0.90.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. The data extraction was checked for accuracy.

The data on the outcome for each trial selected for inclusion in the analysis were extracted into two-by-two tables and summarised using the odds ratio.

**Methods of synthesis**
How were the studies combined?
Effectiveness was evaluated using the Mantel-Haenszel method. The overall adjusted common odds ratio (OR), and its 95% confidence interval (CI) was calculated as a weighted average of the ORs of individual trials to provide an estimate and precision of the overall measure of the effect of treatment. Statistical significance was established with a two-tailed P value of less than or equal to 0.05. The overall crude treatment effect was also calculated after collapsing the tables from each trial into one summary two-by-two table.

How were differences between studies investigated?
The homogeneity of treatment effect across all trials was tested using the method of Breslow and Day (see Other Publications of Related Interest).

Sensitivity analysis: The data were reanalysed after excluding pregnancy losses that were caused by factors that could not be prevented by IVIG treatment or were unrelated to placebo use.

**Results of the review**
Four randomised double-blind placebo controlled studies comprising 255 participants (198 pregnant) were included in the review.

The validity score of included studies ranged from 13 to 14.

There was no significant heterogeneity in the effect of treatment across all trials (Breslow-Day = 5.11; p=0.16).

The estimate of the treatment effect in two of the four studies was in the direction favouring IVIG, whereas in the other two trials, the treatment effect was very small and in favour of the placebo. The common OR was 1.48 (95 CI: 0.84, 2.60, p=0.17), indicating that the live birth rate with IVIG was not significantly higher than with placebo.

The overall absolute treatment effect, in favour of IVIG was 10.1% (95% CI: -4.8, 24.6), and was not statistically significant (chi-squared = 2.02, P=0.16, N=198).

Sensitivity analysis: Excluding pregnancy losses that could not be prevented using IVIG treatment or were unrelated to placebo use resulted in a statistically significant combined OR of 1.86 (95% CI: 1.02, 3.39, p=0.041). The overall absolute treatment effect was 14.4% (chi-squared =3.87, p=0.049, N=186).

**Authors’ conclusions**
This meta-analysis suggests that IVIG may have a role in the treatment of recurrent abortion, but as yet no conclusive evidence is available.

**CRD commentary**
The review answers a well-defined question. Inclusion and exclusion criteria were appropriate. Sufficient details of the
primary studies were given and they were combined appropriately.

It was unclear whether or not only published material was included in the literature search. The validity of included studies was assessed and scored on six criteria. The authors allocated a maximum score of 2 points for completeness of follow-up. However, 2 studies (both receiving 2 points) excluded patients from the trial after randomisation if conception did not occur within 4 or 6 months of treatment. Excluding these participants may have implications on the randomisation procedure.

This is a thorough review and the authors’ conclusions follow from the results. Unfortunately, no conclusive evidence was found. This may have been due to the small number of relevant studies found, and the small overall sample size.

Implications of the review for practice and research
The authors state that the results of this meta-analysis are inconclusive and suggest that further research is necessary to determine whether IVIG use is efficacious in women with recurrent spontaneous abortion.

Because the number of previous pregnancy losses has been shown to be a significant negative prognostic factor, the authors suggest that it should be balanced by stratification in the treatment and control groups. Similarly, they suggest that stratification should be undertaken for primary and secondary types of recurrent abortion, because the response to therapy may vary depending on the category.

Bibliographic details

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Other publications of related interest

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Subject indexing assigned by NLM

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.