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Mini symposium
Analysis of therapies for anovulation and miscarriage

Critical analysis of intravenous immunoglobulin therapy for recurrent miscarriage

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An alloimmune abnormality is believed to be the cause of recurrent miscarriage in couples in whom no other cause can be identified. Because of its immunosuppressive properties, intravenous immunoglobulin (IVIG) is used as a treatment for this disorder. The purpose of this study was to determine whether IVIG improves the chance of successful pregnancy in women with recurrent miscarriage by using individual patient data from efficacy trials. Detailed information on each patient enrolled in these trials was obtained to evaluate the efficacy of IVIG and investigate the effect of clinical variability on pregnancy outcome. Data from 125 patients in the IVIG group and 115 patients in the placebo group were available for analysis. Although the number of previous miscarriages and female age were both negative prognostic factors for successful outcome, there was no significant improvement in successful pregnancy or live birth rate with IVIG. Subgroup analyses indicated that timing of IVIG administration may be important. The results of the present study highlight the importance of stratification for known confounders, so that the role of IVIG can be evaluated in more detail. The collective evidence thus far indicates that IVIG does not have a therapeutic effect that is clinically meaningful.

Key words: immunotherapy/intravenous immunoglobulin/meta-analysis/recurrent miscarriage

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Introduction

Miscarriage is the most frequent complication of human pregnancy, with approximately 3–5% of couples suffering recurrent pregnancy losses (Daya, 1993). The mechanisms that normally prevent a mother from rejecting her semi-allogeneic conceptus are unclear, but it has been postulated that immunological aberrations may lead to recurrent miscarriage in some women. However, there is as yet no definitive diagnostic test that can identify women who have such alloimmune dysfunction. Despite the lack of diagnostic tests, couples with recurrent miscarriage, in whom none of the generally accepted causes (such as uterine, genetic and endocrinological anomalies) can be identified, are offered treatments purporting to improve maternal immunotolerance. The most popular regimen has been active immunization of the female with leukocytes from her male partner (Daya *et al.*, 1994; Daya, 1997).

Passive immunization with intravenous immunoglobulin (IVIG) has recently been proposed as an alternative because of its immunosuppressive properties. It has been suggested that the therapeutic effect of IVIG in humans is mediated by downregulation of systemic natural killer (NK) cells (Kwak *et al.*, 1996; Ruiz *et al.*, 1996). Elevated levels of NK cells have been found in the blood of women having miscarriages of karotypically normal pregnancies (Clark and Coulam, 1995), and

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the presence of increased levels of NK cells in non-pregnant women is associated with a higher probability of miscarriage in a subsequent pregnancy (Aoki *et al.*, 1995). Thus, it is believed that NK cell activity at the implantation site can be abrogated by IVIG, thereby lowering the likelihood of miscarriage.

In a recent meta-analysis of four randomized, placebo-controlled trials, an absolute treatment effect of 10.1% in favour of IVIG was observed (Daya *et al.*, 1998). However, discrepancies have been reported between the results of meta-analysis using aggregate data available from the literature (MAL) and meta-analyses using individual patient data (MAP) (Stewart and Parmar, 1993; Jeng *et al.*, 1995; Oxman *et al.*, 1995). There are several advantages of the MAP approach, including completeness of data collection so that subgroup analyses can be undertaken. Therefore, the purposes of this study were first, to determine whether IVIG improves the chance of successful pregnancy in women with recurrent miscarriage, and second to investigate the effect of clinical variability on pregnancy outcome.

Table I. Details of trials comparing intravenous immunoglobulin (IVIG) with placebo for treatment of recurrent miscarriage

Reference	Study design	No. of patients in trial	No. of patients in meta-analysis	Inclusion criteria	Primary/secondary recurrent miscarriage	Treatment versus control	Timing and dose of infusion
German RSA/ IVIG Group (1994)	Multicentre, randomized, double-blind, central allocation	64 pregnant: 33 IVIG, 31 placebo	23 IVIG, 24 placebo	≥3 SA at 316 weeks, age ≤40 years	1° only (no prior LB)	Verum (5% IVIG) versus 5% human albumin	600 ml (30 g) at positive pregnancy test (5–8 weeks), 400 ml (20 g) every 3 weeks to week 25 ± 1
Christiansen *et al*. (1995)	Randomized, double-blind, sealed envelopes, allocation method not stated	34 pregnant: 17 IVIG, 17 placebo	17 IVIG, 15 placebo	≥3 SA at ≤28 weeks	2° (prior LB) or 1° with ≥1 SA >14 weeks	Nordimmun (IVIG) versus 5% human albumin	35g weeks 5 and 6, 25g weeks 7, 8 and biweekly to week 26, 30g biweekly weeks 28–34 (adjusted by 5g if weight <60 or >80 kg)
Coulam *et al*. (1995)	Multicentre, randomized, double-blind	95 enrolled, 61 pregnant: 29 IVIG, 32 placebo	24 IVIG, 20 placebo	≥2 SA with current partner, age 18–45 years	1° (no prior pregnancy >20 weeks) and 2° (prior LB)	IVIG versus 0.5% albumin	IVIG 500 mg/kg or placebo monthly, starting in follicular phase pre-pregnancy for up to four cycles, until 28–32 weeks
Stephenson *et al*. (1998)	Randomized, double-blind, central allocation	62 enrolled, 39 pregnant: 20 IVIG, 19 placebo	17 IVIG, 13 placebo	≥2 SA at <20 weeks, age 18–45 years	1° (no prior pregnancy >20 weeks) and 2° (prior pregnancy >20 weeks)	Gamimune N (5% IVIG) versus saline	IVIG 500 mg/kg or placebo monthly starting in follicular phase pre-pregnancy for up to six cycles. Treatment in pregnancy was not described
Perino *et al*. (1997)	Multicentre, randomized, double-blind, central allocation	46 pregnant: 22 IVIG, 24 placebo	22 IVIG, 24 placebo	≥3 SA at ≤13 weeks with current partner, age ≤42 years	1° only (no prior LB)	IVIG versus 5% human albumin	500 ml (25 g) on two consecutive days after positive pregnancy test (5–7 weeks gestation) and again 3 weeks later
Jablonowska *et al.* (1999)	Multicentre, randomized, double-blind,	41 pregnant: 22 IVIG, 19 placebo	22 IVIG, 19 placebo	≥3 SA at <20 weeks	1° (no prior LB) or 2° (prior LB)	Gammonativ IVIG versus saline	400 ml (20 g) at viable pregnancy on ultrasound (5-9 weeks) and every 3 weeks (total 5 treatments)

LB = live birth; SA = spontaneous abortion.

The sources of IVIG were as follows:

Christiansen *et al*. (1995): Nordimmun, IVIG (Novo-Nordisk, Gentofte, Denmark).

Coulam *et al*. (1995): IVIG source not provided.

German RSA/IVIG Group (1994): Verum, 5% IVIG (Immuno GmbH, Heidelberg, Germany).

Jablonowska, (1999): Gammonativ IVIG (Pharmacia and Upjohn Plasma Products, Stockholm, Sweden)

Perino *et al*. (1997): IVIG (Sclavo Pharmaceutical Co., Sienna, Italy).

Stephenson *et al*. (1998): Gamimune N, 5% IVIG (Bayer Canada Inc., Etobicoke, Canada).

Table II. Validity criteria and assessment for methodological rigour of each trial

Reference	Randomization	Concealment	Blinding	Co-intervention	Completeness of follow-up	Sample size calculated	Total	Percentage of maximum score (16)	Rank order
German Group (1994)	4	3	2	1	2	2	14	88	1
Christiansen *et al*. (1995)	3	2	2	2	2	2	13	81	2
Coulam *et al*. (1995)	3	1	2	1	2	2	11	69	4
Stephenson *et al*. (1998)	1	3	2	2	2	2	12	75	3
Perino *et al*. (1997)	3	3	2	1	2	2	13	81	2
Jablonowska *et al*. (1999)	1	3	2	1	2	2	11	69	4

Randomization method: 4, within blocks; 3, by computer table; 2, coin tossing; 1, other than above or not stated.
Concealment of randomization: 3, central allocation; 2, using concealed method; 1, no concealment or not stated.
Blinding: 3, triple; 2, double; 1, single; 0, none or not stated.
Co-intervention: 2, none; 1, unlikely or not stated; 0, present.
Completeness of follow-up: 2, complete; 1, <5% of subjects missing; 0, ≥5% of subjects missing.
Sample size calculation: 2, explicitly stated; 1, not done or not stated.

Selection criteria

Trials included in the study

In our recently published MAL of randomized controlled trials of IVIG for the treatment of recurrent miscarriage (Daya *et al*.,1998), the only data available for the analysis were those that could be extracted from the four published papers (The German RSA/IVIG Group, 1994; Christiansen *et al.*, 1995; Coulam *et al.*, 1995; Stephenson *et al.*, 1998). To reduce inconsistencies in eligibility criteria among the trials, the authors were subsequently contacted to provide us with the raw data on all patients enrolled in their trials. For each patient, a data sheet that included patient age, obstetrical history, results of prestudy investigations, intervention group assignment, details of treatment, and information on the outcome of the study pregnancy, was completed and used for analysis. Following acceptance for publication of our MAL manuscript, two more randomized, double-blind, placebo-controlled trials of IVIG were published (Perino *et al.*, 1997; Jablonowska *et al*., 1999). The authors of the Italian study (Perino *et al.*, 1997) were not contacted for additional data because sufficient individual patient data were provided in that paper to include them in the present MAP. The first author of the Swedish study (Jablonowska *et al*., 1999) kindly provided individual patient data for the meta-analysis.

Patients included in the study

Individual patient data were included in the analysis only if the following criteria were met: three or more consecutive miscarriages at <20 weeks gestation with the present male partner; no uterine anomaly; no karyotypic abnormality in the couple; no endocrinological abnormality; and no evidence of autoimmune disease. Because information on karyotype analysis of products of conception from previous pregnancies was available in only a small number of the cases, an abnormal fetal karyotype was not considered a reason for excluding either that loss from the minimum of three, or that couple from the study. No further age restrictions beyond those of the original studies were imposed, thereby allowing women up to the age of 45 years to be included. Women with primary or secondary recurrent miscarriage were coded separately in the database.

The inclusion criteria of the six trials are shown in Table I. For the two trials in which treatment was commenced before conception (Coulam *et al.*, 1995; Stephenson *et al.*, 1998), patients who did not achieve pregnancy within the period specified by the investigators were excluded from this analysis.

Treatment protocols

Details of the treatments used in the six trials are shown in Table I. Although the individual treatment protocols were quite different, two main approaches to IVIG administration were identified. In the North American studies (Coulam *et al.*, 1995; Stephenson *et al.*, 1998), IVIG treatment was begun before conception, in the follicular phase of the menstrual cycle, and continued at regular intervals during the pregnancy. In the European studies (The German RSA/IVIG Group, 1994; Christiansen *et al.*, 1995; Perino *et al.*, 1997; Jablonowska *et al*., 1999), IVIG administration was commenced after implantation upon confirmation of the pregnancy (i.e. between 5 and 7 weeks gestation). IVIG treatment continued at regular intervals during the pregnancy except in the Italian study, in which treatment was discontinued in the first trimester.

Trial quality assessment and statistical analysis

The methodological quality of each trial was quantified using a scoring system which assessed the type of randomization procedure used and whether it was concealed, the use of

blinding, the presence of co-intervention, the completeness of follow-up of trial subjects, and whether a sample size calculation had been performed. Each trial was scored separately by two of us (S.D. and J.G.), and the results were compared. Any disagreement was resolved by consensus. Table II describes the scoring system and shows the results of the quality assessment.

A pregnancy was considered successful if it had progressed to at least 20 weeks gestation. Miscarriage, ectopic pregnancy and therapeutic abortion were considered treatment failures. The live birth rate, length of gestation and birth weight were also compared between the two groups.

The data on the outcome of each trial were summarized using the odds ratio (OR). A test of the homogeneity of treatment effect across all trials was performed using a previously published method (Breslow and Day, 1980). If there was no significant statistical heterogeneity, indicating that the treatment effect in each trial was not significantly different from the overall pooled estimate of treatment effect, the data were pooled using a fixed effects model. An overall adjusted common OR, and its 95% confidence interval (CI), were calculated as the weighted average of the OR of individual trials to provide an estimate of the overall measure of the effect of treatment and the precision of this estimate.

Subgroup meta-analyses were performed for primary and secondary recurrent miscarriage categories and onset of therapy (i.e. before conception or after implantation). Crude estimates of treatment effect (overall and within subgroups) were calculated after summarizing the data in two-by-two tables.

Using logistic regression analysis, predictors of successful pregnancy and live birth were determined for the group as a whole and separately for primary and secondary recurrent miscarriage categories.

Comparisons of groups were made with chi-square and Fisher's exact tests for proportions, *t*-tests for means, and the Mann–Whitney rank sum test for non-parametric data. Statistical significance was established with a two-tailed *P*-value of ≤ 0.05.

Results

After omitting cases which did not meet the inclusion criteria for the study, there were 125 patients in the IVIG group and 115 patients in the placebo group that provided data for analysis. This number of patients provided sufficient power (0.8 or greater) to detect an absolute treatment effect of 15%, i.e. an increase in success rate from 62% in the placebo group to 77% in the IVIG group. The demographic characteristics of the patients in the two groups were not significantly different (Table III).

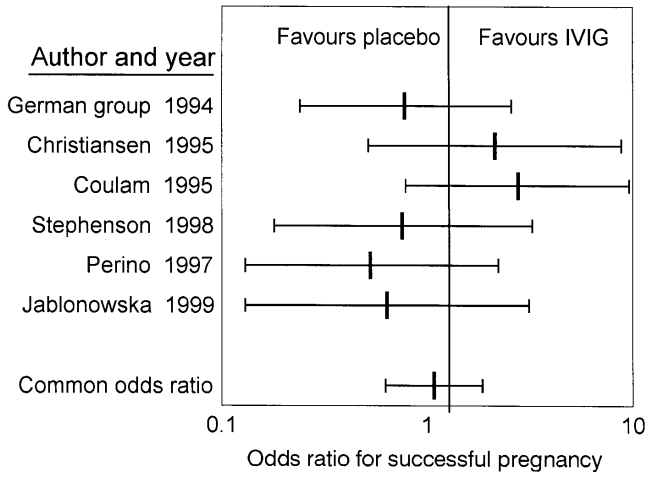

Figure 1. Odds ratio tree of trials comparing the effect of intravenous immunoglobulin (IVIG) with placebo on successful pregnancy outcome. Breslow–Day test for homogeneity of treatment effect = 4.9, *P* = 0.43.

Table III. Patient characteristics in the trials comparing intravenous immunoglobulin (IVIG) with placebo for recurrent miscarriage

Characteristic	Intervention	
	IVIG	Placebo
No. of patients	125	115
Mean (± SD) age (range) (years)[a]	30.6 ± 4.8 (20–42)	31.4 ± 5.5 (19–43)
Proportion of women aged ≥35 years (%)[a]	22	28
Median no. of prior miscarriages (range)	3 (3–6)	3 (3–13)
Proportion of women with >3 prior miscarriages (%)	41	36
Proportion of women with primary recurrent miscarriage (%)	68	75

[a]Age unknown in 14 cases.

Meta-analysis

The point estimate of OR and its 95% CI for each trial and the pooled common OR for pregnancy progressing beyond 20 weeks gestation are shown in Table IV and in the odds ratio tree in Figure 1. The overall success rates were 62.4% (78/125) in the IVIG group and 61.7% (71/115) in the placebo group (OR = 1.08, 95% CI = 0.63–1.86, *P* = 0.78). Pregnancy loss before 20 weeks gestation occurred in 47 women in the IVIG group and 44 women in the placebo group. For women with primary recurrent miscarriage, the success rates were 64.7% with IVIG and 64.0% with placebo (OR = 1.04, 95% CI = 0.54–2.01, *P* = 0.90), and in the secondary recurrent miscarriage group, the respective success rates were 57.5% and 55.2% (OR = 1.18, 95% CI = 0.43–3.21, *P* = 0.74).

Table IV. Results of meta-analysis of intravenous immunoglobulin (IVIG) versus placebo for recurrent miscarriage

Reference	Successful pregnancy			Live birth		
	IVIG	Placebo	Odds Ratio (OR) (95% CI)	IVIG	Placebo	Odds Ratio (OR) (95% CI)
German RSA Group (1994)	14/23	16/24	0.78 (0.24–2.56)	14/23	15/24	0.93 (0.29–3.03)
Christiansen *et al*. (1995)	10/17	6/15	2.14 (0.52–8.81)	9/17	5/15	2.25 (0.54–9.45)
Coulam *et al*. (1995)	13/24	6/20	2.76 (0.79–9.61)	12/24	6/20	2.33 (0.67–8.12)
Stephenson *et al*. (1998)	8/17	7/13	0.76 (0.18–3.24)	8/17	7/13	0.76 (0.18–3.24)
Perino *et al*. (1997)	16/22	20/24	0.53 (0.13–2.22)	16/22	20/24	0.53 (0.13–2.22)
Jablonowska *et al.* (1999)	17/22	16/19	0.64 (0.13–3.11)	17/22	15/19	0.91 (0.20–4.01)
Overall	78/125	71/115	1.08 (0.63–1.86)	76/125	68/115	1.14 (0.66–1.95)

There were eight explained losses at less than 20 weeks in the IVIG group: one ectopic pregnancy, four fetuses with abnormal karyotype (one was electively terminated), one hydatidiform mole, one after a car accident, and one associated with red degeneration of fibroids. There were three explained losses in the placebo group: two ectopic pregnancies and one fetus with an abnormal karyotype. After omitting these cases, the respective success rates were recalculated to be 66.7% and 63.4% (OR = 1.22, 95% CI = 0.69–2.14, $P = 0.49$).

The OR for live birth for each trial and the pooled common OR are shown in Table IV and Figure 2. After 20 weeks gestation, there were two pregnancies in the IVIG group and three in the placebo group that did not result in a live birth. Thus, the overall live birth rates for IVIG and placebo were 60.8% (76/125) and 59.1% (68/115) respectively (OR = 1.14, 95% CI = 0.66–1.95, $P = 0.65$). In the primary recurrent miscarriage group, the respective live birth rates were 62.4% and 61.6% (OR = 1.00, 95% CI = 0.52–1.94, $P = 1.00$), and in the secondary recurrent miscarriage group, the respective live birth rates were 57.5% and 51.7% (OR = 1.34, 95% CI = 0.50–3.62, $P = 0.56$). Two of the losses after 20 weeks were explained: one fetal death from an umbilical cord accident at 30 weeks in the IVIG group and one with severe growth restriction at 23 weeks in the placebo group. After omitting these and the 11 explained losses before 20 weeks (as described above), the respective live birth rates were 65.5% and 61.3% (OR = 1.27, 95% CI = 0.72–2.23, $P = 0.41$).

Figure 3 shows that the magnitude of the effect in women with primary recurrent miscarriage was much larger when treatment was administered before conception (IVIG 14/25 versus placebo 6/19, OR = 2.70, 95% CI = 0.78–9.29) than after implantation (IVIG 41/60 versus placebo 49/67, OR = 0.69, 95% CI = 0.31–1.54). For secondary recurrent miscarriage, the observation was the reverse (pre-conception: IVIG 7/16 versus placebo 7/14, OR = 0.78, 95% CI = 0.18–3.26; post-implantation: IVIG 16/24 versus placebo 9/15, OR = 1.79, 95% CI = 0.43–7.44).

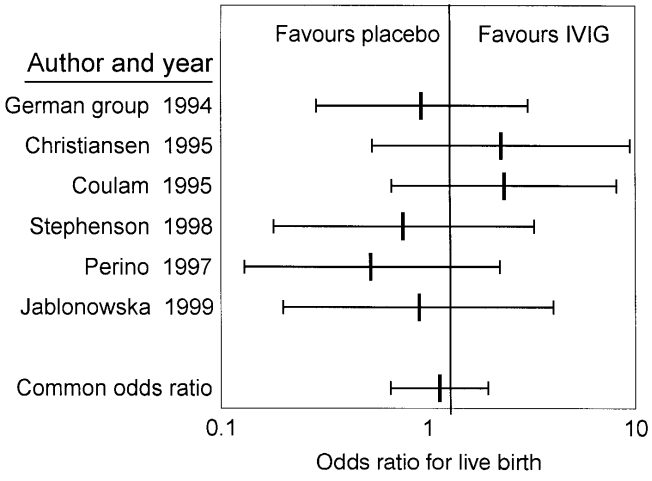

Figure 2. Odds ratio tree of trials comparing the effect of intravenous immunoglobulin (IVIG) with placebo on live birth outcome. Breslow–Day test for homogeneity of treatment effect = 3.7, $P = 0.60$.

Logistic regression analysis

Logistic regression analysis of the data demonstrated that the number of previous miscarriages (OR = 0.56) and female age (OR = 0.90) were significant predictors of successful pregnancy (Figure 4). Most of the variability in pregnancy

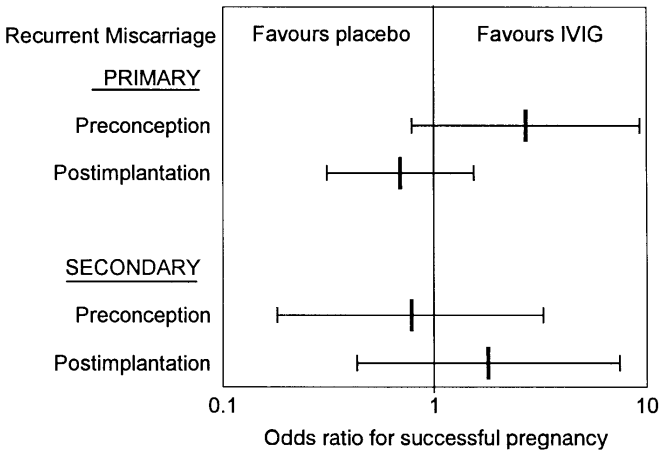

Figure 3. The effect of timing of administration of intravenous immunoglobulin (IVIG) on successful pregnancy outcome.

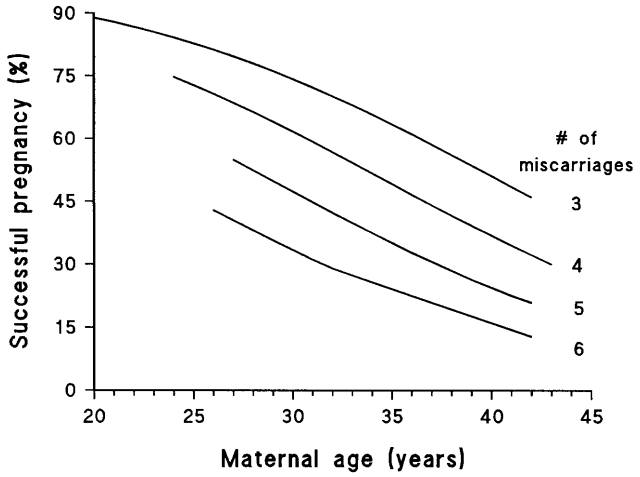

Figure 4. The effect of female age and history of previous miscarriages on the predicted probability of successful pregnancy. Based on 222 cases: 141 with three previous miscarriages; 47 with four miscarriages; 24 with five miscarriages; and 10 with six miscarriages.

success was accounted for by these two variables. The use of IVIG had no significant effect on the probability of success (P = 0.57). Although pre-conceptional treatment was a significant predictor of outcome, it had no effect on the predictive model once female age and number of previous miscarriages had entered the model. For primary recurrent miscarriage, the final model that predicted successful pregnancy included female age (OR = 0.91) and number of previous miscarriages (OR = 0.60). For secondary recurrent miscarriage, the significant predictors of successful pregnancy were number of previous miscarriages (OR = 0.45) and female age (OR = 0.90).

The regression analysis produced similar results when live birth was used as the outcome. Female age (OR = 0.92) and number of previous miscarriages (OR = 0.56) were the only variables in the final model that predicted live birth. The use of IVIG, either before conception or after implantation, had no effect on the probability of live birth. The result was similar in women with primary recurrent miscarriage, with female age (OR = 0.91) and number of previous miscarriages (OR = 0.60) being the only variables in the final model. In secondary recurrent miscarriage, only number of previous miscarriages (OR = 0.49) had an effect on live birth rate.

There was no difference between the groups in the mean gestational age at which the pregnancy was lost or delivered, or in the mean birth weight of live born infants (the number of cases for which data were available are indicated in brackets). The mean gestational age at pregnancy loss for women with unexplained losses was 9.0 weeks in the IVIG group and 8,8 weeks in the placebo group; the range was 4–21 weeks in the IVIG group (n = 39) and 5–27 weeks in the placebo group (n = 41) (P = 0.79). For live births, the mean gestational age was 39 weeks in both groups, with a range of 27–42 weeks in the IVIG group (n = 62) and 24–41 weeks in the placebo group (n = 61) (P = 0.41). The mean birth weight of live-born babies was 3280 ± 789 g (range 605–5030 g; n = 70) in the IVIG group and 3190 ± 719 g (range 700–4200 g; n = 65) in the placebo group (P = 0.49).

Discussion

The results of this meta-analysis and logistic regression analysis of individual patient data indicate that, at the present time, there is insufficient evidence to demonstrate that the use of IVIG in the treatment of unexplained recurrent miscarriage is efficacious. Although a preference for IVIG was observed, the effect size was marginal and not of statistical significance. The results of this meta-analysis of individual patient data are in keeping with other reports (Stewart and Parmar, 1993; Jeng *et al.*, 1995; Oxman *et al.*, 1995) which have indicated that the MAL approach to summarizing data from randomized trials produces an overestimate of the effect of treatment compared with the MAP approach [the observed common OR for IVIG use were 1.48 (Daya *et al.*, 1998) and 1.08 respectively]. One of the advantages of MAP compared with MAL is the ability to undertake subgroup and multivariate analyses to investigate factors that may have an effect on the outcome. Other advantages include detailed data checking, confirmation of the quality of randomization and completeness of follow-up. The use of MAP allows better interpretation of the results that are obtained and, consequently, more widespread endorsement and dissemination of the inferences that are made.

The urgency of reaching a definitive conclusion in the issue of IVIG use for recurrent miscarriage cannot be emphasized enough, given the relatively short supply of IVIG and its expense ($20 per gram in Canada, resulting in a cost of up to $7000 per pregnancy) (Clark and Daya, 1998). Also, in rare situations, serious and life-threatening reactions to IVIG can occur (Duhem *et al.*, 1994), Finally, patients can be spared the pain and grief associated with false expectations that an

ineffective treatment might work. At present, the available data indicate that if there is a beneficial effect, it is quite small and unlikely to be of clinical importance.

A shortcoming of this study is that, despite pooling the data from six trials, the total number of cases available for analysis was only 240. Although this sample size gave the study sufficient power to detect an absolute treatment effect of 15% or greater, smaller effect sizes cannot be detected without increasing the number of cases. Nevertheless, this meta-analysis of data from individual patients raises several issues that require further evaluation. First, the magnitude of the odds ratio was marginally greater for secondary recurrent miscarriage (1.18, 95% CI = 0.43–3.21) compared with primary recurrent miscarriage (1.04, 95% CI = 0.54–2.01), even though these estimates individually were not statistically significant. However, judging from the 95% CI around these estimates of the treatment effect, one can speculate that if IVIG has any beneficial effect, it may be in the secondary recurrent miscarriage group, in which the upper limit of the 95% CI was much higher than that in the primary recurrent miscarriage group. If this hypothesis can be supported by further study (given that there were only 69 cases in the secondary recurrent miscarriage group available for study), then the mechanism for IVIG efficacy in this group will need to be reassessed.

A second issue that requires further study is that of appropriate timing of administration of IVIG, i.e. should the treatment be administered before conception or after implantation? The purported mechanism of NK cell involvement in the miscarriage process, and the fact that IVIG has been shown to reduce NK cell numbers and cytotoxicity within 7 days of treatment (Kwak *et al.*, 1996), suggest that, for benefit to be derived, treatment should be commenced before implantation. In this way, cytotoxicity from NK cells can be minimized, if not eliminated, thereby avoiding any damaging effect to the implanting embryo/trophoblast unit. Using such reasoning, efficacy may be more likely to be demonstrated if treatment is begun before conception occurs. The results of this meta-analysis provide some support for this suggestion; the respective OR were 1.59 and 0.88 for treatment commenced before conception or after implantation. However, subgroup analyses indicate that the timing of treatment may also depend on the type of recurrent miscarriage. In primary recurrent miscarriage, pre-conceptional treatment appears to be more efficacious than treatment administered after implantation (OR 2.70 versus 0.69 respectively). In contrast, the converse appears to be true in secondary recurrent miscarriage (OR 0.78 versus 1.79). Clearly, this issue can only be resolved by conducting appropriate trials that are stratified not only for the type of recurrent miscarriage, but also for the timing of IVIG administration.

A third issue relates to the dose of IVIG that should be used. There has been no dose–response study of IVIG in women with recurrent miscarriage to identify the optimal dose. The dose of IVIG used in the trials selected for this study was variable, and contrasts sharply with the report of a Japanese case series in which a significantly higher amount of IVIG was administered (Yamada *et al.*, 1998). In that study, IVIG was infused intravenously over the course of 5 days at a dose of 20 g/day (for a total dose of 100 g) at gestational weeks 4–7 in women with primary recurrent miscarriage. The treatment was restricted to women with a history of four or more consecutive miscarriages with unexplained aetiology. Excluding the two patients who subsequently had another miscarriage of a karyotypically abnormal pregnancy, this high-dose option showed promise, with all nine of the remaining patients having a successful outcome. However, the additional therapy (either aspirin, heparin or prednisone) that was administered to several of the patients makes it more difficult to attribute the positive outcome to the large dose of IVIG used. Nevertheless, the Japanese study findings raise the possibility that a therapeutic effect may be observed only with a much higher dose of IVIG given over a short period of time, rather than over the course of several weeks, as was used in the other trials.

A fourth issue pertains to the effect on outcome of female age and previous miscarriage history. It is well known that as the age of the woman increases, her reproductive efficiency declines, in part because of an increase in the likelihood of miscarriage. The negative effect of female age was clearly evident in this study. Also, as has been shown previously (Daya *et al.*, 1994) the number of prior miscarriages is a negative prognostic factor. The problem of confounding that these prognostic factors can introduce is not insignificant and points to the need to control for previous miscarriage history and female age in any study of treatment for recurrent miscarriage.

Collectively, these issues highlight the complexity of the task of evaluating the efficacy of IVIG. A randomized trial of sufficient power and with stratification for primary versus secondary recurrent miscarriage, pre-conceptional versus post-implantational administration of IVIG, number of previous miscarriages and female age is necessary before one can determine if IVIG is of any benefit to couples with unexplained recurrent miscarriage. The results of the present study provide information on subgroups in which treatment may be helpful, but IVIG should not be offered as a therapeutic option to couples with unexplained recurrent miscarriage unless they are part of a trial that takes into account the currently known confounders.

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