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ORIGINAL ARTICLE *Early pregnancy*

Intravenous immunoglobulin and idiopathic secondary recurrent miscarriage: a multicentered randomized placebo-controlled trial

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BACKGROUND: Idiopathic secondary recurrent miscarriage may be associated with an abnormal maternal immune response to subsequent pregnancies. Intravenous immunoglobulin (IVIG) has been studied in randomized controlled trials (RCTs) with conflicting results. Therefore, a definitive trial was proposed.

METHODS: We conducted an investigator-initiated, multicentered, randomized, double-blinded, placebo-controlled trial comparing IVIG with saline in women with idiopathic secondary recurrent miscarriage, defined as a history of at least one prior ongoing pregnancy followed by three or more consecutive unexplained miscarriages. Subjects received either IVIG 500 mg/kg or the equivalent volume of normal saline. Preconception infusions were administered 14–21 days from the projected next menstrual period. With documentation of pregnancy, the subject received the same infusion every 4 weeks until 18–20 weeks of gestation. The primary outcome was an ongoing pregnancy of at least 20 weeks of gestation.

RESULTS: A total of 82 patients enrolled, of whom 47 had an index pregnancy. All ongoing pregnancies resulted in live births. Therefore, the live birth rates were 70% (16/23) in the IVIG group and 63% (15/24) in the control group ($P = 0.760$); odds ratio (OR) 1.37 [95% confidence interval (CI) 0.41–4.61]. Including only clinical pregnancies (embryo with cardiac activity at 6 weeks of gestation), the live birth rates were equivalent, 94% (16/17) and (15/16), respectively ($P > 0.999$); OR 1.07 (95% CI 0.06–18.62). Meta-analysis of randomized controlled trials (RCTs) evaluating IVIG for idiopathic secondary recurrent miscarriage revealed live birth rates of 70% (31/44) in the IVIG group and 62% (28/45) in the control group ($P = 0.503$); common OR 1.44 (95% CI 0.59–3.48).

CONCLUSIONS: This is the largest RCT to date in which IVIG was evaluated in women with idiopathic secondary recurrent miscarriage; no treatment benefit was found. The meta-analysis, which combined our study results with two prior RCTs, also showed no significant effect of treatment with IVIG.
ClinicalTrials.gov NCT00606905.

Key words: recurrent miscarriage / intravenous immunoglobulin / randomized controlled trial / live birth / meta-analysis

Introduction

Miscarriage is the most common complication of pregnancy. With inclusion of preclinical pregnancies, at least 30% end in miscarriage (Wilcox *et al.*, 1988). In the general reproductive population, 50–70% of miscarriages of less than 10 weeks of gestation at the time of demise are associated with numeric chromosome errors, such as trisomy, monosomy and polyploidy (Jacobs and Hassold, 1987; Ohno *et al.*, 1991). Therefore, chromosome testing can be useful to determine whether a miscarriage is 'explained', due to a

presumed random numeric chromosome error, or 'unexplained', which may indicate that further evaluation for maternal and paternal factors is warranted (Stephenson and Kutteh, 2007).

Recurrent miscarriage, defined as three or more consecutive miscarriages, is a prevalent health problem that affects ~1–2% of couples who are trying to establish a family (Roman, 1984). Recurrent miscarriage is associated with parental translocations, maternal endocrine and uterine factors and the antiphospholipid syndrome. Despite evaluation, in ~40% of couples with recurrent miscarriage no factor is identified which termed idiopathic (Stephenson, 1996).

Idiopathic recurrent miscarriage has traditionally been associated with alloimmune factors. Recently, uterine $CD^{56+/16-}$ natural killer cells have been implicated (Lachapelle *et al*., 1996; Clifford *et al*., 1999; Quenby *et al*., 1999). *In vitro* studies suggest that pregnancy may result in uterine T-cell activation along the T-helper-2 (Th-2) pathway, resulting in blocking antibodies which mask trophoblast antigens (Wegmann *et al*., 1993). Activation along the Th-1 pathway results in the production of abortogenic cytokines (Reinhard *et al*., 1998; Lim *et al*., 2000; Raghupathy *et al*., 2000; von Wolff *et al*., 2000). Maternal HY-restricting HLA class II alleles are associated with a decreased chance of a live birth in women with secondary recurrent miscarriage with a firstborn boy (Nielsen *et al*., 2009). Although such mechanisms are intriguing, there is a paucity of validated tests to assess the maternal immune response to pregnancy. Despite this, active and passive immunotherapeutic trials for idiopathic recurrent miscarriage have been reported.

Paternal mononuclear cell immunization has proven not to be effective (Ober *et al*., 1999; Scott, 2003). Passive immunotherapy with intravenous immunoglobulin (IVIG) may offer benefit in idiopathic secondary (at least one prior ongoing pregnancy), but not idiopathic primary (no prior ongoing pregnancy) recurrent miscarriage. In 2007, Hutton *et al*. (2007) published a meta-analysis of seven randomized controlled trials (RCTs) of IVIG for treatment of idiopathic recurrent miscarriage. Overall, IVIG did not appear to be of benefit, based on a common odds ratio (OR) of 1.28 [95% confidence interval (CI) 0.78–2.10]. With stratification, there was evidence of benefit in women with idiopathic secondary recurrent miscarriage, based on four RCTs (Christiansen *et al*., 1995, 2002; Stephenson *et al*., 1998; Jablonowska *et al*., 1999). The overall live birth rate was 64% (30/47) in the IVIG group and 39% (17/44) in the control group ($P = 0.03$); common OR of 2.71 (95% CI 1.09–6.73), although the authors advised viewing their conclusions with caution because of small sample sizes with heterogeneity of subjects.

IVIG is a highly purified and virally inactivated fractionated blood product made from pooled human plasma, which makes it costly to use and not without risk. Since the effectiveness of IVIG for couples with a history of idiopathic secondary recurrent miscarriage remains controversial, we conducted an investigator-initiated, multicentered, randomized, double-blinded, placebo-controlled trial.

Materials and Methods

Study population

Women from 18 to 45 years of age who had a history of idiopathic secondary recurrent miscarriage with their present partner, and in whom the most recent conception took less than 1 year, were eligible to participate in the study. The study protocol was approved by the institutional review boards of all participating centers; written informed consent was obtained. It was also approved by Health Canada and the USA Food and Drug Administration as an investigator-initiated trial prior to recruitment, which began in November 1999.

Secondary recurrent miscarriage was defined as at least one ongoing pregnancy of 20 or more weeks of gestation, followed by three or more unexplained miscarriages of <20 weeks. Miscarriages were documented by a urinary or serum βhCG test, ultrasound or pathology. Non-euploid (trisomy, monosomy, polyploidy or unbalanced structural chromosome rearrangement) miscarriages were excluded, since they were 'explained'.

Idiopathic secondary recurrent miscarriage was defined as a negative screening protocol for recurrent miscarriage, consisting of cytogenetic analyses of both partners, maternal thyroid stimulating hormone, prolactin and antiphospholipid antibodies, consisting of anticardiolipin IgG and IgM <3.0 multiples of the median, or <20 IgG units per liter or IgM units per liter and the lupus anticoagulant according to published guidelines (Brandt *et al*., 1995), endometrial assessment, either mid-luteal phase progesterone of ≥8 ng/ml or an in-phase endometrial biopsy (Dubowy *et al*., 2003), and intrauterine cavity evaluation by hysteroscopy, hysterosalpingogram or sonohysterogram. All of the screening evaluations were completed locally and had to be negative within the year prior to enrolment, with the exception of the cytogenetic analyses.

Randomization was performed centrally by a computer program in blocks of four, with stratification for study center. Each center-specific randomization schedule was sent to the Investigational Drug Pharmacy/Transfusion Laboratory directly. The infusion labels contained identifying information but not allocation. The women and their doctors, health care and study personnel were unaware of treatment allocation.

Subjects assigned to the treatment group received IVIG (Canadian Blood Services IVIG, Gamimune or Gamunex, Talecris Biotherapeutics, Clayton, USA) at a dose of 500 mg/kg. Subjects in the control group received the equivalent volume of normal saline. All subjects received preconception infusions, which were administered 14–21 days from the projected next menstrual period. The infusion rate was 60 ml/hr for the first hour, then increased to a maximum of 180 ml/hr. If conception did not occur within six menstrual cycles, the subject's participation ended. With documentation of pregnancy, the subject received the same infusion every 4 weeks until 18–20 weeks of gestation, with adjustment for weight based on her prior visit.

Pregnancy was confirmed with a serum βhCG of at least 5 mIU/ml, drawn 1–2 days after a missed menses; it was repeated 1 week later. Transvaginal ultrasound was performed at 6 weeks of gestation. All subjects were offered close monitoring and supportive therapy until the end of the first trimester, with at least three ultrasounds, direct contact with the local investigator and telephone or direct contact with study personnel every 2 weeks, which was continued until 20 weeks of gestation and then every 4 weeks until delivery. At the end of the first trimester, the subject was transferred for ongoing care. Pregnancy outcome was obtained from the obstetrician and/or hospital records.

The index pregnancy was the first pregnancy in the study, unless it resulted in a non-euploid miscarriage, ectopic or molar pregnancy or genetic termination. If one of these exclusion outcomes occurred, it was classified as a non-index pregnancy; the subject could re-enter and receive the same infusion, with double-blinding being maintained; the subsequent pregnancy would be the index, unless it again resulted in an exclusion outcome.

If the index pregnancy resulted in a euploid (46,XX or 46,XY) miscarriage or chromosome testing was not performed, the subject could re-enter and receive the alternate infusion (saline if randomized to IVIG for the index pregnancy, or vice versa), with double-blinding being maintained. This re-entry was for compassionate reasons only; these pregnancy outcomes were not included in the primary analysis.

No concomitant medication for recurrent miscarriage was allowed; this was confirmed at each infusion. Fertility medications and *in vitro* fertilization (IVF) were allowed if required with the previous pregnancy.

Classification of index pregnancy

Miscarriages were classified as preclinical, including biochemical (decreasing βhCGs <1500 mIU/ml), anembryonic (ultrasound revealed empty gestational sac, yolk sac only or embryo of <6 weeks size) or clinical, including embryonic demise (crown rump length of 6–9 weeks 6 days size) or early fetal demise (corresponding to 10–19 weeks 6 day size).

Ongoing pregnancies were classified as preterm (<37 weeks) or term.

Outcome measures

The primary outcome was an ongoing pregnancy of at least 20 weeks gestation; all resulted in live births, therefore, live birth rates were reported. Failure was defined as a euploid miscarriage or a miscarriage without chromosome results. Secondary outcomes were clinical ongoing pregnancy rates and adverse maternal and fetal outcomes.

Sample-size calculation

On the basis of the two prior randomized trials (Christiansen *et al*., 1995; Stephenson *et al*., 1998) and more stringent eligibility criteria, we calculated a sample size of 178 women would be required to detect an increase in the ongoing pregnancy rate from 39 to 64%, using a fecundity rate of 75% in 6 months, a dropout rate of 10% and a two-sided significance test of 0.05 and a power of at least 80%.

Recruitment was temporarily stopped in February 2008 because of slow recruitment and a request for analysis before further IVIG would be donated to the US centers. After the last pregnant subject reached 20 weeks of gestation, an interim analysis was performed. The treatment effect was much smaller than estimated; therefore, enrollment was terminated in January 2009 for final analysis.

Statistical analysis

For descriptive statistics, mean with standard deviations (SD) and range, or, median with interquartile range (IQR) was used. Baseline differences between groups were analysed by the Student's *t* or the Mann–Whitney statistics, depending on the distributions for continuous variables, and by chi-square or Fisher's exact statistics for categorical variables.

We calculated live birth rates, with ORs and 95% CIs. The study was designed to evaluate the effect of IVIG on pregnancy and not on the ability to conceive, therefore, analysis included only subjects who had an index pregnancy.

A meta-analysis, as described by Hutton *et al*. (2007), of two RCTs evaluating IVIG for treatment of idiopathic secondary recurrent miscarriage (Stephenson *et al*., 1998; Jablonowska *et al*., 1999), with the addition of our RCT, was performed. RCTs were included if the evaluation of secondary recurrent miscarriage was negative for a translocation in either partner, maternal anticardiolipin antibodies and lupus anticoagulant and normal for maternal thyroid function and uterine cavity assessment. We excluded two of the four RCTs (Christiansen *et al*., 1995, 2002) that Hutton *et al*. included because some of the women tested positive for antiphospholipid antibodies, therefore, they did not have idiopathic secondary recurrent miscarriage. A fixed effects model meta-analysis was carried out using statistical software R version 2.9.2 (www.rproject.org). Tests for heterogeneity were run to confirm that a random effects model yielded similar results. Mantel–Haenszel common OR with 95% CI was obtained for discrete and overall data.

The trial was registered with ClinicalTrials.gov (NCT00606905) in January 2008; recruitment started before clinical trials registration was required.

Results

Between November 1999 and February 2008, a total of 82 women were recruited (Fig. 1) from seven centers: university of British Columbia, University of Chicago, University of Tennessee-Memphis, University of Toronto, Ottawa University, Yale University and McMaster University. About 77 of the 82 women were randomly assigned to either the IVIG or the control group; five withdrew their consent before randomization. Fifteen subjects in the IVIG group did not have an index pregnancy; five withdrew prior to completion of the six preconception infusions, nine did not conceive and one had an ectopic pregnancy (non-index pregnancy). Fifteen subjects in the control group did not have an index pregnancy; five withdrew prior to completion of the six preconception infusions, six did not conceive, three had non-euploid miscarriages (47,XX,+22, 69,XXX and 48,XX,+21,+12) and one had a genetic termination (non-index pregnancies). None of the five women with a non-index pregnancy re-entered.

There were 47 women with an index pregnancy; 23 received IVIG and 24 received saline infusions. The mean (range) number of preconception infusions in the IVIG group was 2.7 (1–6) and 2.5 (1–5) in the control group, *P*-value was non-significant. There were no infusion violations, either prior to conception or during the antenatal course. There were no adverse effects that required the allocation to be unmasked.

Four of the 23 women who received IVIG infusions conceived in a clomiphene citrate cycle and one in a cryopreserved IVF cycle. Four of the 23 women required medications with one or more infusions; two received diphenhydramine and acetaminophen, one received naproxen and one received acetaminophen for myalgia, headaches, nausea, fever or chills. Three women developed minor rashes and one developed a headache; medication was not prescribed. One woman developed shortness of breath and coughing, which settled with a slower infusion rate.

Four of the 24 women who received saline infusions conceived in a clomiphene citrate cycle, one in a letrazole cycle and two in an IVF cycle. Two women developed gastrointestinal symptoms with the infusions; one required colonoscopy.

The distribution of demographic and pregnancy history variables is shown in Table I; the groups were similar overall and when stratified for centers (data not shown), all *P*-values were non-significant.

The live birth rates are shown in Table II. Including only women with four or more prior miscarriages, the live birth rates were 64% (9 of 14) in the IVIG group and 54% (7 of 13) in the control group ($P = 0{\cdot}704$), OR 1.54 (95% CI 0.33–7.27).

Including only clinical pregnancies, defined by the presence of an embryo with cardiac activity at 6 weeks, the live birth rates were 94% in both groups. Including only women with four or more prior miscarriages, the live birth rates were 90% (9 of 10) in the IVIG group and 87.5% (7 of 8) in the control group ($P > 0.999$), OR 1.29 (95% CI 0.07–24.38).

In the IVIG group, there were seven female and nine male newborns, of which 15 were healthy term with a mean birthweight of

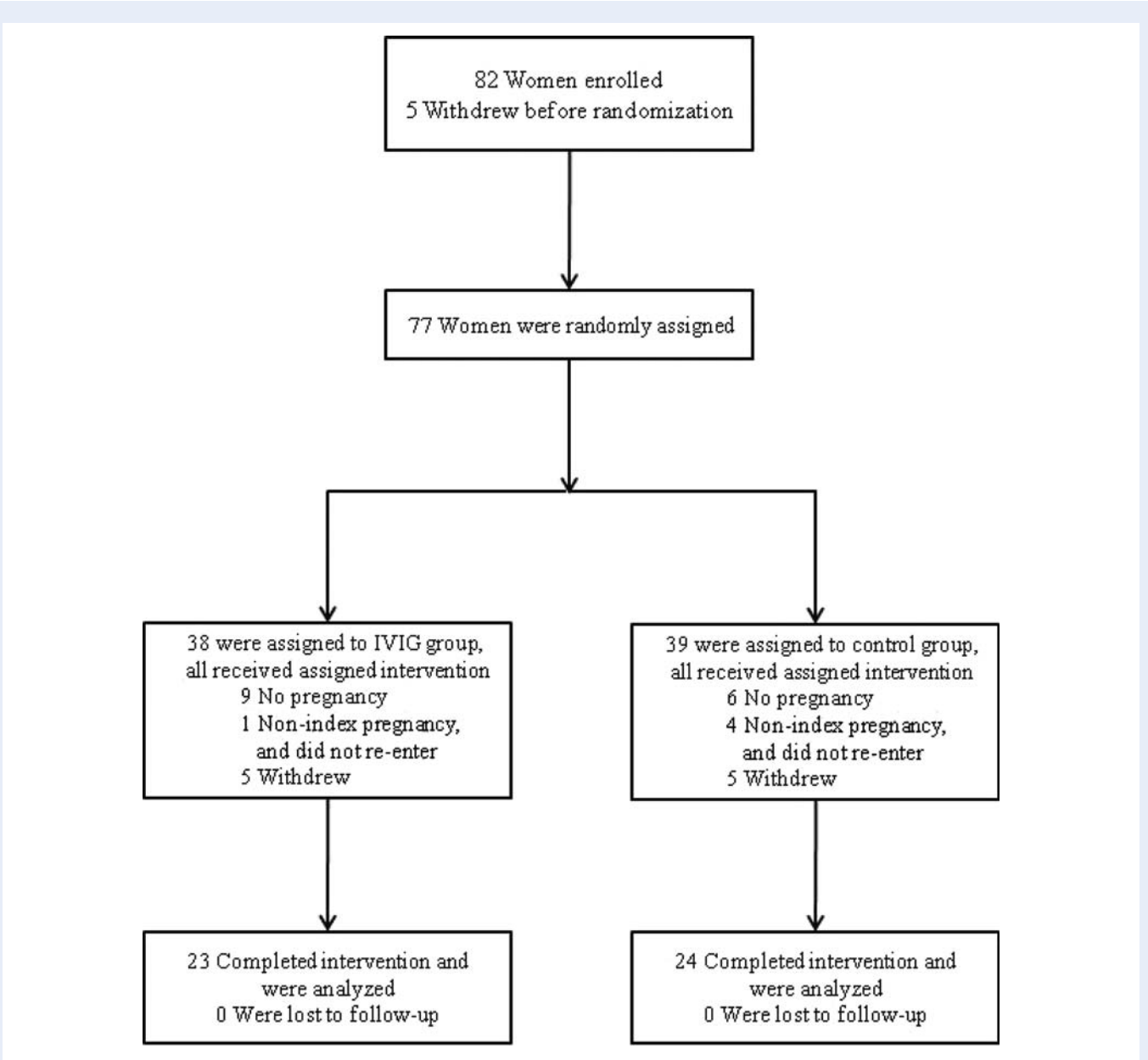

Figure 1 Assignment, treatment and analysis. Women who completed the intervention were those who had an index pregnancy.

3711 g (SD 499; 3120–4820) and 1 was preterm, delivering at 26 weeks following the HELLP Syndrome. In addition, there were three biochemical, two anembryonic, one yolk sac and one fetal miscarriage.

In the control group, there were 12 female newborns, including one set of term female twins and a growth restricted (1675 g) preterm at 36 weeks, and four male newborns, including a term with Down Syndrome (47,XY,+21) and a term 47,XYY with a multicystic dysplastic kidney. There were 11 healthy term and 2 healthy preterm newborns with a mean birthweights of 3271 g (SD 543; 2240–4167) and 3140 g (SD 590; 2240–4167), respectively. Excluding the twins, the mean birthweight of the healthy term newborns ($n = 9$) was 3358 g (SD 557; 2240–4167), which was not significantly different from the IVIG group ($P = 0.123$). In addition, there were four biochemical, four anembryonic and one embryonic miscarriage.

Eight women with an unsuccessful index pregnancy re-entered, receiving the alternate infusion and one subject inadvertently received the same infusion. Five conceived; one of two who received IVIG and two of three who received saline had live births. The two unsuccessful outcomes were both biochemical miscarriages.

The results of the meta-analysis of IVIG for idiopathic secondary recurrent miscarriage are shown in Fig. 2.

Discussion

This is the largest RCT of IVIG for women with idiopathic secondary recurrent miscarriage. Exclusion of prior miscarriages with documented chromosome errors, which resulted in the number of prior miscarriages being greater than four in both groups, served to improve

the homogeneity of the cohort but contributed to the slow enrolment. Women were randomly assigned to receive IVIG or saline, with the first infusion administered prior to ovulation. The study was designed to evaluate the effect of IVIG on pregnancy, therefore, only women who had an index pregnancy were included in the analysis. The interim analysis revealed a much smaller treatment effect than expected, therefore, recruitment was terminated. Primary analysis revealed that IVIG was not of benefit.

Sub-analysis revealed that with documentation of an embryo with cardiac activity at 6 weeks of gestation, the live birth rates in women receiving IVIG or saline were identical and much higher than expected, based on previous RCTs.

Table I Characteristics of the women at enrolment.

Characteristic	IVIG group ($n = 23$)	Control group ($n = 24$)
Mean maternal age at enrolment (SD; range)	36 years (5; 25–44)	35 years (4; 26–43)
Race		
White	20 (87%)	21 (87.5%)
Other	3 (13%)	3 (12.5%)
Mean BMI* at enrolment (SD; range)	26 (4; 20–38)	25 (5; 18–38)
Smoking status		
Present or passive smoker	2 (8.7%)	3 (12.5%)
Past smoker	2 (8.7%)	3 (12.5%)
Non-smoker	19 (82.6%)	18 (75.0%)
Median number of prior pregnancies ≥20 weeks (IQR)	1 (1, 1)	1 (1, 2)
Mean maternal age at prior pregnancy ≥20 weeks (SD; range)	31 years (5.4; 20–39)	29 years (5.9; 17–40)
Mean number of prior miscarriages (SD; range)	4.2 (1.3; 3–8)	5.1 (2.9; 3–16)
Prior miscarriages with chromosome results	19/96 (20%)	20/121 (17%)
Mean maternal age at prior miscarriages (SD; range)	35 years (4.8; 25–43)	–
Mean paternal age at enrolment (SD; range)	38 years (6.7; 23–50)	37 years (5.5; 28–49)

*Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

Although IVIG pilot studies reported encouraging success rates in women with idiopathic secondary recurrent miscarriage, results from prior RCTs have reported contradictory results (Christiansen *et al*., 1995, 2002; Stephenson *et al*., 1998; Jablonowska *et al*., 1999). Our meta-analysis consists of the prior RCTs of Stephenson *et al*., Jablonowska *et al*., and this study.

The single-centered RCT of Stephenson *et al*. (1998) included women with at least two unexplained miscarriages. Although this may initially suggest less stringent criteria, prior miscarriages with documented numeric chromosome errors or unbalanced translocations were excluded because they were 'explained'. At this center, chromosome testing of the second and all subsequent miscarriages was standard of care, therefore, this resulted in a more homogeneous cohort with euploid miscarriages, which, theoretically, would have been more likely to benefit from IVIG. Stephenson *et al*. (2002) reported that 46% of miscarriages in a recurrent miscarriage cohort were non-euploid, using conventional cytogenetic analysis +/− whole genome comparative genomic hybridization. Chromosome testing of prior miscarriages was also performed in the present study, although less consistently. Otherwise, the present trial was similar to the prior trial by Stephenson *et al*. in regard to the diagnostic screening protocol, dosing of IVIG, and timing and frequency of infusions. The live birth rates in both trials were comparable.

In the Jablonowska *et al*. (1999) trial, women with at least three miscarriages were included, with a similar diagnostic screening protocol as the present trial. Infusions were initiated when embryonic cardiac activity was documented by transvaginal ultrasound, therefore, this trial only included clinical pregnancies. The clinical live birth rates were higher in the present trial than in Jablonowska *et al*.; 94% (16/17) compared with 73% (8/11) in the IVIG groups and 94% (15/16) compared with 70% (7/10) in the control groups, suggesting that preconception care may be of benefit.

Preconception care, consisting of either IVIG or saline infusions prior to ovulation in this trial, may improve subsequent pregnancy outcome in women with idiopathic secondary recurrent miscarriage. With the infusions initiated prior to ovulation, rather than with embryonic cardiac activity as in other trials, the clinical live birth rates in the IVIG and control groups were both higher than expected. The effectiveness of preconception care has been demonstrated in women who are at increased risk of adverse pregnancy outcomes (Schutte *et al*., 2009). Clifford *et al*. (1997) previously showed that close monitoring and supportive prenatal care improves subsequent pregnancy outcome in couples with idiopathic recurrent miscarriage.

In summary, our study revealed that IVIG was not of benefit in women with idiopathic secondary recurrent miscarriage. Although the RCT was terminated following an interim analysis, the

Table II Index pregnancy outcomes in women who received IVIG and in controls.

Outcome	IVIG group ($n = 23$)	Control group ($n = 24$)	OR (95% CI)*	*P*-value
Live birth rate	16/23 (70%)	15/24 (63%)	1.37 (0.41–4.61)	0.760
Live birth rate, excluding biochemical miscarriages	16/20 (80%)	15/20 (75%)	1.33 (0.30–5.93)	>0.999
Live birth rate, excluding miscarriages <6 weeks of gestation	16/17 (94%)	15/16 (94%)	1.07 (0.06–18.62)	>0.999

*Odds ratio (95% confidence interval).

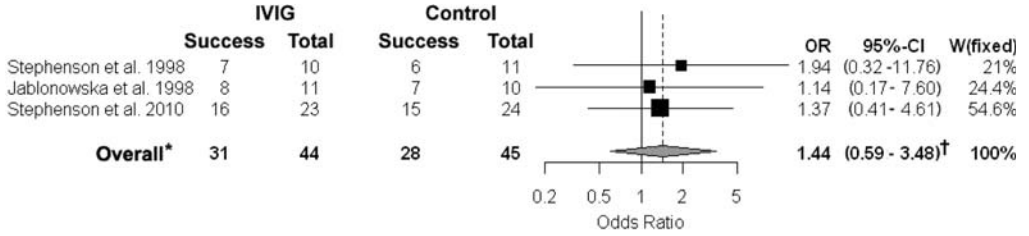

Figure 2 Meta-analysis of live birth rates in randomized placebo-controlled trials of IVIG for idiopathic secondary recurrent miscarriage. *$P = 0.503$. †Test for heterogeneity: $\chi^2(2) = 0.17$, $P = 0.918$.

meta-analysis, which combined these results with two other RCTs, also showed no significant effect of treatment with IVIG, although the overall CI is wide, suggesting that a clinically important potential effect of therapy could not be ruled out. A larger, definitive RCT could be undertaken, but given the results of the meta-analysis, adequate funding could be difficult due to the large sample size that would be required.

Authors' roles

M.D.S. designed the study, obtained funding, supervised data collection from all sites, conducted data analysis and interpretation and wrote the manuscript. M.D.S. enrolled subjects, supervised their care, W.H.K. obtained site funding. M.D.S., W.H.K., S.P. and C.L. enrolled subjects, supervised their care and collected data. W.H.K., S.P. and C.L. critically reviewed the manuscript. P.S. and E.H. enrolled subjects, collected and entered data from all sites and critically reviewed the manuscript. P.S. verified the final data set, assisted with data analysis and prepared the figures and tables. C.H.L. conducted data analysis, provided interpretation and statistical support and critically reviewed the manuscript.

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