Prevention of recurrent spontaneous abortion by intravenous immunoglobulin: a double-blind placebo-controlled study

B.Jablonowska1,4, A.Selbing1, M.Palfi2, J.Ernerudh2, S.Kjellberg1 and B.Lindton3

1Department of Obstetrics and Gynecology, 2Department of Transfusion Medicine and Clinical Immunology, University Hospital, S-581 85 Linköping and 3Department of Obstetrics and Gynecology, Huddinge University Hospital, S-141 86 Huddinge, Sweden

4To whom correspondence should be addressed

The aim of this study was to evaluate the therapeutic efficacy of intravenous immunoglobulin (IVIG) in the prevention of recurrent spontaneous abortion (RSA). In a double-blind, randomized, placebo-controlled study, 41 women with a history of unexplained recurrent spontaneous abortion were treated with IVIG or saline infusions during pregnancy. The birth of a child was considered a successful outcome. The overall success rate was 77% in the IVIG group compared with 79% in the placebo group. For women with primary RSA the success rates were 82 (IVIG) and 89% (placebo), and for women with secondary RSA the rates were 73 (IVIG) and 70% (placebo). We found no statistically significant difference in treatment results between IVIG and placebo.

Key words: intravenous immunoglobulin/recurrent spontaneous abortion

Introduction

Recurrent spontaneous abortion (RSA) is defined as three or more consecutive pregnancy losses and the condition affects 1% of all women (Clifford et al., 1994). RSA is classified as either primary (never achieved a live birth) or secondary (normal pregnancy followed by recurrent abortion) (Heine and Mueller-Eckhardt, 1994). It has been suggested that treatment with i.v. immunoglobulin could be an alternative to immunotherapy with allogenic leukocytes in patients with RSA (Carreras et al., 1988).

The results of pilot studies were promising. The rate of successful pregnancies was 82% for women with RSA (Mueller-Eckhardt et al., 1989; Christiansen et al., 1992). In a later study by Mueller-Eckhardt et al. (1991), the success rate for IVIG treatment was 75% in primary and 60% secondary RSA patients.

We report here our results from a double-blind, randomized, placebo-controlled study on i.v. immunoglobulin in the treatment of unexplained RSA.

Materials and methods

Study design

A double-blind, randomized, placebo-controlled study was done to evaluate the efficacy of i.v. immunoglobulin in the prevention of RSA. The study was approved by the Local Ethics Committee and the Medical Products Agency. The patients were classified as belonging to a primary or a secondary RSA group. Within each RSA group women were separately, centrally randomized by using sealed envelopes at the hospital pharmacy to IVIG or placebo treatment as soon as a transvaginal ultrasound scan had identified fetal heart activity. Based on the assumption that the absolute difference in success rate was 30%, and to obtain an increase from the stipulated 50–80%, we estimated that 80 women (40 in the IVIG and 40 in the placebo group), were needed to detect a statistically significant difference (P < 0.05) with reasonable power.

The study was run at the Departments of Obstetrics and Gynecology University Hospital, Linköping and Huddinge University Hospital.

Patients

Patients with primary RSA (without a live birth) or secondary (a live birth followed by consecutive spontaneous abortions) were included. RSA was defined as three or more consecutive fetal losses before the 20th gestational week. All previous pregnancy losses were confirmed by ultrasound or by histology. Data were taken from the hospital records. Inclusion criteria are presented in Table I. Women with enrollment in other clinical studies or previous inclusion in this study were excluded.

Treatment protocol

Women who fulfilled inclusion criteria were randomized to the IVIG or placebo group. Randomization was done separately for women with primary and secondary RSA.

IVIG and saline (placebo) could not be distinguished, and the codes were blind for both the patients and the hospital staff. IVIG and placebo were distributed 2 h after request and in identical, non-transparent plastic bags. Women received IVIG (20 g Gammonativ®, 400 ml) or placebo (saline, 400 ml) every 3 weeks on five occasions if a viable pregnancy was confirmed by ultrasound before each treatment. By mistake, one patient with a successful outcome of her pregnancy in the IVIG group received only four infusions.

Study medication

Gammonativ® (Pharmacia & Upjohn Plasma Products, Stockholm, Sweden) is a lyophilized powder of normal serum immunoglobulin of human origin aimed for i.v. use. The content of IgA in Gammonativ® is very low (<0.02% of total protein content) and therefore IgA deficiency is not a contraindication for Gammonativ® treatment. Gammonativ® 20 g in 400 ml sterile water was prepared by the hospital pharmacy within 2 h before it was given to the patient as an i.v. infusion.
Informed consent given

Intrauterine pregnancy diagnosed by ultrasound

Laboratory analysis of blocking antibodies performed

No ongoing

No serological sign of hepatitis B, hepatitis C or HIV infection

(<all except four patients, who received the first infusion at 8

weeks gestation or with a birthweight exceeding 999 g.

The mean weight of the newborns was 3493 g

(range 1090–5030) in the IVIG group and 3530 g (range 2780–

4200) in the placebo group. The mean gestational ages were

38.9 weeks (range 27–42 weeks) in the IVIG group and 39.6

weeks (range 38–41 weeks) in the placebo group. There was

only one preterm delivery, in the IVIG group. No congenital

malformations were observed in the newborns.

Six women belonging to the IVIG group reported mild skin

rashes and itching (n = 1), moderate skin rashes and itching

(n = 1), elevated body temperature (n = 2), flush (n = 1)

and severe vaginal bleeding (n = 1). Two women in the

placebo group reported severe itching (n = 1) and mild vaginal

bleeding (n = 1).

Discussion

We examined the efficacy of IVIG to prevent recurrent spontane-

ous abortion and found that there was no significant difference

in rates of successful pregnancies between IVIG and placebo

treatment. The criteria for eligibility to our study prevented

inclusion of women with anticardiolipin antibodies, elevated

APTT and presence of antinuclear antibodies. The study group

was selected to investigate RSA of unknown cause. In a

retrospective, recently published overview, data available on

the possible causes of failure due to spontaneous abortion,

recurrent miscarriage and treatment have been reported (Bulletti

et al., 1996). It has been suggested that some of the idiopathic

recurrent miscarriages might be due to immunological factors

(Lim et al., 1996) and the derangement in cytokine profiles
during pregnancy would be influential in determining a T helper
cells type 1 or T helper cells type 2 immune response
(Mosmann et al., 1986). In our study 37 women were included

in gestational weeks 6–7 after transvaginal ultrasound scanning
had identified fetal heart activity. Three women were included
in gestational week 8 and one in gestational week 9. In the

Danish study, all patients were enrolled and infusions were

started in the fifth gestational week (Christiansen et al., 1995).

In the German study, patients were enrolled between 5 and 8

weeks of pregnancy (The German RSA/IVIG group, 1994).

Thus, we found no statistically significant differences in

treatment results between IVIG and placebo.

Background characteristics of the women in the IVIG and

placebo groups are presented in Table III. The prevalence of

recurrent spontaneous abortion in the IVIG and placebo groups

is presented in Table IV.

Table II. Outcome of pregnancy in relation to treatment with intravenous

immunoglobulin (IVIG) or placebo in 41 women with recurrent spontaneous

abortion (RSA)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Delivery</th>
<th>Abortion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Primary RSA</td>
<td>9/11</td>
<td>82</td>
</tr>
<tr>
<td>(n = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>8/9</td>
<td>89</td>
</tr>
<tr>
<td>Secondary RSA</td>
<td>8/11</td>
<td>73</td>
</tr>
<tr>
<td>IVIG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>7/10</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td>17/22</td>
<td>77</td>
</tr>
<tr>
<td>(n = 41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>15/19</td>
<td>79</td>
</tr>
</tbody>
</table>

Discussion

We examined the efficacy of IVIG to prevent recurrent spontane-

ous abortion and found that there was no significant difference

in rates of successful pregnancies between IVIG and placebo

treatment. The criteria for eligibility to our study prevented

inclusion of women with anticardiolipin antibodies, elevated

APTT and presence of antinuclear antibodies. The study group

was selected to investigate RSA of unknown cause. In a

retrospective, recently published overview, data available on

the possible causes of failure due to spontaneous abortion,

recurrent miscarriage and treatment have been reported (Bulletti

et al., 1996). It has been suggested that some of the idiopathic

recurrent miscarriages might be due to immunological factors

(Lim et al., 1996) and the derangement in cytokine profiles
during pregnancy would be influential in determining a T helper
cells type 1 or T helper cells type 2 immune response
(Mosmann et al., 1986). In our study 37 women were included

in gestational weeks 6–7 after transvaginal ultrasound scanning
had identified fetal heart activity. Three women were included
in gestational week 8 and one in gestational week 9. In the

Danish study, all patients were enrolled and infusions were

started in the fifth gestational week (Christiansen et al., 1995).

In the German study, patients were enrolled between 5 and 8

weeks of pregnancy (The German RSA/IVIG group, 1994).
Table III. Background data of the women in the study

<table>
<thead>
<tr>
<th></th>
<th>IVIG</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Age at the first infusion (years)</td>
<td>30.0ª</td>
<td>21–39</td>
</tr>
<tr>
<td>No of previous abortions</td>
<td>3ª</td>
<td>3–6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.2ª</td>
<td>19.0–36.8</td>
</tr>
</tbody>
</table>

ªNo statistical difference between groups (Mann–Whitney U-test), *NSª, *NSª, *NSª.

IVIG = intravenous immunoglobulin.

Table IV. Prevalence of recurrent spontaneous abortion (RSA) in the study group

<table>
<thead>
<tr>
<th>No of previous abortions</th>
<th>IVIG</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 22</td>
<td>n = 19</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

IVIG = intravenous immunoglobulin.

Treatment was initiated before conception in the American trial (Coulam et al., 1995) and in the Canadian trial (Stephenson et al., 1998). In this way, women who would succumb to very early spontaneous abortion were included. The selection criteria and the time of the first infusion of IVIG or placebo might account for the higher pregnancy rate in this study. However, we have observed few abortions at gestational ages <6 weeks in the group of women enrolled to participate in the study. Thus, using the patient selection criteria and treatment protocol reported in the present trial, IVIG seems to lack significant therapeutic effectiveness. We also found that 79% of women in the placebo group had babies, which was far better than the presumed 50% that we derived from historical data and used in our calculations. A recent study (Clifford et al., 1997) showed that nearly 70% of women with first trimester unexplained recurrent spontaneous abortion could achieve a livebirth in the next pregnancy with supportive care alone. The success rate was nearly 80% if women were aged <40 years and number of previous miscarriages was less than six.

Due to the result of the half time evaluation, the study was terminated and only half of the planned number of patients was included. This makes the estimate of the true treatment results for IVIG and placebo more uncertain, i.e. the 95% confidence intervals were wide for all groups. Hence, our data are insufficient to test the original hypothesis.

The results of studies published before this study were promising (Mueller-Eckhardt et al., 1989, 1991; Christiansen et al., 1992). Before this study was completed, three placebo-controlled studies were published. One study showed that IVIG treatment was beneficial (Coulam et al., 1995) whereas two other studies could not demonstrate that IVIG treatment was efficient (The German RSA/IVIG Group, 1994; Christiansen et al., 1995). However, when the results of these placebo-controlled trials were summarized, a significant result was achieved (Christiansen, 1996). The success rate was 64% in the IVIG group and 47% in the placebo group ($P < 0.05$). Recently two placebo-controlled studies (Perino et al., 1997; Stephenson et al., 1998) have shown no effect of IVIG in RSA patients.

We observed, like other authors (Clifford et al., 1994), that some of the couples had difficulties in becoming pregnant and it is also known that patients who achieve pregnancy more quickly might also have a better prognosis (Clark and Coulam, 1996). It is therefore not certain that the observed ‘baby rate’ after three consecutive spontaneous abortions is close to 80%.

We used saline as placebo in this study in contrast to most previously published placebo-controlled studies where albumin was used in different concentrations: 5% albumin (The German RSA/IVIG Group, 1994), 1.5% albumin (Christiansen et al., 1995) and 0.5% (Coulam et al., 1995). The role of albumin as placebo has been questioned (Rewald et al., 1995). An immunomodulating effect of albumin in concentrations >0.5% could not be excluded (Coulam et al., 1995). In a recently published study, saline was used as placebo (Stephenson et al., 1998).

A pregnancy loss is an emotional event for the couple. The positive role of psychological influence (‘tender loving care’) has been demonstrated for pregnancy success in women with RSA (Stray-Pedersen and Stray-Pedersen, 1984). The excellent outcome of pregnancy after unexplained recurrent first trimester miscarriage with supportive care alone has been documented recently (Clifford et al., 1997). We can neither deny nor verify that we have had such an effect in both IVIG and placebo groups in our study.

To conclude, we found that women with RSA have a better prognosis than presumed and that IVIG does not improve the prognosis compared to placebo in a setting where the couples are given extra care.

Acknowledgements

This study was supported financially by Pharmacia & Upjohn AB, Plasma Products. We are grateful to all the colleagues who provided patients who participated in this study.

References


Intravenous Ig for recurrent abortion


Received on June 29, 1998; accepted on November 12, 1998