Possible Effect of Intravenous Immunoglobulin Therapy for Unexplained Secondary Recurrent Miscarriage

*Saad F.A., *Shahata M.A.M. and **Christiansen O.B.

* Recurrent Pregnancy Loss Clinic, Department of Obstetrics and Gynecology, Women's Hospital
Hamad Medical Corporation, Doha, Qatar

**Fertility Clinic 4071, Rigshospitalet, Copenhagen, Denmark

Abstract:
Objective. To review the role of intravenous immunoglobulin (IVIG) in the prevention of recurrent miscarriage (RM).

Methods. In a prospective controlled clinical trial, 40 women with a history of unexplained RM were treated with IVIG, according to a specific protocol and compared to another 40 women who had the same condition and treated with tender loving care and vitamins only. The birth of a child of more than 28 weeks gestation was considered a successful outcome.

Results. The overall success rate was 60% in the IVIG group compared with 52.6% in the control group (P = 0.65). The success rates for women with primary RM were 56.3% for IVIG group and 68.8% for the control group (P = 0.72). The success rates for women with secondary RM were 62.5% and 41.7% respectively (P = 0.25). None of the previous results is statistically significant.

Conclusion. Women with unexplained RM in general have a good prognosis. IVIG did not improve the prognosis significantly in the total group of patients compared with controls. However, further investigations are needed to explore whether the 21% therapeutic benefit of IVIG in patients with secondary RM indicates that the treatment is efficient in this subset of patients.

Introduction:
Recurrent miscarriage (RM) is defined as three or more consecutive pregnancy losses and the condition affects 1% of all women (Clifford et al., 1994). Passive immunization with intravenous immunoglobulin (IVIG) was proposed as a promising treatment in uncontrolled trials (Mueller-Eckhardt et al. 1989, 1991; Christiansen et al., 1992). So far about seven placebo-controlled trials of IVIG treatment of patients with unexplained recurrent miscarriage have been published with diverging results. Three trials (Coulam et al., 1995; Christiansen et al., 1995; Christiansen et al., 2002) gave evidence of a 24-34% therapeutic gain from IVIG compared with placebo, whereas the other four trials (The German RSA/IVIG Group, 1994; Perino et al., 1997; Stephenson et al., 1998; Jablonowska et al., 1999) could not find any beneficial effects.

We report here our results from a prospective controlled clinical trial on IVIG in the treatment of unexplained RM. Only patients with at least three miscarriages were included and a higher dose of IVIG was given, using an intensive protocol, in order to optimize the chance of detecting a possible treatment effect.

Materials and Methods:
Study design:
A prospective, controlled clinical trial was done to evaluate the efficacy of IVIG in the prevention of unexplained RM. The study was approved by the local Research and Ethics Committee.

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 control group) were needed to detect a statistically significant difference (P < 0.05) with reasonable power.

The study was run at the Recurrent Pregnancy Loss Clinic (RPL Clinic), Department of Obstetrics and Gynecology, Hamad Medical Corporation, Doha, Qatar.

Patients:
RM was defined as three or more consecutive fetal losses before the 20th gestational week. Patients with unexplained primary RM (without a previous live birth) or secondary RM (at least one live birth followed by consecutive miscarriages) were included. All previous pregnancy losses were confirmed by ultrasound or by histology. Inclusion criteria are presented in Table I.

Patients who received IVIG were required to have normal serum IgA, normal liver and kidney function tests and no serological evidence of hepatitis B, hepatitis C or HIV infection.
They had full explanation of the IVIG treatment and its possible side effects. An informed consent was taken.

A control group, who had the same inclusion criteria, was also selected. They were recruited from a database of patients who attended the RPL Clinic during the same period and who refused to have the IVIG therapy. Those patients did not have any active treatment other than tender loving care, folic acid and multivitamins. They were matched for maternal age, number of last miscarriages and clinical type of last miscarriages (primary or secondary). If there were several suitable (matching) controls within a category then the first one was selected irrespective of the outcome of pregnancy.

Table I: The criteria for inclusion in the study

<table>
<thead>
<tr>
<th>Criteria for Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least three confirmed successive and unexplained miscarriages including losses in the 1st and 2nd trimesters.</td>
</tr>
<tr>
<td>Normal chromosomal analysis of the couple.</td>
</tr>
<tr>
<td>Normal finding at examination by hysterosalpingography or hysteroscopy.</td>
</tr>
<tr>
<td>Normal thyroid function tests (thyroid stimulating hormone, free thyroxin).</td>
</tr>
<tr>
<td>No evidence of autoimmune rheumatic diseases or insulin-dependent diabetes mellitus.</td>
</tr>
</tbody>
</table>

Positive pregnancy test as documented by serum β-hCG

*β-hCG = Human chorionic gonadotropin

**IVIG Treatment protocol**

Women who fulfilled inclusion criteria were admitted to the Day-Care Unit for IVIG therapy at 5-6 weeks gestational age. An intravenous catheter is inserted with 500 ml of normal saline. Vital signs were checked before starting IVIG, 15 minutes later and at the end of the infusion. An IVIG dose of approximately 0.5 g/kg of body weight was then infused at an initial rate of 20 drops/minutes and then increased after 15 minutes to 60 drops/minutes if the vital signs were normal and no adverse reaction was noticed on the patient. The patient was encouraged to drink at least 12 liters of water during the infusion to counteract the side effects of the treatment. These side effects were recorded properly in the progress notes.

If the obstetric history of the patient indicated 1 s1 trimester miscarriages only, then two more infusions were given at 7 and 9 weeks gestation using the same doses and precautions as for the first dose. If the patient had a previous unexplained 2nd trimester pregnancy loss, then the IVIG infusions were continued every 3 weeks until the possibility of miscarriage is excluded.

Before starting the repeated IVIG doses an ultrasound scan was performed to confirm viability of the fetus. If the gestational sac was seen without evidence of fetal viability, then the treatment is cancelled and considered as failure. If transvaginal ultrasound failed to show any evidence of intrauterine pregnancy, then serial B-hCG (human chorionic gonadotropin) is recommended to rule out ectopic pregnancy. Patients with biochemical and ectopic pregnancies were excluded from the study and replaced by other candidates.

**Study medication**

Nordimmum® (HemaSure A/S, Sauntesvej 13, DK-2820 Gentofte, Denmark) is a lyophilized powder of normal serum immunoglobulin of human origin aimed for i. v. use. Nordimmum contained 4.6% human IgG, 1.5% human albumin, 4.6% sucrose and 0.15 mol/l sodium. Nordimmum was dissolved in the accompanying bottle of sterile water using aseptic technique and given to the patient immediately.

**Measures of effect**

The treatment is considered successful if the pregnancy resulted in the delivery of a live born child of more than 28 weeks gestation.

**Statistics**

All data were entered into and analyzed with SPSS program version 9. Categorical variables were analyzed using either the i test or Fisher’s exact test. The Student’s t-test was used to compare the background and other numerical data. Relative risks (RR) and their 95% confidence limits (95% CI) were given when appropriate. A P value of < 0.05 was considered statistically significant.

**Results:**

From June 1999 to June 2001, a total of 562 patients attended the RPL Clinic. During the same period, 40 patients fulfilled the criteria of inclusion and received IVIG (study group). They were compared with another 40 patients (control group), who are matched for maternal age, number of previous miscarriages and type of previous miscarriages. There were 16 primary and 24 secondary aborters in each group. Background characteristics of the women in the IVIG and control groups are summarized in Table II.

Treatment was started at gestational weeks 5-6 in all except three patients, who received the first infusion at 7(n = 2) or 8(n = 1) gestational weeks. After the first IVIG dose, one woman had ectopic pregnancy and three were considered biochemical pregnancies as their serum β-hCG was declining without evidence of pregnancy on transvaginal ultrasound. All those four women were excluded from the study and replaced with new candidates.

As evident from Table III, 24 of the 40 patients in the IVIG group had live births (60%), compared to 21 of the 40 controls...
Possible Effect of Intravenous Immunoglobulin Therapy...

Table II: Background data of the women in the trial *

<table>
<thead>
<tr>
<th></th>
<th>IVIG** (n = 40)</th>
<th>Controls (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first infusion (years)</td>
<td>33.1 ± 5.8</td>
<td>31.6 ± 5.3</td>
</tr>
<tr>
<td>No. of previous miscarriages</td>
<td>4.4 ± 1.5</td>
<td>4.2 ± 1.2</td>
</tr>
<tr>
<td>No. of previous deliveries</td>
<td>1.5 ± 1.6</td>
<td>1.5 ± 1.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.3 ± 5.4</td>
<td>30.3 ± 5.6</td>
</tr>
</tbody>
</table>

* No significant difference between groups (Student’s t-test)  ** IVIG = Intravenous Immunoglobulin.

Table III: Effect of clinical type and number of previous miscarriages on the live birth rate.

<table>
<thead>
<tr>
<th></th>
<th>IVIG* Group</th>
<th>Control Group</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sub-groups</td>
<td>24/40</td>
<td>60</td>
<td>21/40</td>
<td>52.5</td>
</tr>
<tr>
<td>Primary RM**</td>
<td>9/16</td>
<td>56.3</td>
<td>11/16</td>
<td>68.8</td>
</tr>
<tr>
<td>Secondary RM**</td>
<td>15/24</td>
<td>62.5</td>
<td>10/24</td>
<td>41.7</td>
</tr>
<tr>
<td>&gt; 4 Miscarriages</td>
<td>12/24</td>
<td>46.2</td>
<td>12/15</td>
<td>36</td>
</tr>
<tr>
<td>!5 Miscarriages</td>
<td>5/14</td>
<td>35.7</td>
<td>4/14</td>
<td>28.6</td>
</tr>
</tbody>
</table>

* IVIG = Intravenous immunoglobulin  ** RM = Recurrent miscarriage

Table IV: Obstetric outcome in IVIG and Control groups.

<table>
<thead>
<tr>
<th></th>
<th>IVIG* Group</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean birth weight (g) ± SD (range)</td>
<td>3096 ± 639 (1465 - 3940)</td>
<td>3087 ± 627 (1890 - 3910)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean gestational age (wk) ±SD (range)</td>
<td>37.4 ± 2.4 (30 - 42)</td>
<td>38.4 ± 1.9 (34 - 41)</td>
<td>NS</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>6/24 (25%)</td>
<td>3/18 (16.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>3/24 (12.5%)</td>
<td>3/18 (16.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Admission to NICU**</td>
<td>2/24</td>
<td>1/18</td>
<td>NS</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 5 minutes</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Presently above 28 weeks</td>
<td>0</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>

* IVIG = Intravenous immunoglobulin  ** NICU = Neonatal Intensive Care Unit

(52.5%). This 7.5% difference in favor of IVIG is not statistically significant (P=0.65, RR 1.1, 95% CI: 0.8-1.7). More favorable effect of IVIG (21% success gain, RR 1.5, 95% CI 0.9-2.6) is shown in the subgroup of patients with secondary RM. The obstetric outcome of the successful pregnancies in both groups is shown in Table IV.

Side effects in the IVIG group included headache (12/40, 30%), feeling cold (7/40, 17.5%), asthmatic symptoms (3/40, 7.5%), elevated body temperature (2/40) and vomiting (2/40). All of these symptoms were transient, mild, occurred toward the end of the infusion, and did not require more than symptomatic treatment. Although the infusion rate was reduced dur-
ing the reaction but it was not stopped in any of the cases.

Discussion:

Recurrent miscarriage is a genuine problem in the Middle East where women have higher incidence of obesity, polycystic ovaries and diabetes. They have also cultural tendency to have large families and continue to get pregnant even at late reproductive age. At this age, various immunologic abnormalities that interfere with successful pregnancy become common. These immunologic abnormalities appear to be caused by a shift in the immune response away from the so-called Th2 (humoral) pattern that promotes pregnancy toward the so-called Th1 (cellular) pattern that is deleterious to reproductive outcome (Piccinni et al., 1998; Sacks et al., 1999).

In fact, IVIG treatment for RM has been controversial. Several studies have shown significant benefit of IVIG treatment (Coulam et al., 1995; Christiansen et al., 1995). However, other studies have failed to confirm this beneficial effect (The German RSA/IVIG Group, 1994; Perino et al., 1997; Stephenson et al., 1998; Jablonska et al., 1999).

In the German multicentre trial, IVIG was no more effective than the albumin placebo (RR 0.9, 95% CI 0.6-1.4). In the American trial, IVIG was 1.7 fold (95% CI 0.9-2.9) more effective than placebo (Coulam et al., 1995). In the Danish trial among women with secondary RM, IVIG was 1.8 fold (95% CI 0.7-5.1) more effective than placebo (Christiansen et al., 1995). In the Canadian trial, IVIG was ineffective in primary RM at 1.8 fold (95% CI 0.3-11.3) more effective than placebo in secondary RM (Stephenson et al., 1998). In the Italian trial, IVIG was 0.7 fold (95% CI 0.1-3.6) less effective than placebo (Perino et al., 1997).

In the Swedish trial, Jablonska et al. (1999) could not find any significant difference in treatment results between IVIG and placebo. The overall success rate was 77% in the IVIG group compared with 79% in the placebo group. The apparently higher success rates in both groups compared to our results (60% and 52.5% respectively) may be attributed to the late inclusion of the patients in the Swedish study, at gestational weeks 6-7, after the transvaginal ultrasound scanning had identified fetal heart activity; while in our study the patients were enrolled at gestational weeks 5-6.

The contradictory results of the trials of IVIG treatment of RM might be explained by different selection criteria of the patients, especially with regard to the number of previous fetal losses, different starting time of the infusions and different IVIG doses. RM patients with only two previous miscarriages generally exhibit a good prognosis, whereas the prognosis worsens and the evidence of an immunological cause increases in women with a higher number of miscarriages (Christiansen et al., 1998; Carp et al., 2001; Pfeiffer et al., 2001). In several previous trials, the starting time of infusions was at the first ultrasonic detection of fetal heart action in gestational weeks 6-7 (The German RSA/IVIG Group, 1994; Jablonska et al., 1999).

Initiation of treatment at that time may be too late to prevent early miscarriages because it may take weeks for the effects of IVIG to be complete, whereas the spontaneous chance of live birth increases after the detection of fetal heart action. The IVIG doses generally given in published trials have been significantly lower than those given in most autoimmune diseases (Ronda et al., 1993).

Daya et al. (1998) performed a meta-analysis of four randomized, double-blind trials comparing IVIG with placebo for treatment of RM. Two of the trials showed an increase in successful pregnancy outcome with IVIG treatment and two did not. The overall OR was 1.5 (95% CI, 0.8-2.6) in favor of IVIG, with an absolute treatment effect of 10.1% (95% CI, 4.8-24.6). This meta-analysis suggested that IVIG might have a role in the treatment of secondary RM.

As evident from table III, we examined the efficacy of IVIG to prevent unexplained RM and found that it does not prevent further losses among women with primary RM. A potential effect has been demonstrated in patients with secondary RM, as the live birth rate was 62.5% in the IVIG group compared to 41.7% in the control group (RR 1.595% CI 0.9-2.6).

The beneficial effect of IVIG therapy on patients with secondary RM was recently supported by a randomized, double-blind, placebo controlled trial (Christiansen et al., 2002). They found a 58% live birth rate in the IVIG group compared to 24% in the placebo group (P < 0.02. RR 2.595% CI 1.2-5.4).

Severe side effects of IVIG are rare in well-selected patients. Mild side effects including fever, malaise, myalgia and headache occur in 4% of patients (Thornton 1993). In our study, the women had a higher incidence of minor and transient side effects (up to 30%). However, no severe side effects were reported in our cases.

In conclusion, Women with unexplained RM in general have a good prognosis. IVIG did not improve the prognosis significantly in the total group of patients compared with controls. However, further investigations are needed to explore whether the apparent therapeutic benefit of IVIG in patients with secondary RM indicates that the treatment is efficient in this subset of patients.
References:


