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Clinical and Applied Immunology Reviews 2 (2002) 187–199

Clinical and Applied Immunology Reviews

Intravenous immunoglobulin (IVIG) therapy for immunologic abortion

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Received 5 November 2001; Received in revised form 27 February 2002; Accepted 4 March 2002.

Abstract

Recurrent pregnancy loss associated with immunologic abnormalities has been termed immunologic abortion. Immunologic abortion occurs primarily in women over the age of 30 years and may affect either natural or in-vitro fertilization (IVF)-induced pregnancy. In this article, we review the humoral and cellular immunologic abnormalities that have been associated with this form of recurrent abortion, and we discuss treatment options for women with this disorder. In particular, we have focused on intravenous immunoglobulin (IVIG) treatment for immunologic abortion. We analyzed 14 studies of IVIG therapy for recurrent loss of natural or IVF-induced pregnancies. Factors associated with successful use of IVIG were: (a) Older mean patient age; (b) inclusion of women with immunologic abnormalities; (c) initiation of IVIG therapy prior to conception; and (d) repeated administration of IVIG at physiologic intervals during pregnancy. When used according to these parameters, IVIG therapy is safe and effective for women with immunologic abortion. Appropriate patient selection and rational timing of IVIG administration are crucial factors that determine the success of this treatment.

Keywords: Abortion; IVIG; Miscarriage; Autoimmunity; Natural killer cells

1. Introduction

Recurrent abortion is a growing problem in our society, particularly among women over 30 years of age [1,2]. In these women, recurrent abortion occurs with both natural and in-vitro fertilization (IVF) techniques [3–5], and there is increasing evidence that immunologic factors

Abbreviations: ALI, allogeneic lymphocyte immunization; IVF, in-vitro fertilization; IVIG, intravenous immunoglobulin; NK, natural killer cells.

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1529-1049/02/$ – see front matter
PII: S1529-1049(02)00046-6

play an important role in the failure of both natural and IVF-induced pregnancies [6–13]. These factors include various humoral abnormalities such as antiphospholipid antibodies, antithyroid antibodies, antinuclear antibodies, antiovarian antibodies and increased IgM levels, as well as cellular components such as increased natural killer cells and decreased suppressor T-cells. The immunologic factors may be associated with toxicity to the trophoblast, placenta or fetus, leading to recurrent pregnancy loss [14–18]. The association of recurrent natural or artificial pregnancy loss with immunologic abnormalities has been termed immunologic abortion.

Treatment of immunologic abortion has been controversial [19–39]. In this article, we review the immunologic factors that are associated with recurrent pregnancy loss, and we discuss the treatment options for women with immunologic abortion. In particular, we have focused on intravenous immunoglobulin (IVIG) treatment for this disorder, and we have performed a critical analysis of factors that determine the success or failure of IVIG trials for recurrent loss of natural or IVF-induced pregnancies.

2. Immunologic abortion

Recurrent abortion is a growing problem in industrialized countries where women are delaying childbearing into their 30s and 40s [1,2]. A population-based study from Sweden found that the risk of abortion almost tripled from 8.7% at age 24 to 24.7% at age 35 [2]. By age 42 the risk of abortion was 51%, and by age 45 the risk was 74.7% [2]. In younger women with recurrent abortion, a number of risk factors have been identified, including gene mutations, structural abnormalities of the uterus, poorly controlled diabetes and smoking [1]. However in the older age group, various immunologic abnormalities that interfere with successful pregnancy become common [40–45]. 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 [44,45]. This shift may be an adjustment of the immune response from the reproductive mode of younger women to the pathogen-defense mode of older women [43]. Because of this immunologic association with recurrent pregnancy loss, the term immunologic abortion has been used to describe women with recurrent abortion and the immunologic abnormalities described below.

Various IVF techniques have been advocated for women with recurrent abortion. Although IVF treatment may be useful for women with anatomic or genetic abnormalities, the overall success rate with IVF has only been on the order of 12–24% [5,32,36]. In older women with documented immunologic abortion, the success rate with IVF may be as low as 1–2% [39]. Since IVF failure may be due to the same immunologic factors that interfere with natural pregnancy in these women, the concept of immunologic abortion has been extended to include loss of both natural and IVF-induced pregnancies [4,18,36].

The concept of immunologic abortion was established with the recognition that recurrent miscarriage is associated with the presence of antiphospholipid antibodies, including the lupus anticoagulant [6,16,17]. Experimental evidence indicates that active production or passive infusion of these antibodies can induce fetal loss in mice [16], and a direct effect of these complex antibodies on vascular thrombogenesis in the placental circulation has been postulated

[17]. At the same time, other autoimmune phenomena have been linked to recurrent abortion [7–11,18]. In retrospective studies, antinuclear antibodies were found to be five times more common in women with unexplained recurrent miscarriage compared to women with successful pregnancies [7], and antithyroid antibodies were reported to be twice as common in women who miscarried compared to fertile controls [8,9]. It has been postulated that antithyroid antibodies are associated with subtle abnormalities in thyroid function that contribute to pregnancy loss [9]. Recent studies have indicated a role for antiovarian antibodies in recurrent failure of natural and IVF-induced pregnancy [18]. Other non-specific humoral abnormalities such as increased IgM levels [6] and IgA deficiency [40] have been associated with autoimmunity and may be markers of immunologic abortion [6,35]. In addition, endometriosis is associated with autoantibody production in both serum and peritoneal fluid, and this autoimmune response may contribute to fetal wastage [41].

In addition to these humoral abnormalities, disorders of cellular immune function have been noted in women with recurrent miscarriage [12–15]. Increased numbers of natural killer (NK) cells have been found in as many as 52% of these women [12], and increased activation of macrophages and NK cells has been noted in recurrent aborters [12–15]. Activation of these cells may be triggered by sperm or trophoblast antigens and may occur prior to conception or very early in pregnancy [13]. Excessive activation may be the consequence of a decrease in suppressor/cytotoxic CD8 T-cells, resulting in an increased CD4/CD8 T-cell ratio [35]. Alloreactivity related to anti-lymphocyte antibodies may play a role in these cellular changes [34], and dysregulation of the cellular immune response may also explain production of the autoantibodies described above. Thus immunologic abortion encompasses a broad range of immune dysfunction that goes beyond a particular autoantibody or cellular component. This immune dysfunction may be present prior to conception and may persist beyond the first trimester of pregnancy [7,8,13]. Although treatment aimed at the consequence of immune dysfunction may be useful (such as anticoagulation for antiphospholipid antibodies), a more logical approach is a therapy aimed at the underlying immune disorder [35], as discussed below.

We initially characterized immunologic abortion in a cohort of 47 women [35]. We have now extended this evaluation to a cohort of 83 women with at least three recurrent miscarriages (Tables 1 and 2). The mean patient age was 37 years with a range of 28–49 years, and the median age was 37 years. The mean number of prior abortions was 3.7 with a range of 3–12, and the median number of abortions was three. Among these women, 83% had never had a successful pregnancy (primary recurrent abortion) while 17% had one prior successful pregnancy (secondary recurrent abortion). Twenty-two women (27%) used natural fertilization methods while 61 (73%) used IVF techniques (Table 1). IVF failure was defined as successful implantation with subsequent embryonic or fetal demise.

In this extended cohort, the most common immunologic abnormality was the presence of antithyroid antibodies (53%), followed by antiphospholipid antibodies (36%), increased natural killer cells greater than 12% of total lymphocytes (35%), antinuclear antibodies (25%), increased IgM level (22%), increased CD4/CD8 T-cell ratio (14%) and antiovarian antibodies (11%). In addition, IgA deficiency was found in two patients, and seven patients had endometriosis (Table 2). Patients with increased CD4/CD8 T-cell ratios had normal levels of CD4 T-cells but decreased CD8 T-cells. Further testing in these patients revealed low or ab-

Table 1
Clinical characteristics of women with recurrent abortion

Variable	Value
Number of patients	83
Mean age, years (range)	37 (28–49)
Median age, years	37
Mean number of abortions (range)	3.7 (3–12)
Median number of abortions	3
Number of patients (%) with:	
–Primary recurrent abortion	69 (83)
–Secondary recurrent abortion	14 (17)
In-vitro fertilization (%)	61 (73)
No in-vitro fertilization (%)	22 (27)

sent suppressor/cytotoxic (CD57) CD8 T-cells. In 70% of patients, more than one immunologic abnormality was detected. In particular, the non-specific findings of increased IgM levels, increased CD4/CD8 T-cell ratios, IgA deficiency and endometriosis were always associated with a targeted immunologic abnormality, particularly the presence of antiphospholipid antibodies and antithyroid antibodies. None of the patients had clinical diseases associated with these immunologic abnormalities.

In summary, immunologic abortion appears to be prevalent in older women with recurrent failure of natural or artificial pregnancy. Many of these women have multiple immunologic abnormalities, reflecting a poorly characterized underlying immune dysfunction that contributes to pregnancy loss.

3. Treatment of immunologic abortion

Treatment of immunologic abortion has been controversial. The initial association with the lupus anticoagulant syndrome and antiphospholipid antibody, which promotes vascular thrombosis, prompted the use of anticoagulant strategies using aspirin and heparin [19,20]. Although this approach has been successful in about 50% of cases, significant bleeding oc-

Table 2
Immunologic abnormalities in women with recurrent abortion[a]

Test result	% Positive
Antiphospholipid antibodies	36%
Antithyroid antibodies	53%
Antinuclear antibodies	25%
Antiovarian antibodies	11%
Increased natural killer cells	35%
Increased IgM level	22%
Increased CD4/CD8 T-cell ratio	14%
IgA deficiency	2%
Endometriosis	8%

[a]Note that 70% of patients had more than one immunologic abnormality.

curs in about 16% of women [21], and fatal hemorrhage has been reported in at least one patient [22]. Subsequent recognition of other immunologic factors prompted the use of immunomodulatory treatments for women with recurrent miscarriages. Corticosteroid therapy has been shown to be ineffective for immunologic abortion, and this treatment is associated with numerous complications during pregnancy, especially pre-term delivery [23]. Allogeneic lymphocyte immunization (ALI) usually involving maternal immunization with paternal lymphocytes has been used successfully in some women with immunologic abortion [24]. However the overall response rate has not been encouraging, and ALI has been associated with severe allergic reactions and painful scarring at the immunization site [25]. The procedure is also nonstandardized and labor-intensive.

IVIG treatment for immunologic abortion has also been controversial [26–39]. Several studies have shown significant benefit of IVIG treatment in women with recurrent miscarriages or IVF failure using either standard-dose (400–500 mg/kg) or low-dose (200–250 mg/kg) IVIG regimens [33–39]. However, other studies have failed to confirm this beneficial effect [26–32]. A major yet often unrecognized problem with the latter studies involves poor patient selection, with de facto inclusion of younger women and deliberate exclusion of older women [26–32]. The resultant comparison between younger women who have a high pregnancy success rate without any treatment has significantly biased the outcome of these studies against IVIG therapy [46]. Other problems include lack of patient screening for immunologic abnormalities [26,27,31,32], exclusion of patients with these abnormalities [28–30] and use of irrational or excessive IVIG regimens [26–32]. These concerns are discussed below.

Our initial evaluation of low-dose IVIG therapy (200 mg/kg) for immunologic abortion indicated that this treatment appeared to be effective for women with recurrent abortion following natural or IVF-induced pregnancy [35]. In that study, IVIG was administered as a single dose prior to conception and then at monthly intervals through the end of the second trimester of pregnancy. We employed the same treatment approach in the extended cohort described above (Fig. 1). Of the 83 patients, 61 underwent IVIG therapy while 22 patients refused treatment. Of the 61 treated patients, 40 became pregnant and had pregnancy outcomes that could be evaluated. There was no difference in mean age, number of prior abortions, use of IVF therapy or type of immunologic abnormalities between the women who became pregnant and those who did not. Of the 40 pregnant women, 35 received IVIG therapy (or intended to receive it) for 26–30 weeks of gestation. Of these patients, 31 (89%) had a term pregnancy while four patients miscarried during the first trimester. The karyotype of the abortus was not determined in these patients. Five patients discontinued IVIG therapy after 10–12 weeks of gestation, and four of these women (80%) had successful pregnancies. The fifth discontinued treatment at 10 weeks and miscarried at 15 weeks of gestation. The karyotype of the abortus was normal.

Of the 22 patients who refused IVIG therapy, 15 patients subsequently became pregnant and 13 (87%) had first-trimester miscarriages. The overall pregnancy success rate in the IVIG-treated group (88%) compared to the untreated group (13%) was statistically significant ($P = 0.001$). There was no difference between the treated and untreated women in terms of mean age, number of prior abortions, use of IVF therapy or type of immunologic abnormalities.

As in our previous study [35], IVIG was well tolerated by the extended cohort (Table 3). A stereotypical infusion reaction characterized by chills, nausea and vomiting was seen in 10%

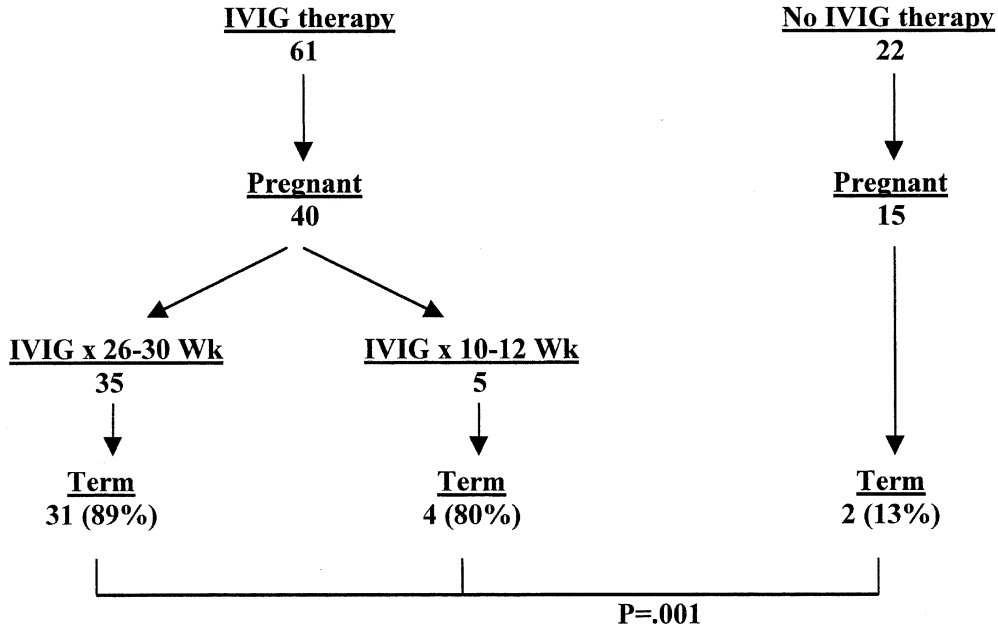

Fig. 1. Pregnancy outcomes in 83 study subjects.

of patients. This reaction could be avoided by changing the brand of IVIG, suggesting that it was probably due to a brand-specific preservative in the IVIG preparation [35]. None of the patients discontinued IVIG therapy because of this side effect. Significant toxicity to mother or fetus was not seen. Although renal insufficiency has recently been associated with intensive IVIG therapy (1.2–2.0 gms/kg over 3–5 days) [52], this complication did not occur with the low-dose IVIG regimen used in the study. IVIG was always administered by slow infusion, and rate-related reactions to the IVIG were not encountered.

In summary, our extended cohort study confirmed that IVIG therapy is safe and effective for women with immunologic abortion. The study also suggested that a longer course of IVIG might be more effective in these women because fetal loss may occur after the first trimester (see below).

Table 3
Side effects of IVIG therapy during 40 pregnancies

Side effect	Number (%) positive
Infusion reactions	4 (10%)
Headache	4 (10%)
Preterm labor	3 (8%)
Ectopic pregnancy	1 (3%)
Intrauterine growth retardation	0
Fetal abnormalities	0

Table 4
IVIG regimens for recurrent abortion

	References
1. Initiation	
Prior to conception: within 1–3 weeks	29, 31–39
Following conception: within 5–8 weeks	26–28, 30
2. Treatment duration	
Prior to conception only	29, 31, 32, 37
Following conception to week 25–34	26–28, 30, 33–36
Following conception to week 7–16	38, 39
3. IVIG dosing	
Standard dose: 400–500 mg/kg per dose	26–33, 36–39
Low dose: 200–250 mg/kg per dose	34, 35
4. Dosing interval[a]	
"Non-physiologic": 1–14 days between doses	27, 28, 31
"Physiologic": 3–4 weeks between doses	26, 30, 33–36, 39

[a]Designation based on approximate 23–day half-life of IgG.

4. Critical analysis of IVIG trials

For the purpose of this analysis, the five largest trials that showed no beneficial effect of IVIG therapy in women with recurrent natural pregnancy loss were chosen from the medical literature [26–30]. In addition, two trials that showed no benefit of IVIG in recurrent IVF failure were added to the analysis [31,32]. These studies were compared with three published trials that demonstrated a significant beneficial effect of IVIG therapy in women with recurrent abortion following natural or IVF-induced pregnancy [33–35]. In addition, four trials showing a beneficial effect of IVIG therapy exclusively in IVF failure were included in the analysis [36–39]. The studies were compared primarily on the basis of patient selection and the IVIG regimen used. Patient selection was analyzed in terms of patient age, number of prior abortions, primary or secondary abortion status and immunologic screening. The IVIG regimen was assessed in terms of timing of initial infusion, timing of subsequent infusions, interval between infusions, dosing of IVIG and duration of treatment during pregnancy (Table 4).

The results of the critical analysis of negative and positive IVIG trials are shown in Tables 5–7. Negative trials were characterized by selection of younger patients with a mean age of 31.9 ± 2.5 years [26–32]. These trials included patients in their early twenties and excluded patients over 40 years old. Three of the studies excluded patients with immunologic abnormalities [28–30], and the remaining four trials failed to screen for these abnormalities [26,27,31,32]. In four trials, IVIG therapy was initiated after conception was achieved [26–28,30], while in the other three trials IVIG was given exclusively prior to conception [29,31,32]. In three of the trials [27,28,31], IVIG was given in a modified acute therapeutic regimen with multiple doses administered at intervals of 1–14 days. In two trials [26,30], IVIG was given at three-week intervals following conception. In two trials [29,32], a single dose of IVIG was given prior to conception (Table 5).

Table 5
Failed IVIG trials

Study/year/reference	N	Mean age (years)	Immunologic screening	IVIG treatment		Pregnancy success (%)
				Prior to conception	Post-conception	
German Group, 1994 [26]	64	30	No	No	Yes	61**
Christiansen et al., 1995 [27]	34	31	No	No	Yes	53**
Perino, 1997 [28]	46	30	Exclusion*	No	Yes	68**
Stephenson, 1998 [29]	62	35	Exclusion*	Yes	No	50**
Jablonowska et al., 1999 [30]	41	30	Exclusion*	No	Yes	77**
Balasch et al., 1996 [31]	12	31	No	Yes	No	0
Stephenson and Fluker, 2000 [32]	51	36	No	Yes	No	15**

N, Number of patients.
*Exclusion: Women with immunologic abnormalities were excluded from the study.
**Not significantly different from age-matched controls who were not treated with IVIG.

The seven positive IVIG trials shared a number of features (Table 6). Six of seven trials excluded women under 27 years old [33–36,38,39], and five of seven trials included women over 40 years old [33–36,39]. The mean patient age was 36.4 ± 1.4 years, and the difference in patient age between the positive and negative studies was significant ($P = 0.0013$, Table 7). Four of the studies used positive immunologic screening as a basis for patient inclusion [34,35,37,38]. In all seven trials, IVIG therapy was initiated prior to conception, and in five of the seven trials IVIG was continued at chronic physiologic intervals of 3–4 weeks (approximating the half-life of circulating IgG) through the second or third trimester of pregnancy [33–36,39]. In the other two studies [37,38], the addition of short-course IVIG therapy was shown to be superior to heparin and aspirin alone in the treatment of recurrent IVF failure.

Table 6
Successful IVIG trials

Study/year/reference	N	Mean age (Years)	Immunologic screening	IVIG treatment		Pregnancy success (%)
				Prior to conception	Post-conception	
Coulam et al., 1995 [33]	95	35	Exclusion*	Yes	Yes	62**
Kiprov et al., 1996 [34]	35	36	Yes	Yes	Yes	80
Stricker et al., 2000 [35]	47	37	Yes	Yes	Yes	92**
Coulam et al., 1994 [36]	29	37	No	Yes	Yes	70
Sher et al., 1998 [37]	52	35	Yes^{+}	Yes	No	42**
Sher et al., 1998 [38]	45	36	Yes^{++}	Yes	Yes	51**
Scher et al., 2000 [39]	30	39	Yes	Yes	Yes	86

N, Number of patients.
*Exclusion: Women with immunologic abnormalities were excluded from the study.
**Significantly better than age-matched controls who were not treated with IVIG.
$^{+}$Screening for antiphospholipid antibodies.
$^{++}$Screening for antithyroid antibodies.

Table 7
Characteristics of failed and successful IVIG trials for recurrent abortion[a]

1. Mean patient age: 31.9±2.5 years old*:
   a. Inclusion of women 20–26 years old (6/7 trials).
   b. Exclusion of women over 40 years old (6/7 trials).
2. Exclusion of women with immunologic abnormalities (3/7 trials), or failure to screen for immunologic abnormalities (4/7 trials).
3. Initial IVIG treatment following conception (4/7 trials), or IVIG therapy limited to period prior to conception (3/7 trials).
4. Repeated IVIG therapy at non-physiologic intervals during pregnancy ("acute" regimen) (4/4 trials).

Characteristics of successful IVIG trials[b]

1. Mean patient age: 36.4±1.4 years old*:
   a. Exclusion of women 20–26 years old (6/7 trials).
   b. Inclusion of women over 40 years old (5/7 trials).
2. Inclusion of women with immunologic abnormalities (4/7 trials).
3. Initial IVIG treatment prior to conception, with continuing IVIG therapy during pregnancy (6/7 trials).
4. Repeated IVIG administration at physiologic intervals during pregnancy ("chronic" regimen) (5/6 trials).

[a] References 26–32
[b] References 33–39
*$P=0.0013$

The number of prior abortions, primary vs. secondary abortion status and dosing of IVIG per infusion did not impact the outcome of the studies.

5. Study design issues in IVIG trials

The results of our analysis demonstrate the lack of standardization of IVIG trials that has made comparison of these trials virtually impossible and contributed to the ongoing controversy over IVIG therapy (Tables 4 and 7). Major differences were found in patient selection and timing of IVIG regimens. In particular, the significantly younger mean patient age, initiation of IVIG therapy following conception and/or use of shorter intensive (acute "non-physiologic") IVIG regimens in negative trials tended to invalidate the conclusions of these studies (Table 7). Conversely, the significantly older mean patient age, initiation of IVIG therapy prior to conception and use of chronic physiologic IVIG regimens (corresponding to the approximate 23-day half life of circulating IgG) appear to be the major factors that determined the success of the positive studies (Table 7). Thus our analysis demonstrated the crucial importance of appropriate patient selection and timing of IVIG administration in the treatment of immunologic abortion with IVIG.

Three of the seven negative IVIG trials used large amounts of IVIG in non-physiologic treatment intervals of 1–14 days [27,28,31]. This approach is based on the IVIG regimens used to treat acute, established immunologic disorders such as Kawasaki's disease, immune thrombocytopenic purpura and Guillain-Barre syndrome. However, if recurrent abortion is due to failure of the Th1 to Th2 switch necessary for successful pregnancy [43–45], an acute IVIG regimen would be inappropriate to alter or prevent this chronic immunologic dysfunc-

tion. The incipient process that leads to abortion would require chronic physiologic dosing of IVIG that is initiated prior to the immunologic changes of conception and that approximates the half life of circulating antibody [46]. In this regard, the use of lower doses of IVIG at longer intervals is based on the concept that the immunomodulatory effect of IVIG is qualitative rather than quantitative [47–51]. Thus a low dose of IVIG should be effective in modulating the Th1 to Th2 switch necessary for successful pregnancy [34,49–51]. Although the exact mechanism of IVIG therapy is still not understood, modulation of lymphocyte reactivity and cytokine production is probably at the core of the immune response to IVIG [47–51]. Thus a low dose of IVIG initiated prior to conception appears to be adequate for immune modulation during pregnancy, and a significant response to this treatment can be achieved (Fig. 1).

In our extended cohort, IVIG therapy was continued through the end of the second trimester in most patients. The rationale for this length of treatment is based on studies showing a 25% abortion rate in the second trimester for women with immunologic abnormalities [7,8]. Indeed, in the women who discontinued IVIG after the first trimester, one of five (20%) miscarried. Furthermore, in our critical analysis the study that utilized the longest IVIG treatment regimen (15 weeks) had the highest pregnancy success rate among the negative IVIG trials [30] (Table 5). Conversely, the two studies that used short-course IVIG therapy in conjunction with heparin and aspirin for IVF failure had the lowest success rates among the positive IVIG trials [37,38] (Table 6). Since IVIG is relatively expensive, shorter treatment courses for immunologic abortion would certainly be attractive. The high success rate with longer treatment suggests that the six-month regimen should remain the standard, particularly in older women with limited pregnancy potential, pending larger trials of a short-course IVIG protocol.

It has been argued that only randomized controlled trials should be used to evaluate IVIG therapy for recurrent abortion, and six of the seven negative trials described above conformed to this study design [26–30,32]. However, poor patient selection and suboptimal IVIG dosing appear to have undermined the optimal design of these trials (Table 7). In contrast, only one of the seven positive IVIG trials was a randomized controlled trial [33], and three of the seven positive studies were non-randomized cohort-controlled studies [35,37,38]. However it has been shown that cohort-controlled trials do not produce a bias toward a treatment effect when compared to randomized controlled trials [53,54], and the results of randomized and non-randomized studies appear to be similar [55–58]. Given the chronic shortages of IVIG products, the expense of IVIG therapy and the reluctance of women to be randomized to placebo treatment during pregnancy, it is uncertain whether appropriately randomized IVIG trials can be implemented. Future randomized and cohort-controlled studies of IVIG therapy should address the issues of patient selection and IVIG dosing outlined above.

An additional problem is the variability of fertilization success in older women with immunologic abortion. In our extended cohort, 34% of patients failed to become pregnant after testing for immunologic abnormalities. The variability of fertilization success underscores the difficulty in evaluating IVIG therapy in this older female population. At the same time, recognition and understanding of immunologic abortion will allow newer IVIG treatment approaches, such as “front-loading” IVIG infusions over the months prior to natural conception or IVF. Newer approaches to IVIG therapy will require larger well-designed studies of women with immunologic abortion.

6. Summary

Immunologic abortion encompasses a broad range of immunologic abnormalities that are associated with recurrent failure of natural or IVF-induced pregnancy. IVIG therapy appears to be safe and effective for older women with this disorder. Pending the results of larger controlled clinical trials, monthly administration of low-dose IVIG initiated prior to conception and continuing through the end of the second trimester of pregnancy appears to be the optimal treatment regimen for these patients. Appropriate patient selection and valid timing of IVIG administration are crucial factors that determine the success of this treatment.

Acknowledgments

The authors thank Drs. Norbert Gleicher, Joanne Kwak-Kim, Alan Beer, Jonathan Scher, Christo Zouves, Elliot Main, Tom Jackson, Carl Kirsch, Yehuda Shoenfeld and Michel Kazatchkine for helpful discussion. We also thank Kathy Guirant, Annie Wong, John Brooks and Billi Goldberg for technical assistance and David Thomas for manuscript preparation.

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