

# Comparison of the effect of aspirin and heparin with or without intravenous immunoglobulin in treatment of recurrent abortion with unknown etiology: A clinical study

Zeinab Nazari,  
Javad Ghaffari<sup>1</sup>,  
Aghdas Ebadi

Obstetric and Gynecologist, Fellowship of Oncology, <sup>1</sup>Associate Professor of Allergy and Clinical Immunology, Department of Pediatrics, Mazandaran University of Medical Sciences, Sari, Iran

**Address for correspondence:**

Prof. Javad Ghaffari, Department of Pediatric Immunology and Allergy, Bou Ali Sina Hospital, Pasdaran Boulevard, Sari, Iran. E-mail: javadneg@yahoo.com

## Abstract

**Introduction and Objective:** Abortion is the most common complication of pregnancy, defined as spontaneous expulsion of products of conception before 24 weeks of pregnancy or termination of pregnancy with a fetus weighing <500 g. The aim of this study was to compare the efficacy of intravenous immunoglobulin (IVIG) in combination regimens with aspirin and heparin versus aspirin and heparin combination alone in women with idiopathic recurrent abortion. **Materials and Methods:** This randomized, clinical trial was performed at Imam Khomeini Hospital in Sari-Iran between March 2010 and March 2013. Sixty people were randomly allocated into two groups. The control group was treated by subcutaneous enoxaparin 40 mg daily up to 24 weeks associated with aspirin 80 mg daily up to 37 weeks of gestation. The intervention group received IVIG 200 mg/kg monthly up to 24 weeks of gestation with enoxaparin and aspirin for the same therapeutic period and the same dose as the control group. **Results:** Three patients (10%) in the intervention group had abortion and 25 (90%) had live births with mean birth weight  $3.5 \pm 0.9$  kg. Four patients (13%) in the control group had abortions, and 28 (87%) had live births with birth weight  $3.4 \pm 1.2$  kg ( $P = 0.74$ ). The difference was not statistically significant. **Conclusions:** It seems that employing the heparin and aspirin combination therapeutic regimen is appropriate for idiopathic abortions and avoids the high cost of IVIG use and its complications.

**Key words:** Aspirin, heparin, intravenous immunoglobulin, recurrent abortion

## INTRODUCTION

Abortion is the most common complication of pregnancy. Recurrent abortion occurs in 3% of all cases of abortion and approximately half (60-40%) are classified as idiopathic.<sup>[1]</sup> The risk of subsequent abortion is about 30-40% after two or three consecutive miscarriages. The rate of recurrent abortion is about 70% in women who have a positive

history of abortion as well as high levels of antibodies.<sup>[2]</sup> Despite much of the information that has been published about immunologic aspects of recurrent abortion, there is no agreement about the mechanism of action or the effect of therapeutic interventions. In cases of repeated abortion, the number of natural killer cells in cervical mucus is much

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higher than normal.<sup>[3]</sup> Some autoantibodies also play a role in recurrent abortion.<sup>[4]</sup> Antiphospholipid syndrome is one of the important curable causes of recurrent abortion (prevalence 7-25%) with a 90% prevalence of abortion in women with antiphospholipid syndrome and a rate of live births of more than 70% among women who undergo treatment. Treatment with heparin, aspirin, intravenous immunoglobulin (IVIG) singly or combination therapy, and even steroid therapy have been useful and effective.<sup>[5-8]</sup> Treatment with aspirin has different results in different studies.<sup>[7-9]</sup> Enoxaparin, a low molecular weight heparin, accelerates the formation of anti-trypsin three and thrombin, causes inactivation of thrombin and inhibits the conversion of fibrinogen to fibrin. It also has thromboprophylactic effects and inhibits intravascular endothelial damage in the mother and trophoblast by binding to antiphospholipid antibodies and anti-gamma interferon antibodies.<sup>[7-12]</sup> IVIG is used due to a suppressor effect, neutralizing autoantibodies, reducing natural killer cell activity, and reducing production of certain cytokines in autoimmunity and idiopathic recurrent abortion.<sup>[10-13]</sup> The aim of this study was to compare the efficacy of IVIG in combination with aspirin and heparin versus aspirin and heparin alone in women with idiopathic recurrent abortion referred to the Obstetrics and Gynecology Department of Imam Khomeini Hospital in the North of Iran.

## MATERIALS AND METHODS

In this randomized clinical trial, the sample size of 30 in each group would give an error of 5% and power of 80%. Inclusion criteria were: Recurrent abortion (at least 3 times), defined as spontaneous expulsion of the products of conception before 24 weeks of pregnancy or termination of pregnancy with fetal weight <500 g. Exclusion criteria were other causes of abortion such as structural deformities and anatomical defects of uterus, karyotype abnormalities in the parents, patients with thrombophilia defects, thyroid dysfunction or history of maternal diabetes, aspirin sensitivities, gastric ulcer, hypertension, antihypertensive drug therapy, and women who received anticoagulants for other causes during pregnancy. After explaining the protocol for the patients and obtaining written informed consent, a precise medical history, and physical examination was performed. Laboratory assessments included excluding diabetes, thyroid dysfunction and hyperprolactinemia, determining both parental karyotypes, sonography, hysterosalpingography, serum prolactin measurement, antiphospholipid antibody, anticardiolipin antibody, factor V Leiden, protein C and protein S, and immunoglobulins IgA, IgM, IgG. Any patient with a known cause for abortion was excluded, and only patients who had an idiopathic abortion were included. A total of 60 patients

were randomly allocated into two groups and enrolled as soon as a pregnancy test was positive. The control group ( $n = 32$ ) was treated with subcutaneous enoxaparin (Sanofi, France) 40 mg daily up to 24 weeks associated with aspirin (aburaihan.co.ir, Iran) 80 mg daily up to 37 weeks of gestation. The intervention group ( $n = 28$ ) received IVIG (Intratec, Biotest, Germany) 200 mg/kg monthly up to 24 weeks of gestation with enoxaparin and aspirin for the same therapeutic period and doses as the control group. IVIG was infused monthly over 8-10 h and its side effects including chill, fever, rash, hives, hypotension or anaphylactic shock recorded. Successful treatment was defined as a live birth. Obstetric complications such as preeclampsia (blood pressure >140/90 associated with proteinuria), preterm labor, gestational diabetes, and fetal complications including low birth weight and obvious congenital defects, the mean gestational age of the fetus were recorded. Any side effects of the medications, urticaria, bleeding, pain, irritation or hematoma at the injection site, ecchymosis, were also recorded. All women routinely received vitamins including folic acid and iron compounds in the both groups.

All demographic and therapeutic outcome data were collected by research structured questionnaires and analyzed using Version 16.0. (Chicago, SPSS Inc.) with descriptive and analytic statistical tests. We used Student's *t*-test for quantitative variable and  $\chi^2$  tests for the qualitative variable.  $P < 0.05$  was considered significant.

## RESULTS

Initially, 68 patients were randomly divided into two intervention (Group A) and control (Group B) groups; Group A consisted of 35 women and Group B including 33 patients. Finally, 8 cases were excluded based on exclusion criteria. Random allocation was performed based on the consort method [Figure 1].

The mean age of the patients in Group A was  $29.7 \pm 3.1$  years (min age = 21 years and max age = 36 years) and in Group B was  $31.2 \pm 2.1$  years (min age = 20 years and max age = 40 years). There was no significant statistical difference in age between the two groups ( $P = 0.72$ ) [Table 1].

In the intervention Group A, an abortion was observed in 3 patients and the rest (25) had live births with the mean birth weight of  $3.5 \pm 0.9$  kg. Four patients in the control Group B, (13%) had an abortion following prescription of medication and 28 had live births with the mean birth weight of  $3.4 \pm 1.2$  kg ( $P = 0.74$ ). All of the patients in Group A had delivery via cesarean section (C/S) while in Group B, 27 patients (87%) underwent C/S ( $P = 0.42$ ). The number of patients with intrauterine growth retardation

**Figure 1: Random allocation of eligible and enrolment patients based on consort method**

Assessed for eligibility (n = 68)		
Enrolment	60	Randomized (n = 60) Excluded (n = 8): Not meeting inclusion criteria
Allocation	Allocated to intervention (n=28): Received allocated intervention IVIG 200 mg/kg monthly up to 24 weeks of gestation with enoxaparin 40 mg/daily up to 24 weeks and aspirin 80 mg/daily up to 37 weeks of gestation	Allocated to control (n=32): Received subcutaneous enoxaparin associated with aspirin 80 mg/daily up to 37 weeks of gestation
Follow-up Analysis	Lost to follow-up (give reasons) (n=0) Analyzed (n=28)	Lost to follow-up (give reasons) (n=0) Analyzed (n=32)

IVIG: Intravenous immunoglobulin

or preeclampsia in Group A was 3 (13%) and 2 (7%) and in Group B was 4 (10%) and 2 (6%), respectively. There were no statistically significant differences between the two groups [Table 2]. The drug side effects in the control group included 2 cases (7%) with ecchymosis and 4 cases (13%) with local induration at the injection site. In addition, fever and chills occurred in 1 case and palpitations in another case in the intervention group.

One neonate in the intervention group died from cyanotic congenital heart disease due to total anomalous pulmonary venous return at 48 h after birth.

## DISCUSSION

Abortion is one of the most important complications of pregnancy and recurrent abortion causes of 3% of all cases. Although, various treatments have been proposed for this problem, various protocols are still associated with different results and comprehensive studies have commenced.

The mean age of the studied patients was a  $30.4 \pm 3.0$  year which is in agreement with the prevalence of abortion reported by other studies. As >87% of live births occurred in both of our study groups, we demonstrated the high effectiveness of these two therapeutic regimens in patients with recurrent abortion. The incidence of abortion in the group receiving aspirin and enoxaparin alone versus the group receiving aspirin and enoxaparin and IVIG was not statistically significant.

Triolo *et al.* in a study of subcutaneous low molecular weight heparin plus aspirin versus IVIG in the treatment of recurrent fetal loss associated with antiphospholipid antibodies showed that the effect of IVIG plus aspirin was less than that of low molecular weight heparin plus aspirin.<sup>[14]</sup> As in the first group, the rate of live births was 57% versus 84% in the second group. Similar to our study, they concluded that IVIG was no more effective than heparin and aspirin in the treatment of recurrent abortion.

**Table 1: Demographic data and medical history of both groups**

Groups variables	Intervention group A	Control group B	P
Population (n)	28	32	—
Mean age (years)	29.7±3.1	31.2±2.1	0.72
Mean number of abortion	3.2±1.2	2.6±0.4	0.66
Previous delivery, n (%)	4 (13.3)	16 (53.2)	0.44
Previous live birth, n (%)	2 (6.6)	12 (4)	0.34
Mean age of gravida (week)	11.4±3.2	10.8±2.1	0.51
Mean time from the last abortion (years)	3.3±1.4	2.9±1.1	0.70
Current D and C	18 (60)	17 (56.5)	0.41
Positive family history of abortion, n (%)	0 (0)	0 (0)	—

**Table 2: Characteristics of outcomes of intervention both groups**

Outcome	Case group (%)	Control group (%)	P
Abortion in end of study	3 (10)	4 (13)	0.531
Live birth in end of study	25 (90)	28 (89)	0.654
Mean neonatal birth weight	3.5±0.9	3.4±1.2	0.443
Cesarean section	25 (100)	27 (96)	0.653
IUGR	3 (12.3)	4 (10)	0.646
Preeclampsia	2 (7)	3 (6)	0
Preterm delivery	6 (20)	8 (26)	0.552

IUGR: Intrauterine growth retardation

Hutton *et al.* in 2007, conducted a review of seven placebo-controlled studies, similar to ours, with heparin and aspirin compared with IVIG. They found that IVIG had no greater benefit than placebo when used after recurrent abortion with results similar to ours. In addition, the birth weight, gestational age, and preterm delivery were not significantly different.<sup>[15]</sup>

Stricker *et al.* performed a systematic review of the use of IVIG for the treatment of recurrent miscarriage. The results of their study revealed that the rate of live births in the IVIG group (18%) was significantly higher than in other group without IVIG (13%).<sup>[13]</sup> In another study by this author, the effect of using IVIG in the treatment of immune related recurrent abortions was higher than in the group without treatment with IVIG.<sup>[16]</sup>

It should be noted that the cases included in the study by Stricker and Triolo were women with recurrent abortion due to antiphospholipid syndrome and anticardiolipin antibodies, whereas, our study demonstrated that treatment with IVIG was effective for pregnant women with idiopathic recurrent abortion probably due to an immune reaction. Farid *et al.* in a similar study showed a statistically significant association between treatment with IVIG and live births in women with recurrent abortion. The differences in the results of the various studies may be due to sample size and more importantly, the cause of abortion.<sup>[17]</sup> A study on recurrent spontaneous abortion conducted by Winger and Reed has shown that the combination of IVIG and anticoagulation therapy was more significant and effective than the anticoagulant alone. They also claimed that the combination therapy of IVIG and the TNF inhibitor, adalimumab (Humira), and an antithrombotic like etanercept (Enbrel) or, compared with the combination of IVIG, and anticoagulation therapy was not significantly different, but in comparing the anticoagulant as a sole therapeutic agent it was significant.<sup>[18]</sup>

Fawzy *et al.* in a study on idiopathic recurrent miscarriage have shown that treatment with enoxaparin alone or in combination with prednisolone or aspirin compared to placebo had a very favorable effect, but the differences were not significant. This study showed that the treatment was centered on enoxaparin. The results of their study are similar to ours, but they were not using IVIG, and we have not used prednisolone.<sup>[19]</sup> Dendrinis *et al.* performed a study to evaluate the effect of the combination of heparin and aspirin versus IVIG in the treatment of recurrent abortion with positive antiphospholipid antibodies. They found that the rate of live birth was significantly higher in the first group. Enoxaparin was also the main drug in the study with efficacy.<sup>[20]</sup>

The results of the previous studies show that although the idiopathic recurrent abortion tests were negative, they could have an autoimmune, idiopathic or coagulation cause that responded to anticoagulant therapy or IVIG. On the other hand, the incidence of side effects was higher in the control group compared to the group receiving IVIG; however, none of the cases required discontinuation and withdrawal from the study.

In addition, the rate of complications of pregnancy in the present study was similar to other studies. All of the newborns except one that had no congenital problems detected in the early physical examination, however, one developed central cyanosis due to persistent fetal circulation in the early hours after birth.

Although IVIG is reported to cause the side effects, such as fever, chills, back or chest pain, and anaphylaxis, we observed fever and chills only in 1 patient that was prevented with a slow injection rate and the use of acetaminophen.<sup>[21]</sup>

## CONCLUSION

The combination regimen of heparin and aspirin could be considered as a standard treatment protocol in idiopathic recurrent abortion. Due to the high cost of IVIG and its complications in patients taking this drug, its use should be discontinued. Furthermore, further studies with a greater sample size are recommended before and after pregnancy.

Limitation of our study is nonevaluation of a cellular immune factor, some thrombophilic factor, and other unrevealed factors that may be an influence on results of this study.

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## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Salat-Baroux J. Les avortements spontanés à répétition. *Reprod Nutr Dev* 1988;28:1555-68.
2. Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, *et al.*, editors: *Williams Obstetrics*. New York: McGraw Hill, 2014, 24<sup>th</sup> edition. p. 350-76.
3. Clifford K, Flanagan AM, Regan L. Endometrial CD56+ natural killer cells in women with recurrent miscarriage: A histomorphometric study. *Hum Reprod* 1999;14:2727-30.
4. Kaider AS, Kaider BD, Janowicz PB, Roussev RG. Immunodiagnostic evaluation in women with reproductive failure. *Am J Reprod Immunol* 1999;42:335-46.
5. Geva E, Amit A, Lerner-Geva L, Yaron Y, Daniel Y, Schwartz T, *et al.* Prednisone and aspirin improve pregnancy rate in patients with reproductive failure and autoimmune antibodies: A prospective study. *Am J Reprod Immunol* 2000;43:36-40.
6. Yokoo T, Takakuwa K, Ooki I, Kikuchi A, Tamura M, Tanaka K. Alteration of TH1 and TH2 cells by intracellular cytokine detection in patients with unexplained recurrent abortion before and after immunotherapy with the husband's mononuclear cells. *Fertil Steril* 2006;85:1452-8.
7. Dolitzky M, Inbal A, Segal Y, Weiss A, Brenner B, Carp H. A randomized study of thromboprophylaxis in women with unexplained consecutive recurrent miscarriages. *Fertil Steril* 2006;86:362-6.
8. Tempfer CB, Kurz C, Bentz EK, Unfried G, Walch K, Czizek U, *et al.* A combination treatment of prednisone, aspirin, folate, and progesterone in women with idiopathic recurrent miscarriage: A matched-pair study. *Fertil Steril* 2006;86:145-8.

9. Tulppala M, Marttunen M, Söderstrom-Anttila V, Foudila T, Ailus K, Palosuo T, *et al.* Low-dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: Effect on prostacyclin and thromboxane A2 production. *Hum Reprod* 1997;12:1567-72.
10. British Columbia Provincial Blood Coordinating Office. IVIG Utilization Management Handbook. 1<sup>st</sup> ed. British Columbia, Canada: BC Provincial Blood Coordinating Office; 2002.
11. Chen C, Danekas LH, Ratko TA, Vlasses PH, Matuszewski KA. A multicenter drug use surveillance of intravenous immunoglobulin utilization in US academic health centers. *Ann Pharmacother* 2000;34:295-9.
12. Hanna K, Poulin-Costello M, Preston M, Maresky N. Intravenous immune globulin use in Canada. *Can J Clin Pharmacol* 2003;10:11-6.
13. Stricker RB, Steinleitner A, Winger EE. Intravenous immunoglobulin (IVIG) therapy for immunologic abortion. *Clin Appl Immunol Rev* 2002;2:187-99.
14. Triolo G, Ferrante A, Ciccia F, Accardo-Palumbo A, Perino A, Castelli A, *et al.* Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. *Arthritis Rheum* 2003;48:728-31.
15. Hutton B, Sharma R, Fergusson D, Tinmouth A, Hebert P, Jamieson J, *et al.* Use of intravenous immunoglobulin for treatment of recurrent miscarriage: A systematic review. *BJOG* 2007;114:134-42.
16. Stricker RB, Winger EE. Update on treatment of immunologic abortion with low-dose intravenous immunoglobulin. *Am J Reprod Immunol* 2005;54:390-6.
17. Farid R, Jabbari F, Ahanchian H, Saghafi N, Mohsenian Z, Moghiman T. Evaluating the Success Rate of Treating Immunologic Abortion WITH Low Dose Intravenous Immunoglobulin. Poster Presentation, The First Middle East-Asia Allergy Asthma Immunology Congress, Dubai, UAE; 26-29 March, 2009.
18. Winger EE, Reed JL. Treatment with tumor necrosis factor inhibitors and intravenous immunoglobulin improves live birth rates in women with recurrent spontaneous abortion. *Am J Reprod Immunol* 2008;60:8-16.
19. Fawzy M, Shokeir T, El-Tatongy M, Warda O, El-Refaiey AA, Mosbah A. Treatment options and pregnancy outcome in women with idiopathic recurrent miscarriage: A randomized placebo-controlled study. *Arch Gynecol Obstet* 2008;278:33-8.
20. Dendrinis S, Sakkas E, Makrakis E. Low-molecular-weight heparin versus intravenous immunoglobulin for recurrent abortion associated with antiphospholipid antibody syndrome. *Int J Gynaecol Obstet* 2009;104:223-5.
21. Ghaffari J, Gharegozlou M, Mohammadzadeh E, Nazari Z. Adverse reaction following intravenous immunoglobulin in primary immunodeficiency patients. *J Mazandaran Univ Med Sci* 2007;17:114-21.