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Original Article

Immunoglobulin Therapy in Recurrent Pregnancy Loss

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Abstract

Objective: **Recurrent pregnancy loss is a global issue. This study was planned in order to evaluate the effects of high dose intravenous immunoglobulin (IV Ig) in primary and secondary unexplained miscarriages in patients of recurrent pregnancy loss.**

Patients and Methods: Total 168 couples having history of primary or secondary recurrent pregnancy loss were included in the study. They were divided into IVIg group and control group. IVIg group was given 50 gm of IVIg on monthly basis. Control group was provided with normal saline drip at same intervals. Statistical package for social sciences 19(SPSS 19) was used to analyze the data.

Results: Women receive IVIg treatment (primary + secondary recurrent pregnancy loss) shows significantly higher percentage of live birth as compare to control group (81%; p<0.000). Percentage of full term live birth is also significantly increased in IVIg group in comparison with control group (76.2%; p < 0.000). In primary recurrent pregnancy loss total percentage of live births and full term live births were 85.3 and 79.4% in IVIg group while in control group it was 26.9% and 19.2% (p<0.000). In secondary recurrent pregnancy loss percentage of total number of live birth and full term live births in IVIg group is 78% and 74% in comparison with control group 32% and 26% respectively (p<0.000).

Conclusion: High dose intravenous immunoglobulin has a beneficial role in patients of primary and secondary recurrent miscarriages.

Key words: High dose immunoglobulin, Primary recurrent miscarriage, Secondary pregnancy loss.

Introduction

Spontaneous pregnancy loss (SPL) is a common worldwide problem. It is an emotional and physical trauma for couples. About 15% of all clinically recognized pregnancies end up in spontaneous loss. Many pregnancies terminated even before their clinical recognition. Live births results in only about 30% of all conceptions.[1]

About 1-2% of couples face the problem of recurrent miscarriages (RM) and it is well known disturbing and distressing dilemma for them. RM also known as recurrent pregnancy loss (RPL) or habitual abortion is defined as loss of 03 or more continuous pregnancies before 20 weeks of gestation.[2] RPL is further classified as either primary (never achieved a live birth) or secondary RPL (normal pregnancy followed by recurrent abortions).[3] There are multiple causes of RPL like cervical incompetence, uterine problems, chromosomal abnormalities, endocrinological problems, autoimmune defects such as anti-phospholipid syndrome and microbial infections.[4,5] Although a large number of autoantibodies to cells and tissue components particularly anticardiolipin antibodies and others like antithyroglobulin, anti-phosphatidylserine, antiphos-phatidylethanolamine, antiphosphatidylinositol, anti-phosphatidylglycerol and antiphosphatidic acid and anticoagulant antibodies have been found in many patients having problem of RPL. But still presence of these antibodies does not clearly indicate that whether these are the causes or consequences of pregnancy loss. That's why besides the postulation of immunological etiology, the cause of RPL is still unknown and pregnancy loss is often described as idiopathic, spontaneous or unexplained RPL .[6]

In order to avert the RPL, multiple treatment options like IVIgs, low molecular weight heparin with or without aspirin, prednisolone and progestin, paternal lymphocyte immunization have been studied.[7,8] Purified human plasma collected from thousands of healthy donors is used in order to make IVIg preparation. Being a therapeutic immunomodulatory agent it contains a wide variety of natural antibodies, non pathogenic natural autoantibodies, antibodies against exogenous antigens (bacteria, viruses, etc.), Fab fragments of IgG, immunomodulating peptides (CD4,

CD8, CD95, etc.), and various cytokines (interleukin [IL]–2, IL-4, IL-10, transforming growth factor–ß, etc.).[9] Although different studies depicted the encouraging effects of IVIg in patients of RPL but there is still ambiguity regarding patients selection criteria and dosage of IVIg.[10,11,12] That's why we planned this study in order to evaluate the effects of high dose IVIg in primary and secondary unexplained miscarriages in patients of RPL.

Material and Methods

Subjects: This retrospective study was performed at Salma and Kafeel Medical Centre Islamabad from January 2012 to December 2012. Couples with history of 3 or more recurrent abortions and unexplained etiology were recruited and their pelvic ultrasound, hysterosalpingography, endometrial biopsy, hormonal analysis including LH, FSH, Prolactin, Progesterone, Estrogen, Thyroid stimulating hormone, TORCH profile, liver, kidney function tests and antiphospholipid antibodies in some cases were done. A total of 168 patients having normal TORCH profile and hormonal levels were included in this study.

Treatment: Patients were divided into two groups. One was labeled as IVIg group and the other one was categorized as control group. IVIg group was given 50 grams of intravenous immunoglobulin (IVIg). It was started within 2 weeks of attempted conception. After establishment of pregnancy, same dose of IVIg was continued on monthly basis up to term. Control group was provided with normal saline drip at same intervals.

Statistical analysis: Statistical package for social sciences 19(SPSS 19) was used to analyze the data. Baseline characteristics of participants were measured as mean ± SD. In order to compare the percentages between IVIg and control group Chi-square test was applied. $p<0.05$ was considered significant.

Results

Patients of RPL who participated into study were divided into IVIg group (n=84) and control group (n=84). Base line characteristics of all participants were measured (Table 1). The outcome of pregnancies is shown in table 2. Women who received IVIg treatment showed significantly higher percentage of live births (81%) as compared to control group (31%) ($p<0.000$) (OR 9.481, 95%CI 4.64-19.37). Percentage of full term live birth is also significantly increased in IVIg group (76.2%) in comparison with control group (23.8%) (OR 10.24, 95% CI 5.03-20.83). Total percentage of fetal loss upto and after 13 weeks is significantly high in control group 28.6% and 26.2% as compare to IVIg group 7.1% and 4.8% (OR 0.19, 95%CI 0.07-0.50) (OR 0.141, 95% CI 0.05-0.43) respectively.

Couples were then divided in to two groups according to type of miscarriage (primary or secondary). Baseline characteristics of individuals having primary RPL are depicted in table 3. These women also show greater treatment response to IVIg group. Total percentage of live births and full term live births were 85.3 and 79.4% in IVIg group while in control group it was 26.9% and 19.2% (OR 15.74, 95%CI 4.35-56.92) (OR 16.20, 95% CI 4.50-58.35) respectively. In control group total percentage of fetal loss up to and after 13 weeks is significantly high (26.9%) and (23.1%) as compared to IVIg group (2.9%) and (2.9%) (OR 0.082, 95% CI 0.009-0.720) (OR 0.101; 95%; CI 0.011-0.901) respectively.

Baseline characteristics of women having history of secondary RPL are shown in table 5. Percentage of total number of live birth and full term live births in IVIg group is 78% and 74% in comparison with control group 32% and 26% respectively (OR 7.534, 95% CI3.08-18.44) (OR 8.10, 95%CI 3.31-19.80). Percentage of fetal loss upto 13 weeks in control group

Table 1: Baseline characteristics of participants

S No.	**Characteristics of participants**	IVIG Group (n=84)	Control Group (n=84)
1.	Maternal age at enrolment (mean ± SD)	29.21 ± 6.38	32.69 ± 7.25
2.	Paternal age at enrolment (mean ± SD)	33.86 ± 7.80	36.28 ± 6.46
3.	No of previous miscarriages (mean ± SD)	3.62 ± 0.88	3.67 ± 1.02
4.	Cumulative number of previous pregnancies	366	376
5.	Cumulative number of previous miscarriages	304	308
6.	Primary recurrent miscarriages (n)	34	28
7.	Secondary recurrent miscarriages (n)	50	56

Table 2: Index pregnancy outcome in women who received IVIG treatment and in controls				
S No.	**Out come**	**IVIG Group**	**Control Group**	**p-value***
1.	Total number of pregnancies (n)	84	84	
2.	Total number of live births, n (%)	68(81)	26(31)	0.000**
3.	Total number of full term live births, n (%)	64(76.2)	20(23.8)	0.000**
4.	Total number of pre term live births, n (%)	04(4.8)	06(7.1)	0.514
5.	Total number of first trimester fetal loss upto 13 wks (n %)	06(7.1)	24(28.6)	0.000**
6.	Total number of fetal loss after 13 wks, n (%)	04(4.8)	22(26.2)	0.000**
7.	Total number of intrauterine deaths	06(7.1)	12(14.3)	0.134
8.	In case of live births, Total number of SVD, n (%)	52(61.9)	10(11.9)	0.000**
9.	In case of live births, Total number of C-section, n (%)	16(19)	16(19)	1.000

*Chi-square test was applied, ** p<0.05 was considered significant

Table 3: Baseline characteristics of participants having primary recurrent miscarriages			
S No.		IVIG Group (n 34)	Control Group (n 26)
1.	Maternal age at enrolment (mean ± SD)	28.09±5.43	33.15±7.70
2.	Paternal age at enrolment (mean ± SD)	31.79±5.20	35.42±6.00
3.	No of previous miscarriages (mean ± SD)	3.65±0.95	3.38±0.85
4.	Cumulative number of previous pregnancies(n)	146	110
5.	Cumulative number of previous miscarriages (n)	124	88

Table 4: Index pregnancy outcome in women receiving IVIG and in control group in case of primary recurrent abortions				
S No.	Out come	IVIg Group	Control Group	p-value*
1.	Total number of pregnancies (n)	34	26	
2.	Total number of live births, n (%)	29(85.3)	07(26.9)	0.000**
3.	Total number of full term live births, n (%)	27(79.4)	05(19.2)	0.000**
4.	Total number of pre term live births, n (%)	02(5.9)	02(7.7)	0.781
5.	Total number of first trimester fetal loss upto 13 wks, n (%)	01(2.9)	07(26.9)	0.007**
6.	Total number of fetal loss after 13 wks, n (%)	01(2.9)	06(23.1)	0.016**
7.	Total number of intrauterine deaths	03(8.8)	06(23.1)	0.125
8.	In case of live births, Total number of SVD, n (%)	19(55.9)	01(3.8)	0.000**
9.	In case of live births, Total number of C-section, n (%)	10(29.4)	06(23.1)	0.582

*Chi-square test was applied. **p<0.05 was considered significant

Table 5: Baseline characteristics of participants having secondary recurrent miscarriages			
S No.		IVIg Group (n=50)	Control Group (n=50)
1.	Maternal age at enrolment (mean ± SD)	29.98 ± 6.90	31.38 ± 6.59
2.	Paternal age at enrolment (mean ± SD)	35.2 6 ± 8.93	35.90 ± 6.46
3.	No of previous miscarriages (mean ± SD)	3.58 ± 0.83	3.68 ± 1.02
4.	Cumulative number of previous pregnancies(n)	220	222
5.	Cumulative number of previous miscarriages (n)	179	184

Table 6: Index pregnancy outcome in women receiving IVIg and in control in case of secondary recurrent abortions

S No.	Out come	IVIG Group	Control Group	p-value*
1	Total number of pregnancies (n)	50	50	
2	Total number of live births, n (%)	39(78)	16(32)	0.000**
3	Total number of full term live births, n (%)	37(74)	13(26)	0.000**
4	Total number of pre term live births, n (%)	02(4)	03(6)	0.646
5	Total number of first trimester fetal loss upto 13 wks, n (%)	05(10)	14(28)	0.022**
6	Total number of fetal loss after 13 wks, n (%)	03(6)	14(28)	0.003**
7	Total number of intrauterine deaths	03(6)	06(12)	0.295
8	In case of live births, Total number of SVD, n (%)	34(68)	08(16)	0.000**
9	In case of live births, Total number of C-section, n (%)	06(12)	08(16)	0.564

Chi-square test was applied **p<0.05 was considered significant

and IVIg group is 28% and 10% respectively (OR 0.29, 95%CI 0.09-0.87) while fetal loss after 13 weeks in control group and IVIg group is 28% and 6% respectively (OR 0.16, 95% CI 0.04-0.615).

Discussion

Intravenous immunoglobulin being a safe preparation is considered to be an effective therapy in spontaneous miscarriages. In general, the purpose of IVIg treatment is to enhance passive immunity in women suffering from RPL. This treatment may have valuable effect by improving the person's antibody levels and antigen-antibody reaction potential. Our study demonstrated the significantly (p<0.05) high birth rate of 81% (68/84) after giving the high dose IVIg treatment. While in control group it was 31% (26/84). Our results are in accordance with a recent study conducted by Yamada in 2012. Results revealed that after giving daily infusion of 20 g of intact type immunoglobulin for 5 days during early gestation live birth rate was 73.3% (44/60). While after exclusion of pregnancies with abnormal chromosome karyotype live birth rate increased upto 89.8% (44/49).[12]

The results of use of IVIg in different studies are controversial. Primarily the results of IVIg administration in pregnancy loss were encouraging. In a study conducted on twenty women with history of spontaneous recurrent abortions the therapeutic effect of IVIg was significant. After IVIg treatment the overall success rate was 82-86%.[13] At that time it was proposed that passive IVIg therapy can be used in patients of RPL as a substitution of providing active immunity by allogenic leukocytes.[14] In a study conducted by Mueller-Eckhardt et al. (1991) the success rate for IVIg treatment was 75% in primary and 60% secondary recurrent spontaneous abortion patients.[15] Later three placebo-controlled studies were published. One study revnealed that IVIg treatment was effective whereas two other studies demonstrated that IVIg treatment was not beneficial.[16,17,18] However, after summarizing the results of these placebo controlled trials, a significant result was achieved[19] and it was suggested that IVIg could be more effective in women having the history of secondary RM or repeated second trimester intrauterine fetal deaths.[20] In the largest randomized controlled trial (RCT) in which IVIg was evaluated in women with idiopathic secondary RM; no treatment benefit was found. The meta-analysis, which combined this study results with two prior RCTs, also showed no significant effect of treatment with IVIg for idiopathic secondary RM.[21] A computerized search in Medline, Embase, Central, Ovid Medline In-Process, and Other Non-Indexed Citations Databases and randomized controlled trial registries was performed. Abstracts of the American Society of Reproductive Medicine and European Society of Human Reproduction and Embryology annual meetings and reference lists of identified reports were searched. IVIg was not found to be beneficial when women with combined or with primary and secondary RM were analyzed separately.[22] This also signifies the treatment therapy regarding primary and secondary miscarriages. In primary recurrent abortions results were 85.3% (29/34) as compared to control group 26.9% (7/26). In secondary RPL rate of live births in IVIg group was 78% (39/50). In control group it was 32% (16/50). A systematic review of eight trials involving 442 women evaluates the medium dose IVIg therapy to treat recurrent miscarriage. It shows a significant increase in live births following IVIg use in women with secondary RM, while those with primary miscarriage did not experience the same benefit.[10] The meta-analysis of 5 RCTs indicate a higher proportion of successful pregnancies with medium dose IVIg in

secondary recurrent SPL. IVIg treatment was not effective for primary recurrent SPL.[11] Sun et al in 2010 demonstrated that in patients with unexplained RSA receiving IVIg therapy, pregnancy rate (93.3%) and live birth rate (87.5%) was highly significant as compare to that in control group.[23] Massive immunoglobulin therapy in women with RSA of unknown cause shows significant results.[24] Study conducted in 2012 demonstrated the beneficial effect of high dose intravenous immunoglobulin therapy (HIVIg) (daily infusion of 20 gms of intact type immunoglobulin for 5 days during early gestation) in severe cases of unexplained RSA. In 60 women with history of 4-8 RSAs after administration of HIVIg live birth rate was 73.3% (44/60). While after exclusion of pregnancies with abnormal chromosome karyotype live birth rate increased upto 89.8% (44/49).[12]

Conclusion and Recommendation

Although this study supports that patients with history of RMs might get advantage from high dose IVIg therapy,but still there is a need for large sample sized studies in order to substantiate the effectiveness of multiple doses IVIg therapy in RPL.[8]

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