Effect of Intravenous immunoglobulin on Th1 and Th2 lymphocytes and improvement of pregnancy outcome in recurrent pregnancy loss (RPL)

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**A B S T R A C T**

Background: Women with elevated natural killer (NK) cell frequency and function during pregnancy, suffer from recurrent pregnancy loss (RPL). In the present study, the possible effect of intravenous immunoglobulin (IVIG) administration on Th1 and Th2 cell frequency, cytokine secretion, and expression of transcription factors is compared between RPL patients and control group.

Materials and methods: Totally, 44 women with a history of RPL (32 women as treated group and 12 as control group) were enrolled in the study. The frequency of Th1 and Th2 lymphocytes, the expression of transcription factors related to these cells and the serum levels of associated cytokines were assessed by flowcytometry, real-time PCR and ELISA, respectively. All, assessments were performed both before and after treatment with IVIG.

Results: A significant reduction in Th1 lymphocyte frequency, transcription factor expression and cytokine levels were observed in IVIG-treated group, while all the above parameters indicated a significant increase for Th2 lymphocytes. Th1/Th2 ratio decreased significantly (p value < 0.0001) at the end of treatment and 28 out of 32 (87.5%) women in IVIG-treated group had live birth in comparison with 5 out of 12 (41.6%) in untreated group.

Conclusion: IVIG administration proves to be an efficient therapeutic strategy which is able to enhance the success rate of pregnancy through a shift in Th2 responses. Furthermore, IVIG presents efficacy for the treatment of reproduction failures especially in subjects with immune cell abnormalities and increased NK cell level and function.

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1. Introduction

Recurrent miscarriage (RM) or recurrent pregnancy loss (RPL) remains a global issue and is increasing across the world. RPL is classically determined as three or more pregnancy losses happening before the 20th week of gestation and is associated with genetic, anatomic, hormonal, infectious and immunological abnormalities, while almost 50% of RPL cases are idiopathic [1]. Recent evidence provides support for the notion that immunological factors play an important role in the maintenance of pregnancy because tolerance in the maternal immune system is required to prevent immune response against paternally inherited genes and paternal antigens in embryo or fetus. Any disturbance in this immune-tolerance has been demonstrated to result in immunological attack, rejection of embryo and pregnancy loss [2,3].

T cells and their subtypes, especially helper T cells, play essential roles in immune responses and immune regulation. T
helper1 and T helper2, two major subtypes of T helper cells, are of particular importance during gestation and a controlled balance between them is necessary for a successful pregnancy. Th1-type cells and their associated cytokines, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and interleukin-2 (IL-2), are dominant cell types involved in reproductive failures, but in normal pregnancies there is a shift toward Th2-type cells and cytokines, IL-4, IL-5 and IL-13 [3,4,5].

A tolerance in the maternal immune response is required to prevent the activation of cellular immunity against the antigens present in early embryo or fetus, as a semi-allograft. Any disruption in the mechanisms underlying the regulation of maternal immune response may lead to poor pregnancy outcomes [3]. This highlights the need to develop proper and effective therapeutic strategies for patients suffering from reproductive failure. There are numerous line of evidence in the literature confirming the efficacy of intravenous immunoglobulin (IVIG) for autoimmune and immunodeficiency disorders and infertility [6–8]. Within the recent years, a variety of studies and randomized trials have been performed to investigate the efficacy of IVIG in RPL patients. It is estimated that most of the cases with idiopathic RPL suffer from immune-related abnormalities. Therefore, IVIG seems to provide a source of hope for treating patients with idiopathic RPL according to its probable mechanisms of action [3].

As an immunomodulator, IVIG protects embryo from attack by the maternal immune system via different mechanisms [9]. Important mechanisms of action for IVIG include reducing the activity of natural killer (NK) cells, increasing the activity of suppressor T cells [10], blocking the function of anti-HLA antibodies which are produced against paternal inherited genes and their encoded products, preventing complement activation, down-regulation of stimulatory Fc receptors (FcγRI and FcγRII) [11] and up-regulation of inhibitory receptors (FcγRIIB) [12] on the surface of different immune cells [6,10,13].

Some of the previous studies have indicated that treatment with IVIG in RPL patients especially those with elevated levels of NK and Th1 cells is promising and may improve the pregnancy outcomes [3,14,15]. Graphou et al. exhibited that IVIG treatment in patients with elevated NK cells (alloimmune abnormalities) results in a shift toward Th2 cells in Th1/Th2 balance and leads to a normal balance between Th1 and Th2 in autoimmune abortions, women with elevated anti-phospholipid antibodies (APAs) [16]. This finding was also confirmed by Yamada et al. who demonstrated that IVIG is able to decrease the Th1/Th2 lymphocyte ratio in patients with recurrent spontaneous abortion (RSA) [17].

These studies reinforce the notion that one of the mechanisms through which IVIG performs its functions is related to Th1/Th2 ratio. In actual, IVIG is able to create a shift toward Th2-type responses which are useful for a normal and healthy pregnancy. In the current study, the effects of IVIG on cellular abnormalities associated with reproductive failure are investigated and the frequency, balance and cytokines of Th1 and Th2 cells are evaluated.

### 2. Materials & methods

#### 2.1. Study population

44 women (mean age: 34.2 ± 0.6) with a history of RPL, referred to Alzahra Hospital of Tabriz University of Medical Sciences from February 2015 to March 2016, were included in the study. The study was approved by the Research Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1395.316). The inclusion criteria for the subjects are summarized in Table 1. An informed consent were obtained from all of the subjects. Totally, 32 women with a history of RPL and 12 women as control group were enrolled in the study. Prior to inclusion, all patients were investigated for anatomic, endocrine, genetic and infectious abnormalities and confirmed as negative for these parameters.

According to previous studies, it is approved that NK cells are among the most abundant cells in the decidua especially in pregnancy and there is a balance in NK cells proportion between decidua and peripheral blood. In the other words, cellular immune abnormalities which is elevated rate of NK cells in patients will face reproductive failure and the role of these lymphocyte is approved in miscarriages [18,19], so we analyzed the rate of NK cells in subjects before the enrollment. All of the subjects had cellular immune abnormalities including elevated frequency and cytotoxicity of CD3+CD56+NK cells. NK cell cytotoxicity was evaluated by flowcytometry technique using K562 target cells. As effector cells, isolated PBMCs of patients, were incubated with pre-stained K562 target cells and propidium iodide for 2 h in 37°C and 5% CO2. The target cells dead by NK cells, are permeabilized to propidium iodide. The percentage of dead target cells containing propidium iodide, shows NK cells cytotoxicity rate [20].

All partners of the subjects had normal semen status with no chromosomal abnormalities and none of them was smoking (Table 1). To evaluate cellular ratios compared with control and IVIG groups, 32 normal pregnant and 32 non-pregnant women (mean age: 34.2 ± 0.6) with no immune cell abnormalities were included in the study.

#### 2.2. IVIG treatment protocol

The first injection of IVIG was administered for patients in a dose of 400 mg/kg body weight as soon as pregnancy was confirmed with β-hCG test. Afterwards, the infusions were repeated once every 4 weeks until 28–32 weeks of gestation.

#### 2.3. Blood sampling

Peripheral blood was collected twice from all subjects. The first sampling was done at the time of positive pregnancy test before the first IVIG administration followed by assessing the frequency of Th1 and Th2 cells. The second sampling was conducted after the last injection or after 28–32 weeks of gestation for post-treatment investigation.

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### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treated group</th>
<th>Untreated group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Age(year ± SD)</td>
<td>33.8 ± 3.6</td>
<td>34.1 ± 3.4</td>
</tr>
<tr>
<td>Recurrent miscarriage(number ± SD)</td>
<td>3.3 ± 1.4</td>
<td>3.2 ± 1.1</td>
</tr>
<tr>
<td>Primary RM</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Secondary RM</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Gestational ages of previous miscarriages(weeks ± SD)</td>
<td>12.9 ± 6.2</td>
<td>13.2 ± 5.9</td>
</tr>
<tr>
<td>Abnormal NK cell levels(number, percent)</td>
<td>36, 50%</td>
<td>7, 58.3%</td>
</tr>
<tr>
<td>Abnormal NK cell cytotoxicity(number, percent)</td>
<td>20, 62.5%</td>
<td>8, 66.6%</td>
</tr>
</tbody>
</table>

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2.4. Isolation of peripheral blood mononuclear cells (PBMCs)

PBMCs were isolated from heparinized blood samples by adding 1.077 g/mL of Ficoll (lymphosep) (Biosera, UK) and centrifugation at 450 × g for 25 min followed by washing twice with phosphate buffered saline (PBS) (Sigma, Germany). Prior to flow cytometry analysis, 10% of the isolated cells were cultured in a medium containing 10% heat-inactivated fetal calf serum (FCS), 100 U/mL of penicillin, and 200 mM l-glutamine. Subsequently, 10 ng/mL of PMA (eBiosciences, San Diego, CA, USA) was added to the medium, and cells were incubated for 5 h at 37°C with 5% CO2. At the end of incubation time, the cultured cells were used for RNA extraction and flow cytometry analysis and the supernatant was exploited for cytokine assessment using enzyme linked immuno-sorbent assay (ELISA).

2.5. Expression analysis of (T-bet, GATA-3) transcript levels

To evaluate the mRNA expression of transcription factors related to Th1, Th2 cells, total RNA was extracted by RNX-PLUS Solution (SinaClon, Tehran, Iran) and then complementary DNA (cDNA) was synthesized using RevertAid Reverse Transcriptase kit (Thermo Fisher, Waltham, MA, USA). SYBR Green method of polymerase chain reaction (PCR) was selected for the analysis of T-bet and GATA-3 mRNA levels. β-2 microglobulin [β2 M] was used as the reference gene and standard curves were plotted according to six standards made by using 10-fold serial dilutions of a concentrated sample of the genes. The standard condition for SYBR Green method of PCR in the first step was 10 s at 95°C. This was repeated for 40 cycles of denaturation (10 s at 95°C), followed by 30 s at 60°C for annealing and extension. An electrophoresis analysis on 2% agarose gel and DNA sequencing by Biosystems (SEQLAB, Germany) was performed to confirm the amplification.

2.6. Th1- and Th2 frequency and intracellular cytokine assessment

Th1 and Th2 cells were detected among PBMCs using flowcytometric analysis. Prior to test, the sample was prepared by incubating 5 × 10⁶ of PBMCs with 10 ng/mL of phorbol 12-myristate 13-acetate (PMA) and 0.5 M ionomycin at 37°C in a 5% CO2 humidified incubator for 5 h. Chemical stimulators like Monensin (eBiosciences, San Diego, CA, USA) were utilized to improve the staining of intracellular cytokines. Before cell staining, the cells were washed and then incubated with monoclonal antibodies against the surface and intracellular antigens like anti-CD4-APC (BD Biosciences), fluorescein isothiocyanate (FITC)-labeled anti-IFN-γ (Becton Dickinson, Franklin Lakes, NJ, USA), and anti-IL-4-phycocerythrin (PE) (Becton Dickinson).

2.7. Cytokine release analysis (IFN-γ, TNF-α, IL-10, IL4)

Secretion of Th1- (IFN-γ, TNF-α), and Th2-related (IL-10 and IL4) cytokines was analyzed by ELISA in the supernatant obtained from cultured PBMC (Biosource, Nivelles, Belgium). In brief, the wells of a 96-well plate were precoated overnight with 100 μL of coating antibody followed by washing with phosphate buffered saline (PBS) containing 0.005% Tween and incubating with blocking buffer for 1 h on a shaker. 100 μL of samples or standards were added to the wells and the plate was put for 1 h on a shaker. After washing, the wells were first incubated with 100 μL of biotinylated antibody for 1 h and then with 100 μL of horseradish peroxidase (HRP)-conjugated streptavidin for 30 min. After washing, 100 μL of tetramethylbenzidine substrate solution was added to the wells. The reaction was terminated after 30 min and the absorbance values were measured at 450 nm by a Medgenix ELISA reader (BP-800, Biohit, USA). The concentration of samples was calculated using the appropriate standard calibration lines and the Softmax software of the reader.

2.8. Statistical analysis

Statistical analysis was performed using SPSS PC Statistics (version 19.0; SPSS). Paired T-test was used in order to compare the results of immunologic studies before and after IVIG treatment in IVIG group and control group, also we used unpaired T test to compare the statistical differences between control group and IVIG group. ANOVA (analysis of variance) test used for multiple comparisons between four groups (IVIG group, normal pregnant, non-pregnant and control group) and showed statistical difference between four groups and then paired T test applied for multiple comparisons. Linear-by-linear association chi-square test was performed to test linear trend among the groups of immune variables, response rate of the variables and pregnancy outcome. P-values < 0.05 were reported to be statistically significant.

Fig. 1. mRNA expression level of T-bet and GATA-3 in IVIG-treated and control groups. (IVIG group n = 32, control group n = 12) At the time of positive pregnancy test, the mRNA expression level of T-bet in IVIG group was significantly higher in comparison with the end of pregnancy (p value = 0.0002). Also, the mRNA expression of GATA-3 significantly increased post-treatment (p value < 0.0001), while there was no significant differences in control groups before and after treatment (p value = ns). (p ≤ 0.05: statistically significant).
Table 2
Th1 and Th2 cell alterations in IVIG-treated and control group.

<table>
<thead>
<tr>
<th>mRNA expression of transcription factors in activated PBMC (fold change)</th>
<th>Treated group</th>
<th>Untreated group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td></td>
</tr>
<tr>
<td>T-bet</td>
<td>1</td>
<td>0.75 ± 0.18</td>
<td>0.0002</td>
</tr>
<tr>
<td>GATA-3</td>
<td>1</td>
<td>2.60 ± 0.89</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Cytokine secretions (pg/ml)

<table>
<thead>
<tr>
<th></th>
<th>Treated group</th>
<th>Untreated group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF-γ</td>
<td>1364 ± 958.5</td>
<td>658.8 ± 432.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>TNF-α</td>
<td>1992 ± 1046</td>
<td>816.8 ± 564.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-4</td>
<td>83 ± 70.73</td>
<td>116.8 ± 95.6</td>
<td>NS</td>
</tr>
<tr>
<td>IL-10</td>
<td>53 ± 34.84</td>
<td>152.8 ± 76.37</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Cell frequency in PBMC (%)

<table>
<thead>
<tr>
<th></th>
<th>Treated group</th>
<th>Untreated group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th1(CD4⁺ IFN-γ⁺) cells</td>
<td>40.94 ± 7.25</td>
<td>32.16 ± 7.66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Th2(CD4⁺IL-4⁺) cells</td>
<td>1.175 ± 0.73</td>
<td>1.706 ± 0.81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Th1/Th2 ratio</td>
<td>26.66 ± 7.12</td>
<td>19.09 ± 4.53</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Fig. 2. The frequency of Th1 and Th2 in IVIG-treated and untreated group. (IVIG group n = 32, control group n = 12) There was an obvious decrease in the frequency of Th1 cells after IVIG administration (p value < 0.0001), while the rate of Th2 cells indicated a significant increase (p value < 0.0001). As a result, a significant reduction in Th1/Th2 balance was observed in IVIG-treated group (p value < 0.0001). (p ≤ 0.05: statistically significant).
3. Results

3.1. Pre-treatment evaluation of NK cell frequency and cytotoxicity

Flow cytometric assessment of cellular abnormalities showed that half of the patients (16 out of 32) in IVIG group had elevated NK cell frequency; and NK cell cytotoxicity was increased in 20 out of 32 patients, while there were 7 out of 12 and 8 out of 12 elevated rate of NK cell frequency and cytotoxicity, respectively, in control group.

3.2. mRNA expression levels of transcription factors related to Th1 and Th2 cells in IVIG treated and untreated groups

T-bet and GATA-3 mRNA levels were evaluated and compared between IVIG treated group and control groups. As shown in Fig. 1, the mRNA level of T-bet decreased in IVIG treated group at the end of the treatment (28–32 weeks of gestation). By contrast, the mRNA level of GATA-3 indicated a significant increase in IVIG group compared with control. There was no significant difference in the mRNA rate of T-bet and GATA-3 in control group pre and post-treatment (Fig. 1 and Table 2).

3.3. Th1 and Th2 frequency in IVIG treated and untreated groups

The frequency of CD4+ IFN-γ-producing Th1 cells, and CD4+ IL-4-producing Th2 cells as well as Th1/Th2 balance were measured before and after treatment with IVIG in both IVIG treated and control groups by flow cytometry. Post-infusion results showed a decrease in the percentage of Th1 cells, while the percentage of Th2 cells increased after IVIG treatment. As a result, Th1/Th2 balance was also affected, and the ratio was significantly reduced in IVIG group (Fig. 2 and Table 2).

Data analysis in normal pregnant and non-pregnant women demonstrated that there is almost no differences in the cellular proportion of Th1 cells, but Th1 frequency is lower than control and IVIG-treated groups with cellular abnormalities. Th2 frequency was the same in normal pregnant and non-pregnant women, but significantly higher in comparison with control and IVIG-treated groups (Fig. 3 and Table 3).

3.4. Cytokine secretion levels of Th1 and Th2 cells in IVIG-treated and –untreated groups

At the end of the treatment with IVIG in RPL women, cytokine secretion of PBMCs was measured in the supernatant obtained from cultured cells. The results showed a lower concentration of Th1-associated cytokines including IFN-γ and TNF-α after IVIG treatment in IVIG group in comparison with control group, while the level of cytokine secretion by Th2 cells, especially IL-10, increased significantly compared with both the time of positive pregnancy test and control group. IFN-γ and TNF-α secretion level were affected significantly (p value = 0.0015, 0.0002, respectively), IL-10 increased noticeably (p value = 0.0176) but IL-4 was not affected so much (p value = 0.453) in IVIG group in comparison with control group after IVIG administration. The analysis of untreated group and comparison of groups before treatment, exhibited almost no difference at the end of IVIG therapy (Fig. 4 and Table 2).

3.5. Pregnancy outcome and live birth rate in IVIG-treated and –untreated groups

RPL women who received IVIG treatment showed a considerably higher success rate of pregnancy outcome. 28 out of 32 (87.5%) women in treated group had a live birth and the pregnancy of 4
women ended in miscarriage (two miscarried fetuses had Normal fetal karyotypes, while there was not performed any fetal chromosomal study in two other miscarriages). In untreated group, 5 out of 12 pregnancies (41.6%) ended in live birth and other pregnancies ended in miscarriage. (Normal fetal karyotypes were detected in five miscarried fetuses, and no fetal chromosomal study was performed in two other miscarriages) (Table 4).

4. Discussion

As a growing problem, approximately 15% to 25% of pregnancies face clinically recognized recurrent miscarriages [21]. RPL women often show different etiologies such as genetic, anatomic, hormonal, and infectious abnormalities, while almost 50% of RPL cases are idiopathic. Immune-mediated abnormalities are common especially in patients with idiopathic RPL [22,23]. Different studies have demonstrated that cellular immune abnormalities such as elevated NK cell frequency and cytotoxicity can negatively affect pregnancy outcome [24,25]. To date, several therapeutic agents have been suggested for the clinical management of RPL. Among the different treatment approaches used for RPL patients, IVIG therapy has received increasing attention in recent years.

IVIG was used for the first time in the late 1980s for the treatment of reproductive failure. Subsequently, this approach was also applied to treat other immune system disorders [26]. The mechanism of action of IVIG in recurrent miscarriage is not completely understood, but it has been suggested that immune response is modulated by IVIG through suppressing immune responses against the fetus or stimulating the regulatory responses, like inhibition of the activity of NK cells [27] and antibody production [13], enhancement of the proportion and function of regulatory T cells, inhibition of stimulatory Fc receptors and deposition of complement components [28–30].

Table 4

<table>
<thead>
<tr>
<th>Pregnancy outcome in IVIG-treated and untreated patients.</th>
<th>No. of patients</th>
<th>No. of live birth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>32</td>
<td>28(87.5%)</td>
</tr>
<tr>
<td>Untreated</td>
<td>12</td>
<td>5(41.6%)</td>
</tr>
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</table>
In the present study, etiology-based selection of RPL patients seems to be beneficial and improves the pregnancy outcome at the end of IVIG therapy. 47% of women included in this study exhibited abnormal levels of NK cells and 63% indicated abnormal cytotoxicity of NK cells. Based on this, these biomarkers were exploited for patient selection. Additionally, another evaluation was done for comparison of Th1 and Th2 proportion in normal pregnant and non-pregnant women with RPL patients before IVIG therapy; data associated to this assessment demonstrated that there is an imbalance between Th1 and Th2, elevated rate of Th1 and decreased level of Th2, in RPL patients in comparison to normal pregnant women. The data summarized in Table 3 and Fig. 3, confirmed the role of these lymphocytes in the success or failure of pregnancy process.

According to previous studies, IVIG treatment shows higher efficacy in patients with cellular immune abnormalities [3]. On the other hand, we included in our study normal pregnant and non-pregnant healthy women with no immune cell abnormalities in order to compare the frequency of Th1, Th2 cells between these healthy women and patients with cellular immune abnormalities. At the end of study, the healthy women showed a lower frequency of Th1 cells in comparison with IVIG and control groups, while their Th2 rates were significantly higher than patients with cellular abnormalities.

Study of Graphuo et al. investigated the effect of IVIG on RSA of immune etiologies and Th1/Th2 balance in alloimmune or autoimmune abnormalities. The results of their study demonstrated that IVIG shifts the responses toward Th2 and decreases Th1/Th2 ratio [16]. In another report, Yamada et al. examined the effect of massive IVIG (MOVIG) on the peripheral blood Th1/Th2 ratio in RSA women and analyzed the frequency of Th1, Th2 cells and related cytokines before and after treatment. Th2 frequency and IL-4 and IL-10 levels increased after treatment, while the frequency of Th1 cells and the levels of their associated cytokines decreased. Overall, this study revealed that MOVIG is able to decrease Th1/Th2 ratio in RSA patients [17].

In the study of Lee et al. which focused on assessing RPL etiology, 91 out of 189 had idiopathic RPL and 98 cases had known etiology in which immune cell abnormalities such as elevated rate of NK cells were investigated. 49 out of 91 and 62 out of 98 (111 out of 189, 58.7%) women had immune cell abnormalities and received the treatment. There was observed minor differences in the success result in patients with known etiology and cellular abnormalities (87.1%) and patients with unknown etiology and cellular abnormalities (81.6%). This study demonstrates that etiology-based treatment with IVIG, especially in patients with immune cell abnormalities, proves to be more effective and leads to an improved pregnancy outcome.

In accordance with previous reports, the results of our study revealed that patients with known etiology, especially immune-cell abnormalities, are appropriate candidates for IVIG administration during pregnancy. Also, IVIG is able to modulate harmful responses in the immune system to protect the early embryo or fetus. The elevated frequency of NK cells is a criterion which we used to select the subjects. According to our analyses performed after treatment, IVIG is capable of reducing Th1-associated responses and cytokine secretion, the mRNA level of T-bet decreased significantly after IVIG administration, which are detrimental to a successful pregnancy and instead, IVIG elevates Th2 frequency, and the levels of transcription factors and cytokines. GATA-3 was also effected noticeably, when it is compared between IVIG and control group after treatment and in IVIG group pre and post-treatment. As a result, Th1/Th2 balance is affected by IVIG, and a decrease in the ratio is observed through a shift toward Th2 responses.

5. Conclusion

In this study, we found that IVIG treatment in etiology-based enrollment of patients may be used as a beneficial approach to improve therapeutic outcome. Also, our results demonstrated that IVIG is an effective agent for the treatment of RPL women especially those patients with immune cell abnormalities. As an immunomodulator, IVIG is able to create a shift toward Th2 type responses and cytokine secretion and can decrease Th1/Th2 ratio, thus improving pregnancy outcome.

References


