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ORIGINAL ARTICLE

Altered Expression of the *HLA-G* and *IL10RB* Genes in Placental Tissue of Women with Recurrent Pregnancy Loss

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SUMMARY

Background: **Several lines of evidence strongly suggest that the contribution of human leukocyte antigen-G (HLA-G) and interleukin 10 receptor (IL10R) to maternal immunological tolerance toward paternal alloantigens of the embryo limits the activation and function of the maternal immune system. This study is aimed to assess the variation of the mRNA expression levels of *HLA-G* and *IL10RB* genes in placental tissue of women with recurrent pregnancy loss (RPL).**
Methods: **Placental tissue samples were collected from 78 women with a history of at least two consecutive miscarriages and 40 healthy women with no history of pregnancy loss. The expression of *HLA-G* and *IL10RB* in placental tissue specimens was evaluated by the quantitative real-time PCR (qPCR) method. Moreover, the correlation between the expression levels of these genes and clinicopathological parameters was analyzed.**
Results: **The results showed that the expression of *HLA-G* was down-regulated in placental tissues samples of RPL patients compared to healthy subjects, while the expression of *IL10RB* was up-regulated, but none of them was statistically significant (p-value > 0.05). The mRNA expression levels of *HLA-G* and *IL10RB* in placental tissue of RPL patients were negatively correlated with age and number of miscarriages (p-value > 0.05). A significant positive correlation was observed between the expression levels of *HLA-G* and *IL10RB* in women with RPL (p-value < 0.05).**
Conclusions: **The altered expression of *HLA-G* and *IL10RB* in placental tissue may contribute to the pathogenesis of RPL and therefore serve as potential therapeutic targets for its prevention.**
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KEYWORDS

recurrent pregnancy loss, placental tissue, *HLA-G*, *IL10RB*

INTRODUCTION

As an extremely distressing experience for women, recurrent pregnancy loss (RPL) is one of the complicated and challenging dilemmas in the field of reproductive medicine [1,2]. According to the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) guidelines, RPL is now defined as two or

more consecutive failed clinical pregnancies [3,4]. Approximately, 2 - 5% of reproductive-age couples trying to conceive suffer from RPL [1]. RPL is a multifactorial condition which originates from the complex interactions between multiple genetic, lifestyle, and environmental factors [5,6]. Although several etiological factors such as parental chromosome abnormalities, uterine anomalies, endocrine and metabolic disorders, endometrial dysfunction, autoimmune diseases, inherited thrombophilia, and infections have been suggested as key contributors of RPL [1, 2], the underlying causes of disease are still unknown in almost half of the cases.

The maternal immunological tolerance to the semi-allogeneic fetus is essential in a successful pregnancy. Failure in the molecular cross-talk at the maternal-fetal interface may lead to various adverse pregnancy outcomes such as RPL, preeclampsia, and other pathological conditions [7-9]. Over the last decades, several mechanisms have been suggested to describe how the fetal-placental unit escapes from maternal immune system rejection during early pregnancy [9-11]. In this regard, limitations on activation and function of natural killer (NK) cells, macrophages, dendritic cells (DCs), T cells, B cells, and natural killer T (NKT) cells have been proposed [10-12]. The human leukocyte antigen-G (HLA-G) is a non-classical major histocompatibility complex class I (MHC-I) molecule with a pivotal regulatory role in the establishment of fetal-induced maternal immunological tolerance [13-15]. HLA-G is almost exclusively expressed by extravillous trophoblasts (EVTs) of the placenta at the fetal-maternal interface and provides immunoprotection for the semi-allogeneic embryo against attacks of the maternal NK cells [16]. Interleukin 10 (IL10) is a potent anti-inflammatory immunosuppressive cytokine with a fundamental role in dampening immune responses and maintaining maternal-fetal immune tolerance [17]. IL10 mediates its biological activities by binding to heterotetrameric IL10 receptor (IL10R) complex, which consists of two ligand-binding subunits (IL10Rα or IL10R1) (encoded by the *IL10RA* gene) and two accessory signaling subunits (IL10Rβ or IL10R2) (encoded by the *IL10RB* gene) [17-19]. IL10R is expressed in a wide variety of cell types including placental trophoblasts, decidual stromal cells (DSCs), macrophages, and decidual natural killer (dNK) cells [17]. Upon binding of IL10 to its receptor complex, the synthesis of proinflammatory cytokines is suppressed through activation of Janus kinase-signal transducer and activator of transcription (JAK-STAT) and inhibition of nuclear factor κ-light-chain enhancer of activated B cells (NF-κB) signalling pathways [17].

Emerging evidence indicates the involvement of the dysregulated expression levels of *HLA-G* in the pathogenesis of RPL [20-23]. The expression levels of *HLA-G* have been reported to be down-regulated in RPL patients compared to healthy controls [20,21]. However, other studies contradict these findings [22,23]. Moreover, to the best of the authors' knowledge, no studies have so far investigated the relationship between altered expression levels of *IL10RB* and the occurrence of RPL. Accordingly, the present study was aimed to determine the involvement of the altered mRNA expression levels of *HLA-G* and *IL10RB* genes in placental tissue in the pathogenesis of RPL. The correlation between expression levels of *HLA-G* and *IL10RB* genes in placental tissue and clinicopathological characteristics was also explored.

MATERIALS AND METHODS

Subjects

Between May 2018 and September 2020, Seventy-eight women with a history of at least two consecutive failed clinical pregnancies before 20 weeks gestation and no previous live births (mean age ± standard deviation (SD); 32.92 ± 6.48 years, range 23 - 49) (mean number of miscarriages ± SD; 2.89 ± 0.96 years, range 2 - 6), as well as forty healthy women with a history of induced abortion (mean age ± SD; 28.57 ± 4.21 years, range 20 - 40), were included into this study. The studies were carried out in the medical genetic laboratory at the Assisted Reproductive Technology (ART) Center, Eastern Azerbaijan Branch of Academic Center for Education, Culture and Research (ACECR), Tabriz, Iran. Patients with any of the following criteria were excluded from the study: chromosomal abnormalities, uterine malformations, autoimmune diseases, hormonal imbalances, inherited thrombophilia, and genital infections. Demographic and clinical data, including age, number of live births, history of spontaneous miscarriages, induced abortions, ectopic pregnancies, stillbirths, preterm births, low birth weight, and infertility therapy were collected by a structured questionnaire. All procedures were done according to the relevant guidelines and the study was approved by the Institutional Review Board /Independent Ethics Committee (IRB/IEC) of the Tabriz University, Tabriz, Iran (Ethical Approval Code: IR.TABRIZU.REC.1398.020). In line with the principles of the World Medical Association's Declaration of Helsinki, written informed consent was obtained from all women after explaining the objectives and procedures of the study.

RNA extraction and cDNA synthesis

Placental tissues were obtained during the surgical abortion procedure or uterine curettage and immediately washed with phosphate-buffered saline (PBS) solution to remove maternal blood, followed by cutting into small pieces. The small placental tissue samples were immersed into RNAlater® RNA Stabilization Reagent (Qiagen, Hilden, Germany) and stored at -20°C until further processing. Total RNA was extracted from 100 mg placental tissue using a Tri-Pure® isolation reagent kit (Roche Applied Science, Penzberg, Germany) according to the manufacturer’s instructions. To eliminate genomic DNA contamination, the extracted RNAs were treated with RNase-free DNase I (Thermo Scien-

Table 1. List of primer sequences used for quantitative real-time polymerase chain reaction (qPCR) in the study.

	Sequence of primer	AL (bp)	Ta (°C)
HLA-G	F 5′ - CACGCACAGACTGACAGAATG - 3′	99	60
	R 5′ - GTCGCAGCCAATCATCCACT - 3′		
IL10RB	F 5′ - TGAGCAAACAACCCATGACGA - 3′	237	61
	R 5′ - TCATCCGACAATGGAAAGGAGA - 3′		
GAPDH	F 5′ - ACAACTTTGGTATCGTGGAAGG - 3′	101	60
	R 5′ - GCCATCACGCCACAGTTTC - 3′		

AL - amplicon length, Ta - annealing temperature, HLA-G - Human leukocyte antigen-G, IL10RB - Interleukin 10 receptor subunit beta, GAPDH - Glyceraldehyde 3-phosphate dehydrogenase.

Table 2. Correlation of placental HLA-G and IL10RB expression levels with age and number of abortions in patients with RPL.

	HLA-G	IL10RB
Age		
r	-0.147	-0.105
p-value	0.198	0.360
Number of abortions		
r	-0.156	-0.101
p-value	0.173	0.381

HLA-G - Human leukocyte antigen-G, IL10RB - Interleukin 10 receptor subunit beta, RPL - Recurrent pregnancy loss.
p-value was calculated by Pearson's correlation coefficient.

tific, Wilmington, DE, USA) based on the manufacturer's recommendations. The concentration and purity of the extracted RNAs were determined using a NanoDrop® ND-1000 UV-Vis Spectrophotometer (ThermoFisher Scientific™, Waltham, MA, USA). Subsequently, 1 µg of total RNA was reverse transcribed to complementary DNA (cDNA) using SuperScript® III First-Strand Synthesis System (Invitrogen, Grand Island, NY, USA) as mentioned in the manufacturer's protocol. Briefly, a random hexamer primer (1 µL) was added to the total RNA and incubated at 25°C for 5 minutes followed by 20 minutes of incubation at 42°C.

Quantitative real-time PCR (qPCR)

The expression levels of *HLA-G* and *IL10RB* genes in the placental tissue samples of RPL women and healthy controls were quantified by SYBR Green I-based qPCR technique on a StepOnePlus™ Real-Time PCR Systems (Applied Biosystems, Foster City, CA, USA). The qPCR assays were also carried out in triplicate using AccuPower® 2X GreenStar™ qPCR Master Mix (Bioneer, Daejon, South Korea) whose specific primers are listed in Table 1. PCR reactions contained 100 ng cDNA, 12.5 µL of 2X GreenStar™ qPCR Master Mix and 2 µL of each primer pair (10 pmol/µL) in a final volume of 25 µL. The PCR cycling reactions were conducted for 5 minutes at 94°C, followed by 40 cycles of denaturation at 94°C for 30 seconds, 30 seconds at temperatures given in Table 1 for each primer pair, and then 30 seconds at 72°C. The glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) mRNA level was utilized as an internal control to normalize the expression of *HLA-G* and *IL10RB* genes. No template control (NTC) reactions served as negative controls.

Statistical analysis

Statistical analysis of data was achieved using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). P-values less than 0.05 were regarded as statistically significant. The Kolmogorov-Smirnov test was employed to check the normality of the data and normally distributed variables were expressed as mean ± standard deviation (SD). Student's *t*-test was utilized to compare the mean expression levels of *HLA-G* and *IL10RB* in the placental tissue samples of RPL patients and healthy subjects. Pearson's correlation coefficient was also applied to determine the correlation between the expression levels of *HLA-G* and *IL10RB* and clinicopathological features.

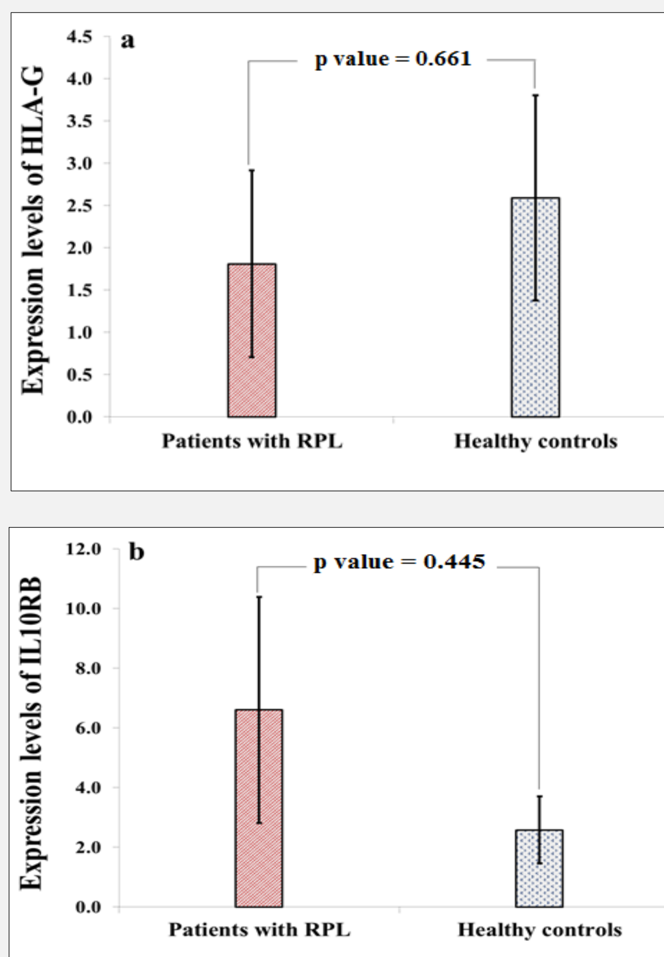

Figure 1. Expression levels of placental *HLA-G* and *IL10RB* genes in patients with RPL and healthy controls.

a) Down-regulation of placental *HLA-G* expression in patients with RPL compared with healthy controls (Fold change = 1.431, p-value = 0.661, 95% CI = - 4.2911 to 2.7317). b) Up-regulation of placental *IL10RB* expression in patients with RPL compared with healthy controls (Fold change = 2.5537, p-value = 0.455, 95% CI = - 6.5903 to 1.4624).

RESULTS

Placental expression levels of HLA-G and IL10RB in RPL patients and healthy subjects

The mRNA expression levels of *HLA-G* and *IL10RB* genes in the placental tissue samples of RPL patients and healthy controls were quantified by qPCR. Kolmogorov-Smirnov test was utilized to explore the normality of data which confirmed the normal distribution of the mRNA expression levels of *HLA-G* and *IL10RB* genes (p-value > 0.05). Based on cycle threshold (Ct) values, the relative expression levels of *HLA-G* and *IL10RB* genes were determined using the equation of $2^{-\Delta\Delta CT}$. As shown in Figure 1a, the mRNA expression levels of the *HLA-G* gene were up-regulated in the placental tissue samples of healthy subjects when compared with RPL patients (Fold Change (FC) = 1.431), although it was not statistically significant (95% Confidence Interval (95% CI): - 4.2911 to 2.7317; p-value = 0.661). RPL Patients exhibited slightly higher mRNA expression levels of *IL10RB* gene in the placental tissue samples (FC = 2.553) (95% CI: - 6.5903 to 1.4624; p-value = 0.455) (Figure 1b).

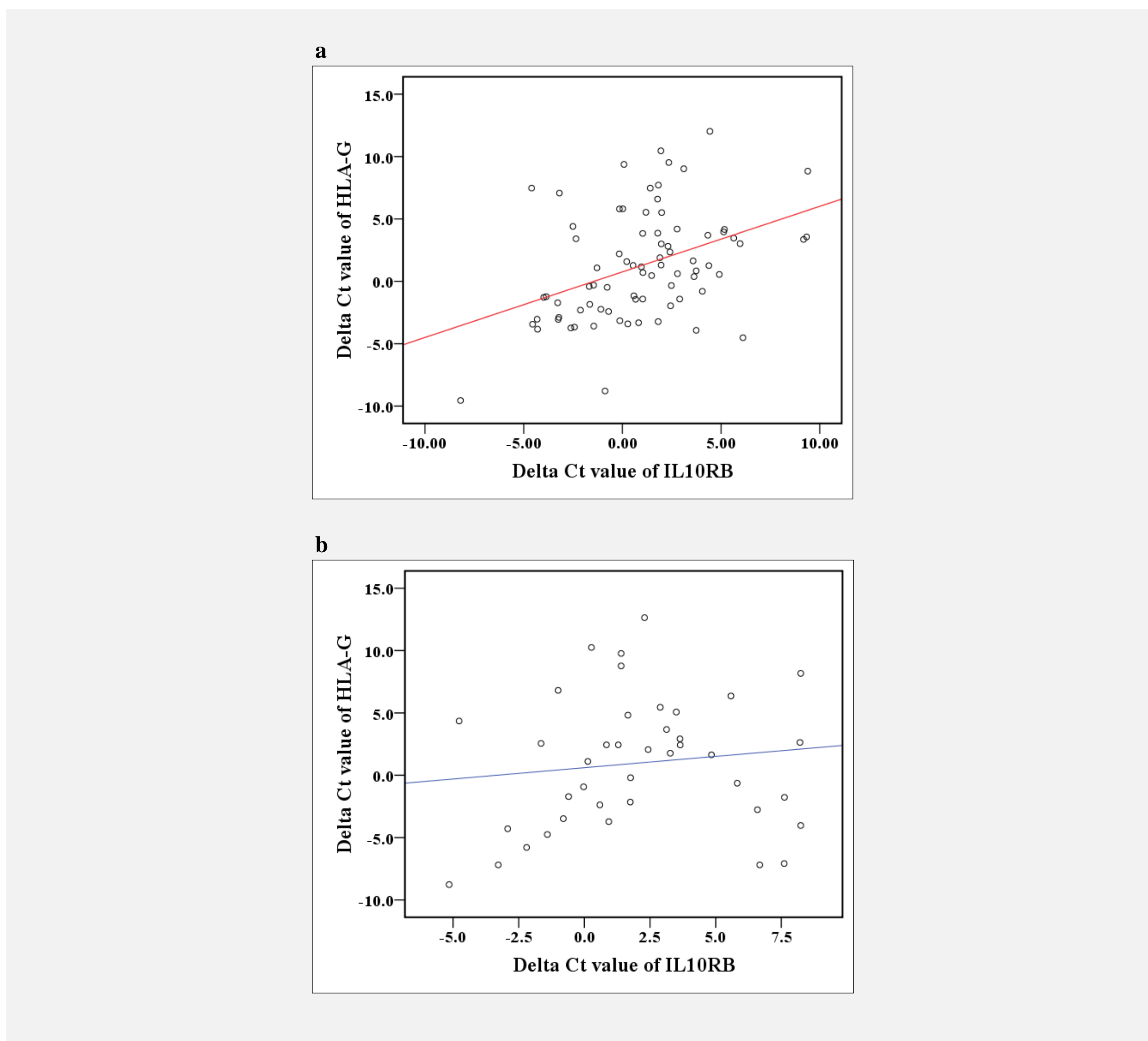

Figure 2. Correlation between expression levels of placental *HLA-G* and *IL10RB* genes in patients with RPL and healthy controls.

a) Significant positive correlations between the expression levels of placental *HLA-G* and *IL10RB* genes in patients with RPL (r = 0.405, p-value 0.0001). b) No significant correlation between the expression levels of placental *HLA-G* and *IL10RB* genes in healthy controls (r = 0.123, p-value = 0.449).

Correlation between mRNA expression levels of HLA-G and IL10RB genes in RPL patients and healthy subjects

A significant positive correlation was found between the mRNA expression levels of *HLA-G* and *IL10RB* genes in the placental tissue samples of RPL patients (r = 0.405, p-value = 0.0001) (Figure 2a); while no significant correlation was detected between mRNA expression levels of *HLA-G* and *IL10RB* genes in the placental tissue samples of healthy controls (r = 0.123, p-value = 0.449) (Figure 2b).

Correlation between mRNA expression levels of *HLA-G* and *IL10RB* genes and clinicopathological parameters

The correlation of mRNA expression levels of *HLA-G* and *IL10RB* genes in the placental tissue samples of RPL patients with age and number of abortions was also evaluated. A negative correlation was found between mRNA expression levels of *HLA-G* (r = - 0.147) and *IL10RB* (r = - 0.105) in RPL patients and their age, although it was not statistically significant (p-value > 0.05) (Table 2). Furthermore, mRNA expression levels

of *HLA-G* (r = - 0.156) and *IL10RB* (r = - 0.101) in patients were negatively, but insignificantly, correlated with number of abortions in RPL patients (p-value > 0.05) (Table 2).

DISCUSSION

The human placenta has a roughly disc-shaped structure and is a transient vital organ formed at the interface between the mother and developing fetus. The placenta mediates respiratory gases exchange and transfer of nutrients and metabolic waste products during pregnancy [24]. Immunologically, the embryo and its placenta are semi-allogeneic, which must be tolerated by the maternal immune system to establish a healthy pregnancy [25]. Thus far, several key strategies have been suggested to explain the adaptation of the maternal immune system to paternally inherited antigens in the fetal-placental unit, however, many aspects of maternal immune tolerance have not been elucidated [9-11]. Compelling evidence showed that fetally-derived trophoblast cells act as effector cells in sustaining maternal-fetal immune tolerance via secreting the different cytokines and chemokines [26,27]. At the fetal-maternal interface, EVTs are in close contact with decidual leukocytes such as dNK cells, macrophages, T helper cells, and cytotoxic T cells [28]. Among these leukocytes, dNK cells constitute more than 70% of maternal immune cells in decidua basalis with a play key regulatory role in trophoblast invasion, placental vascular development, and immune balance [29]. EVT-expressed HLA-G serves as a ligand for direct interaction with the inhibitory receptor, i.e., killer cell immunoglobulin-like receptor (KIR) 2DL4 (KIR2DL4) on the surface of dNK cells [30]. Upon binding of HLA-G to KIR2DL4, signals are conveyed into the cell to inactivate dNK cells and protect the fetus against allogeneic dNK-mediated cytolysis [31]. Additionally, a subset of dNK cells that expresses immunoglobulin-like transcript 2 (ILT2) (also called leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1)) are inhibited by HLA-G, reducing the cytotoxicity of dNK cells [32]. Meanwhile, soluble HLA-G (sHLA-G) secreted by EVTs binds to KIR2DL4 on dNK cells and stimulates the secretion of proinflammatory/proangiogenic cytokines and chemokines such as IL6, IL8, IL23, tumor necrosis factor-α (TNF-α), macrophage inflammatory protein-3α (MIP-3α), MIP-1δ, MIP-1α, and MIP-2β by dNK cells which, in turn, mediates EVTs invasion into the maternal decidua [33]. The sHLA-G secreted by EVTs can also induce type 1 regulatory T ($T_{reg}1$) cells to produce IL10 to limit immunological aggression to the fetus [31]. Therefore, the cross-talk between expressed/secreted HLA-G by EVTs and decidual immune cells coordinates a series of complex events with a vital role in a successful pregnancy. Additionally, IL10 stands out as an important molecule in tuning the maternal immune responses at the maternal-fetal interface [34]. In the decidua, IL10 is expressed by placental villous trophoblasts, Tregs, and dNK cells, and exerts its biological activities through IL10R [17]. As a signaling subunit of the IL10R complex, IL10Rβ is expressed in a broad range of cell types [35,36]. Once the IL10/IL10Rα/IL10Rβ complex is assembled, IL10Rα-associated Janus kinase 1 (JAK1) and IL10Rα-associated tyrosine kinase 2 (Tyk2) are activated, which, in turn, phosphorylate the intracellular domain of IL10Rα and subsequent activation of STAT3 [36]. Activated STAT3 also acts as a transcriptional factor and regulates the expression of target genes involved in anti-inflammatory response via binding to STAT3-binding elements of IL10-responsive genes [37]. It has also been demonstrated that IL10 inhibits the activity of NF-κB transcription factors in different cell types that regulates the expression of many genes such as IL12 and TNF-α [38]. Noteworthy, IL10Rβ is a component of other human class II family of cytokine receptors (CRF2) including IL22, IL26, and INFλ [39]. Overall, these findings indicate that IL10Rβ may concurrently regulate the secretion of a large array of cytokines and chemokines from different cells in decidua basalis during pregnancy. Accordingly, it was hypothesized that altered mRNA expression levels of *HLA-G* and *IL10Rβ* genes in the placenta may contribute to the susceptibility of RPL. This hypothesis was tested by quantifying the mRNA expression levels of these genes in the placental tissue samples of RPL patients and healthy subjects using the qPCR method. Lower *HLA-G* expression was detected at mRNA level in the placental tissue samples of RPL patients compared to healthy controls, but not statistically significant (p-value > 0.05). In line with our findings, Mosaferi et al. identified the decreased mRNA and protein levels of HLA-G in the placental tissues of RPL cases compared to healthy subjects [20]. Similarly, Akhter et al. observed a low level of *HLA-G* in extravillous cytotrophoblast cells from RPL patients as compared with healthy controls [21]. Eskicioğlu et al. reported the higher expression of HLA-G in decidua samples of women with healthy pregnancies compared to those suffering from recurrent miscarriages [22]. However, there was no statistically significant difference between groups [22]. These findings lead us to conclude that low levels of HLA-G expression in the placenta might be a potential risk factor for RPL. As far as we know, this is the first report investigating the mRNA expression levels of the *IL10RB* gene in placental tissues samples of RPL patients using the qPCR procedure. Based on the literature review, two studies have so far examined the expression of IL10R in placental tissues, cytotrophoblast, and endometrial cells [40,41]. The mRNA expression levels of IL10RB were up-regulated in placental tissue samples of RPL patients compared to healthy controls, but not statistically significant (p-value > 0.05), in line with the findings of Vigano et al. who demonstrated a significant enhancement in the mRNA expression levels of IL10R in early pregnancy compared with cycling endometrium using a semiquantitative RT-PCR method [40]. Immunohisto-

chemical analysis showed that the expression of IL10, but not its receptor, was significantly decreased in the placental tissues [41].
In conclusion, HLA-G and IL10Rβ may play important roles in regulating immune tolerance during pregnancy. Moreover, altered expression of *HLA-G* and *IL10RB* genes in the placenta may contribute to the pathogenesis of RPL.

Acknowledgment:
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Availability of Data and Material:
The confirmed data in this study are available upon reasonable request from the corresponding author.

Ethical Approval:
All procedures involving human participants were in line with the ethical standards of the institutional research committee.

Informed Consent:
The study was approved by the Institutional Review Board /Independent Ethics Committee (IRB/IEC) of the University of Tabriz, Tabriz, Iran. Informed written consent was also obtained from all participants.

Declaration of Interest:
The authors declare that there is no conflict of interest regarding the publication of this paper.

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