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GENETICS

The HLA-G 14-bp polymorphism and recurrent implantation failure: a meta-analysis

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Abstract
Purpose The human leucocyte antigen-G (HLA-G) 14-bp insertion/deletion polymorphism was implicated in recurrent implantation failure (RIF), but individual published studies showed inconclusive results. Thus, a meta-analysis was performed to clarify the effect of HLA-G 14-bp polymorphism on RIF risk.
Methods A comprehensive search for relevant articles was conducted. The odds ratios (ORs) and 95% confidence intervals (CIs) for HLA-G 14-bp polymorphism and RIF were calculated.
Results A total of five studies were included. In studies conducted in RIF patients and controls who had at least one spontaneous pregnancy, meta-analysis revealed no statistically significant association between the HLA-G 14-bp polymorphism and RIF in allele contrast and all genetic models in the overall population, but significant association was found in the population of Caucasian origin under allele contrast (OR = 1.73, 95% CI, 1.20, 2.50) and genetic models of +14 bp/+14 bp vs. −14 bp/−14 bp (OR = 3.09, 95% CI, 1.43, 6.65). In studies conducted in RIF patients and controls who had successful pregnancy following IVF-ET, the meta-analysis showed that there was statistically significant association between the HLA-G 14 bp polymorphism and RIF in allele contrast (OR = 1.74, 95% CI, 1.13, 2.67) and genetic models of +14 bp/+14 bp vs. −14 bp/−14 bp (OR = 10.20, 95% CI, 2.47, 42.14) and dominant model (OR = 4.34, 95% CI, 1.72, 10.92). No publication bias was found in the present studies.
Conclusions This meta-analysis suggested that the HLA-G 14-bp insertion allele may increase the risk of RIF in Caucasians. Further studies with large sample size of different ethnic populations are necessary.

Keywords HLA-G · Polymorphism · RIF

Introduction

Recurrent implantation failure (RIF) was one of the most common causes of unsuccessful pregnancy in women receiving in vitro fertilization and embryo transfer (IVF-ET). Although there was no consensus on the definition of RIF, implantation failure following two or more embryo transfer cycles of high-grade embryos was most widely accepted. The exact prevalence rate of RIF was difficult to determine because of the varied definitions used to describe the disease. Etiology of RIF is complex, and in some women, the pathogeny of RIF is often not clear. Numerous factors influenced successful implantation in IVF-ET, including female factors (uterine anatomy, endometrium, and thrombophilia) and embryonic factors (genetics, sperm contribution, and immunologic factors) [1]. The couples with RIF may benefit from many treatments including immunological tests and therapy, intratubal transfer of zygotes and embryos, blastocyst transfer, sequential embryo transfer of cleavage stage embryos and blastocysts, assisted hatching, co-cultures, and pre-implantation genetic screening for aneuploidy screening [2]. Recently, several lines of genetic-association studies have revealed associations between the RIF risk and certain genetic polymorphisms,

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including tumor protein P53, cyclooxygenase-2 (COX-2), methylenetetrahydrofolate reductase (MTHFR), thymidylate synthase (TS), nuclear factor kappa B (NF-κB), plasminogen activator inhibitor-1, vascular endothelial growth factor, and leukocyte antigen-G [3–9]. Among these candidate RIF-susceptibility genes, the human leucocyte antigen-G (HLA-G) gene was one of the most extensively explored.

The HLA-G gene located on chromosome 6p21.3 was composed of eight exons and seven introns [10]. HLA-G proteins included four membrane-bound (HLA-G1, G2, G3, and G4) and three soluble (HLA-G5, G6, and G7) forms, which was detected only in trophoblast, thymus, cornea, nail matrix, pancreas, and erythroid and endothelial precursors [11]. HLA-G had a lower level of polymorphism than other HLA class molecules I. The extensively studied polymorphism in the non-coding region was a 14-bp insertion/deletion in exon 8, which had a role on HLA-G alternative splicing and HLA-G messenger RNA (mRNA) stability [12]. Compared with the genotypes of +14 bp/−14 bp and −14 bp/−14 bp, the homozygous genotype (+14 bp/+14 bp) was associated with lower mRNA and soluble HLA-G levels [12, 13]. Therefore, it seemed that HLA-G 14-bp polymorphism may play a momentous role in the modulation of HLA-G expression, and women with RIF may have a higher frequency of individuals with the 14-bp insertion. A number of epidemiological studies investigated the association between the HLA-G 14-bp polymorphism and susceptibility to RIF [14–16]. However, these studies yielded apparently inconclusive results, which might be due to differences in the studied populations and limited sample sizes. Therefore, we conducted a systematic review and meta-analysis of the results of previously published studies to clarify this inconsistency and to establish the relationship between the HLA-G 14-bp polymorphism and susceptibility to RIF.

Materials and methods

Literature search strategy

Electronic searches were conducted by two authors independently in the following databases: PubMed, EMBASE, and CNKI (China National Knowledge Infrastructure) for all eligible articles on the association between the HLA-G 14-bp polymorphism and RIF risk (up to March 12, 2017). The following keywords were used: ("human leukocyte antigen g" or "HLA-G") and ("polymorphism" or "genotype" or "genetic" or "mutation" or "variant") and ("recurrent implantation failure" or "repeated implantation failure" or "RIF" or "implantation failure" or "in vitro fertilization or intracytoplasmic sperm injection" or "IVF" or "ICSI" or "assisted reproductive techniques" or "ART"). The language of the studies was not restricted. Reference lists of identified studies and related reviews were reviewed to identify additional studies that may be not indexed by the electronic searches.

Inclusion and exclusion criteria

Studies included in the meta-analysis had to meet all of the following criteria: (1) case–control studies, (2) studies that evaluated the association of the HLA-G 14-bp polymorphism with RIF, and (3) studies with sufficient data for calculating odds ratios (ORs) and the 95% confidence intervals (CI). The exclusion criteria were (1) studies in which the genotype or allele frequency could not be calculated; (2) studies that were review articles, letters, case reports, abstracts, and editorials; and (3) studies that were family-based studies.

Data extraction

Based on the inclusion criteria, the following information was extracted from eligible included studies by two authors independently: the first author's name, year of publication, country, ethnicity, sample size, inclusion criteria of cases and controls, distribution of genotypes, and Hardy–Weinberg equilibrium (HWE) in controls. $P < 0.05$ was considered to be a significant deviation from the HWE. Disagreements were discussed and resolved with consensus.

Statistical analysis

We accessed the association between the HLA-G 14-bp polymorphism and RIF risk by using different comparison models, including an allelic model, a codominant model, a dominant model, and a recessive model. ORs and the corresponding 95% CIs were used to measure the strength of the models. The heterogeneity between studies was evaluated by a chi-square-based Q test [17] and I^2 statistic [18]. The Q test ($P < 0.1$) was interpreted as significant heterogeneity among the studies; then, the random-effects model was used; otherwise, the fixed-effects model was applied. I^2 statistic was calculated to quantify the heterogeneity: $I^2 < 25\%$, $I^2 = 25$–50%, $I^2 = 50$–75%, and $I^2 > 75\%$, indicated no, moderate, large, and extreme heterogeneity, respectively [18]. Subgroup analysis was performed by ethnicity, HWE in controls (yes or not). The Begg rank correlation test and Egger weighted regression test were conducted to assess the potential publication bias ($P < 0.05$ was considered statistically significant). All statistical analyses were performed using STATA® software version 10.0 (StataCorp LP, College Station, TX, USA).

Results

Studies included in the meta-analysis

In this study, we retrieved a total of 193 articles after a search of PubMed, EMBASE, and CNKI databases, of which 24 were selected for full-text review based on their titles and abstracts. After the full-text evaluation, according to the inclusion/exclusion criteria, five publications were ultimately selected into analysis [14–16, 19, 20].

As shown in Table 1, the meta-analysis considered four studies for the HLA-G 14-bp polymorphism and RIF risk, with 137 RIF patients and 246 controls who had at least one spontaneous pregnancy [14, 15, 19, 20]; three studies for the HLA-G 14-bp polymorphism and RIF risk with 78 RIF patients and 102 controls who had successful pregnancy following IVF-ET [15, 16, 20]. Of the five studies, four studies were conducted in Caucasians and one in a mixed-race population [14]. In two of the five included studies, the criteria for the inclusion of RIF patients were at least two unsuccessful embryo transfers [14, 16]; in the other included studies, the criteria for the inclusion of RIF patients were at least three unsuccessful embryo transfers [15, 19, 20]. The distribution of genotypes among controls was consistent with HWE in all studies.

The HLA-G 14-bp polymorphism and RIF susceptibility

A summary of findings on the association between the HLA-G 14-bp polymorphism and RIF risk in studies conducted in RIF patients and controls who had at least one spontaneous pregnancy is shown in Table 2. In the overall population, meta-analysis revealed no statistically significant association between the HLA-G 14-bp polymorphism and RIF in allele contrast and all genetic models (+14 bp vs. −14 bp: OR = 1.11, 95% CI, 0.46, 2.67, $I^2 = 86.1\%$, $P_{\text{heterogeneity}} < 0.001$; +14 bp/+14 bp vs. −14 bp/−14 bp: OR = 1.11, 95% CI, 0.15, 8.14, $I^2 = 85.5\%$, $P_{\text{heterogeneity}} < 0.001$; +14 bp/−14 bp vs. −14 bp/−14 bp: OR = 1.39, 95% CI, 0.38, 5.02, $I^2 = 76.2\%$, $P_{\text{heterogeneity}} = 0.01$; dominant model: OR = 1.34, 95% CI, 0.35, 5.11, $I^2 = 80.4\%$, $P_{\text{heterogeneity}} < 0.001$; recessive model: OR = 0.88, 95% CI, 0.22, 3.55, $I^2 = 81.1\%$, $P_{\text{heterogeneity}} < 0.001$). In the subgroup analysis by ethnicity, significant association between the HLA-G 14-bp polymorphism and RIF risk was found in the population of Caucasian origin under allele contrast and genetic model of +14 bp/+14 bp vs. −14 bp/−14 bp (+14 bp vs. −14 bp: OR = 1.73, 95% CI, 1.20, 2.50, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.71$; +14 bp/+14 bp vs. −14 bp/−14 bp: OR = 3.09, 95% CI, 1.43, 6.65, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.70$) (Table 2). The distribution of genotypes among controls was consistent with HWE in all studies; thus, we did not perform the subgroup analysis by HWE in controls.

In studies conducted in RIF patients and controls who had successful pregnancy following IVF-ET, the meta-analysis showed that there was statistically significant association between the HLA-G 14-bp polymorphism and RIF risk in allele contrast and genetic model of +14 bp/+14 bp vs. −14 bp/−14 bp and dominant model (+14 bp vs. −14 bp: OR = 1.74, 95% CI, 1.13, 2.67, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.56$; +14 bp/+14 bp vs. −14 bp/−14 bp: OR = 10.20, 95% CI, 2.47, 42.14, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.97$; dominant model: OR = 4.34, 95% CI, 1.72, 10.92, $I^2 = 52.1\%$, $P_{\text{heterogeneity}} = 0.12$) (Table 3). All the studies included in the meta-analysis were conducted in Caucasians, and the distribution of genotypes among controls was consistent with HWE in all studies, so we did not perform the subgroup analysis by ethnicity and HWE in controls.

Heterogeneity analysis

There was moderate or large heterogeneity among studies in most overall comparisons. To explore sources of heterogeneity across studies, subgroup analyses by ethnicity and HWE in controls were conducted.

For the studies conducted in RIF patients and controls who had at least one spontaneous pregnancy, there was extreme heterogeneity among studies in all comparisons (Table 2). To explore sources of heterogeneity across studies, subgroup analyses by ethnicity and HWE in controls were conducted. There was no heterogeneity in the studies of Caucasians in allele contrast and genetic models of +14 bp/+14 bp vs. −14 bp/−14 bp and recessive model (Table 2). Since the distribution of genotypes among controls was consistent with HWE in all studies, HWE in controls could not explain the heterogeneity.

For the studies conducted in RIF patients and controls who had successful pregnancy following IVF-ET, although there was no heterogeneity among studies in allele contrast and genetic model of +14 bp/+14 bp vs. −14 bp/−14 bp, there was still large heterogeneity among studies in other genetic models (Table 3). All the studies included in the meta-analysis were conducted in Caucasians, and the distribution of genotypes among controls was consistent with HWE in all studies; thus, we cannot perform the subgroup analyses by ethnicity and HWE in controls to explore sources of heterogeneity across studies.

Publication bias

Begg's test and Egger's test were performed to assess the publication bias of the literatures (Tables 2, 3), which showed that there was no strong evidence of publication bias for studies published on the association of the HLA-G 14-bp polymorphism and RIF patients.

Table 1 Characteristics and distribution of HLA-G genotype of studies included in the present meta-analysis

Study (year)	Ethnicity (country)	Inclusion criteria for cases	Inclusion criteria for controls 1	Inclusion criteria for Controls 2	Numbers			Genotype									HWE in control, *P* value
					Cases	Controls 1	Controls 2	Cases			Controls 1			Controls 2			
								Ins/ins	Ins/del	Del/del	Ins/ins	Ins/del	Del/del	Ins/ins	Ins/del	Del/del	
Nardi Fda S et al. (2016)	Mixed (Brazil)	≥2 unsuccessful embryo transfers in ART	≥2 successful previous pregnancies without a history of gestational complications		49	34		2	31	16	13	18	3				Controls 1:0.35
Lashley LE et al. (2014)	Caucasian (Netherlands)	≥3 consecutive IVF failures with high-quality and fresh embryos.	≥one spontaneous pregnancy and no record of secondary infertility	A live child birth after one IVF or ICSI treatment	24	48	48	6	16	2	10	18	20	6	25	17	Controls 1:0.13 Controls 2:0.49
Enghelabifar M et al. (2014)	Caucasian (Iran)	≥2 failed IVF-ET, using at least 6 appropriate cleaved embryos		Successful implantation following IVF-embryo transfer	40		39	7	33	0				9	22	8	Controls 2:0.42
Sipak-Szmigiel O et al. (2009)	Caucasian (Poland)	≥3 IVF failures	≥2 children, none experienced RSA		50	71		12	27	11	12	30	29				Controls 1: 0.38
Hviid TV et al. (2004)	Caucasian (Denmark)	≥3 unsuccessful IVF treatments	≥2 uncomplicated pregnancies and live births and no miscarriages	Successful twin pregnancy after first IVF	14	93	15	4	5	5	10	52	31	0	9	6	Controls 1: 0.09 Controls 2: 0.10

Table 2 Meta-analysis of the association between the HLA-G 14-bp polymorphism and RIF risk in studies conducted in RIF patients and controls who had at least one spontaneous pregnancy

Comparisons	No. of studies	Subgroup	OR (95% CI)	Test of heterogeneity		Publication bias	
				P value	I^2 (%)	Begg's test	Egger's test
+14 bp vs. −14 bp	4	All	1.11 (0.46, 2.67)	<0.001	86.1	1.00	0.90
	3	Caucasian	*1.73(1.20,2.50)*	*0.71*	*0*		
+14 bp/+14 bp vs. −14 bp/−14 bp	4	All	1.11 (0.15, 8.14)	<0.001	85.5	0.73	0.49
	3	Caucasian	*3.09(1.43,6.65)*	*0.70*	*0*		
+14 bp/−14 bp vs. −14 bp/−14 bp	4	All	1.39 (0.38, 5.02)	0.01	76.2	1.00	0.86
	3	Caucasian	2.20 (0.59, 8.19)	0.03	70.4		
Dominant model	4	All	1.34 (0.35, 5.11)	<0.001	80.4	1.00	0.81
	3	Caucasian	2.36 (0.83, 6.69)	0.09	59.3		
Recessive model	4	All	0.88 (0.22, 3.55)	<0.001	81.1	0.73	0.43
	3	Caucasian	1.68 (0.90, 3.16)	0.53	0		

Discussion

In recent years, interest in genetic factors that was implicated in the pathogenesis of RIF has spurred a great number of association studies on polymorphisms of different genes [21–23]. To date, epidemiological studies have indicated that the HLA-G 14-bp polymorphism may play an important role in the risk of RIF, but the results were inconclusive. Thus, the meta-analysis was undertaken to assess whether the HLA-G 14-bp polymorphism was associated with RIF risk. To the best of our knowledge, this is the first meta-analysis of the relationship between the HLA-G 14-bp polymorphism and the risk of RIF.

In this meta-analysis, we addressed the association between the HLA-G 14-bp polymorphism and RIF susceptibility in Caucasian population in allele contrast and genetic model of +14 bp/+14 bp vs. −14 bp/−14 bp with no heterogeneity, no matter the controls had at least one spontaneous pregnancy or had successful pregnancy following IVF-ET.

Fetus was considered as a semi-allograft for maternal immune system. There were particular mechanisms that modulated the maternal immune system during pregnancy, protecting the semi-allogeneic fetus from maternal graft rejection responses. HLA-G was believed to take part in the immunosuppression in the process of embryo implantation and embryo development. It was suggested that lower concentrations of HLA-G increased allocytotoxic T lymphocyte responses and resulted in a Th1-type cytokine profile, whereas high concentrations of HLA-G suppressed the allocytotoxic T lymphocyte response and induced a Th2-type cytokine response [24]. Several treatment modalities with Th1/Th2 elevation have been previously reported to be effective in women with RIF [25–27]. Moreover, it was showed that low levels of soluble HLA-G (sHLA-G) in maternal blood were associated with a risk of spontaneous abortion during the first trimester in IVF patients [28], and there was a statistically significant association between sHLA-G positive pre-implantation blastocysts and pregnancy success in IVF [29, 30]. The HLA-G 14-bp ins phenotype was expressed at a significantly lower level HLA-G mRNA and soluble HLA-G than the HLA-G 14-bp del phenotype [12, 13, 31], possibly providing an explanation for the increased frequency of 14-bp insertion in women with RIF. In aggregate, these findings supported the idea that the 14-bp insertion allele was associated with an increased risk of RIF in IVF. We speculated that HLA-G 14-bp insertion may be associated with reduced soluble HLA-G expression, which

Table 3 Meta-analysis of the association between the HLA-G 14-bp polymorphism and RIF risk in studies conducted in RIF patients and controls who had successful pregnancy following IVF-ET

Comparisons	No. of studies	OR (95% CI)	Test of heterogeneity		Publication bias	
			P value	I^2 (%)	Begg's test	Egger's test
+14 bp vs. −14 bp	3	1.74 (1.13, 2.67)	0.56	*0*	1.00	0.68
+14 bp/+14 bp vs. −14 bp/−14 bp	3	10.20 (2.47, 42.14)	0.97	*0*	1.00	0.31
+14 bp/−14 bp vs. −14 bp/−14 bp	3	3.57 (0.50, 25.71)	0.05	67.7	1.00	0.55
Dominant model	3	4.34 (1.72, 10.92)	0.12	52.1	0.30	0.49
Recessive model	3	1.55 (0.73, 3.29)	0.12	53.3	0.30	0.38

leaded to immune system intolerance against embryo and thereby promoted development of RIF.

Nevertheless, this meta-analysis also had some limitations. First, there were only few articles included in the present meta-analysis, so the sample size was relatively small and may not provide sufficient statistical power. Moreover, the included studies were carried out mainly in Caucasians, and ethnic differences may reflect different linkages to the polymorphism determining the RIF risk. In Caucasian populations, the frequencies of +14 bp and −14 bp are nearly equal; however, in African populations, the allele with the deleted 14-bp sequence may dominate [32]. Therefore, more studies with larger sample size are warranted to validate these findings, especially in different ethnic populations. Second, haplotype analysis could provide additional information, and would have been more powerful than single polymorphism analysis. It was suggested that the HLA-G*01:01:02a and HLA-G*01:01:02b alleles and the 14-bp ins polymorphism was significantly presented in women with failure implantation after IVF treatment [33]. However, in our meta-analysis, the haplotype analysis was not performed because of inadequate data. Third, we only included published studies in the meta-analysis, and thus the possibility of publication bias may not be excluded, although the results of Begg's test and Egger's test showed that publication bias is unlikely. Fourth, we did not further assess the potential gene–gene interactions and gene–environment interactions, due to the lack of sufficient information from the included studies. Fifth, the HLA-G 14-bp ins/del genotype of the men may be the risk factor of RIF. It was suggested that the concentration of sHLA-G in seminal plasma samples was significantly associated with the HLA-G 14-bp ins/del genotype of the men, and seminal sHLA-G may be an immunomodulatory factor before and at the time of conception [34]. Unfortunately, we cannot evaluate the association between the HLA-G 14-bp polymorphism of the men and RIF due to the lack of sufficient information from the included studies.

In conclusion, this meta-analysis suggested that the HLA-G 14-bp insertion allele may increase the risk of RIF in Caucasians. Further studies with large sample size of different ethnic populations are necessary. In addition, other probable genetic risk factors interacting with the HLA-G 14-bp polymorphism should be investigated.

References

1. Simon A, Laufer N. Repeated implantation failure: clinical approach. Fertil Steril. 2012;97:1039–43.
2. Urman B, Yakin K, Balaban B. Recurrent implantation failure in assisted reproduction: how to counsel and manage. B. Treatment options that have not been proven to benefit the couple. Reprod BioMed Online. 2005;11(3):382–91.
3. Feng Y, Wu YY, Lin XJ, Yang L, Luo ZJ, Zhou YH, et al. Associations between the codon 72 polymorphism of the TP53 gene and the risk of recurrent implantation failure. J Obstet Gynaecol Res. 2016;42(2):184–9.
4. Salazar LA, Inostroza M, Jara C, Vega F, García R, Ciuffardi I, et al. Association of -765G>C polymorphism of the COX-2 gene with recurrent embryo implantation failure in southern Chilean women. Clin Chim Acta. 2010;411(21–22):1822–4.
5. Choi Y, Kim JO, Shim SH, Lee Y, Kim JH, Jeon YJ, et al. Genetic variation of methylenetetrahydrofolate reductase (MTHFR) and thymidylate synthase (TS) genes is associated with idiopathic recurrent implantation failure. PLoS One. 2016;11(8):e0160884.
6. Luo L, Li DH, Li XP, Zhang SC, Yan CF, Wu JF, et al. Polymorphisms in the nuclear factor kappa B gene association with recurrent embryo implantation failure. Genet Mol Res. 2016;15(2): gmr7759.
7. Salazar Garcia MD, Sung N, Mullenix TM, Dambaeva S, Beaman K, Gilman-Sachs A, et al. Plasminogen activator inhibitor-1 4G/5G polymorphism is associated with reproductive failure: metabolic, hormonal, and immune profiles. Am J Reprod Immunol. 2016;76(1):70–81.
8. Jung YW, Kim JO, Rah H, Kim JH, Kim YR, Lee Y, et al. Genetic variants of vascular endothelial growth factor are associated with recurrent implantation failure in Korean women. Reprod BioMed Online. 2016;32(2):190–6.
9. Nardi Fda S, Slowik R, Wowk PF, da Silva JS, Gelmini GF, Michelon TF, et al. Analysis of HLA-G polymorphisms in couples with implantation failure. Am J Reprod Immunol. 2012;68(6):507–14.
10. Geraghty DE, Koller BH, Orr HT. A human major histocompatibility complex class I gene that encodes a protein with a shortened cytoplasmic segment. Proc Natl Acad Sci U S A. 1987;84:9145–9.
11. Carosella ED, Moreau P, Le Maoult J, Le Discorde M, Dausset J, Rouas-Freiss N. HLA-G molecules: from maternal-fetal tolerance to tissue acceptance. Adv Immunol. 2003;81:199–252.
12. Hviid TV, Hylenius S, Rorbye C, Nielsen LG. HLA-G allelic variants are associated with differences in the HLA-G mRNA isoform profile and HLA-G mRNA levels. Immunogenetics. 2003;55:63–79.
13. Hviid TV, Rizzo R, Christiansen OB, Melchiorri L, Lindhard A, Baricordi OR. HLA-G and IL-10 in serum in relation to HLA-G genotype and polymorphisms. Immunogenetics. 2004;56(3):135–41.
14. Nardi Fda S, Slowik R, Michelon T, Manvailer LF, Wagner B, Neumann J, et al. High amounts of total and extracellular vesicle-derived soluble HLA-G are associated with HLA-G 14-bp deletion variant in women with embryo implantation failure. Am J Reprod Immunol. 2016;75(6):661–71.
15. Lashley LE, van der Westerlaken LA, Haasnoot GW, Drabbels JJ, Spruyt-Gerritse MJ, Scherjon SA, et al. Maternal HLA-C2 and 14 bp insertion in HLA-G is associated with recurrent implantation failure after in vitro fertilization treatment. Tissue Antigens. 2014;84(6):536–44.
16. Enghelabifar M, Allafan S, Khayatzadeh J, Shahrokh Abadi K, Hasanzadeh Nazarabadi M, Moradi F, et al. Association of the maternal 14-bp insertion/deletion polymorphism in the histocompatibility leukocyte antigen G gene with recurrent implantation failure. Iran J Reprod Med. 2014;12(9):641–6.
17. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med. 1997;127:820–6.
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.
19. Sipak-Szmigiel O, Cybulski C, Wokołorczyk D, Lubiński J, Kurzawa R, Baczkowski T, et al. HLA-G polymorphism and in vitro fertilization failure in a Polish population. Tissue Antigens. 2009;73(4):348–52.
20. Hviid TV, Hylenius S, Lindhard A, Christiansen OB. Association between human leukocyte antigen-G genotype and success of

in vitro fertilization and pregnancy outcome. Tissue Antigens. 2004;64(1):66–9.
21. Cho SH, Chung KW, Kim JO, Jang H, Yoo JK, Choi Y, et al. Association of miR-146aC>G, miR-149C>T, miR-196a2T>C, and miR-499A>G polymorphisms with risk of recurrent implantation failure in Korean women. Eur J Obstet Gynecol Reprod Biol. 2016;202:14–9.
22. Vagnini LD, Nascimento AM, Canas Mdo C, Renzi A, Oliveira-Pelegrin GR, Petersen CG, et al. The relationship between vascular endothelial growth factor 1154G/A polymorphism and recurrent implantation failure. Med Princ Pract. 2015;24(6):533–7.
23. Kuroshli Z, Gourabi H, Bazrgar M, Sanati M, Zamani EM. The relationship between HLA-G gene polymorphisms and repeated implantation failure in infertile couples undergoing assisted reproductive technique. Iran J Allergy Asthma Immunol. 2015;14(5):535–42.
24. Kapasi K, Albert SE, Yie S, Zavazava N, Librach CL. HLA-G has a concentration-dependent effect on the generation of an allo-CTL response. Immunology. 2000;101(2):191–200.
25. Virro MR, Winger EE, Reed JL. Intravenous immunoglobulin for repeated IVF failure and unexplained infertility. Am J ReprodImmunol. 2012;68:218–25.
26. Winger EE, Reed JL, Ashoush S, El-Toukhy T, Ahuja S, Taranissi M. Degree of TNF-a/IL-10 cytokine elevation correlates with IVF success rates in women undergoing treatment with adalimumab (Humira) and IVIG. Am J Repro Immunol. 2011;65:610–8.
27. Nakagawa K, Kwak-Kim J, Ota K, Kuroda K, Hisano M, Sugiyama R, Yamaguchi K. Immunosuppression with tacrolimus improved reproductive outcome of women with repeated implantation failure and elevated peripheral blood TH1/TH2 cell ratios. Am J Reprod Immunol 2015;73(4):353–361.
28. Pfeiffer KA, Rebmann V, van der Ven K. Soluble histocompatibility antigen levels in early pregnancy after IVF. Hum Immunol. 2000;61:559–64.
29. Yie SM, Balakier H, Motamedi G, Librach CL. Secretion of human leukocyte antigen-G by human embryos is associated with a higher in vitro fertilization pregnancy rate. Fertil Steril. 2005;83:30–6.
30. Rebmann V, Switala M, Eue I, Grosse-Wilde H. Soluble HLA-G is an independent factor for the prediction of pregnancy outcome after ART: a German multi-centre study. Hum Reprod. 2010;25:1691–8.
31. Chen XY, Yan WH, Lin A, Xu HH, Zhang JG, Wang XX. The 14 bp deletion polymorphisms in HLA-G gene play an important role in the expression of soluble HLA-G in plasma. Tissue Antigens. 2008;72:335–41.
32. Hviid TV. HLA-G in human reproduction: aspects of genetics, function and pregnancy complications. Hum Reprod Update. 2006;12(3):209–32.
33. Costa CH, Gelmini GF, Wowk PF, Mattar SB, Vargas RG, Roxo VM, et al. HLA-G regulatory haplotypes and implantation outcome in couples who underwent assisted reproduction treatment. Hum Immunol. 2012;73(9):891–7.
34. Dahl M, Perin TL, Djurisic S, Rasmussen M, Ohlsson J, Buus S, et al. Soluble human leukocyte antigen-G in seminal plasma is associated with HLA-G genotype: possible implications for fertility success. Am J Reprod Immunol. 2014;72(1):89–105.