Int J Fertil Steril
International Journal of Fertility & Sterility
Homepage: https://www.ijfs.ir/
Systematic Review
Vol 17, No 4, October-December 2023, Pages: 231-235

Association between Serum HLA-G Levels in The First Trimester of Pregnancy and The Onset of Preeclampsia: A Systematic Review and Meta-analysis Study

Salome Maghsudlu, M.D.[1], Mohamed Ghazanfari Hashemi, Ph.D.[2], Vahid Talebi, Ph.D.[3], Elham Vahabi, M.D.[4], Sanaz Sharifpour, M.D.[5], Ramtin Hajibeygi, M.D.[6], Farajolah Maleki, Ph.D.[7*]

1. Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Radiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Radiology, Isfahan University of Medical Sciences, Isfahan, Iran
4. Department of Gynecology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran
5. Islamic Azad University Tehran Medical Branch, Tehran, Iran
6. Department of Cardiology, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
7. Non-Communicable Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran

Abstract

Human leukocyte antigen G (HLA-G) levels are among the biomarkers suggested for pre-eclampsia (PE). This study is aimed at determining the possible relationship between low soluble HLA-G (sHLA-G) levels in maternal blood at the beginning of pregnancy and subsequent PE. We searched the international scientific databases of Web of Science, Embase, PubMed, Cochrane, and Scopus. We extracted the studies investigating the relationship between the serum levels of HLA-G in the first trimester of pregnancy and the onset of PE using the appropriate keywords. The collected data were analyzed using the random-effects meta-analysis model and STATA (version 14). A total of 5 studies met the eligibility criteria, and the total sample size was 668 subjects. The mean and SD age of case subjects was 31.41 ± 4.16 years, while it was 30.56 ± 3.5 for control subjects. According to the findings, there was an inverse relationship between HLA-G serum level in the first trimester of pregnancy and the subsequent onset of PE, standard mean difference (SMD)=-1.51 [95% confidence interval (CI): -2.26, -0.75, I2=90.8%, P=0.000]. Based on these results, low sHLA-G level in early pregnancy has a positive correlation with subsequent PE, and the significant role of sHLA-G in the early stages of placentation can be proven.

Keywords: First Trimester, Preeclampsia, Pregnancy

Citation: **Maghsudlu S, Ghazanfari Hashemi M, Talebi V, Vahabi E, Sharifpour S, Hajibeygi R, Maleki F. Association between serum HLA-G levels in the first trimester of pregnancy and the onset of preeclampsia: a systematic review and meta-analysis study. Int J Fertil Steril. 2023; 17(4): 231-235. doi: 10.22074/IJFS.2023.559787.1349**

Introduction

Pre-eclampsia (PE) is regarded as one of the most common disorders of pregnancy, which is usually manifested by the onset of hypertension along with proteinuria after the 20th week of pregnancy (1). Previous epidemiological data showed that about 3-5% of pregnancies worldwide are pregnancies are affected by PE (2). This condition not only leads to morbidity and mortality in some pregnant women but also causes fetus health issues such as growth restriction and preterm birth (3, 4).

The main feature of PE is defected placentation. The reduced ability of trophoblasts to invade the placental spiral arteries, as well as incomplete endothelial remolding of these arteries are considered the main mechanisms leading to the onset of PE (5). Despite the above-mentioned, clear-cut information cannot be provided on the exact pathogenesis of PE since various factors play a role in this regard (6). Risk factors including a genetic background of hypertension, maternal age, diabetes, cardiovascular conditions, and obesity have been listed to be associated with PE (7-9). In the case of the immune system, inflammatory conditions have been demonstrated to play a critical role in PE pathogenesis (10, 11). In this regard, through a review of the conducted studies, increased levels of inflammatory cytokines and declined levels of regulatory and anti-inflammatory cytokines have been found to play a role (12-15). Moreover, decreased frequency of immune cells with regulatory properties and

Received: 10/August/2022, Revised: 02/January/2023, Accepted: 16/January/2023
***Corresponding Address: P.O.Box: 6931738677, Non-Communicable Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran**
Email: maleki-f@medilam.ac.ir

Royan Institute
International Journal of Fertility & Sterility

increased number of immune cells with inflammatory properties during all stages of pregnancy have been focused on as the main features of PE (16). Uncontrolled immune activation and pro-inflammatory condition during the early weeks of gestation and in the first trimester of pregnancy are associated with the onset of PE after the 20th week of pregnancy (17). Several efforts have been done to find inflammatory biomarkers in early gestation to predict PE (18).

Many factors are involved in the immune system regulation at the feto-maternal interface, among which human leukocyte antigen G (HLA-G) is believed to be a critical factor that prevents fetus immune rejection and provide fetal growth and appropriate placentation. During a normal pregnancy, extravillous trophoblasts express an abundant amount of HLA-G (19). Interestingly, upregulated expression of HLA-G in trophoblasts is simultaneous with the invasive ability (20). HLA-G has several isoforms, which are different in subunits and the existance of soluble forms. HLA-G1 and HLA-G5 are the most frequent soluble ones and consist of four subunits (21). During pregnancy, HLA-G1 regulates the proliferation and activation of T cells and NK cells to support feto-maternal immune tolerance (22). HLA-G5 has been shown to regulate and control the production of cytokines by alloantigen-activated T cells (23). In the case of patients with PE, studies have shown that placental trophoblasts are defective in upregulating HLA-G expression and the serum level of soluble HLA-G is significantly lower than in patients without PE (24, 25). However, most studies in this regard have been done in cases with PE in their second or third trimester of pregnancy (26, 27). To determine the possible role of HLA-G in the onset of PE it is necessary to investigate the expression of this molecule during the first few weeks of pregnancy and the placentation process.

The role of HLA-G and its potential use as a biomarker to predict the onset of PE is currently unclear. Therefore, the current study aimed to review and analyze the published data available on the association of serum HLA-G during the first trimester of pregnancy and the onset of PE.

Materials and Methods

We conducted this systematic evidence review according to best practices and report our findings according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist (28).

Search strategies

A comprehensive search was performed to extract the published studies on the relationship between the sHLA-G serum level in the first trimester of pregnancy and the onset of PE. The keywords used included “pregnancy”, “human leukocyte antigen G”, “HLA-G”, “preeclampsia”, “first trimester”, “onset of preeclampsia”, “PE", “frequency, and “genotype. Different combinations of these keywords and Boolean operators (“OR” and “AND”) were used for searching international databases, including ISI, PubMed, Embase, and Scopus. Google Scholar was also searched to find the studies not included in the mentioned databases (Table 1). Also, the references of the extracted studies were checked to find potentially relevant studies. All records were then imported into the endnote and duplicated records were deleted.

Table 1: Search strategy used in each database in this review

Electronic database	Search terms (including truncations)
ISI	“Pregnancy" OR “First Trimester”
	AND "Genotype"
	AND “Human leukocyte antigen G” OR “HLA-G”
	AND “Onset of Preeclampsia” OR “PE"
PubMed	“Preeclampsia”OR “PE"
	AND
	" Pregnancy" OR“First Trimester”
	AND “Human leukocyte antigen G” OR “HLA-G”
Scopus	“Human leukocyte antigen G” OR “HLA-G”
	AND "Genotype"
	AND “Preeclampsia”OR “PE
	AND “First Trimester of pregnancy”
Embase	“First Trimester of pregnancy”
	AND
	“Human leukocyte antigen G” OR “HLA-G”
	AND
	“Onset of Preeclampsia” OR “Preeclampsia "

Study selection

After deleting the duplicated studies, the titles and abstracts of the remaining were checked to find the eligible studies based on the following inclusion and exclusion criteria:

Inclusion criteria were the original case-control studies on the relationship between the sHLA-G serum level in the first trimester of pregnancy and the onset of PE with extractable intended data and available full texts. Exclusion criteria included review articles, meta-analyses, congress abstracts, studies in languages other than English, and retracted papers.

Using studies eligible based on the above criteria were selected by two of the authors independently while they were rechecked and confirmed by all authors.

Data extraction

Data from the selected studies were extracted by two different authors. Data such as the related data, including authors’ names, location, publication date, age and the number of case and control participants, gestational age, and sHLA-G serum level (ng/ml) were extracted by two of the authors. Data were reviewed for potential mistakes by other authors and then confirmed by all authors.

Risk of bias in individual studies (Quality assessment)

The Newcastle-Ottawa scale (NOS) for cross-sectional and case-control studies was used to assess the risk of bias in individual studies (18) with 9 points for case-control studies and 8 points for cross-sectional studies indicating high quality and low risk of bias: 1-3, 4-6, and 7-9, were categorized as of low, intermediate, and high quality, respectively for case-control studies and 1-3, 4-5, and 6-8 were categorized as low, intermediate, and high quality, respectively for cross-sectional studies (Table 2).

Risk of bias across studies

Publication bias was evaluated by Begg's Funnel plots and Egger test. P<0.05 were considered valid for heterogeneity.

Data synthesis and analysis

Variables such as the sample size, mean, and standard deviation of expected data were grouped. Each study's weight was assigned based on its inverse variance. The Q test and I^2 index were done at an α-level error of lower than 10% significance to assess test heterogeneity within the included studies. To analyze our collected heterogeneous data, the random effect model was utilized. Moreover, Stata Version 14.2 was used to analyze all of the data statistically.

Results

The present meta-analysis included five original studies published on the relationship between sHLA-G serum level in the first trimester of pregnancy and the onset of PE (Table 3). The study selection process is shown in Figure 1. The total sample size was 668 (155 case subjects and 513 control subjects), with mean ages of 31.41 ± 4.16 and 30.56 ± 3.5 years for the case and control subjects, respectively. The overall estimate of the standard mean difference between groups using the random-effects model was -1.51 [95% confidence interval (CI): -2.26, -0.75, I2=90.8%, P=0.000] (Fig.2). Accordingly, it can be concluded that a significant relationship was found between HLA-G serum level in the first trimester of pregnancy and the onset of PE in pregnant women, and the risk of developing PE later in pregnancy was increased by low sHLA-G serum levels. Based on Figure 3, no evidence of publication bias was found employing Begg's funnel plots and Egger test.

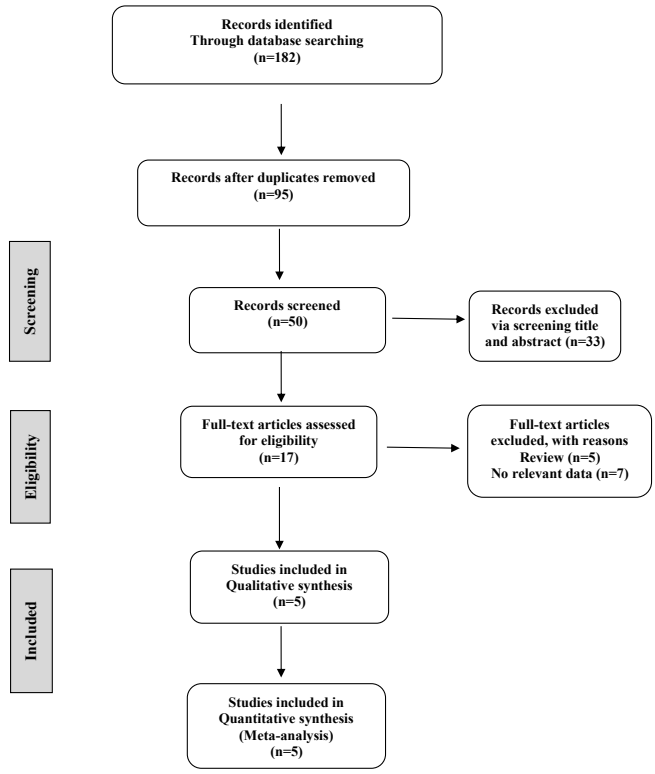

Fig.1: Prisma flow diagram illustrating the selection of articles.

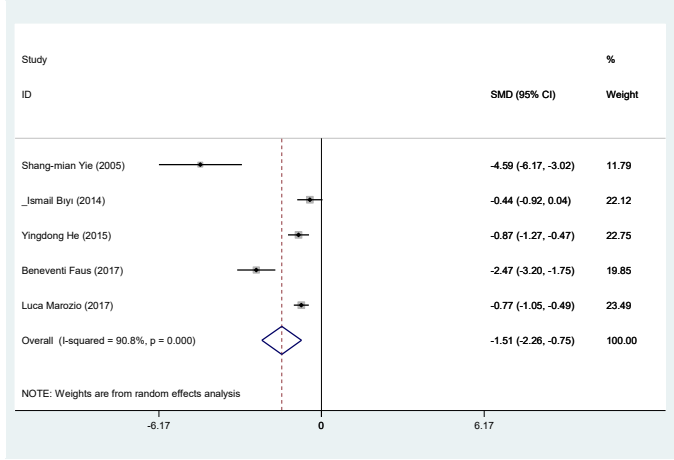

Fig.2: Forest plots for case-control studies of the relationship between the variables of HLA-G serum level in the first trimester of pregnancy and onset of PE in the investigated studies with 95% confidence interval (based on random model). PE; Preeclampsia, HLA-G; Human leukocyte antigen G, SMD; Standard mean difference, and CI; Confidence interval.

Table 2: Risk of bias in individual studies

First author's name	Type of study	Selection				Comparability	Outcome			Total
		1	2	3	4	1	1	2	3	
Yie et al. (29)	Case-control	*	*			*	*	*		5
Biyik et al. (30)	Case-control	*			**	*	**			6
Beneventi et al. (31)	Case-control	*	*	*	*	*	*	*	*	8
Marozio et al. (32)	Case-control	*	*			*	**			5
He et al. (33)	Case-control	*	*	*		*	**			6

Table 3: Characterizations of articles reviewed in the present study

First Author (reference)	Publication year	Sample size		Mean age ± SD		Gestational age ± SD		sHLA-G serum level (ng/ml) ± SD	
		Case	Control	Case	Control	Case	Control	Case	Control
Yie et al. (29)	2005	12	12	28 ± 5	29.8 ± 2.2	8.2 ± 6.6	7.8 ± 0.5	125 ± 16.87	195 ± 13.4
Biyik et al. (30)	2014	19	154	28.7 ± 6.64	27.24 ± 6.21	12.48 ± 0.7	12.3 ± 0.8	23.89 ± 12.82	36.91 ± 30.72
Beneventi et al. (31)	2017	17	42	34.26 ± 1.76	36.2 ± 1.3			22.32 ± 5.2	47 ± 11.3
Marozio et al. (32)	2017	65	234	31.7 ± 4.8	31.7 ± 4.9			96.86 ± 14.42	105.4 ± 10.03
He et al. (33)	2015	42	71	32.03 ± 2 .63	30.8 ± 2.9			2.52 ± 2.38	5.26 ± 3.53

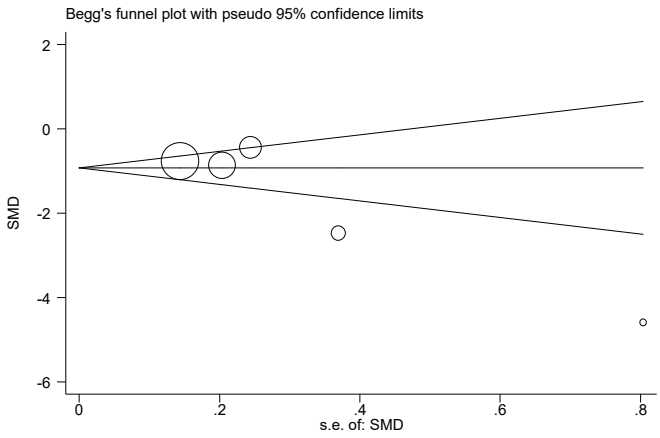

Fig.3: Begg's funnel plot for publication bias diagram in the investigated studies, the circles show the weight of the studies. SMD; Standard mean difference.

Discussion

Based on our findings, it seems that a clinical index determination for severe PE prediction especially in the first trimester is crucial, since its development has a negative effect on the prognosis of the mother and her baby. Therefore, the present meta-analysis was performed to investigate the controversial results on the potential relationship between serum levels of sHLA-G in the first trimester of pregnancy, and the onset of PE in pregnant women. To our knowledge, this is the first meta-analysis investigating this potential relationship. Our results suggest a significant relationship between sHLA-G serum level in the first trimester of pregnancy and the onset of PE.

Through our literature review, some studies were found to address the relationship between HLA-G and gestational time, including those in the current meta-analysis. For instance, Alegre et al. (34) and Yie et al. (29), have conducted studies in which a comparison is made between pregnant and non-pregnant women in terms of plasma sHLA-G levels. Based on their results, in the case of pregnant women, sHLA-G levels were detectable, while it was not the case for non-pregnant women. Another study, it was found by Klitkou et al. (35) that sHLA-G levels they were lower in fetal blood in comparison to the maternal blood, which shows the role of the placenta as a barrier. Besides, they observed that throughout the 20 weeks of gestation, sHLA-G levels were lower in maternal blood compared to fetal blood. Interestingly, a recently conducted study showed the possible association of sHLA-G with PE (36), while another recent study reported that sHLA-G levels did not predict complicated pregnancies (including PE). However, it should be noted that the latter study addressed various types of complicated pregnancies, and the selected sample size was found to be relatively small (30).

Through the study conducted by Yie et al. (29), the following results were obtained: a decrease occurred in the serum and placental HLA-G levels during PE in comparison to normal pregnancy, and a significant association was found between serum and placental levels of HLA-G. The results indicate that in maternal plasma, the trophoblast is the main source of sHLA-G. In a report by Steinborn et al. (37), it was revealed that lower sHLA-G levels are shown in women with placental abruption in comparison to the ones in normal pregnancy at the same gestational age.

It has also been found that below 43.5 IU/mL sHLA-G levels at the end of the first trimester lead to an increase in developing placenta-mediated complications, particularly severe PE. This usually happens through the later course of pregnancy which is reported to be related to abnormal placentation and placental abruption (32). Recent studies regarding the HLA-G and its association with PE have also highlighted the role of HLA-G in PE. A study published in 2020 suggested that placental down-regulation of HLA-G and its receptors contribute to the onset of PE through disturbance in interferon immune activation (38). Another recent study in 2021 has shown that not only decreased placental expression of HLA-G may be associated with PE, but changes in HLA-G isoform may also be a critical factor in PE (39).

The small sample size and address only sHLA-G levels constitute the limitations of this study. Accordingly, we cannot totally rule out the possibility that it could be a source of bias. However, our results showed that sHLA-G1 levels were independent of other factors such as body mass index (BMI).

Conclusion

To summarise, in comparison to the normal controls, plasma sHLA-G1 levels were found to be significantly lower in women with late-onset severe PE. One could conclude that although the low sHLA-G1 expression is shown to be significantly related to the occurrence of PE,

high sHLA-G1 levels may be considered as one of the factors to maintain a normal pregnancy. Although first-trimester sHLA-G1 seems to have predictive values for PE, large-scale cohort studies are needed to justify this.

Acknowledgements

There is no financial support and conflict of interest in this study.

Authors Contributions

S.M., F.M.; Designed the conception of the study. M.Gh.H., V.T., E.V.; Focus on the statistical analysis. S.Sh., R.H., S.M.; Technical support and conceptual advice. All authors contributed to the draft of the manuscript, revised it critically, and approved the final version.

References

1. Dekker GA, Robillard PY. Preeclampsia: a couple's disease with maternal and fetal manifestations. Curr Pharm Des. 2005; 11(6): 699-710.
2. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ. 2013; 347: f6564.
3. Omani-Samani R, Ranjbaran M, Amini P, Esmailzadeh A, Sepidarkish M, Almasi-Hashiani A. Adverse maternal and neonatal outcomes in women with preeclampsia in Iran. J Matern Fetal Neonatal Med. 2019; 32(2): 212-216.
4. Souza JP, Gülmezoglu AM, Vogel J, Carroli G, Lumbiganon P, Qureshi Z, et al. Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. Lancet. 2013; 381(9879): 1747-1755.
5. Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. Biol Reprod. 2003; 69(1): 1-7.
6. Sircar M, Thadhani R, Karumanchi SA. Pathogenesis of preeclampsia. Curr Opin Nephrol Hypertens. 2015; 24(2): 131-138.
7. Das UN. Cytokines, angiogenic, and antiangiogenic factors and bioactive lipids in preeclampsia. Nutrition. 2015; 31(9): 1083-1095.
8. Hod T, Cerdeira AS, Karumanchi SA. Molecular mechanisms of preeclampsia. Cold Spring Harb Perspect Med. 2015; 5(10): a023473.
9. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet. 2016; 387(10022): 999-1011.
10. Marusic J, Prusac IK, Tomas SZ, Karara JR, Roje D. Expression of inflammatory cytokines in placentas from pregnancies complicated with preeclampsia and HELLP syndrome. J Matern Fetal Neonatal Med. 2013; 26(7): 680-685.
11. Redman CW, Sargent IL. Pre-eclampsia, the placenta and the maternal systemic inflammatory response--a review. Placenta. 2003; 24 Suppl A: S21-S27.
12. Pinheiro MB, Martins-Filho OA, Mota AP, Alpoim PN, Godoi LC, Silveira AC, et al. Severe preeclampsia goes along with a cytokine network disturbance towards a systemic inflammatory state. Cytokine. 2013; 62(1): 165-173.
13. Tosun M, Celik H, Avci B, Yavuz E, Alper T, Malatyalioğlu E. Maternal and umbilical serum levels of interleukin-6, interleukin-8, and tumor necrosis factor-alpha in normal pregnancies and in pregnancies complicated by preeclampsia. J Matern Fetal Neonatal Med. 2010; 23(8): 880-886.
14. Gharesi-Fard B, Mobasher-Nejad F, Nasri F. The expression of T-helper associated transcription factors and cytokine genes in preeclampsia. Iran J Immunol. 2016; 13(4): 296-308.
15. Tok A, Seyithanoğlu M, Ozer A, Erkayıran U, Karaküçük S, Çelebi A. The serum level of soluble CXCL16 is increased in preeclampsia and associated with hepatic/renal damage. J Matern Fetal Neonatal Med. 2021; 34(9): 1435-1440.
16. Ahn H, Park J, Gilman-Sachs A, Kwak-Kim J. Immunologic characteristics of preeclampsia, a comprehensive review. Am J Reprod Immunol. 2011; 65(4): 377-394.
17. Founds SA, Terhorst LA, Conrad KP, Hogge WA, Jeyabalan A, Conley YP. Gene expression in first trimester preeclampsia placenta. Biol Res Nurs. 2011; 13(2): 134-139.
18. Tangerås LH, Austdal M, Skråstad RB, Salvesen KÅ, Austgulen R, Bathen TF, et al. Distinct first trimester cytokine profiles for gestational hypertension and preeclampsia. Arterioscler Thromb Vasc Biol. 2015; 35(11): 2478-2485.
19. Rizzo R, Vercammen M, van de Velde H, Horn PA, Rebmann V. The importance of HLA-G expression in embryos, trophoblast cells, and embryonic stem cells. Cell Mol Life Sci. 2011; 68(3): 341-352.
20. Guillard C, Zidi I, Marcou C, Menier C, Carosella ED, Moreau P. Role of HLA-G in innate immunity through direct activation of NF-kappaB in natural killer cells. Mol Immunol. 2008; 45(2): 419-427.
21. Carosella ED, Rouas-Freiss N, Paul P, Dausset J. HLA-G: a tolerance molecule from the major histocompatibility complex. Immunol Today. 1999; 20(2): 60-62.
22. Jiang F, Zhao H, Wang L, Guo X, Wang X, Yin G, et al. Role of HLA-G1 in trophoblast cell proliferation, adhesion and invasion. Biochem Biophys Res Commun. 2015; 458(1): 154-160.
23. Lombardelli L, Aguerre-Girr M, Logiodice F, Kullolli O, Casart Y, Polgar B, et al. HLA-G5 induces IL-4 secretion critical for successful pregnancy through differential expression of ILT2 receptor on decidual CD4- T cells and macrophages. J Immunol. 2013; 191(7): 3651-3662.
24. Hackmon R, Koifman A, Hyodo H, Glickman H, Sheiner E, Geraghty DE. Reduced third-trimester levels of soluble human leukocyte antigen G protein in severe preeclampsia. Am J Obstet Gynecol. 2007; 197(3): 255. e1-5.
25. Steinborn A, Varkonyi T, Scharf A, Bahlmann F, Klee A, Sohn C. Early detection of decreased soluble HLA-G levels in the maternal circulation predicts the occurrence of preeclampsia and intrauterine growth retardation during further course of pregnancy. Am J Reprod Immunol. 2007; 57(4): 277-286.
26. Zhu X, Han T, Yin G, Wang X, Yao Y. Expression of human leukocyte antigen-G during normal placentation and in preeclamptic pregnancies. Hypertens Pregnancy. 2012; 31(2): 252-260.
27. Darmochwal-Kolarz D, Kolarz B, Rolinski J, Leszczynska-Gorzelak B, Oleszczuk J. The concentrations of soluble HLA-G protein are elevated during mid-gestation and decreased in pre-eclampsia. Folia Histochem Cytobiol. 2012; 50(2): 286-291.
28. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009; 62(10): e1-34.
29. Yie SM, Li LH, Li YM, Librach C. HLA-G protein concentrations in maternal serum and placental tissue are decreased in preeclampsia. Am J Obstet Gynecol. 2004; 191(2): 525-529.
30. Bıyık I. Maternal serum soluble HLA-G in complicated pregnancies. J Matern Fetal Neonatal Med. 2014; 27(4): 381-384.
31. Beneventi F, Locatelli E, De Amici M, Martinetti M, Spinillo A. Soluble HLA-G concentrations in obese women during pregnancy and in cord blood. J Reprod Immunol. 2017; 119: 31-37.
32. Marozio L, Garofalo A, Berchialla P, Tavella AM, Salton L, Cavallo F, et al. Low expression of soluble human leukocyte antigen G in early gestation and subsequent placenta-mediated complications of pregnancy. J Obstet Gynaecol Res. 2017; 43(9): 1391-1396.
33. He Y, Chen S, Huang H, Chen Q. Association between decreased plasma levels of soluble human leukocyte antigen-G and severe pre-eclampsia. J Perinat Med. 2016; 44(3): 283-290.
34. Alegre E, Díaz-Lagares A, Lemaoult J, López-Moratalla N, Carosella ED, González A. Maternal antigen presenting cells are a source of plasmatic HLA-G during pregnancy: longitudinal study during pregnancy. Hum Immunol. 2007; 68(8): 661-667.
35. Klitkou L, Dahl M, Hviid TV, Djurisic S, Piosik ZM, Skovbo P, et al. Human leukocyte antigen (HLA)-G during pregnancy part I: correlations between maternal soluble HLA-G at midterm, at term, and umbilical cord blood soluble HLA-G at term. Hum Immunol. 2015; 76(4): 254-259.
36. Djurisic S, Hviid TV. HLA class Ib molecules and immune cells in pregnancy and preeclampsia. Front Immunol. 2014; 5: 652.
37. Steinborn A, Rebmann V, Scharf A, Sohn C, Grosse-Wilde H. Placental abruption is associated with decreased maternal plasma levels of soluble HLA-G. J Clin Immunol. 2003; 23(4): 307-314.
38. Wedenoja S, Yoshihara M, Teder H, Sariola H, Gissler M, Katayama S, et al. Fetal HLA-G mediated immune tolerance and interferon response in preeclampsia. EBioMedicine. 2020; 59: 102872.
39. Persson G, Stæhr CS, Klok FS, Lebech M, Hviid TVF. Evidence for a shift in placental HLA-G allelic dominance and the HLA-G isoform profile during a healthy pregnancy and preeclampsia. Biol Reprod. 2021; 105(4): 846-858.