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Association Between Maternal Soluble Human Leukocyte Antigen-G and Pre-eclampsia: A Case–control Study

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Abstract

Introduction: Pre-eclampsia is a severe complication in pregnancy that is typified by high blood pressure (BP) and generalized endothelial ailment after 20 weeks of pregnancy. There is a growing body of evidence that maternal-fetal immune tolerance impairment is a contributor to its pathogenesis. Human leukocyte antigen-G (HLA-G) is a non-classical major histocompatibility complex class I molecule, is mainly expressed in the trophoblast cells and essential in the maternal-fetal immune tolerance during pregnancy.

Objectives: This study aims to detect the soluble isoform of HLA-G (sHLA-G) in maternal blood and use it as a potential biomarker of pregnancy complications.

Methods: A case-control study included 120 pregnant women, 60 with a pre-eclampsia and 60 normotensives pregnant as controls. Concentrations of sHLA-G in maternal serum were detected using an enzyme-linked immunosorbent assay (ELISA). The comparative study of biomarker levels in the groups and the predictive power of sHLA-G was carried out with the help of statistical analyses.

Results: The levels of maternal serum sHLA-G were lower in women with pre-eclampsia than in controls (38.6 ± 10.4 U/mL vs. 62.3 ± 14.7 U/mL, $p < 0.001$). The logistic regression analysis proved that reduced sHLA-G was a common factor that predisposed to pre-eclampsia. Analysis using the ROC curve revealed moderate accuracy, as reflected by an area under the curve (AUC) of 0.79.

Conclusion: These results indicate that lower maternal levels of sHLA-G may associated with pre-eclampsia. Maternal sHLA-G measurement could be an interesting biomarker to monitor high-risk pregnancy and identify early diagnosis and risk.

Keywords: Biomarker, Maternal immune tolerance, Pre-eclampsia, Pregnancy complications, Soluble human leukocyte antigen-G.

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Introduction

Pre-eclampsia is a pregnancy-related multisystem complication, where hypertension and dysfunction of organs are observed following 20 weeks of pregnancy [1]. It is the cause of between 3% - 8% of all pregnancies all over the world and is among the most common causes of maternal and perinatal morbidity and mortality [2-4]. Although there has been extensive research on the pathophysiological processes that lead to pre-eclampsia, the exact pathophysiological processes are still not clearly understood. Recent studies indicate that failure to stabilize the placenta, endothelial dysfunction, and deregulated maternal immune activities are very important in the pathogenesis of the disease [5, 6]. To have a successful pregnancy, the immune system of the mother and the semi-allogenic fetus have to interact on a very fine balance. HLA-G is one of the major molecules that play a role in the maintenance of maternal-fetal immune tolerance, which is a non-classical major histocompatibility complex class I molecule that is mainly expressed by extravillous trophoblast cells [4]. In contrast to classical HLA molecules, HLA-G has a low polymorphism and potent immunomodulatory activity that inhibits the natural killer (NK) cells, cytotoxic T lymphocytes, and antigen-presenting cells, as well as immune-mediated rejection of the unborn child [7, 8]. HLA-G, through these processes, helps in the development of immune tolerance and normal placenta growth.

HLA-G is provided in membrane-bound and soluble isoforms. The sHLA-G may be identified in maternal blood and has been suggested as a potential biomarker of pregnancy results [9, 10]. It has been found that various research studies examined the relationship between maternal circulating sHLA-G levels and pregnancy complications, especially pre-eclampsia. Indicatively, previous studies found that a lowering of the maternal plasma sHLA-G levels during pregnancy was found to raise the risk of pre-eclampsia and intrauterine growth restriction (IUGR) [11, 12].

Besides the individual clinical studies, systematic reviews and meta-analyses have also supported the role of sHLA-G in pre-eclampsia. The recent meta-analysis has shown that the maternal circulating levels of sHLA-G had significantly decreased in the pregnancies affected by pre-eclampsia in contrast to the healthy controls, therefore, showing the diagnostic potential of this biomarker [13]. Nevertheless, the clinical usefulness of maternal sHLA-G is still uncertain, and the present study can help in this area in the following ways. Second, it compares reduced sHLA-G levels and the risk of pre-eclampsia through statistical modeling. Third, it studies the diagnostic performance of the maternal sHLA-G based on receiver operating characteristic (ROC) analysis. Lastly, it adds more information on the involvement of immune tolerance mechanisms in pre-eclampsia pathogenesis, which may help justify the use of sHLA-G as a biomarker to detect the disease early.

Pre-eclampsia is a multisystem condition, with onset of hypertension and dysfunction of the organ present after 20 weeks of gestation period and is a leading cause of maternal and perinatal morbidity and mortality across the globe [14]. Even though the exact pathogenesis of it is not entirely known, there is an increasing amount of evidence that the maladaptation of the immune system between the mother and fetus is a key factor in the pathogenesis of diseases. In the list of molecules that mediate maternal-fetal immunity tolerance, HLA-G has become a source of significant immune response regulation in pregnancy [15].

HLA-G is a non-classical major histocompatibility complex class I molecule whose expression is mainly seen on extravillous trophoblasts in the maternal-fetal interface [16]. HLA-G, in contrast to classical class I molecules of the HLA, has limited polymorphism and also has strong immunomodulatory effects, which help in the maintenance of maternal immune tolerance to the semi-allogeneic fetus. HLA-G suppresses NK cells, cytotoxic T lymphocytes, and antigen-presenting cells and, thus, inhibitor of maternal immune rejection of the developing fetus [17]. Besides having isoforms bound by the membrane, sHLA-G are also discharged into maternal circulation and can be detected in maternal serum during pregnancy.

Several studies have been conducted to establish the relationship between the levels of circulating sHLA-G and pregnancy complications, especially pre-eclampsia [12, 18]. Among the first studies examining this association, Steinborn et al. [11] had reported that low maternal plasma levels of sHLA-G in the second trimester were linked to an elevated risk of later in pregnancy acquiring pre-eclampsia and IUGR. Such results indicated that the reduced concentrations of sHLA-G might indicate the dysfunctional activity of trophoblasts or a lack of maternal immunological tolerance in the initial phase of gestation. The clinical importance of maternal sHLA-G levels has since been further explored using subsequent clinical studies as a marker of pregnancies with complications associated with placental dysfunction. Laskowska et al. [19] compared the maternal serum level of sHLA-G in pregnancies with IUGR and pre-eclampsia as compared with normal controls and found that there were different levels of sHLA-G in the affected pregnancies relative to the normal controls. Their results revealed that there is the possibility of abnormal expression of sHLA-G correlated with pathological placenta development and the dysfunction of maternal immune interactions with the fetus.

Longitudinal studies have more recently found further evidence to support the role of sHLA-G in the pathogenesis of pre-eclampsia [13, 20]. Jacobsen et al. [12] prospectively measured the levels of sHLA-G in the maternal circulation during pregnancy and postpartum and found that women with pre-eclampsia exhibited greatly reduced levels of sHLA-G than did the normotensive pregnant women and proposed that immunoregulatory signaling was impaired in the impacted pregnancies. Other associations with lower levels of sHLA-G included the links with indicators of placental dysfunction that also connected immune dysregulation with maladjusted placental development. Besides individual clinical studies, there are a number of systematic reviews and meta-analyses examining the predictive ability of sHLA-G as a predictor of pre-eclampsia. In a systematic review study, Maghsudlu et al. [18] established that maternal serum sHLA-G levels in the first trimester were significantly low in women who ended up developing pre-eclampsia, indicating that sHLA-G could be used as an early biomarker of the disease. On the other hand, a recent meta-analysis conducted by Bhattarai et al. [13] validated that the levels of circulating sHLA-G among the mothers were significantly lower in pre-eclamptic pregnancies than in the normotensive controls, although heterogeneity among the studies signified that further large-scale studies are required.

These results highlight the importance of the immune regulation by HLA-G to the normal placentation and the sustenance of a successful pregnancy.The lowering or varied release of HLA-G can affect invasion of the trophoblast and maternal immune tolerance, and therefore, this contributes to the onset of pre-eclampsia. Nevertheless, although there is growing evidence on the role of sHLA-G in pregnancy complications, there is a need to conduct further clinical research to determine the diagnostic and prognostic utility of sHLA-G as a biomarker to early diagnose pre-eclampsia.

Materials and Methods

Study design and participants

The present case-control research was done to determine maternal serum levels of sHLA-G in pre-eclampsia-complicated pregnancies. A total of 120 pregnant women were the subjects in the study, and they visited the antenatal clinics of Ibn-Gazwan teaching hospital during 20th June, 2025 to 1st February, 2026. The respondents were separated into two groups: 60 women with pre-eclampsia and 60 normotensive pregnant women as controls, based on the gestational age. Pre-eclampsia was diagnosed in line with the diagnostic criteria used by the American College of Obstetricians and Gynecologists, which include systolic BP 140 mmHg and diastolic BP 90 mmHg at least twice after 20 weeks of gestation, and proteinuria (>300 mg in 24 h of the urine sample) or maternal organ dysfunction. The last menstrual period was used to determine gestational age, which was confirmed by first-trimester ultrasonography whenever available.

Inclusion and exclusion criteria

Women aged between 18 and 40 years, who are pregnant and have singleton pregnancies with a gestation period of 28 - 36 weeks, considered eligible for inclusion in the study. The women were also not allowed to have a history of chronic hypertension diagnosed before pregnancy, diabetes mellitus, autoimmune diseases, kidney or liver disease, multiple pregnancy, fetal congenital anomalies known, current infections, or inflammatory diseases at the time of recruitment. The application of these exclusion criteria was to reduce the possibility of confounding factors that may affect the circulating immune biomarkers and the interpretation of these levels of sHLA-G in the mother.

Sample collection and serum preparation

For each participant, 5 mL of maternal venous blood was collected under sterile conditions and placed in gel tubes. Women who have pre-

eclampsia were not given any treatment before the collection of blood. The samples were left to clot at room temperature and centrifugation was done at a rate of 3000 rpm over 10 min to separate the serum. To avoid degradation of proteins, the resultant serum was aliquoted into sterile microtubes and kept at a temperature of -20 ˚C awaiting laboratory analysis.

Quantification of sHLA-G

A commercially available ELISA kit (Human sHLA-G ELISA Kit, BioVendor Research and Diagnostic Products, Brno, Czech Republic) was used to measure the concentrations of sHLA-G in the maternal serum by following the instructions of the manufacturer. Before analysis, thawing of serum samples was done on ice followed by gentle mixing of the samples. Monoclonal antibodies against human HLA-G were used on microplate wells and standards, controls and serum samples were added in duplicate. After incubation, the unbound components were eliminated by washing with phosphate-buffered saline with tween-20. Following further steps of washing streptavidinhorseradish peroxidase conjugate was introduced. The enzyme reaction was observed on tetramethylbenzidine substrate solution and the reaction was terminated by adding of sulfuric acid. The concentration of serum sHLA-G was determined using a standard calibration curve constructed using known concentrations that were contained in the assay kit. The detection range was 5 - 200 U/mL, intra and inter assay coefficients of variation were found to be less than 10% and assay was found to be reproducible.

Ethical approval

The Institutional Research Ethics Committee of Al-Zahraa College of Medicine approved the study protocol and reviewed it (E/T 66). All the work had been done according to the ethical standards of the World Medical Association and the standards of the Declaration of Helsinki concerning research on human beings. All participants were supplied with informed consent in written form before being included in the study.

Statistical analysis

IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) was used to conduct statistical tests. Continuous variables were in the form of mean and standard deviation (SD), and frequencies and percentages expressed the categorical variables. The test of normality of data was determined by the Shapiro-Wilk test. The independent samples t-test and Mann-Whitney U test were used to assess differences between groups because the variables were normally distributed and non-normally distributed, respectively. The chi-square test was used to compare categorical variables. Logistic regression analysis was used to determine the association between maternal serum sHLA-G levels and the risk of pre-eclampsia and the outcome given in odds ratio (OR) and 95% confidence interval (CI).The diagnostic accuracy of sHLA-G to predict pre-eclampsia was evaluated based on ROC curve analysis, and the AUC was measured. Low sHLA-G was defined as serum levels below the median value of the study population (or a predefined cutoff based on ROC analysis). A p-value of less than 0.05 was taken to be statistically significant.

Results

Participant characteristics

The final analysis involved a total of 120 pregnant women, with 60 pregnant women being diagnosed with pre-eclampsia and 60 normotensive pregnant controls. None of the participants dropped out of the study because of missing data or insufficient samples. Table 1 represents the baseline demographic and clinical aspects of the study population. The pre-eclampsia and the control group had a mean maternal age of 29.4 ± 5.2 and 28.7 ± 4.9 years, respectively, and the difference was not statistically significant ($p = 0.48$). Likewise, no significant difference was reported in the gestational age at sampling in the two groups (32.1 ± 3.4 weeks vs 31.8 ± 3.6 weeks; $p = 0.62$). The body mass index (BMI) was not different between the pre-eclamptic patients and the controls (28.2 ± 3.1 kg/m^2 vs 27.9 ± 3.3 kg/m^2; $p \leq = 0.55$). Nevertheless, systolic and diastolic BP were found to be significantly greater among women having pre-eclampsia ($p < 0.001$). The results show that the study samples were balanced on the major demographic factors and reduced the possibility of confounding factors.

Maternal serum sHLA-G levels

The sHLA-G in maternal serum was measured successfully in all the participants. The circulating levels of sHLA-G were lower in pre-eclamptic women than in the normotensive pregnant controls, as seen in table 2. The average level of serum sHLA-G in pre-eclampsia patients was 38.6 ± 10.4 U/mL, and in the control group it was significantly higher (62.3 ± 14.7 U/mL). This was statistically significant ($p < 0.001$), which was equivalent to a decrease of about 38% in the circulating sHLA-G levels in pre-eclamptic patients. Figure 1 depicting the sHLA-G levels in both groups shows that there is an evident shift in values in women with pre-eclampsia towards lower values.

Table 1: Baseline characteristics of the study population.

Variable	Pre-eclampsia (n = 60)	Control (n = 60)	p-value
Maternal age (years)	29.4 ± 5.2	28.7 ± 4.9	0.48
Gestational age (weeks)	32.1 ± 3.4	31.8 ± 3.6	0.62
BMI (kg/m²)	28.2 ± 3.1	27.9 ± 3.3	0.55
Systolic BP (mmHg)	152 ± 12	112 ± 9	<0.001
Diastolic BP (mmHg)	96 ± 8	72 ± 7	<0.001

Table 2: Maternal serum sHLA-G levels.

Group	Mean sHLA-G (U/mL)	SD	p-value
Pre-eclampsia (U/mL)	38.6	±10.4	-
Control (U/mL)	62.3	±14.7	<0.001

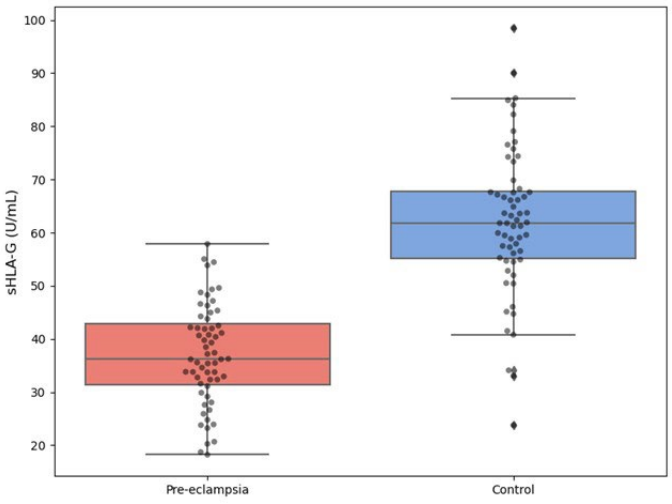

Figure 1: The distribution of maternal serum sHLA-G levels.

Association between sHLA-G levels and risk of pre-eclampsia

The logistic regression analysis was conducted in order to determine the correlation between the maternal serum sHLA-G and pre-eclampsia risk.The low maternal serum sHLA-G levels in the univariate analysis had significant relation with the increased risk of pre-eclampsia (OR = 2.96, 95% CI: 1.78 - 4.93; $p < 0.001$). A multivariate logistic regression model was then conducted, as a measure to account for the possible confounding factors, and thus adjusted for maternal age and BMI. Table 3 demonstrates that at the adjusted level, levels of sHLA-G in the maternal serum were significantly related to pre-eclampsia, adjusted OR = 2.84, 95% CI: 1.61 - 5.02; $p = 0.001$),Conversely, the BMI (OR = 1.12, 95% CI: 0.98 - 1.27; $p = 0.09$)or maternal age (OR = 1.04, 95% CI: 0.97 - 1.12; $p = 0.21$)) did not have any statistically significant relationship with pre-eclampsia. These results show that low maternal serum sHLA-G concentrations only had a significant association with the possibility of being affected by pre-eclampsia whilst BMI and maternal age did not have an important effect in the adjusted model (Figure 1).

Diagnostic performance of maternal sHLA-G

The ROC curve analysis was conducted to determine the discriminating nature of maternal serum sHLA-G levels in the pre-eclamptic and normotensive pregnancies. Figure 2 illustrates that the AUC was 0.79 (95% CI: 0.71 - 0.87), which is stated to be moderate diagnostic accuracy. Optimal cut-off value of sHLA-G was calculated using the Youden index, in which a value of 45 U/mL gave a sensitivity of 72%, and specificity was 75% when it was used to identify pre-eclampsia.

Table 3: Multivariate logistic regression analysis for risk of pre-eclampsia.

Variable	OR	95% CI	p-value
Low sHLA-G	2.84	1.61 - 5.02	0.001
BMI	1.12	0.98 - 1.27	0.09
Maternal age	1.04	0.97 - 1.12	0.21

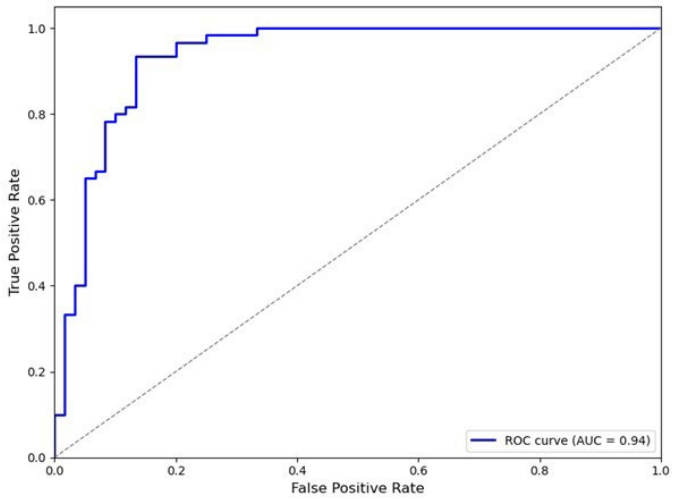

Figure 2: The diagnostic performance of sHLA-G for predicting pre-eclampsia.

Correlation analysis

There was a correlation analysis done to assess the relationship between maternal serum sHLA-G levels and clinical parameters. The levels of sHLA-G were significantly negatively correlated with systolic BP $r = -0.42$, $p < 0.001$) and diastolic BP ($r = -0.39$, $p < 0.001$). Conversely, they did not show any significant relationship between the levels of sHLA-G and the maternal age or the gestational age of the sampled mothers. These results indicate that reduced levels of sHLA-G in circulation are related to the severity of hypertensive manifestations during pregnancy.

Discussion

The current paper has shown that maternal serum sHLA-G concentrations in pre-eclampsia are considerably lower than those of normotensive pregnant controls which is go in line with previous studies [21, 22]. The finding augers well in the supposition that maternal- fetal immune tolerance is impaired and is involved in the pathogenesis of pre-eclampsia. The decrease in the circulating sHLA-G was independently linked to pre-eclampsia when possible confounding variables were removed; this indicates that it can be used as a useful biomarker in determining women at a higher risk.

HLA-G is a non-classical major histocompatibility complex class I, which is expressed at a high level on the extravillous trophoblast cells. It has strong immunomodulatory effects, which are caused by its interaction with the maternal NK cells, cytotoxic T lymphocytes, and antigen-presenting cells receptors, which are inhibitory in nature [23]. These interactions inhibit maternal immune activation to fetal antigens, which induces maternal fetal tolerance as well as normal placentation. The reduction in the maternal sHLA-G seen in pre-eclampsia could indicate the poor functioning of the trophoblasts and the reduced ability to regulate immunity at the maternal-fetal interface.

This research is aligned with the previous studies which showed lower levels of maternal circulating sHLA-G in pre-eclamptic pregnancies [13, 18]. A number of studies have shown that low concentrations of sHLA-G are linked to immune tolerance disruption between mothers and their fetuses as well as pre-eclampsia onset [24, 25]. Indicatively, researches reported by Rizzo, Campioni and other [26, 27]. indicated that the disturbed production of sHLA-G has been associated with the deregulation of immune responses and decreased anti-inflammatory signaling, which could be a predisposing factor in pregnancy complications. On the same note, other researchers found that low levels of sHLA-G in circulation correlate with pathological pregnancies and therefore HLA-G has been implicated in protecting immune tolerance during pregnancy [5, 28]. Additionally, evidence of recent meta-analyses pooled show that women with pre-eclampsia have significantly lower levels of maternal serum sHLA-G than do normotensive controls, especially during the first and third trimesters [13]. Combined with the data of the current research, these results, along with their alignment with the findings of the current study, confirm the hypothesis that the lack of sHLA-G is related to the immunopathogenesis of pre-eclampsia due to the lack of immune control between mothers and fetuses.

The low sHLA-G may result in excessive activation of maternal cytotoxic immune cells and resultant abnormal trophoblast invasion and defective spiral artery remodelling. The result of this maladaptation of the placenta consists of placental hypoperfusion, augmented oxidative stress, and systemic dysfunction of endotheliums, which are characteristic of pre-eclampsia [29].This hypothesis is also supported in our correlation analysis, which indicates that the less the sHLA-G is, the higher the levels of systolic and diastolic BP, indicating that the stricter the hypertensive manifestations.

Besides its mechanistic ability, sHLA-G could be of clinical use as a predictive biomarker. In the present study, ROC analysis showed that maternal serum sHLA-G had moderate diagnostic effectiveness

(AUC = 0.79) in the ability to separate pre-eclamptic pregnancies and controls. Even though the sensitivity and specificity of sHLA-G alone do not make it a useful diagnostic tool, it could be useful as part of a multi-marker panel together with other biomarkers in the early detection of at-risk pregnancies.

Limitations and Future Directions

The results of the current research can be viewed through a number of limitations. First, the cross-sectional structure does not provide an opportunity to develop the causal relationship between decreased levels of maternal sHLA-G and the occurrence of pre-eclampsia. Longitudinal research is necessary to find out whether lowered sHLA-G starts the disease manifestations and can be sure not to miss the development of the disease is not missed in its development. Second, the sample size was large enough to identify meaningful group differences, but might have lacked sufficient power to provide finer subgroup analyses. Third, sHLA-G was only measured at one point in time, and this lacks the dynamic changes that occur in immune regulation during pregnancy. Also, other immunologic and angiogenic biomarkers that have been demonstrated to play a role in pre-eclampsia, including sFlt-1 and placental growth factor (PlGF), were not evaluated in the study, which precludes the possibility of combining predictive models.

The future research must aim at combining the maternal sHLA-G values with the already known and newer biomarkers, such as sFlt-1 and PlGF, to come up with a strong and clinically viable predictive algorithm to detect pre-eclampsia at an early stage. Cohort studies with serial measurements in various trimesters would be of great help to understand the temporal variation of sHLA-G and its implications on disease development. Moreover, exploring the pathophysiological processes of HLA-G inhibition in trophoblasts, such as epigenetic control and inhibition by microRNA, can be used to understand new therapeutic points that can be used to ameliorate immune tolerance in high-risk pregnancies.

Conclusion

The current research shows that the sHLA-G level of maternal serum is very low in women with pre-eclampsia than in pregnant controls with normal BP. In addition to that, the reduction of sHLA-G was also independently related to the high risk of pre-eclampsia, which confirms the idea that the disturbance of maternal-fetal immunity tolerance is a key factor in pre-eclampsia development. These results indicate that circulating sHLA-G by the mother is a possible biomarker in the early identification of pre-eclampsia especially when used in combination with other clinical and biochemical risk factors.The findings also reflect the significance of immunoregulatory responses in the normal pregnancy process, and they suggest the possibility of abnormal placentation through the dysregulation of HLA-G. Prospective and mechanistic investigations in the future are justified to prove the predictive worth of sHLA-G and explain further the molecular pathways that control the expression of HLA-G. Besides this, the therapeutic potential of regulating the expression of HLA-G should be explored and could offer new options in managing and preventing pre-eclampsia in high-risk gestation.

Acknowledgements

None.

Conflict of Interest

None.

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