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ORIGINAL ARTICLE

Maternal serum glycodelin levels in preeclampsia and its relationship with the severity of the disease

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ABSTRACT

Purpose: Preeclampsia, in which insufficient trophoblastic invasion is thought to be one of the underlying mechanisms, is a common pregnancy disorder. Glycodelin is a regulator of immunosuppression, fertilization, implantation, and placentation. Because of its inhibitory effects on trophoblastic activity, trophoblast invasion is disturbed when its levels alter. We aimed to analyze serum glycodelin levels in preeclampsia and evaluate whether it correlates with the severity of disease.

Methods: This is a prospective case–control study conducted in a research and training hospital between March and September 2016. In this study, a total of 55 preeclamptic and 65 healthy pregnants were included. Preeclamptic patients were divided into two subgroups: 25 severe and 30 mild. Maternal serum glycodelin levels were measured using enzyme-linked immunosorbent assay.

Results: Glycodelin levels were higher in preeclamptic group as compared with controls (71.38 ± 22.78 versus 42.32 ± 12.28 ng/ml, $p < .001$). Also, it was higher in severe preeclampsia than the mild group (84.19 ± 24.58 versus 60.71 ± 14.4 ng/ml, $p < .001$). Glycodelin was positively correlated with systolic and diastolic blood pressures ($r = 0.637$ and $r = 0.714$, respectively, $p < .001$), aspartate and alanine aminotransferases ($r = 0.369$, $p = .006$ and $r = 0.377$, $p = .005$) and proteinuria ($r = 0.342$, $p = .011$). Moreover, it was correlated with birth weights and gestational age at delivery ($r = -0.386$, $p = .004$ and $r = -0.394$, $p = .003$, respectively). The role of glycodelin to diagnose preeclampsia was evaluated by receiver operating curve (ROC) curve. Area under the curve for glycodelin is 0.897 with $p < .001$. The sensitivity of glycodelin was 83.6% and the specificity was 80% at a threshold >53.64 ng/ml. Moreover, area under the curve for glycodelin to diagnose severe preeclampsia is 0.788 with $p < .001$. The sensitivity of glycodelin was 59% and the specificity was 93.3% at a threshold >83.97 ng/ml.

Conclusion: Glycodelin may be a promising marker in predicting the presence and severity of preeclampsia.

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Introduction

Preeclampsia (PE), which is a pregnancy-specific multisystem disorder, is one of the leading causes of maternal and fetal mortality and morbidity [1]. It approximately affects 3–14% of all pregnancies [2]. It has catastrophic consequences such as eclampsia, disseminated intravascular coagulation, pulmonary edema, placental abruption and hemorrhage, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), intrauterine growth retardation, iatrogenic preterm birth, fetal, and maternal death [3]. However, it is definitely defined as new onset hypertension in the presence of proteinuria or in the absence of proteinuria new onset hypertension accompanied by thrombocytopenia, renal insufficiency, doubling of serum creatinine, impaired liver function, pulmonary edema, cerebral or visual problems after 20th gestational week by current guidelines, the pathophysiology, and early diagnosis of the disease is still challenging [4].

The exact pathophysiological mechanism of PE is not fully elucidated. Abnormal placentation, systemic inflammatory response, imbalance in pro and antiangiogenic factors, oxidative stress, hydrogen sulphides, renin–angiotensin–aldosterone system that all leads to endothelial dysfunction are known to play role in the initiation and clinical manifestations of the disease [5].

Placental development plays a crucial role in the pathophysiology of PE. Vascularization to structure

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feto-maternal vascular surface and trophoblast invasion of spiral arteries are the main steps of placentation [6]. Shallow cytotrophoblast invasion that has been demonstrated in defective maternal artery remodeling results in placental ischemia and high resistance blood flow in intervillous space leads to placental PE [7]. The invasion of trophoblasts into maternal spiral arteries could be affected by several factors including inflammatory cells such as macrophages and decidual/uterine natural killer cells and cytokines, matrix metalloproteinases, growth factors, cellular environment, and oxygen tension [5].

Glycodelin, previously known as placental protein 14, is one of the glycoproteins of lipocalin group. It is a 180 amino acids containing glycoprotein with a molecular weight of 28 kDa and encoded by a single gene located at chromosome 9q34. It is a secretory glycoprotein functioning in cell proliferation, differentiation, adhesion, and motility [8]. Glycodelin has four isoforms (glycodelin-A, -S, -F, and -C) and differences in glycosylation affect each characteristic function. Its expression has a unique temporo-spatial pattern and it is the most important progesterone-related glycoprotein in uterus. It is released into the uterine cavity from the secretory decidual glands. In normal pregnancies glycodelin reaches its highest levels in both maternal serum and amniotic fluid at 10th–16th gestational weeks. Recent studies have demonstrated that glycodelin has the potential to regulate various processes, including immunosuppression, fertilization, implantation, and placentation [9,10]. Glycodelin participates in early placental development through its modulatory effect on immune cells and cytotrophoblasts. The recruitment of macrophages and monocytes to the implantation site contributes to placental remodeling by inducing apoptosis of trophoblasts and decidual cells [11]. Glycodelin inhibits proliferation and induces apoptosis of monocyte cell lines and peripheral blood monocytes via mitochondrial pathway and activating NF-kB [12,13]. In addition to these functions, glycodelin has an invasion suppressive effect via extracellular signal-regulated kinases pathway. It down-regulates matrix metalloproteinase-2 and urokinase plasminogen activator activity and suppresses the invasion of JAR cells and invasion of immortalized first-trimester normal extravillous cytotrophoblast cells [14].

The main hypothesis of the present study is that maternal serum glycodelin levels should differ between preeclamptic women and healthy pregnants and also between severe and mild preeclamptic patients, since glycodelin is a glycoprotein, that is thought to play a crucial role in placentation and take part in pathogenesis of PE. We aimed to evaluate the glycodelin levels in preeclamptic patients and determine whether it correlates with clinical findings and severity of the disease.

Materials and methods

This is an observational, prospective, case–control study conducted in a research and training hospital between March and September 2016. This study protocol was approved by the local ethics committee (Saglik Bilimleri University, Bursa Yuksek Ihtisas Research and Training Hospital Ethics Committee with protocol number 2011-KAEK-25-2016-1808) and each participant was given a written informed consent. Also, it complies with the Declaration of Helsinki.

Study participants

In this study, a total of 55 pregnant women who admitted to our obstetrics clinic for delivery and were diagnosed as PE according to the criteria below and 65 pregnants who have no known hypertension or pregnancy complication between 18 and 40 years old were recruited to the study. In our study, power calculation was performed. To calculate minimum sample size for study and control groups, a pilot study was conducted and, according to mean glycodelin values of two groups found in pilot study, the effect size was calculated as 0.73 and to attain 80% power according to related effect size value, at least 40 subjects were suggested to be included in each group. Considering possible data loss, sample size was finally determined as $n = 55$ for the study group and $n = 65$ for the control group. The PE patients were divided into two subgroups according to the severity of the disease as mild ($n = 30$) and severe ($n = 25$).

The exclusion criteria of the present study were as follows: chronic hypertension, pregestational and gestational diabetes, multiple gestation, active labor, preterm labor, premature rupture of membrane, chorioamnionitis, severe liver or kidney failure, intrauterine growth restriction, the patients who had a history of hematological diseases, any systemic inflammatory/autoimmune conditions, malignancy, cervical intraepithelial neoplasia, endometriosis, tobacco use, and use of drugs such as aspirin, antihypertensive agents, and non-steroidal anti-inflammatory drugs. We analyzed patients for prior risk factors and we excluded patients with prior preeclampsia history, higher blood pressures or new paternities.

Demographic features, clinical characteristics, perinatal outcomes and laboratory results of the participants including age, gravida, parity, maternal height

and weight, systolic and diastolic blood pressure, gestational age at delivery, delivery mode, birth weight, Apgar scores at first and fifth minutes, neonatal intensive care unit (NICU) admission, sepsis and respiratory distress syndrome (RDS) development, lipid profile, electrolytes, renal function tests, liver function tests, fasting glucose, and complete blood count parameters were recorded. Body mass index (BMI) was calculated as the weight divided by the square of height (kg/m^2). Also, all patients underwent color and spectral Doppler sonography with Voluson 730 (General Electric Company, Fairfield, CT) device using a 3.5 MHz probe and mean value of resistance index (RI) and pulsatility index (PI) were calculated. In addition to these, maternal serum glycodelin levels were measured and recorded.

Diagnosis of PE

PE was diagnosed based on these criteria: systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg measured while resting and at least twice in 4 h intervals and 0.3 g/24 h or $\geq +1$ proteinuria by dipstick after the 20th gestational week. In the absence of proteinuria, new onset hypertension after 20th week of gestation accompanied by the evidence of systemic disease, including thrombocytopenia, impaired liver function, renal insufficiency, doubling of serum creatinine, cerebral or visual disturbances, and pulmonary edema. Also, severe PE was diagnosed by the presence of any of the followings: systolic blood pressure $\geq$160 mmHg or diastolic blood pressure $\geq$110 mmHg at least on two separate measurements, serum creatinine level $\geq$1.1 mg/dl, hepatic transaminases $\geq$40 IU/ml, platelets $\leq$100,000/μl, pulmonary edema or symptoms of headache, epigastric or right upper quadrant pain, and visual impairment [15].

Biochemical measurements

All routine biochemical and hematological parameters were measured from blood samples which were drawn from the antecubital vein of the patient in sitting position by using a vacutainer system after a 12 h overnight fasting. Blood samples were centrifugated at 3000 rpm for 15 min and sera were stored at $-80\,^{\circ}$C until analysis. Fasting blood glucose, creatinine, and lipid profile were measured by using Abbott Diagnostics C8000l (Abbott, Wiesbaden, Germany) autoanalyzer and hematological parameters were obtained by using the Coulter LH 780 Analyzer (Beckman Coulter Ireland, Inc, Mervue, Galway, Ireland). Serum glycodelin levels were measured with a commercially available kit using an enzyme-linked immunosorbent assay (ELISA) method (Human Glycodelin ELISA kit, catalogue no. CK-E90717, Eastbiopharm Co Ltd, Hangzhou, China). This assay can assess plasma glycodelin concentration between 5 and 500 ng/ml with a lower sensitivity limit of 2.39 ng/ml. All samples were measured in duplicate and mean values were used.

Statistical analysis

All statistical analyses were carried out using SPSS statistical software version 22.0. (IBM Corp released 2012. IBM SPSS statistics for windows, IBM Corp, Armonk, NY). The variables were tested for normal distribution using probability plots and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk test). Continuous, normally distributed variables were reported as mean ± standard deviation and non-normally distributed variables were expressed as median value. Also, categorical variables were shown as frequencies and/or percentages. Categorical variables were compared by Chi-square test or Fisher's exact test. Mann–Whitney *U* test was used for continuous non-normally distributed variables, and independent *t*-test for continuous normally distributed variables. The relationship among continuous and discrete variables was examined by using correlation analysis and Spearman correlation coefficient was computed. A receiver operating curve (ROC) analysis was performed to determine the discriminative role of glycodelin for presence and severity of PE. A multivariate logistic regression analysis was performed by including the parameters which were significantly different between the groups to identify the independent predictors of PE. A p value of $\leq$.05 was considered statistically significant.

Results

A total of 55 preeclamptic women and 65 healthy pregnants were recruited to this study. The demographic characteristics and perinatal outcomes of preeclamptic women and control group are demonstrated in Table 1. There was no significant difference between two groups in terms of age, gravida, BMI, resistance, and pulsatility index of umbilical artery and delivery mode (cesarean section rate). The preeclamptic group had significantly higher systolic and diastolic blood pressures. NICU admission, development of RDS, and sepsis rate were higher in the preeclamptic group as compared with controls but it was not statistically

Table 1. Demographic characteristics and perinatal outcomes of the study group.

	Preeclampsia ($n = 55$)	Control ($n = 65$)	p
Age (years)	29.76 ± 5.4	29.06 ± 4.66	.446[a]
Gravida (*n*)	2 (1:5)	2 (1:4)	.286[b]
Body mass index (kg/m^2)	26.77 ± 2.41	26.2 ± 2.13	.174[a]
Cesarean section (*n*, %)	25 (45.5%)	22 (33.8%)	.194[c]
Gestational age at delivery (week)	36.1 (27:38)	38 (37:40)	<.001[b]
Birth weight (g)	2165.1 ± 675.3	3010.3 ± 520.1	<.001[a]
Systolic blood pressure (mmHg)	150 (140–210)	110 (90–130)	<.001[b]
Diastolic blood pressure (mmHg)	100 (90:140)	70 (55–80)	<.001[b]
Resistance index of umbilical artery	0.66 ± 0.12	0.66 ± 0.11	.880[a]
Pulsatility index of umbilical artery	1.08 ± 0.36	0.99 ± 0.29	.652[a]
Apgar score 1st min	7 (4:9)	8 (6:9)	.037[b]
Apgar score 5th min	8 (6:10)	9 (7:10)	.034[b]
NICU admission (*n*, %)	31 (56.4%)	25 (38.5%)	.06[c]
RDS (*n*, %)	26 (47.3%)	24 (36.9%)	.252[c]
Neonatal sepsis (*n*, %)	16 (29.1%)	13 (20%)	.246[c]

NICU: neonatal intensive care unit; RDS: respiratory distress syndrome.
[a]Independent samples *t* test.
[b]Mann–Whitney *U* test.
[c]Chi-square test.

Table 2. Laboratory parameters of the study group.

	Preeclampsia ($n = 55$)	Control ($n = 65$)	p
Glucose (mg/dl)	86.44 ± 15.99	83.29 ± 15.66	.215[a]
Total cholesterol (mg/dl)	223.95 ± 39.08	232.15 ± 45	.293[b]
HDL (mg/dl)	49.25 ± 8.12	50.4 ± 7.95	.438[b]
LDL (mg/dl)	131.05 ± 19.98	134.62 ± 28.18	.823[a]
AST (IU/L)	54.04 ± 46.94	20.93 ± 8.16	<.001[a]
ALT (IU/l)	42.76 ± 38.33	17.56 ± 9.94	<.001[a]
Sodium (mEq/l)	137.07 ± 1.86	0.68 ± 0.13	.001[a]
Creatinine (mg/dl)	0.87 ± 0.38	138.3 ± 1.86	.001[a]
Potassium (mEq/l)	4.15 ± 0.42	3.95 ± 0.43	.012[b]
Platelet-count ($\times 10^3$/mm^3)	163.236 ± 53.29	231.461 ± 54.14	<.001[b]
Hemoglobin (g/dl)	11.04 ± 1.5	10.79 ± 1.25	.326[b]
Hematocrit (%)	33.1 ± 4.55	32.38 ± 3.08	.214[a]
Glycodelin (ng/ml)	71.38 ± 22.78	42.32 ± 12.28	<.001[a]

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
[a]Mann–Whitney *U* test
[b]Independent samples *t* test.

significant ($p = .06$, $p = .252$, $p = .246$, respectively). Furthermore, gestational age at delivery (36.10 (27:38) versus 38 (37:40) week, $p < .001$), birth weight (2165.1 ± 675.3 versus 3010.3 ± 520.1 g, $p < .001$), Apgar score at first min (7 (4:9) versus 8 (6:9), $p = .037$), and Apgar score at fifth min (8 (6:10) versus 9 (7:10), $p = .034$) were significantly lower in the preeclamptic group as compared with controls.

The laboratory parameters of two groups are presented in Table 2. According to the laboratory parameters, there was no statistically significant difference between two groups except serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, sodium levels, potassium levels, and platelet count. In addition to these findings, maternal serum glycodelin levels were significantly higher in the preeclamptic group as compared with controls (71.38 ± 22.78 versus 42.32 ± 12.28 ng/ml, $p < .001$, respectively).

Table 3. Clinical characteristics and perinatal outcomes of the mild and severe preeclampsia groups.

	Severe preeclampsia ($n = 25$)	Mild preeclampsia ($n = 30$)	p
Age (years)	30.32 ± 6.22	29.3 ± 4.65	.490[a]
Gravida (*n*)	2 (1:4)	2 (1:5)	.578[b]
Parity (*n*)	1 (0:2)	1 (0:3)	.339[b]
Body mass index (kg/m^2)	27.15 ± 2.66	26.45 ± 2.17	.286[a]
Cesarean section (*n*, %)	15 (60%)	10 (33.3%)	.048[c]
Gestational age at delivery (week)	31.12 ± 3.18	36.23 ± 1.43	<.001[b]
Birth weight (g)	1590.8 ± 608.6	2808 ± 352.9	<.001[a]
Systolic blood pressure (mmHg)	180 (150:210)	145 (140:155)	<.001[b]
Diastolic blood pressure (mmHg)	115 (90:140)	95 (90:100)	<.001[b]
Resistance index of umbilical artery	0.68 ± 0.12	0.65 ± 0.12	.302[a]
Pulsatility index of umbilical artery	1.24 ± 0.4	1.12 ± 0.33	.220[a]
Apgar score 1st min	7 (4:9)	8 (6:9)	<.001[b]
Apgar score 5th min	7 (6:10)	9 (7:10)	<.001[b]
NICU admission (*n*, %)	18 (72%)	13 (43.3%)	.033[c]
RDS (*n*, %)	18 (72%)	8 (26.7%)	.001[c]
Neonatal sepsis (*n*, %)	9 (36%)	7 (23.3%)	.303[c]

NICU: neonatal intensive care unit; RDS: respiratory distress syndrome
[a]Independent samples *t* test.
[b]Mann–Whitney *U* test.
[c]Chi-square test.

Clinical characteristics and perinatal outcomes of the mild and severe preeclamptic groups are summarized in Table 3. As it was expected, systolic and diastolic blood pressures were higher in the severe preeclamptic group as compared with the mild preeclamptic group. In subgroup analysis, no significant difference was found between the severe and the mild preeclamptic group in terms of age, gravida, parity, BMI, neonatal sepsis, resistance, and pulsatility index of umbilical artery. The severe preeclamptic group was more likely to have slightly higher cesarean section rate ($p = .048$), lower birth weights ($p < .001$), earlier gestational week at delivery ($p < .001$), lower first and 5th minutes Apgar scores ($p < .001$), and higher NICU admission ($p = .033$) and development of RDS rate ($p = .001$).

The laboratory parameters of severe and mild preeclamptic groups are summarized in Table 4. There was no difference between two groups regarding to glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, hemoglobin, and hematocrit levels ($p > .05$). AST, ALT, creatinine, and potassium levels were significantly higher; sodium and platelet counts were lower in severe preeclampsia. Moreover, glycodelin levels were found to be higher (84.19 ± 24.58 versus 60.71 ± 14.4 ng/ml, $p < .001$, respectively) in the severe preeclamptic group as compared with the mild group.

Maternal glycodelin levels were positively correlated with systolic and diastolic blood pressures ($r = 0.637$ and $r = 0.714$, respectively, $p < .001$), AST and ALT ($r = 0.369$, $p = .006$ and $r = 0.377$, $p = .005$, respectively) and proteinuria ($r = 0.342$, $p = .011$). Also maternal glycodelin levels were weakly negatively correlated with

platelet count ($r = -0.133$, $p = .032$), birth weights ($r = -0.386$, $p = .004$), and gestational age at delivery ($r = -0.394$, $p = .003$).

In a multivariate regression analysis, platelet count $\leq 173.000 \times 10^3/\mu l$ (odds ratio = 8.006, 95% CI 2.548–25.155, $p < .001$) and glycodelin levels >53.64 ng/ml (odds ratio = 18.833, 95% CI 6.24–56.843, $p < .001$) were found to be significant independent predictors of PE after adjusting for other risk factors.

The effect of glycodelin to diagnose PE was evaluated by ROC curve (Figure 1). Area under the curve (AUC) for glycodelin is 0.897 with $p < .001$. The sensitivity of glycodelin was 83.6% and the specificity of glycodelin was 80% at a threshold >53.64 ng/ml. Moreover, the effect of glycodelin to diagnose severe PE was evaluated by ROC curve (Figure 2). AUC for glycodelin is 0.788 with $p < .001$. The sensitivity of glycodelin was 59% and the specificity of glycodelin was 93.3% at a threshold >83.97 ng/ml.

Table 4. Laboratory parameters of severe and mild preeclamptic groups.

	Severe preeclampsia ($n = 25$)	Mild preeclampsia ($n = 30$)	p
Glucose (mg/dl)	83.4 ± 16.01	88.97 ± 15.8	.173[a]
Total cholesterol (mg/dl)	214.72 ± 35.59	239.97 ± 34.81	.334[a]
HDL (mg/dl)	49.68 ± 7.82	48.9 ± 8.48	.727[b]
LDL (mg/dl)	127.48 ± 19.85	134.03 ± 19.93	.132[a]
AST (IU/L)	85.52 ± 54.78	27.8 ± 7.29	<.001[a]
ALT (IU/l)	69.68 ± 42.63	20.33 ± 9.32	<.001[b]
Creatinine (mg/dl)	1.05 ± 0.48	0.72 ± 0.14	.009[a]
Sodium (mEq/l)	136.72 ± 2.2	137.36 ± 1.51	.001[b]
Potassium (mEq/l)	4.21 ± 0.39	4.1 ± 0.45	.012[b]
Platelet-count ($\times 10^3/mm^3$)	142.520 ± 48.71	180.5 ± 51.43	<.001[b]
Hemoglobin (g/dl)	10.71 ± 1.38	11.32 ± 1.56	.132[b]
Hematocrit (%)	32.19 ± 4.13	33.85 ± 4.81	.214[b]
Glycodelin (ng/ml)	84.19 ± 24.58	60.71 ± 14.4	<.001[a]

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
[a]Mann–Whitney *U* test
[b]Independent samples *t* test.

Discussion

In this study, we evaluated the relationship of maternal serum glycodelin levels with PE and whether its serum levels have an association with the severity of the disease. There is only a few data in the literature about the role of glycodelin in obstetrics and gynecology practice.

Glycodelin is known to be an endocrine-related glycoprotein having effects on immune cells,

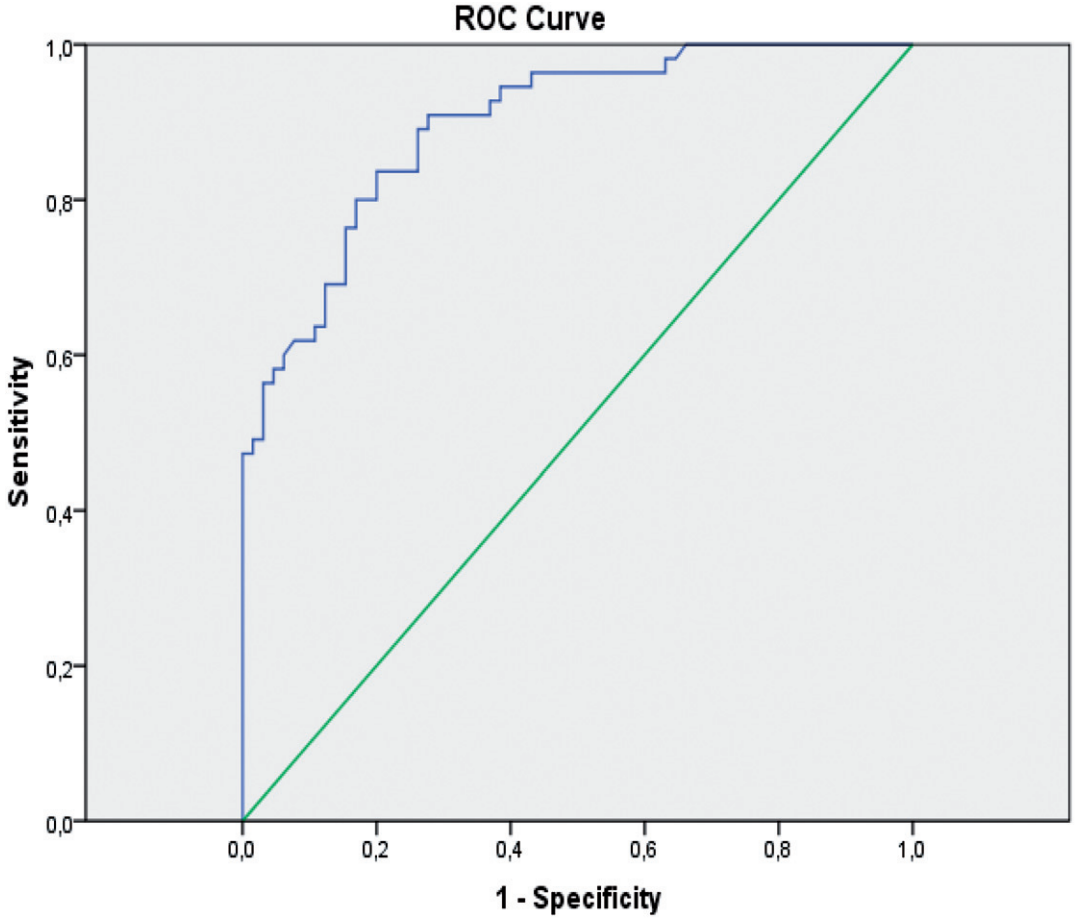

Figure 1. The discriminatory value of glycodelin levels for preeclampsia by receiver operating (ROC) curve analysis.

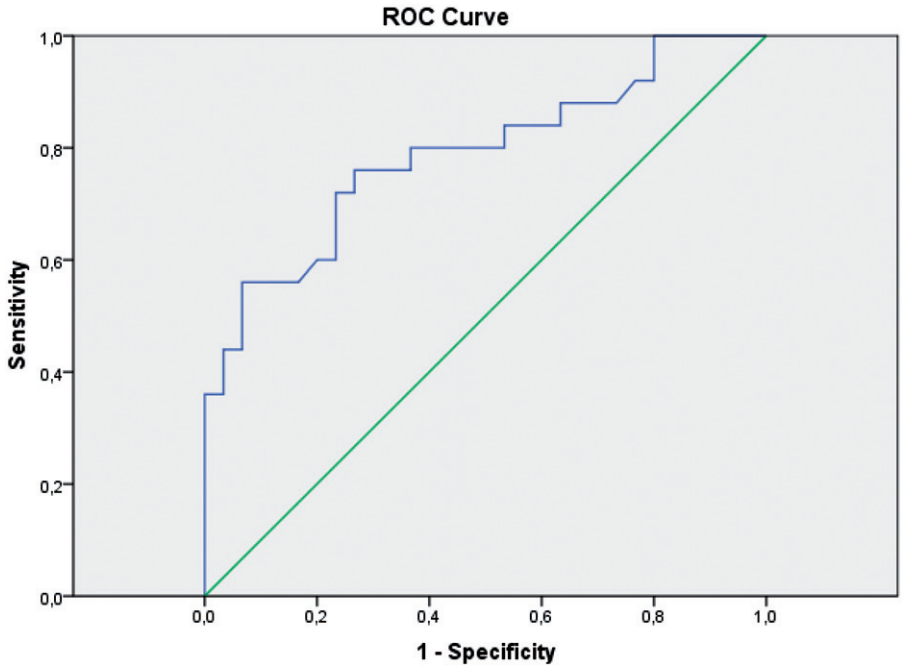

Figure 2. The discriminatory value of glycodelin levels for severe preeclampsia by receiver operating (ROC) curve analysis.

apoptosis, cell adhesion, differentiation, reproduction, and malignant processes. Besides its functions at very early steps of reproduction such as capacitation, immune protection of spermatozoa, modulation of sperm–oocyte binding, acrosome reaction and implantation, glycodelin also has several biological functions in development of some of the endocrine-related cancers such as breast, endometrium, and ovarian cancer [16]. Also, Ciavattini et al. [17] stated that higher expression of glycodelin by immunostaining in pregnancies $\leq$16th gestational week may be suggestive for lower proliferative activity in cervical intraepithelial neoplasia. Since it is a secreted immunosuppressive glycoprotein, it was studied in several other malignant conditions like lung cancer and malignant pleural mesothelioma [18,19]. Moreover, glycodelin was shown to be one of the proteins that is significantly decreased in endometriosis while most of the genes were up regulated during normal window of implantation [16]. The biochemical properties and functions of glycodelin, which can be sorted as induction of cellular differentiation, restriction of malignant cell proliferation, decreasing expression of oncogenes, and increasing expression of tumor suppressor genes may provide an explanation for all the above-mentioned data in the literature [9].

Glycodelin is released from endometrial glands and decidual glandular tissue in response to progesterone, human chorionic gonadotropin, and relaxin [16,20]. It is thought to have functions in feto-maternal defense [21]. Although the underlying mechanism of this has not been completely elucidated yet, the data accumulating in the literature may provide an explanation in the future. It was demonstrated that glycodelin has suppressive effects on mixed leukocyte populations, has modulatory effects on trophoblastic cell line and also has a suppressive effect on natural killer cells *in vitro* [14,22,23].

Serum glycodelin levels were reported to reach its highest level at 6th–12th gestational weeks, decreased to a plateau at the end of second trimester and remained low during the third trimester in a normal pregnancy, which is an indicative of pleiotropic effect of glycodelin in early pregnancy [9]. In the literature, there are data about the role of glycodelin in some of the pregnancy associated conditions such as small for gestational age, intrauterine growth restriction, infectious-inflammatory complications in preterm birth, early pregnancy loss, and recurrent miscarriage [9,24,25].

In a recent study, first-trimester glycodelin levels were investigated and whether small for gestational age at delivery could be predicted according to serum glycodelin levels was analyzed. Although lower levels of glycodelin in first trimester was observed in pregnancies complicated with small for gestational age, its predictivity was poor for small for gestational age at delivery [26].

Tambor et al. [25] searched for several amniotic fluid proteins which were thought to be associated with infectious-inflammatory complications in spontaneous preterm birth. According to this study, glycodelin

is one of the proteins, levels of which alter with the presence of microbial invasion of the amniotic cavity. Furthermore, serum glycodelin levels in patients with threatened abortion were observed to be lower compared to healthy pregnants between 10th and 20th weeks of gestation in another study [27]. Similarly, glycodelin concentrations measured in uterine flushings were significantly lower in women who were suffering from recurrent miscarriage [28].

In addition to aforementioned clinical situations, the role of glycodelin has been investigated in PE in several studies. However, there are inconsistent results for PE in the literature.

In 1983, Bolton et al. [29] reported increased levels of glycodelin in four of seven patients with preeclampsia. In 1986, Lino et al. [30] measured serum concentrations of glycodelin in women whose pregnancies were complicated with gestational hypertension. They found that serum glycodelin levels were higher in the case of gestational hypertension whereas it may not be considered to be a useful marker for clinical management of PE. In 1989, Howell et al. [31] studied serum glycodelin levels in PE for one more time to shed some light on the effects of PE on decidua and to detail the changes in concentrations of glycodelin regarding the severity of the disease. But, their study revealed similar serum glycodelin levels in controls and preeclamptic patients with all grades of severity. In 2005, the expression of glycodelin in decidual tissues obtained from placentas of women whose pregnancies were complicated with intrauterine growth restriction, PE, and HELLP, was compared with those of healthy ones. It was demonstrated that glycodelin expression was significantly reduced in decidual cells of placentas with intrauterine growth restriction, HELLP and PE [24]. In 2010, expressions of serum placental protein 13 and glycodelin in preeclampsia were evaluated. Serum levels of glycodelin were found to be significantly lower in the PE group as compared with controls while placental protein 13 levels were higher in the PE group. There were not any correlations between serum glycodelin levels and severity of the disease whereas levels of placental protein 13 were higher in the mild PE group as compared with the severe PE group. According to this study, Sun et al. [32] asserted that placental protein 13 may be an indicator of disease progression.

In our study, we evaluated 55 preeclamptic patients and concluded that maternal serum glycodelin levels were significantly higher in the preeclamptic group compared with controls and also, it was higher in the severe preeclamptic group as compared with the mild preeclamptic group. Moreover, serum glycodelin levels were found to be positively correlated with systolic/diastolic blood pressures, ALT/AST, and proteinuria. In addition to these findings, serum levels of maternal glycodelin >53.64 ng/ml are suggested to diagnose PE with a sensitivity of 83.6% and with a specificity of 80% and >83.97 ng/ml are suggested to diagnose severe PE with a sensitivity of 59% and with a specificity of 93%. To the best of our knowledge, there is a few data about the correlation of serum glycodelin and clinical and laboratory parameters of PE and also there is no cut-off value to diagnose PE. Previous studies were generally small sample sized, lack of correlation analysis or performed by using decidual tissue not maternal serum samples.

In conclusion, the underlying mechanism of PE is mainly related with defective early placentation, which is associated with defects in trophoblast invasion and spiral artery remodeling, finally leading to improper placental development, placental perfusion, and insufficient transport of nutrients. Faulty in the adaptation of immune cells is an important step in development of insufficient trophoblastic invasion of placenta and consequently failures in the vascular remodeling of spiral arteries [5]. Considering the effect of glycodelin in early pregnancy, especially in regulation of trophoblast invasion and immune cell functions, it is plausible to infer that abnormalities in glycodelin functions may have a significant role in the pathophysiology of preeclampsia [9,33]. However, the data about the relationship of glycodelin with PE and the clinical consequences of defective glycodelin functions in PE is quite limited and controversial.

To sum up, serum glycodelin levels are significantly increased in PE. This increase is more prominent as the severity of the disease increases. Serum levels of glycodelin may be used as a diagnostic tool for PE and in assessing the severity of the disease. But it is obvious that the data in the literature is not enough to make an accurate conclusion about the role of glycodelin in diagnosis and clinical follow-up of PE. Further apprehending of the biological nature of glycodelin will shed light on its functions in pregnancy related conditions such as PE.

Study limitations

There are some limitations of this study. First, this study has a small sample size, which arose from single center. Second, measurement of glycodelin levels in early pregnancy period could be beneficial for determining whether it can be used for early diagnosis of PE in first trimester of pregnancy. Also, another limitation of our study is that we did not compare

glycodelin levels in preeclamptic patients with a more widely accepted parameter such as sFLt/PLGF ratio. This would probably increase the plausibility of our study.

Disclosure statement

The authors report no conflict of interest.

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