Article presented at 1st Int Conf Med Sci of North Technical University /Kirkuk, Iraq (1st ICMS 2023)

Original Article

The Evaluation of Maternal Serum Glycodelin Level as a Marker for the Presence and Severity of Preeclampsia

Ruya Qadri Fawzi, Aseel Ghazi Rifat[1]

Department of Obstetrics and Gynecology, Azadi Teaching Hospital, Iraqi Board of Medical Specialization, Kirkuk, Iraq,
[1]Department of Obstetrics and Gynecology, College of Medicine, Kirkuk University, Kirkuk, Iraq

Abstract

Background: Preeclampsia (PE) is a common multisystemic disorder of pregnancy. Glycodelin is a glycoprotein belongs to the lipocalin superfamily. It acts as a regulator of immunosuppression activity, fertilization, implantation, and placentation. **Objectives:** To analyze serum glycodelin levels in PE and evaluate whether it correlates with the severity of the disease. **Materials and Methods:** A prospective case–control study included 60 women diagnosed with PE (subdivided into 30 pregnant women with mild PE and 30 pregnant women with severe PE) and 30 healthy normotensive pregnant women. Patient with multiple pregnancies, gestational trophoblastic diseases, in active labor, a history of medical diseases, or taking treatment were excluded from the study. Blood samples were taken for biochemical study; serum glycodelin levels were measured using an enzyme-linked immunosorbent assay. **Results:** Patients with PE had significantly higher mean glycodelin levels as compared to the normal group. The glycodelin level ≥37.9 ng/mL had 96.70% sensitivity, 100% specificity, and 98% accuracy for the prediction of PE. The mean glycodelin was significantly higher in severe PE (102.3 ± 51.3) as compared to mild PE (45.2 ± 7.3) in pregnant women ($P < 0.001$). The glycodelin level ≥50.1 ng/mL had 86.7% sensitivity, 80% specificity, and 85% accuracy for the prediction of severe PE. **Conclusions:** Glycodelin is an appropriate marker for the diagnosis of PE and the categorization of disease according to severity.

Keywords: Preeclampsia, severe preeclampsia, glycodelin

Introduction

Preeclampsia (PE) is an idiopathic disorder of pregnancy characterized by proteinuric hypertension. Recent estimates indicate that over 30,000 women die worldwide each year because of PE and its complications, with 98% of these occurring in developing countries. Up to 5% of women will develop PE in their first pregnancy, and although the overwhelming majority of these will have successful pregnancy outcomes, the condition can give rise to severe multisystem complications, including cerebral hemorrhage, hepatic and renal dysfunction, and respiratory compromise.[1]New biomarkers could significantly aid the diagnosis of women suspected of having PE, and that allows for an objective assessment of the disease. Furthermore, because the presence of increased urinary protein is usually a late manifestation of PE, experts have hoped that the use of biomarkers would enable earlier detection or even prediction of the disease.[2]

Glycodelin is a glycoprotein previously known as placental protein 14. It has four isoforms and belongs to the lipocalin protein superfamily.[3]Glycodelin-A is found abundantly in the secretory endometrium, decidua, and amniotic fluid. In humans, glycodelin-A concentration in the decidua rises from implantation and peaks between the 6th and 12th week of gestation, implying a role in early pregnancy.[4]Based on the important role of glycodelin-A in placental angiogenesis through the upregulation of vascular endothelial growth factor[5] and in regulating trophoblast development, differentiation, and immune cell functions, it is reasonable to speculate that deficiency

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_34_23

Address for correspondence: Dr. Ruya Qadri Fawzi, Department of Obstetrics and Gynecology, Azadi Teaching Hospital, Iraqi Board of Medical Specialization, Kirkuk, Iraq.
E-mail: ruya_alkhateeb@yahoo.com

Submission: 10-Jan-2023 **Accepted:** 22-Jan-2023 **Published:** 29-Mar-2024

How to cite this article: Fawzi RQ, Rifat AG. The evaluation of maternal serum glycodelin level as a marker for the presence and severity of preeclampsia. Med J Babylon 2023;20:S95-100.

in the normal functions of glycodelin-A may contribute to the pathophysiology of PE.[6]

The aim of the study is to analyze serum glycodelin levels in PE and evaluate whether it correlates with the severity of the disease.

Materials and Methods

This is a prospective case–control study that was carried out in the Department of Obstetrics and Gynecology of Azadi Teaching Hospital in Kirkuk-Iraq. The duration of the study was 9 months throughout the period from March 1 to November 30, 2020.

The study included 90 Rh+ve women with singleton viable pregnancy at a gestational age >20 weeks as assessed by menstrual dates and confirmed by first trimester ultrasounds scan visiting consultancy clinic or was admitted to the obstetric ward for assessment and management with no prior history of chronic hypertension or pregnancy-related hypertension disorder in a previous pregnancy. All patients were informed about the nature of the study, and verbal consent was obtained from them. Women included in the study were divided into two groups:

Preeclampsia group

Included 60 women present with signs and symptoms of PE and were diagnosed as PE according to the American College of Obstetricians and Gynecologists (ACOG) definition.

Normal group

Included 30 normotensive pregnant women without known pregnancy complications and with matched gestational age.

Pregnant patient with PE was defined according to the ACOG by the presence of hypertension and proteinuria or no proteinuria but with new incident hypertension with either thrombocytopenia (platelets $<100 \times 10^9$/L), or renal impairment or liver dysfunction or pulmonary edema or headache, or visual symptoms.

And they subdivided according to the severity of the condition based on ACOG classification of PE into two groups: 30 pregnant patients with mild, in which blood pressure was less than 160/110 mmHg with proteinuria ≥300 mg in 24 h, or in dipstick urine 1+ and 30 pregnant patients with severe PE systolic blood pressure was ≥160 mmHg or diastolic blood pressure was ≥110 mmHg or both of them with proteinuria ≥500 mg in 24 h, or dipstick urine 2+ or more.[7]

Women in both PE and normal groups with the following criteria were excluded from the study: active labor. Premature rupture of membranes and chorioamnionitis gestational trophoblastic disease. Using drugs such as aspirin, an antihypertensive agent. Chronic medical diseases (hypertension, gestational or pregestational diabetes, renal impairment, chronic liver diseases, hematological disorders).

A detailed history was taken, including the following: age of participants, obstetrical history: last menstrual period, parity, and gestational age, history of chronic medical diseases, and drugs history.

All patients were subjected to a complete physical examination, including vital signs and BMI (body mass index) assessment.

In addition to the routine investigations, which included CBC (hemoglobin, platelets), blood group and Rh, and random blood sugar, the following investigations were done for all participants: liver function test (alanine aminotransferase, aspartate aminotransferase), renal function tests, urinary protein (dipstick testing), serum glycodelin level, umbilical artery Doppler ultrasound for assessing: resistance index and pulsatility index.

Venous blood was drawn from patients was centrifuged at 2000–3000 RPM for 20 min after allowed to clot for 10–20 min at room temperature, and serum glycodelin was measured using enzyme-linked immunosorbent assay kit according to the manufacturer company: MyBioSource, standard curve range: 5–500 ng/mL.

The data of women were analyzed by application of Microsoft Excel program and Statistical Package for Social Sciences (SPSS, IBM Company, Chicago, IL 60606, USA) version 23. The outcomes of the analysis were arranged in scales variables (means and standard deviation) and in categorical variables. The chi-square test was used for categorical variables. An Independent sample *t*-test was used to compare the two means. The receiver operating characteristic (ROC) curve was used to predict the best cutoff values of glycodelin in the diagnosis of PE and PE severity. *P* value of 0.05 or less was regarded as significant.

Ethical approvals

Verbal permission and analytical approval were obtained from each patient prior to collecting data. Names were removed and replaced by identification codes. All information is kept confidential in a password-secured laptop, and data are used exclusively for research purposes.

Administrative approvals were granted from the following

1. The Council of Iraqi Board of Medical Specialization.
2. Approval and agreement of the Department of Obstetrics and Gynecology at Azadi Teaching Hospital.

The study protocol, subject information, and consent form were reviewed and approved by a local ethics committee

according to document number 25 (including the number and the date on January 18, 2023) to get this approval.

Results

The mean age of normotensive pregnant women was (28.2 ± 4.8), and the mean age of PE pregnant women was (29.7 ± 5.7); in normotensive and PE groups, the highest proportion of pregnant women was in the age between 20 and 29 years (70% and 56.7% in normotensive and PE groups, respectively). Regarding BMI, the highest proportion of the population in both groups was overweight (43.3%) in the normal group and (55%) in the PE group. The mean BMI for the normotensive group was (26.2 ± 2.5), and for the PE groups was (26.2 ± 2.1). There were no significant differences observed between normal and PE women regarding age (P = 0.4) and BMI (P = 0.2). We noticed that the highest proportion of the population in both groups was multipara (53.3%) of the normal group and (68.3%) of PE pregnant women. There was no significant difference observed between normal and PE pregnant women regarding parity (P = 0.1), as shown in Table 1.

The mean systolic blood pressure of PE (161.1 ± 17.4) was significantly higher than that of normal pregnant women (113.1 + 10.7) (P < 0.001). The mean diastolic blood pressure of PE (109 ± 12) was also significantly higher than that of normal pregnant women (74.8 ± 6.7) (P < 0.001).

In 86.7% of the normal group, urine was negative for albumin, and no woman in this group had ++ or +++ albumin, while in the PE group, all of them had positive urine for albumin, with 33.3% of them having +++ albumin.

There was a significant difference between the two groups regarding albumin in the urine (P < 0.001), as shown in Table 2.

Patients with PE had significantly higher mean glycodelin levels (73.8 ± 46.3) ng/mL compared to women in the normal group (29.2 ± 3.9) ng/mL (P = 0.001), as shown in Table 3.

ROC curve analysis was constructed for serum glycodelin level as a diagnosis for PE.

The acceptable cutoff point of glycodelin for the risk of PE was 37.9 ng/mL as a large significant area under the curve (AUC = 97%) [Figure 1].

The cutoff level of glycodelin at 37.9 ng/mL had acceptable validity results with 96.70% sensitivity, 100% specificity, 100% positive predictive value, 98.5% negative predictive value and an accuracy of 98% for the diagnosis of PE.

Table 2: Comparison in mean blood pressure and albumin in urine distribution between normal and PE groups

Variable	Normal		PE		*P*
Systolic blood pressure					<0.001*S
Mean ± SD (mmHg)	113.1 ± 10.7		161.1 ± 17.4		
Diastolic blood pressure					<0.001*S
Mean ± SD (mmHg)	74.8 ± 6.7		109 ± 12		
Urine albumin	**No.**	**%**	**No.**	**%**	<0.001**S
Nil	26	86.7	0	–	
+	4	13.3	30	50.0	
++	0	–	10	16.7	
+++	0	–	20	33.3	

S = significant

*Independent sample *t*-test, **Chi-square test

Table 1: Distribution of studied women according to demographic and obstetrical characteristics

Variable	Normal		PE		*P*
	No.	%	No.	%	
Age					0.4* NS
<20 years	0	–	1	1.7	
20–29 years	21	70.0	34	56.7	
30–39 years	9	30.0	22	36.7	
≥40 years	0	–	3	5.0	
Mean ± SD (years)	28.2 ± 4.8		29.7 ± 5.7		0.2** NS
BMI					0.2* NS
Normal	13	43.3	16	26.7	
Overweight	13	43.3	33	55.0	
Obese	4	13.3	11	18.3	
Mean ± SD (kg/m^2)	26.2 ± 2.5		26.2 ± 2.1		0.9** NS
Parity					0.1* NS
Nulliparous	14	46.7	19	31.7	
Multiparous	16	53.3	41	68.3	

NS = not significant

*Chi-square test, **Independent sample *t*-test

Table 3: Comparison in mean glycodelin level between normal and PE groups

Variable	Normal	PE	*P*
	Mean ± SD	Mean ± SD	
Glycodelin (ng/mL)	29.2 ± 3.9	73.8 ± 46.3	<0.001*S

S = significant
*Independent sample *t*-test

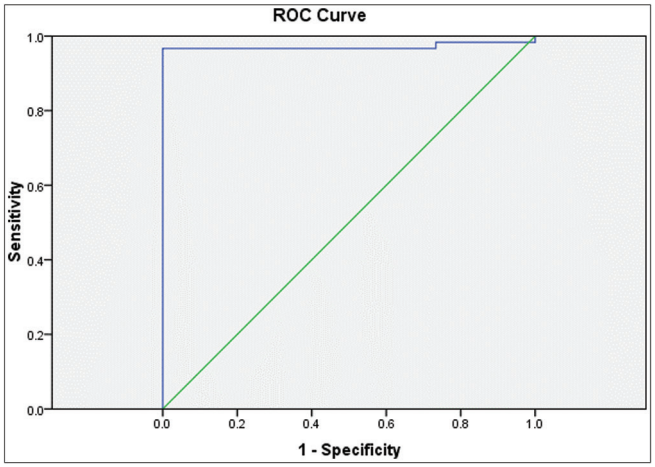

Figure 1: ROC curve of glycodelin for diagnosis of PE (AUC = 0.97)

Table 4: Validity values of glycodelin for diagnosis of PE

Cutoff point (ng/mL)	Sensitivity	Specificity	PPV	NPV	Accuracy
37.9	96.7%	100%	100%	98.5%	98%

NPV: negative predictive value, PPV: positive predictive value

The cutoff point and the corresponding validity values of glycodelin level for diagnosis of PE are shown in Table 4.

As shown in Table 5, the mean glycodelin level was significantly higher among severe PE (102.3 ± 51.3) as compared to mild PE (45.2 ± 7.3) pregnant women ($P < 0.001$).

ROC curve analysis revealed that the acceptable cutoff point of glycodelin for risk of severe PE was 50.1 ng/mL as a large significant AUC = 87% [Figure 2].

The cutoff level of glycodelin at 50.1 ng/mL had acceptable validity results with 86.7% sensitivity, 80% specificity, 80.8% positive predictive value, 88.5% negative predictive value, and accuracy of 85%, for the detection of severe PE, as shown in Table 6 and Figure 2.

Furthermore, the glycodelin level was higher in patients with late compared to early onset disease; however, the difference between them was not statistically significant ($P = 0.9$), as shown in Table 7.

Table 5: Comparison in mean glycodelin level between mild and severe PE

Variable	Mild PE	Severe PE	*P*
	Mean ± SD	Mean ± SD	
Glycodelin (ng/mL)	45.2 ± 7.3	102.3 ± 51.3	**<0.001***S

*Independent sample *t*-test, S = significant

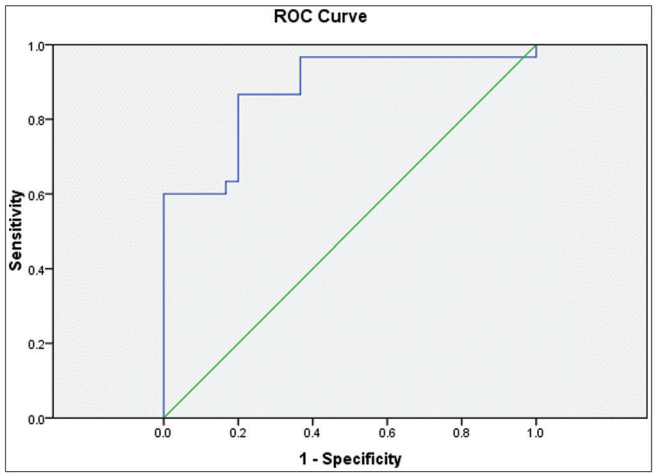

Figure 2: ROC curve of glycodelin for detection of severe PE (AUC = 0.87)

Table 6: Validity values of glycodelin for detection of severe PE

Cutoff point (ng/mL)	Sensitivity	Specificity	PPV	NPV	Accuracy
50.1	86.7%	80%	80.8%	88.5%	85%

NPV: negative predictive value, PPV: positive predictive value

Table 7: Mean of glycodelin level according to PE onset

Variable	<34 weeks	≥34 weeks	*P*
	Mean ± SD	Mean ± SD	
Glycodelin (ng/mL)	73 ± 37.4	74.4 ± 52.7	0.9*NS

NS = not significant
*One-way ANOVA analysis

Discussion

Hypertension is one of the most common health problems in the world,[8] PE is a pregnancy-specific disorder. It is one of the main causes of maternal and perinatal morbidity and mortality globally, with a predominance in low and middle-income countries. It is a multisystemic disorder; however, its etiology and pathophysiology are poorly understood. Exploring new markers is essential in helping physicians to predict and confirm the diagnosis of PE and also assessing the severity of the condition.[9,10]

Glycodelin has been predominantly localized to organs of the genital tract in humans; it has a role in early placental development through its modularity effects on immune cells and cytotrophoblast, and it has several reproduction-related functions.[4]

In Iraq, a case–control study on one hundred pregnant women in 1st trimester was carried out by Ibrahim *et al.*[11] found that serum glycodelin is a good predictor for unruptured ectopic pregnancy. Vijayan *et al.*[12] stated that glycodelin-A stimulates the polarization of monocytes into decidual macrophages for regulation of fetomaternal tolerance and placental development,[13] but there were few studies about the hlycodelin in PE.

The main hypothesis of the present study is that maternal serum glycodelin levels may differ between PE women and healthy pregnancies and also between severe and mild PE patients; for that reason, we aimed to evaluate the glycodelin levels in PE patients and determine whether it correlates with clinical findings and severity of the disease.

In the current study, the mean glycodelin serum level was significantly higher among PE women as compared to normal pregnant women.

It has previously been suggested that placental protein 14 (glycodelin) is a prostaglandin metabolizing enzyme (15-hydroxy prostaglandin dehydrogenase); high levels of prostaglandin are secreted during pregnancy, and these need to be inactivated particularly locally at the site of the placenta, to prevent their induction of premature labor and also to minimize their vasoconstriction and hence potential hypertensive effects. One would expect the secretion pattern of such an inactivation factor to increase throughout pregnancy with a marked reduction in levels immediately prior to parturition. The markedly increased levels of the inactivating factor that is glycodelin in PE patients may be explained based on this hypothesis as a response mechanism to reduce the prostaglandin levels and hence restore normotension.[14]

Our finding coincides with the results of Dundar *et al*.,[15] documenting that higher levels of glycodelin-A in early pregnancy are useful in the prediction of PE and with the study of Iino *et al*.[16] that showed higher serum levels of PP14 (glycodelin) in patients with PE and related that to either increased synthesis or decreased catabolism of glycodelin, which resulted from changes in decidual arteries that have been observed in hypertensive pregnancy.

Further analysis of our data showed that glycodelin level cutoff (>37.9 ng/mL) had acceptable validity results with (96.70% sensitivity, 100% specificity, and 98% accuracy) as a diagnosis for PE.

Consistently Dundar *et al*.[15] study in Turkey showed that glycodelin has good validity results in discrimination between PE and control women, with a sensitivity of 83.6% and specificity of 80% at a cutoff level (>53.64 ng/mL). Actually, maternal health programs in all countries and specifically the low resources countries, are in need of sensitive, specific, and reliable biomarkers for early detection and even prediction of PE since the 1st trimester in order to prevent maternal and neonatal complications and to minimize the economic burden on the national health system.[17]

Furthermore, in the present study, the mean glycodelin level was significantly higher among severe as compared to mild PE pregnant women. The cutoff glycodelin level of >50.1 ng/mL was found to have acceptable validity results (86.7% sensitivity, 80% specificity, and accuracy 85%) for the detection of the severity of the disease.

These are again close to the results of Dundar *et al*.[15] that showed higher glycodelin levels among pregnant women with severe compared to mild PE and revealed that glycodelin is useful in predicting the severity of PE at a cutoff (>83.97 ng/mL) with the sensitivity of 59%, and specificity of 93.3%.

However, the higher cutoff values of glycodelin recorded in the previous study[15] may be related to the differences in the study population and in the kit used for glycodelin estimation.

On the other hand, our results regarding the glycodelin levels in PE disagree with the Howel *et al*.[18] study in which the PP14 (glycodelin) levels in PE were similar to controls in all grades of PE.

Conclusion

- The glycodelin is an appropriate marker for diagnosis of PE at a cutoff value >37.9 ng/mL.
- Our finding of the appreciated role of glycodelin as a diagnosis for PE and its severity needs to be furtherly evaluated in larger, multicenter studies before wider clinical application in the management of PE.
- Further studies are needed to confirm the exact serum profile of glycodelin in normal pregnancy in order to determine the appropriate screening and monitoring schedule of high-risk women.
- Future studies with a different design, including serial measurements of glycodelin levels since early pregnancy in high-risk women, are advised to confirm the role of the concerned biomarker in the early prediction of PE.
- More sophisticated and advanced studies to determine the decidual origin of glycodelin are recommended to confirm the severity of placenta or decidual damage caused by PE.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Edmonds K, Lees C, Bourne T (eds.). Dewhurst's Textbook of Obstetrics & Gynaecology. 9th ed. USA: Wiley Blackwell; 2018. p. 73-80.
2. Acestor N, Goett J, Lee A, Herrick TM, Engelbrecht SM, Harner-Jay C, *et al*. Towards biomarker-based tests that can facilitate decisions about prevention and management of preeclampsia in low-resource settings. Clin Chem Lab Med 2016;54:17-27.
3. Lee CL, Lam KK, Vijayan M, Koistinene H, Seppala M, Ng EHY, *et al*. The pleiotropic effect of glycodelin-A in early pregnancy. Am J Reprod Immunol 2016;75:290-7.
4. Seppala M, Koistinen H, Koistinen R, Hautala L, Chiu PC, Yeung WS. Glycodelin in reproductive endocrinology and hormone-related cancer. Eur J Endocrinol 2009;160:121-33.
5. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. Annu Rev Pathol 2010;5:173-92.
6. Jeschke U, Kunert-Keil C, Mylonas I, Hammer A, Schiessl B, Lomba I, *et al*. Expression of glycodelin A in decidual tissue of preeclamptic, HELLP and intrauterine growth restricted pregnancies. Virchows Arch 2005;446:360-8.
7. Norwitz ER, Zelop CM, Miller DA, Keefe DL, (eds.). Evid Based Obstet Gynecol. USA: Wiley Blackwell; 2019. P. 255-60.
8. Helen AM, Ameer KA. Assessment of knowledge about hypertension among hypertensive patients in Babylon Province. Med J Babylon 2022;19:31-6.
9. Amal FW, Helema YA. Association between gestational hypertension and preeclampsia with spontaneous prelabor rupture of membrane. Med J Babylon 2022;19:281-7.
10. Gathiram P, Moodley J. Pre-eclampsia: Its pathogenesis and pathophysiology. Cardiovasc J Afr 2016;27:71-8.
11. Ibrahim WW, Al-Naddawi AM, Fawzi HA. Role of maternal serum glycodelin as predictor of ectopic pregnancy in first trimester. Int J Women's Health Reprod Sci 2019;7:467-70.
12. Vijayan M, Lee CL, Wong VHH, Wang X, Bai K, Wu J, *et al*. Decidual glycodelin-A polarizes human monocytes into a decidual macrophage-like phenotype through Siglec-7. J Cell Sci 2020;133:jcs244400.
13. Bonney EA. Immune regulation in pregnancy: A matter of perspective? Obstet Gynecol Clin North Am 2016;43:679-98.
14. Bolton AE, Chapman MG, Stoker RJ, Andrew CE, Wass D, Bohn H. The radioimmunoassay of human placental protein 14 (PP14). Clin Chim Acta 1983;135:283-91.
15. Dundar B, Dincgez Cakmak B, Aydin Boyama B, Karadag B, Ozgen G. Maternal serum glycodelin levels in preeclampsia and its relationship with the severity of the disease. J Matern Fetal Neonatal Med 2018;31:2884-92.
16. Iino K, Julkunen M, Sjöberg J, Seppälä M. Is decidua affected in gestational hypertension? Indication by elevated PP14 levels. Acta Obstet Gynecol Scand 1986;65:367-70.
17. Acestor N, Goett J, Lee A, Herrick TM, Engelbrecht SM, Harner-Jay CM, *et al*. Towards biomarker-based tests that can facilitate decisions about prevention and management of preeclampsia in low-resource settings. Clin Chem Lab Med 2016;54:17-27.
18. Howell RJ, Economides D, Teisner B, Farkas AG, Chard T. Placental proteins 12 and 14 in pre-eclampsia. Acta Obstet Gynecol Scand 1989;68:237-40.