AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 4, Issue 04, 2026 ISSN (E): 2993-2149

Maternal Serum Netrin-1 as a New Biomarker of Preeclampsia

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Abstract: Background: The netrin-1 serum is extensively expressed in various tissues such as renal tissues and placenta. It is predominantly implicated in cell migration development, cell adhesion and cell survival. Netrin-1 serum is also important in the formation of the placenta by enhancing the growth of cytotrophoblast and placental vapour development.

Aim: To determine whether the use of serum netrin-1 levels measurement might be linked to preeclampsia or might be a biomarker of preeclampsia.

Patients and Method: The case-control study was done in Alzahraa Teaching Maternity and Pediatrics Hospital / Najaf Governorate / Iraq, in the year period starting 1 st January 2024 to 1 st January 2025. The convenience sampling technique was used to recruit a total of 90 singleton pregnant women. The sample incorporated two groups whereby the case group comprised 45 pregnant women exposed to preeclampsia and the control group comprised of 45 healthy pregnant women (normotensive and never had any medical disease in their history). The serum netrin-1 was measured with the help of an Enzyme-Linked Immunosorbent Assay kit.

Findings: The serum netrin-1 mean showed a significant difference that was found to be elevated at the case group (non-severe and severe preeclampsia) than in the control group. Besides, it was also more pronounced in patients with non-severe preeclampsia than in the control group (P-value=0.001). Moreover, it was much greater in the case of severe preeclampsia patients as compared to non-severe preeclampsia (P-value=0.019). There were also significant positive associations between serum netrin-1 and alanine transaminase, aspartate transaminase, blood urea, serum creatinine and negative significant association between serum netrin-1 and platelet count in case. The sensitivity, the specificity, and the accuracy of serum netrin-1 in the diagnosis of preeclampsia were 93.3, 80 and 86.6 respectively with a cut-off point of 698 pg/ml.

Conclusion: Netrin-1 serum can be considered as a potential biomarker in the prediction and detection of preeclampsia.

Keywords: Netrin-1, Maternal, Preeclampsia.

1. Introduction

Preeclampsia is an acute, pregnancy specific condition of hypertension characterized by new-onset hypertension (>140/90 mmHg) and excessive proteinuria or other end-organ dysfunctions that occur afterward of 20 weeks of gestation (1-2). It has been shown to be a major cause of maternal and perinatal morbidity and mortality with an annual maternal and fetal fatalities of more than 70,000 and 500,000, respectively (3-4). The disease has a clinical spectrum associated

with mild symptoms up to life-threatening complications eclampsia, HELLP syndrome, abruptio placentae, and severe intrauterine growth restriction (5).

The pathophysiological basis of preeclampsia is deeply based on the malfunction of placentation and vascular dysfunction. In a normal pregnancy, extravillous trophoblasts (EVTs) enter the maternal decidua, and substantially remodel the spiral arteries of the uterus into large, low-resistance vessels, which maintain sufficient uteroplacental blood flow (6). The pathological constriction of these arteries is caused by shallow trophoblastic invasion in preeclampsia. The result of such remodeling failure is placenta hypoperfusion and relative hypoxemia coupled with oxidative stress (7). This results in the release of antiangiogenic factors, mainly sFlt-1 and sEng, by the ischemic placenta and a decrease in the concentrations of essential proangiogenic factors, including VEGF and PlGF. This disturbance of angiogenesis eventually triggers maternal endothelial dysfunction on a systemic level and the production of an acute inflammatory reaction (8). Although the benefits of prophylactic low-dose aspirin in high-risk women are known, efficient prediction of disease occurrence with the help of classical maternal risk factors has been a key clinical issue, which highlights the importance of new highly sensitive biomarkers (9).

Since angiogenic dysregulation stands at the center of the pathogenesis of preeclampsia, serum netrin-1 has become an interesting molecule of interest. Netrin-1 is a laminin protein with several domains binding with particular receptors which encompass DCC and UNC5 family to mediate various biological processes (10). Netrin-1 is a key modulator of cell migration, cell adhesion, cell apoptosis, and inflammation, which is widely expressed in human tissues, including the placenta (11).

Above all netrin-1 is a strong regulator of angiogenesis. It also helps in vascular development by enhancing the movement and growth of endothelial cells towards the vascular smooth muscle cells (12). Netrin-1 and its receptors are expressed by trophoblastic and endothelial cells in the human placenta which is the most vascularized mammalian organ and is a crucial part of cytotrophoblast proliferation and normal fetal-placental vascular development (68-70). Since preeclampsia is caused by the inhibition of angiogenesis and superficial placentation, the disturbances in the signal transduction of netrin-1 could be directly connected to the causes of the disease (13). Thus, this research paper will examine the hypothesis on whether maternal serum netrin-1 levels can be connected to preeclampsia and determine its possible clinical application as a new predictive or diagnostic tool of the disease.

2. Patients and Methods

This was a case-control study carried out at Al-Zahraa Teaching Hospital located in Najaf Governorate, Iraq and during a period of one year between the year 1 January, 2024, to 1 January, 2025. The aim of the study was to determine the relationship between maternal serum netrin-1 and preeclampsia. The Scientific Council of Gynecology and obstetrics of the Iraqi board of medical specialization approved the use of the ethical approval. The informed consent was taken and written before the enrolment of all the participants in the study in terms of the objectives of the study and the procedures involved. Anonymity and confidentiality were also ensured and data utilized only to conduct research.

Ninety pregnant women were sampled through a convenient sampling approach and assigned into two equal groups such as a case group (n= 45) of women diagnosed with preeclampsia and a control group (n=45) of pregnant women who were healthy and normotensive and had no history of medical illnesses. Preeclampsia was suspected due to the occurrence of hypertension (systolic blood pressure 140 mmHg or more at least two times at least at 4 hours apart or 160 mmHg or more on one occasion) and proteinuria (urine dipstick 1 or more). The inclusion criteria were women who had singleton pregnancies during the third trimester (2840 weeks of gestational age). The exclusion criteria were urinary tract infection, chronic kidney disease, diabetes mellitus or gestational diabetes, and current smoking.

The use of direct interviews and the structured questionnaire that was created after examining the corresponding literature and tested by the supervisor of the study were the methods of collecting data. Data were on sociodemographic factors, medical and obstetric history, and a history of preeclampsia in the past. Gestational age was calculated with reference to the last menstrual period and checked with the early ultrasound. Standardized clinical examination was conducted that consisted of blood pressure measurement after a five-minute rest in a sitting position based on the guidelines of the international norms. The measurements were done in both arms, and the larger one was taken. The body mass index (BMI) was derived as the weight in kilograms/height in meters squared.

Protein analysis was done on midstream urines. Laboratory research was conducted on venous blood (10 mL) and it included platelet count, liver functioning tests (AST, ALT), and renal functioning tests (urea, creatinine) using the colorimetric assay methods. Serum samples were divided and kept at -20 o C pending analysis. The quantitative enzyme-linked immunosorbent assay (ELISA) of serum netrin-1 levels was conducted according to the instructions of the manufacturer by using the sandwich-ELISA method.

Data were examined with the help of Microsoft Excel 2016 and SPSS version 22. Frequencies, percentages and mean Standard deviation were used to present descriptive statistics. Comparison of differences between groups was done using independent samples t-test and chi-square test. The correlation coefficient of Pearson was used to evaluate correlations among continuous variables. The p-value of less than 0.05 was deemed as statistically significant.

3. Results

A total of 90 pregnant women were enrolled in the current study. The age range in the case group was 16-35, respectively, while it was 16-33 years, respectively, in the control groups were, respectively. There was no significant difference between the study groups regarding age (26.42 ±6.4 years versus 24.80 ±5.0 years) (P-value=0.187) and body mass index (26.55 ±3.1 kg/m^2 versus 27.62 ±2.2 kg/m^2) (P-value=0.068). As shown in table 3.1.

Table 3.1: Distribution of the patients according to the maternal age, body mass index, and gestational age according in the study groups

Variables	Groups		P-value
	Case group Mean ±SD	Control group Mean ±SD	
Age (years)	26.42 ±6.4	24.80 ±5.0	0.187
Body mass index (kg/m^2)	26.55 ±3.1	27.62 ±2.2	0.068
Gestational age (weeks)	36.7 ±3.3	36.2 ±3.4	0.511

The means of alanine transaminase and aspartate transaminase were significantly higher in the case group than in the control group (34.93 ±6.4 IU/L versus 31.64 ±5.9 IU/L and 36.27 ±19.8 IU/L versus 28.8 ±5.9 IU/L, respectively) (P-values were 0.014 and 0.018, respectively). In contrast, the platelets count was significantly lower in the case group than in the control group (210.71 ±91.2 ×10^9/L versus 249.27 ±50.6 ×10^9/L) (P-value was 0.015). There were no significant differences between the study groups regarding the blood urea and serum creatinine (P-values were 0.180 and 0.108, respectively) as shown in table 3.2.

Table 3.2: Distribution of the results of blood pressure, liver function test, renal function test, and platelets count according to the study groups

Investigations	Groups		P-value
	Case group Mean ±SD	Control group Mean ±SD	
Alanine transaminase (IU/L)	34.93 ±6.4	31.64 ±5.9	0.014
Aspartate transaminase (IU/L)	36.27 ±19.8	28.8 ±5.9	0.018

Blood urea (mg/dl)	22.85 ±5.9	19.94 ±7.0	0.180
Serum creatinine (mg/dl)	0.72 ±0.2	0.65 ±0.1	0.105
Platelets count ($\times 10^9$/L)	210.71 ±91.2	249.27 ±50.6	0.015

According to the severity parameters, patients in the case group were categorized as 12 patients had severe preeclampsia and 33 patients had non-severe preeclampsia. The mean of serum netrin-1 was significantly higher in the case group (including non-severe and severe preeclampsia) compared to the control group. In addition, it was higher in patients with non-severe preeclampsia compared to the control group (P-value=0.001). Furthermore, it was significantly higher for patients with severe preeclampsia compared to those with non-severe preeclampsia (P-value=0.019) as shown in figure 3.1.

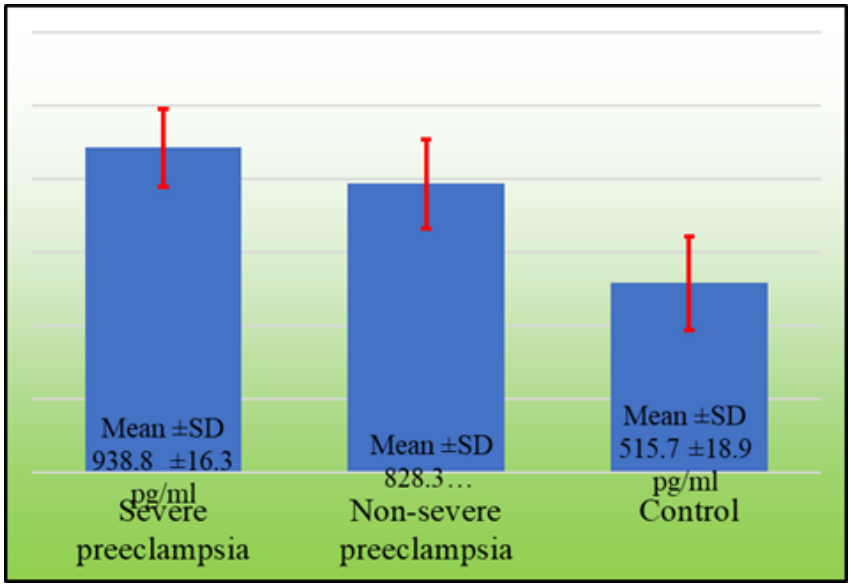

Figure 3.1: Distribution of serum netrin-1 according to the study groups. Control versus preeclampsia: P-value=0.001. Control versus non-severe preeclampsia: P-value=0.001. Control versus severe preeclampsia: P-value=0.001. Non-severe versus severe preeclampsia: P-value=0.019

The ROC curve was used to estimate the best cut-off point of serum netrin-1 in the detection of preeclampsia. Accordingly, the serum netrin-1 level of 698 pg/ml was selected (Figure 3.2).

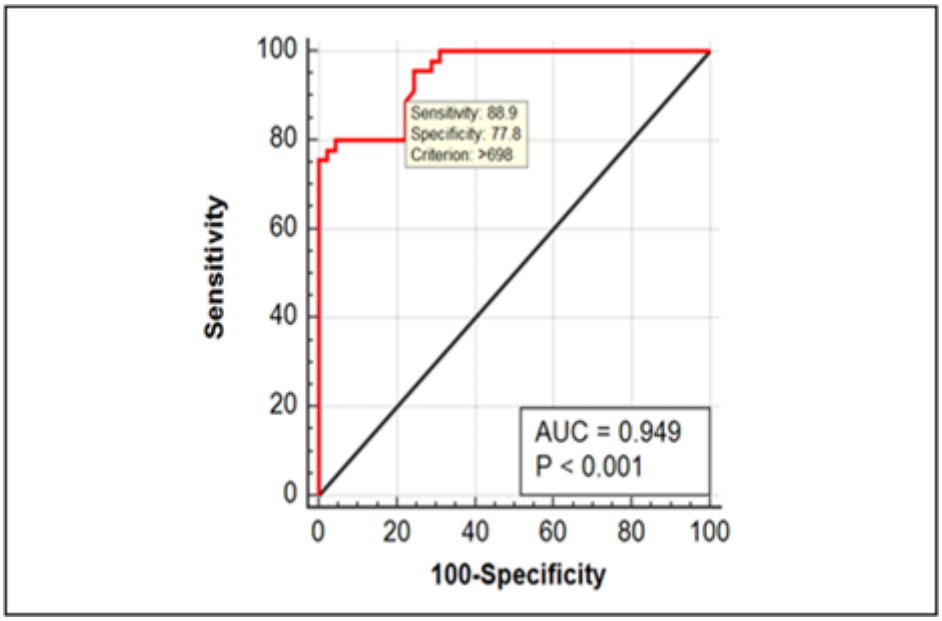

Figure 3.2: ROC curve for serum netrin-1

According to the cut-off point of 698 pg/ml, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of serum netrin-1 in the detection of preeclampsia were 93.3%, 80%, 82.4%, 92.3%, and 86.6%, respectively (Table 3.3).

Table 3.3: Validity of the serum netrin-1 test in detecting preeclampsia

Serum netrin-1	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
>698 pg/ml	88.9%	77.8%	87.5%	80%	83.3%

In the case group, there were significant positive correlations between serum netrin-1 with alanine transaminase, aspartate transaminase, blood urea, and serum creatinine. While a negative significant correlation was obtained between serum netrin-1 and platelet count. As shown in table 3.4.

Table 3.4: Correlation between serum netrin-1 and other variables

Parameters		Serum netrin-1
Systolic blood pressure	Pearson Correlation	0.403
	P-value	0.006
	N	45
Diastolic blood pressure	Pearson Correlation	0.592
	P-value	<0.001
	N	45
Alanine transaminase (IU/L)	Pearson Correlation	0.497
	P-value	0.001
	N	45
Aspartate transaminase (IU/L)	Pearson Correlation	0.365
	P-value	0.014
	N	45
Blood urea (mg/dl)	Pearson Correlation	0.296
	P-value	0.049
	N	45
Serum creatinine (mg/dl)	Pearson Correlation	0.438
	P-value	0.003
	N	45
Platelets count (×109/L)	Pearson Correlation	-0.566
	P-value	<0.001
	N	45

4. Discussion

Preeclampsia should be properly detected and treated promptly because it would lead to improved outcomes of both mothers and babies. Yet, the development of the disease and its severity cannot be forecasted regardless of the advanced equipment of the hospitals. Different predictive models and biomarkers have been elaborated to determine the risk and the progression of preeclampsia[14]. This study tried to evaluate the potential role of serum netrin-1 in the prediction of preeclampsia.

This paper attempted to determine the possible use of serum netrin-1 in prediction of preeclampsia. The present research indicated that the liver functions test that comprised of alanine transaminase and aspartate transaminase were highly influenced by preeclampsia. Similarly, the same findings were also found in other studies that were conducted by Kasraeian

et al. in Iran[15], Javid et al. in India[16], and Oloruntoba et al. Nigeria[17], Bibi et al. in Pakistan[18], and Afroz et al. in Bangladesh[19].

The renal function test that was conducted by measuring the blood urea and serum creatinine levels did not show significant differences between the pregnant women with preeclampsia and those of the current study. Similarly, this was also found to be the case in a study conducted by Alaa et al in Iraq[20]. Conversely, a different research that was conducted by Ekun et al. showed a sharp rise in blood urea and serum creatinine in women who were pregnant with preeclampsia in relation to normal[21]. Salma et al. in the study conducted in Libya discovered that blood urea of women with preeclampsia of pregnant women was significantly high when compared to that of women with normal blood pressure although the serum creatinine was not significantly different[22]. This discrepancy may be associated with the level of preeclampsia in samples of these research.

The platelet count in the pregnant women in the current study with preeclampsia was significantly lower as compared to the platelet count in the control population. Comparatively, an analysis carried out by Gashaw et al. affirmed the fact that platelet count in women with preeclampsia is significantly reduced regardless of the degree of severity levels and whether or not the women have experienced related complications[23]. Research done in the Kingdom of Saudi Arabia by AlSheeha et al. found that, in the preeclampsia group platelet count had significantly diminished compared to the control group[24]. On the same note, Shaifali et al. discovered that the reduction in platelet count in patients with preeclampsia is higher than in other patients, in addition they also concluded that estimation of platelet indices could be regarded as an early, simple and economical procedure in the determination of severity of preeclampsia[25].

The primary research conclusion made during the current study was that the level of serum netrin-1 increased significantly between the level of the control group to the level of pregnant women with non-severe preeclampsia to severe preeclampsia. Moreover, the grade of serum netrin-1 level was positively correlated with blood pressure, liver functioning test, and kidney functioning test and negatively with the platelets count. Similarly, the same findings were reached in a study that was carried out by Yasemin et al. Turkey and relied on the conclusion that serum netrin-1 could be viewed as a new mark that may be used in the diagnosis of preeclampsia[12]. This was also found in the study conducted by Zekiye Soykan who came to the conclusion that the high levels of serum netrin-1 have a strong relationship with the occurrence of preeclampsia. The starting concentration of serum netrin-1 can serve as a significant indicator of assessing the risk of developing preeclampsia in women with gestational hypertensive diseases[13]. Morteza et al. also reported in the same line that the concentration of serum netrin-1 was statistically elevated in the women with preeclampsia compared with that of normotensive pregnant women. Moreover, the serum netrin-1 concentration in severely preeclamptic women was found to be quite high in comparison with non-severe preeclamptic women[26].

The sensitivity, specificity, and accuracy of 698 pg/ml netrin-1 serum used in the present research were 93.3, 80, and 86.6, respectively. Comparatively, in yet another study which was conducted in Turkey, serum netrin-1 levels exceeding 784.9 pg/mL was predictive of the occurrence of preeclampsia with a sensitivity of 72.0% and a specificity of 88.8%[13].

5. Conclusion

The present research find to Serum netrin-1 can be included as one more potential biomarker in preeclampsia prediction. The sensitivity, specificity and accuracy of serum netrin-1 in the detection of preeclampsia were 93.3, 80 and 86.6 with a cut-off point of 698 pg/ml respectively.

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