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The Contribution of Serum Netrin-1 Levels in Early-Onset Preeclampsia Detection

Sarah Kinaan Omar[1], Assist. Prof. Dr. Masryia Rashad Hassein[2]

[1]College of Medicine, Tikrit University, Iraq, Sarahkanaan51@gmail.com
[2]College of Medicine, Tikrit University, Iraq, masriarashad@tu.edu.ia

ABSTRACT:

Background: Netrin-1 is a laminin-related protein involved in angiogenesis, vascular remodeling, trophoblast invasion, endothelial protection, and inflammatory regulation, making it a promising candidate biomarker for early prediction of preeclampsia.

Aim: To evaluate the role of maternal serum Netrin-1 measured during the first trimester as an early biomarker for predicting early-onset preeclampsia and to assess its relationship with maternal and neonatal outcomes.

Patients and Methods: A hospital-based case-control study was conducted at the Department of Obstetrics and Gynecology, Tikrit Teaching Hospital, Salah Al-Din Governorate, Iraq, between October 2025 and June 2026. Ninety pregnant women with singleton pregnancies were enrolled during the first trimester (11–13+6 weeks of gestation). Forty-five women who subsequently developed early-onset preeclampsia constituted the case group, while forty-five normotensive pregnant women served as controls..

Results: Maternal serum Netrin-1 concentrations were markedly lower among women who developed EOPE than among controls (286.4±71.8 vs. 468.9±84.6 pg/mL, $P<0.001$). Women with EOPE experienced significantly poorer maternal outcomes, including earlier delivery, increased cesarean section rate, higher ICU admission, and increased incidence of HELLP syndrome. Neonatal outcomes were also significantly worse, with lower birth weight, lower Apgar scores, higher preterm birth, and increased NICU admission. Serum Netrin-1 demonstrated significant negative correlations with maternal body mass index ($r=-0.311$), systolic blood pressure ($r=-0.671$), diastolic blood pressure ($r=-0.642$), serum creatinine ($r=-0.514$), AST ($r=-0.488$), and ALT ($r=-0.451$), while significant positive correlations were observed with gestational age at delivery ($r=0.557$), birth weight ($r=0.602$), and platelet count ($r=0.463$) (all $P<0.05$). Multivariable logistic regression analysis showed that serum Netrin-1 remained an independent predictor of EOPE after adjustment for maternal risk factors (adjusted OR=0.982, 95% CI=0.974–0.990, $P<0.001$).

Conclusions: Maternal serum Netrin-1 measured during the first trimester is significantly reduced in women who subsequently develop early-onset preeclampsia. Lower serum Netrin-1 concentrations are associated with adverse maternal and neonatal outcomes and remain an independent predictor of disease development. Serum Netrin-1 demonstrates excellent diagnostic accuracy and represents a promising biomarker for early prediction and risk stratification of early-onset preeclampsia.

INTRODUCTION

One of the main causes of maternal and perinatal morbidity and mortality globally, preeclampsia is a hypertension condition of pregnancy that affects 3–5% of pregnant women.Preeclampsia is a multisystemic syndrome that develops in previously normotensive women after 20 weeks of gestation and is characterized by new-onset hypertension and end-organ dysfunction.

It is divided into Early-Onset Preeclampsia (EOP), which occurs before 34 weeks of gestation, and Late-Onset Preeclampsia (LOP), which develops at or after 34 weeks .The underlying mechanisms of these two subtypes differ markedly. EOP is mainly associated with abnormal placentation, resulting from inadequate trophoblastic invasion and defective spiral artery remodeling that lead to placental hypoperfusion and ischemia[4]. In contrast, LOP is more often linked to maternal endothelial dysfunction arising from metabolic or vascular abnormalities. While both forms share similar diagnostic criteria, EOP is typically associated with severe maternal and fetal complications, including intrauterine growth restriction (IUGR), preterm birth, and stillbirth, whereas LOP tends to have milder clinical outcomes[5]. Consequently, identifying reliable predictors for early-onset disease is crucial for effective management, timely intervention, and reduction of adverse outcomes. Despite extensive research, no consistent biochemical marker has yet been validated for predicting EOP[2] .

In this context, netrin-1 has emerged as a potential biomarker of interest. Initially recognized as an axon guidance protein, netrin-1 has since been found to play pivotal roles in angiogenesis, embryogenesis, and vascular remodeling[6]. It exhibits proangiogenic, antiapoptotic, and anti-inflammatory properties, which are fundamental for maintaining endothelial stability and placental development[7]. Studies in animal models have shown that netrin-1 is crucial for placental angiogenesis and fetal survival, underscoring its importance in early gestation[8]. Furthermore, it promotes cytotrophoblast proliferation and vascular branching, both essential for normal placental architecture[9]. These findings suggest that maternal serum netrin-1 levels could reflect placental function and potentially serve as a novel biomarker for early detection of preeclampsia.

Netrin-1 is a member of a family of laminin-related proteins that include many epidermal growth factor-like (EGF) repeats after an N-terminal laminin-type domain. Interactions with certain receptors, such as UNC5B and members of the Deleted in Colorectal Cancer (DCC) family, are the main way that it mediates its effects. Anne Eichmann and associates initially reported the regulating function of netrin-1 and its receptor UNC5B in vascular morphogenesis in 2004, who demonstrated that netrin-1 could inhibit filopodia formation and endothelial sprouting, suggesting an anti-angiogenic function[1]. Subsequent studies, however, provided contrasting evidence, showing that exposure to netrin-1 stimulates endothelial cell proliferation, migration, capillary branching, and tubule formation, supporting its proangiogenic properties [10,11]. Research in human placental tissue has confirmed the expression of netrin-1 and its receptors, highlighting their critical role in cytotrophoblast proliferation and placental vascular branching. Additional research revealed that netrin-1 promotes angiogenesis in part by enhancing endothelial cell survival thru inhibition of apoptosis, an effect mediated by its receptor-dependent signaling[0]. Preeclampsia, intrauterine growth restriction (IUGR), and placental abruption are just a few of the obstetric issues that can result from placental dysfunction, which is known to be caused by disruption of placental angiogenesis during early pregnancy [9].

Aim

The purpose of this study was to assess the potential utility of maternal serum netrin-1 levels as a biochemical marker for early-onset preeclampsia identification and prediction.

PATIENTS AND METHODS.

Study Design

This study was planned as a hospital-based case-control study that was carried out between October 1, 2025, and June 30, 2026, at the Department of Obstetrics and Gynecology, Tikrit Teaching Hospital, Salah Al-Din Governorate, Iraq.

3.1.1 Study Population

A total of **90 pregnant women** attending the antenatal clinics of Tikrit Teaching Hospital during the first trimester of pregnancy were enrolled in the study.

The participants were allocated into two comparable groups:

- **Case group (n = 45):** Pregnant women who subsequently developed **early-onset preeclampsia**, defined as preeclampsia requiring diagnosis before 34 completed weeks of gestation.

Control group (n = 45): Pregnant women who remained normotensive throughout pregnancy and delivered healthy singleton term infants without maternal or fetal complications.

METHODS

Sampling Technique

A consecutive non-probability sampling technique was employed throughout the study period. All eligible pregnant women attending the antenatal outpatient clinics at Tikrit Teaching Hospital during the first trimester were invited to participate. Following recruitment, all participants underwent routine antenatal follow-up until delivery. Women who subsequently developed early-onset preeclampsia were allocated to the case group, whereas women who remained normotensive throughout pregnancy constituted the control group.

Blood Sample Collection and Laboratory Investigations

During the first trimester, venous blood samples were taken from each participant in a completely aseptic setting. Sterile disposable syringes were used to draw 5–10 mL of venous blood from the antecubital vein. After allowing blood samples to coagulate at room temperature, they were centrifuged for ten minutes at 3000 rpm. Before being examined in a lab, the separated serum was put into sterile Eppendorf tubes and kept at -20°C. The following tests were conducted in the lab:

- Serum Netrin-1 concentration (ELISA)
- Liver function tests (AST and ALT)

Ethical Considerations

Prior to starting patient recruitment, the Scientific and Ethical Committee of the Iraqi Board for Medical Specializations and the Research Ethics Committee of Tikrit Teaching Hospital granted ethical approval. The Declaration of Helsinki and its later revisions' ethical guidelines were followed when conducting the study. Before enrolling, each participant was given a thorough description of the goals, methodology, potential advantages, and potential hazards of participation. Each subject provided written informed permission..

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) program (IBM Corp., Armonk, NY, USA) was used to enter, code, verify, and analyze all of the data that had been gathered. The Shapiro-Wilk test was used to determine whether continuous variables were normal. Mean ± standard deviation (SD) was used to express variables that were normally distributed.

RESULTS

Baseline Demographic Characteristics

According to the study, the baseline demographic features of the two study groups were largely similar. There was no significant difference in maternal age between normotensive controls and women who later developed early-onset preeclampsia (31.7 ± 4.6 vs. 30.9 ± 4.8 years, P = 0.421). Similarly, the two groups were similar in terms of gestational age at recruitment (12.2 ± 0.7 vs. 12.1 ± 0.8 weeks, P = 0.573), gravidity (2.6 ± 1.1 vs. 2.4 ± 1.0, P = 0.352), and parity (1.2 ± 0.9 vs. 1.3 ± 0.8, P = 0.618). However, compared to controls, women who later experienced early-onset preeclampsia had a substantially higher body mass index (30.6 ± 3.8 vs. 27.9 ± 3.4 kg/m² P = 0.001).

Table 1: Baseline Demographic Characteristics of the Study Groups

Variable	EOPE (n=45)	Controls (n=45)	P-value
Maternal age (years)	31.7 ± 4.6	30.9 ± 4.8	0.421
BMI (kg/m²)	30.6 ± 3.8	27.9 ± 3.4	**0.001**
Gestational age at recruitment (weeks)	12.2 ± 0.7	12.1 ± 0.8	0.573

Gravidity	2.6 ± 1.1	2.4 ± 1.0	0.352
Parity	1.2 ± 0.9	1.3 ± 0.8	0.618
Urban residence	28 (62.2%)	30 (66.7%)	0.661
Rural residence	17 (37.8%)	15 (33.3%)	

Routine Laboratory Findings

Significant laboratory differences between the research groups were shown by the study. The amounts of AST and ALT were considerably greater in women who later experienced early-onset preeclampsia ($P < 0.001$ for all comparisons).

Table 2: Routine Laboratory Findings

Variable	EOPE	Controls	P-value
AST (U/L)	34.5 ± 9.8	22.8 ± 6.5	<0.001
ALT (U/L)	29.4 ± 8.3	18.5 ± 5.7	<0.001

Serum Netrin-1 Concentration

In comparison to normotensive pregnant controls, the study showed that women who later had early-onset preeclampsia had considerably lower serum Netrin-1 concentrations during the first trimester. There was a highly significant difference ($P < 0.001$) between the mean serum Netrin-1 concentration in cases and controls, which was 286.4 ± 71.8 pg/mL and 468.9 ± 84.6 pg/mL, respectively.

Table 4. 5: Comparison of Serum Netrin-1 Concentrations

Variable	EOPE	Controls	P-value
Serum Netrin-1 (pg/mL)	286.4 ± 71.8	468.9 ± 84.6	<0.001

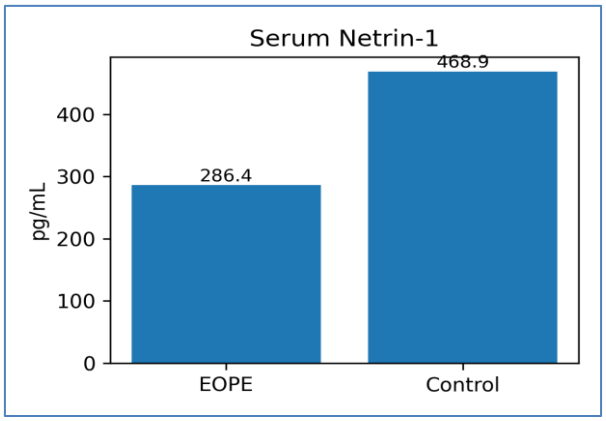

Figure 1: Comparison of Serum Netrin-1 Concentrations

DISCUSSION

In comparison to normotensive pregnant controls, the current investigation showed notable changes in routine laboratory measures in women who later developed early-onset preeclampsia. While hemoglobin concentration only slightly but statistically significantly decreased, women who had EOPE had significantly lower platelet counts along with significantly higher serum creatinine, AST, and ALT concentrations. These results are in line with the existing understanding that placental malfunction leads to extensive maternal endothelial injury, microvascular inflammation, coagulation activation, and organ dysfunction. They also illustrate the multisystem nature of early-onset preeclampsia [11,12].

The main discovery of this study was that women who later experienced early-onset preeclampsia had significantly lower first-trimester serum Netrin-1 concentrations. This finding supports the theory that Netrin-1 plays a role in early placental development and angiogenic control and implies that disruptions in Netrin-1 signaling occur long before the clinical start of hypertension.

Originally discovered as an axonal guidance protein, Netrin-1 is now understood to be a crucial regulator of angiogenesis, trophoblast invasion, endothelial migration, vascular remodeling, and inflammatory regulation (30–33). According to experimental research, Netrin-1 activates DCC receptors to promote endothelial cell proliferation while preserving endothelium survival and vascular stability (12,13). Additionally, Xie et al. (14) demonstrated that in experimental animal models, Netrin-1 enhances vascular growth and promotes placental angiogenesis, while inhibition of Netrin-1 led to decreased placental vascularization and impaired endothelial proliferation. Similarly, Dakouane-Giudicelli et al. (15) showed that Netrin proteins are crucial for controlling placental angiogenesis in the early stages of pregnancy..

The current results are highly consistent with the prospective study conducted by Sert et al. (4), who initially showed that women who subsequently suffered early-onset preeclampsia had considerably lower levels of maternal serum Netrin-1 assessed during the first trimester. They came to the conclusion that serum Netrin-1 might be a useful early biomarker for detecting high-risk women before symptoms develop. Similarly, in pregnancies complicated by preeclampsia, Çekmez et al. (16) found dramatically changed maternal serum Netrin-1 concentrations and proposed that Netrin-1 represents placental endothelial dysfunction. More recently, Berenji et al. (17) showed that the diagnostic performance for early preeclampsia was significantly enhanced when serum Netrin-1 and urinary renal injury molecule-1 were combined.

This evidence has been strengthened by recent research. According to Gothwal et al. (18), when combined with urine KIM-1, serum Netrin-1 offers exceptional discriminatory performance for identifying and classifying the severity of preeclampsia. In a similar vein, Gharib et al. (19) showed that maternal serum Netrin-1 could be a useful biomarker for diagnosing preeclamptic women. Further research on maternal and umbilical cord serum Netrin-1 was conducted by Demirci et al. (20), who found significant correlations between maternal Netrin-1 concentrations, placental function, and fetal fate.

CONCLUSIONS

Pregnant women who later developed early-onset preeclampsia had significantly lower serum Netrin-1 concentrations during the first trimester compared to normotensive pregnant controls. Additionally, women who later developed early-onset preeclampsia had significantly higher frequencies of prior miscarriage, prior preeclampsia, and positive family histories of hypertension and preeclampsia, supporting the role of maternal obstetric and genetic risk factors in the development of the disease..

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