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Elabela is a reliable biomarker for predicting early onset preeclampsia: A comparative study

Amer Ali E *et al*. Prediction of preeclampsia

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Abstract

BACKGROUND

Preeclampsia (PE) is a multisystemic metabolic disease with an undetermined etiology. PE is a worldwide cause of maternal and perinatal morbidity, subdivided into early (EoPE) and late-onset (LoPE) according to 34 wk of gestation as a divider. Many researchers investigated biomarkers for predicting PE to halt its consequences on the feto-maternal outcome. Elabela (Ela) is a newly discovered peptide hormone that was implicated in PE pathogenesis. Earlier rodent studies discussed Ela's role in controlling blood pressure. Moreover, Ela deficiency was associated with PE development.

AIM

To test whether plasma Ela could serve as a reliable marker for predicting PE based on the time of onset (EoPE *vs* LoPE) compared to age and body mass matched healthy controls since no definitive treatment exists for PE but to terminate a pregnancy.

METHODS

This case-control study recruited (n = 90) pregnant who fulfilled inclusion criteria; they were allocated into three groups: EoPE (30/90) (< 34 wk of gestation); LoPE (30/90) (≥ 34 wk of gestation); and healthy pregnant (30/90). Demographic criteria; biochemical, hematological, and maternal plasma Ela levels were recorded for comparison.

RESULTS

Serum Ela was significantly reduced in EoPE compared to LoPE and healthy controls (P = 0.0023). The correlation confirmed a strong inverse relationship with mean atrial blood pressure (r = -0.7, P < 0.001), while gestational age and platelets count showed a moderate correlation with (r = 0.4 with P < 0.0001). No correlation was confirmed between the body mass index (BMI) and urine albumin. The predictive ability of 25 centile serum Ela had an Odds ratio of 5.21, 95% confidence interval (1.28, 21.24), P = 0.02 for predicting EoPE. The receiver operator characteristic curve defined the Ela cutoff value at > 9.156 with 96.7% and 93.3% sensitivity and specificity, P < 0.0001 in predicting EoPE.

CONCLUSION

A strong correlation of serum Ela with PE parameters with excellent sensitivity and specificity in distinguishing EoPE independent of the BMI, age, and blood pressure which makes Ela a recommendable marker in screening. Further research is warranted to explore prognostic and therapeutic applications for Ela in PE.

Key Words: Early onset preeclampsia; Late-onset preeclampsia; Prediction; Elabela; Preeclampsia; Pregnant women

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Core Tip: Preeclampsia (PE) is a worldwide cause of increased maternal and perinatal morbidity; PE is divided into early-onset and late-onset subtypes. The precise pathophysiology of PE is obscured, and currently no treatment exists but to terminate pregnancy. Several researches seek a reliable biomarker to anticipate PE to mitigate its negative effects. Elabela (Ela), a recently discovered peptide hormone secreted by the fetus and human placenta; animal studies confirmed Ela's critical role in maintaining

blood pressure; its deficiency was linked to elevated blood pressure. The purpose of this study was to evaluate the accuracy of Ela in predicting PE based on the time of occurrence.

INTRODUCTION

Preeclampsia (PE), a pregnancy-specific syndrome that increases feto-maternal morbidity and mortality, continues to fascinate scientists[1]. Despite the tremendous advance in the medical field, there is no definitive treatment for this enigmatic syndrome but to terminate the pregnancy. Scientists agree that PE is a 2-stage syndrome. Stage 1, in which defective trophoblast invasion and failure to model placental spiral vessels trigger placental hypoxia, eventually leading to diffuse inflammatory response and vascular endothelial dysfunction within the maternal circulation, is stage 2[2].

A growing body of research was directed to understand the pathophysiology of PE phenotypes; early onset (EoPE) and late-onset (LoPE) are differentiated by gestational age of < 34 wk and > 34 wk, respectively. Furthermore, each type seems to have a different etiology, pathophysiology, and prognosis[3]. The primary issue in PE cases is a placental injury the more significant the placental insult, the graver its consequence. EoPE is a PE phenotype that is less common than LoPE (15% *vs* 80%); it presents higher materno-fetal morbidity in addition to an increased lifetime risk of cardiovascular diseases (CVD). Therefore, many researchers have addressed EoPE to halt its near and long complications and seek reliable prediction biomarkers or preventive interventions like Aspirin therapy[4,5].

Elabela (Ela), a recently discovered peptide hormone (also called Apela/Toddler) is a molecule composed of thirty-two amino acids. It's an endogenous ligand for apelin (APJ), a G-protein receptor[6,7].

There is a diverse expression of APJ receptors in many human tissues, and during pregnancy, it is secreted by the fetus and human placenta. Ela has a series of functions in embryonic life; it promotes skeletal development renewal of embryonic stem cells;

inhibits renal remodeling, angiogenesis, and vascular morphogenesis in embryonic life[8]. In addition, the Ela-APJ system has an essential role in fetal cardiovascular development. It can lower the vascular tone by direct vasodilatory action on the aorta, lowering blood pressure[9].

Early animal studies confirm the vital role of Ela in controlling blood pressure rates, and its deficiency triggered PE development and various congenital disabilities in the offspring. However, human studies presented inconsistent and sometimes conflicting results about its role in PE[10]. This study aimed to examine the reliability of Ela in predicting PE based on time of occurrence (EoPE *vs* LoPE) to alleviate PE-related morbidity.

MATERIALS AND METHODS

Study type and setting

A case-control study was conducted in the University Hospital, a tertiary center in Baghdad/Iraq, from December 2020 to October 2021. The ethics committee of Mustansiriyah University issued the study approval IRB dated (IRB 126 on Nov 25, 2020). Our hospital receives hundreds of patients in many specialties; the maternity wards receive 150-300 cases per month. We sequentially recruited (90) pregnant who were aged and body mass index (BMI) matched. All pregnant gave written consent prior to enrollment; the declaration of Helsinki was followed. Cases that satisfied the study inclusion criteria were grouped into 3 main groups, Early onset PE (EoPE) 30/90; Late-onset PE (LoPE) 30/90 and healthy controls 30/90. PE was defined as newly diagnosed hypertension after twenty weeks of pregnancy in a previously normotensive pregnant with /or without proteinuria. In the absence of proteinuria, PE is defined as hypertension that leads to end-organ damage. Early-onset PE was less than 34 wk; Late-onset PE was more than 34 wk[11].

Inclusion criteria

As follows: (1) Primigravida; age range 18-35 years pregnant with a singleton pregnancy with reliable dating; calculated by LMP and early pregnancy scanning; (2) pregnant should not start antihypertensive drugs; and (3) uneventful medical and surgical history.

Exclusion criteria

As follows: (1) Multiparty, multiple pregnancies, abnormal fetuses, and those with fetal growth restriction; (2) pregnant with a BMI > 30 kg/m^2, age < 18 years or > 35 years; and (3) past medical history of chronic hypertension, diabetes, thyroid, liver, and renal disease.

After a detailed history and clinical examination, which included measuring the blood pressure by sphygmomanometer in rest 4-h apart and measuring BMI. Overnight fast aspiration was made to 10 ccs of venous blood, which was sent for: (1) Complete blood counts, including hemoglobin and platelets; (2) biochemical parameters, including[aspartate aminotransferase (AST), alanine transaminase (ALT), urea, and creatinine; (3) after centrifuging the blood at 3000 rpm/min for 15 min, the sera were refrigerated to -80 °C to analyze Ela later. The estimation was made by the Human Ela ELISA Kit (Cat. No. MBS 3803412) according to the manufacturer's protocol; and (4) urinalysis for albuminuria.

Sample size calculation

It was achieved based on the following formulae[12]. *r* = Stands for the ratio of control to cases, in our study, equal to 2. *P** = denotes the average proportion exposed = proportion of exposed cases + proportion of control exposed /2. In our study the p*= 0.26 + 0.10/2 = 0.36/2 = 0.18; P1-P2 = different in proportion expected based on previous studies. P1 = proportion in cases, P2 = proportion in control. Zβ is the standard normal variant, and it is 0.84 for 80% power of the study. Zα/2 is the standard normal variant, and it is 1.96 at *P* = 0.05 value significance. Sample size = *r* + 1 (p*)(1-

p*)(Zβ + Zα/2)^2 /r (p1- p2)^2 = 2 + 1 (0.18) (1-0.18) (0.84 + 1.96) 2/2 (0.19-0.03)^2 = 3*0.18*0.82 *7.84/2*0.0256 = 70. So the sample size is 70, and we collect 90 participants.

Statistical analysis

The Kolmogorov-Smirnov test checked the data normality. The expression for continuous data was as mean ± SD. ANOVA and Student's *t*-test were used to compare different means when appropriate. Through the use of Pearson correlation analysis, the association between several PE indicators and Ela was evaluated. The correlation was interpreted as weak if *r* is equal to (0.2-0.4), moderate if *r* is equal to (0.4-0.6), strong if *r* is equal to (0.6-0.8), and very strong if *r* is equal to (0.8-1.0). Analysis of covariance (ANCOVA) was used to explore the impact of different PE parameters (taken as independent factors) on serum Ela levels taken as a dependent variable. The Odds ratio (OR), 95% confidence interval (95%CI), and respective *P* value for 25 centiles of serum Ela was tested as a predictive marker in early, late-onset PE and healthy controls. Finally, the receiver operator characteristic curve (ROC) calculated serum Ela cutoff value associated with the highest sensitivity, specificity, and area under the curve (AUC) in predicting early onset PE. Significance was set at a *P* value less than 0.05. All tests were conducted by the SPSS program (version 22.0)[13].

RESULTS

The analysis showed significant differences in all the study variables except for maternal age 26.53 years ± 1.18 years, 28.67 years ± 0.99 years, and 28.33 years ± 1.34 years for the healthy controls, EoPE and LoPE respectively. BMI and blood urea showed insignificant differences across the three groups. Serum Ela scored the highest level among healthy controls, followed by late PE cases and early onset PE highlighted in Table 1 and Figure 1, respectively.

Ela correlation *vs* all study parameters was presented in Table 2; the strongest correlation was for SBP, MAP, and DBP with (*r* = -0.80, -0.70, and -0.64, *P* < 0.0001), respectively. Gestational age and platelets count showed a moderate correlation with (*r*

= 0.44 and 0.48, $P < 0.0001$). None of the BMI, AST, Urea, and albumin in urine was significant. A three-dimensional figure highlighted the correlation of serum Ela concerning gestational age and degree of hypertension in Figure 2.

ANCOVA in Table 3 confirmed that none of the study variables had an impact on serum Ela as P value was > 0.05. In Table 4, the Odds ratio and 95%CI were tested to evaluate the predictive power of 25 centile serum Ela showed the highest Odds for predicting early onset PE with OR of 5.21, 95%CI (1.28, 21.24), $P = 0.02$. The ROC curve defined the Ela cutoff value at > 9.156 with 96.7%, 93.3%, sensitivity and specificity, and $P < 0.0001$ in predicting early onset PE, Figure 3.

DISCUSSION

Analysis showed a significant reduction of serum Ela in EoPE compared to LoPE and healthy controls. Ela correlated inversely and strongly with mean atrial blood pressure and moderately and positively with gestational age and platelet count. Ela did not correlate with BMI and urine albumin. None of the study variables impacted serum Ela levels. A 25-centile serum Ela had a significant Odds ratio for predicting EoPE.

In accordance with our result, Wang *et al*[14] confirmed a meaningful reduction of Ela concentration among EoPE *vs* healthy pregnant.

Conversely, Pritchard *et al*[15] examined Ela levels in healthy controls *vs* PE cases in addition to a subgroup analysis in PE cases below 34 wk of gestation *vs* matched age controls. Their result shows no statistical differences for both comparisons. Since earlier animal models support Ela's role in PE pathogenesis, deficient rats in Ela had impaired placental and fetal development. The authors proposed that Ela levels are of no value once PE is clinically manifested[15]. Likewise, Huanga study did not recommend Ela levels in predicting gestational hypertension by screening pregnant in the first and second-trimester[16].

Panaitescu *et al*[17] declared higher Ela levels in PE (LoPE and EoPE) *vs* healthy pregnant ($P = 0.32$, < 0.001) at a gestational age of 37 and 30 wk, respectively. Different sampling times might explain the difference in our results. Still, serum Ela at EoPE was

lower than LoPE; they attributed this to the different pathophysiology of the two subgroups of PE. Moreover, they discussed the long-term CVD risk among EoPE, which underlies insufficient protection by low Ela levels during pregnancy[18].

Deniz *et al*[19] investigated Ela serum levels among PE (36 wk), healthy pregnancy (38 wk), and their neonates' blood. Ela was significantly low among PE cases, and that reduction was positively linked to PE severity in line with Ho *et al*[20] study. Furthermore, Deniz *et al*[19] correlated maternal Ela to low birth weight in the newborn. Reduced levels of Ela among PE cases caused insufficient placenta angiogenesis, which consequently reduced birth weight[21]. Georgiadou *et al*[22] tested Ela at 11-14 wk of pregnancy as a predictive marker of PE. Normal weight pregnant destined to have PE showed meaningfully reduced levels. However, Ela showed a wide variance in affected cases; moreover, it was BMI dependent, for it was not recommended for screening. However, a potential therapeutic avenue for Ela was proposed because it promotes extra villous trophoblastic differentiation.

Ela plays a crucial role in early developing fetuses and placenta by increasing trophoblast penetration into the uterine wall and angiogenic sprouting[8], reinforcing Ela's role in preventing EoPE, a PE subtype caused by under-penetration of placental vessels. Scientists agree that PE is a 2-stage syndrome. First, defective trophoblast triggers placental hypoxia; this is (stage 1). Once PE is clinically evident around the 20th week of gestation (stage 2), the placenta will secret placental factors and cytokines to overcome reduced fetal blood supply and trigger a systemic maternal inflammatory cascade, a PE hallmark[23]. Apelin emerges later to promote fetal angiogenesis, placental vessel tone, and energy homeostasis[24].

Ela levels are high early in pregnancy and tend to decrease around 34 wk to be replaced by Apelin, which explains the difference in Ela's reliability among PE cases[8]. That was highlighted in our result by the three-dimensional figure showing the inverse correlation between serum Ela *vs* mean arterial blood pressure and a positive correlation with gestational age; it can be noted that the lowest serum Ela is seen at 27-33 wk, *i.e.*, early onset PE.

Inconsistency in reporting Ela links to Early, late, and normal controls may be due to many factors[25]. First, inconsistency in gestational age at sampling time. Second, the use of different commercial kits. Third, the inclusion of heterogenous BMI participants[26-28]. Although earlier works have examined Ela's role in PE onset, they did not address confounders that might impact Ela levels (proven by ANCOVA test) which forms the current study novelty. Interestingly BMI, gestational age, mean arterial pressure, and platelets count did not affect Ela levels, which added validity to our marker and implied its intimate link to PE pathogenies.

Earlier research discussed an Ela-BMI dependence among normal-weight women in LoPE but not for EoPE; the authors attribute this insignificant to a smaller size sample[21].

Our result highlighted Ela's role in EoP by OR of 5.21, $P = 0.02$; conversely, LoPE had an OR of 1.80 and an insignificant P value. Additionally, the ROC estimated Ela cutoff value at > 9.156 with 96.7%, 93.3%, and $P < 0.0001$ sensitivity and specificity, respectively, in discriminating EoPE.

Many acknowledge PE as a 2-stage syndrome[23]. However, PE's first stage fits with EoPE alongside the mother's long-life risk of cardiovascular disease; Panaitescu *et al*[17] discussed that the CVD risk among EoPE underlies insufficient protection by low Ela levels during pregnancy.

Ela plays a crucial role in early developing fetuses and placenta by increasing trophoblast penetration into the uterine wall and angiogenic, reinforcing Ela's role in preventing EoPE, a PE subtype caused by under-penetration of placental vessels[29].

Qi *et al*[30] declared that Ela levels were markedly low among missed abortion cases *vs* healthy pregnant women, which suggests Ela's critical role in supporting early pregnancy prosperity.

Ela is Apelin's endogenous receptor against; Ela- and Apelin-APJ signaling orchestrates important aspects of placental growth by promoting extra-villous trophoblastic differentiation and invasiveness to the uterus, improving uterine blood supply, decreasing oxidative stress, and suppressing placenta apoptosis. Animal

models support Ela's role in PE pathogenesis. Ela-deficient rats had impaired placental and fetal development[20,31].

On the systemic level, Ela- and Apelin improve the cardiac output by producing nitric oxide that has vasodilatory action on the vasculature. Low Apelin concentrations were reported in cases with high blood pressure due to reduced vascular hemostasis protection[25,32,33].

Ho *et al*[20] discussed that Ela infusion in preeclamptic rates improved hypertension and albuminuria. Yang *et al*[32] reported that exogenous Ela infusion additionally ameliorates pulmonary hypertension by causing pulmonary vessel remodeling in rats.

Study limitation: Being a single center study and the small number of included studies due to scare number of published research. So, the current results need to be verified in large scale multi-centric studies. PE is a syndrome that is affected by race, a parameter we did not address. We hoped to recruit more patients; however COVID-19 pandemic affected many work aspects[34].

Study strengths: The study was well-powered with tight inclusion criteria; it estimated the risk ratio and Ela cutoff value in predicting EoPE with a reliable AUC and high sensitivity and specificity. Furthermore, Ela's independency of gestational age, BMI, and mean arterial pressure, with high specificity and sensitivity, adds more credibility to Ela's prediction power. Moreover, the therapeutic application suggested by earlier researchers may unveil prognostic application in the long run for reducing CVS risk for postpartum women.

CONCLUSION

Ela, a recently discovered peptide hormone, was found to be a reliable marker for screening EoPE independence of BMI, age, and blood pressure. It differentiated EoPE with high sensitivity specificity and a significant area under the curve. Ela's intimate link with predictors of PE opens a therapeutic and preventive avenue for Ela in PE.

ARTICLE HIGHLIGHTS

Research background

Preeclampsia (PE) is a multisystemic disease that can cause problems for both the mother and the baby. It can start early or late, depending on how far along the pregnancy is. Elabela (Ela) is a recently found peptide hormone that was linked to the development of PE. Since the only safe way to treat PE is to end a pregnancy, the goal of this study was to see if plasma Ela could be used as a reliable way to predict PE based on the time of onset.

Research motivation

Endogenous ligand for apelin (APJ) receptors are found in many different parts of the human body, and Ela is produced by the fetus and placenta during pregnancy. Ela has a number of roles in embryonic life. During embryonic life, it stops renal remodeling, angiogenesis, and vascular morphogenesis. Also, the Ela-APJ system is very important for the development of the heart and blood vessels in a fetus. It can lower the tone of the blood vessels by directly relaxing the blood vessels in the aorta. This lowers blood pressure.

Research objectives

To determine the reliability of Ela in predicting PE based on time of incidence early (EoPE) *vs* late (LoPE) in order to reduce PE-related morbidity.

Research methods

In a case-control study, pregnant women were divided into three groups: EoPE (30/90) (34 wk of gestation), LoPE (30/90) (34 wk of gestation), and healthy pregnant (30/90). Demographic criteria were examined, as well as biochemical, hematological and maternal plasma Ela levels.

Research results

Serum Ela was significantly reduced in EoPE compared to LoPE and healthy controls ($P = 0.0023$); Ela had a strong inverse relationship to mean atrial blood pressure ($r = -0.7$, $P < 0.001$), and a moderate correlation with gestational age and platelets count ($r = 0.4$, $P < 0.0001$. The predictive ability of 25 centile serum Ela had an odds ratio of 5.21, 95% confidence interval (1.28, 21.24), $P = 0.02$ for predicting EoPE. Ela's cutoff value (> 9.15) distinguished EoPE with 96.7%, 93.3%, sensitivity and specificity, and $P < 0.0001$.

Research conclusions

Ela is a highly recommended marker in screening due to its high sensitivity and specificity in differentiating EoPE from other conditions such as body mass index, age, and blood pressure.

Research perspectives

Ela's specificity and sensitivity, independent of gestational age, body mass index, and mean arterial pressure, lend credence to Ela's ability to predict. As an added bonus, the therapeutic use proposed by previous researchers may eventually reveal prognostic application for lowering CVS risk in postpartum women. Further study is required to verify its usefulness in clinical settings.

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Figure 1 Showing serum elabela across the study participants. PE: Preeclampsia.

Figure 2 A three-dimensional figures showing the inverse correlation relationship between serum elabela with mean arterial blood pressure and the positive correlation with gestational age. It can be noted seen that the lowest serum elabela is seen at 27-33 wk; early onset preeclampsia. GA: Gestational age; MAP: Mean arterial blood pressure.

Figure 3 The receiver operator characteristic curve for serum elabela as a diagnostic marker in early *vs* late pre-eclampsia cases. Area under the curve = 0.986, $P < 0.0001$.

Table 1 Demographic criteria of the study participants (*n* = 90)

Variable	Control (*n* = 30), mean ± SD	*P* value	Late-PE (*n* = 30), mean ± SD	Early-PE (*n* = 30), mean ± SD	*P* value
Age (yr)	26.53 ± 1.18	0.39 NS	28.33 ± 1.34	28.67 ± 0.99	0.39 NS
BMI (kg/m^2)	24.93 ± 0.34	0.77 NS	26.19 ± 0.29	26.96 ± 3.42	0.77 NS
Gestational age (wk)	34.93 ± 0.20^b	0.0001	36.30 ± 0.19^a	30.70 ± 0.34^c	0.0001
Systolic BP (mmHg)	106.00 ± 1.48^b	0.0001	152.33 ± 1.71^a	152.33 ± 1.64^a	0.0001
Diastolic BP (mmHg)	82.67 ± 1.85^b	0.0001	103.00 ± 1.80^a	102.66 ± 1.79^a	0.0001
Mean arterial BP (MAP)	90.44 ± 1.21^b	0.0001	119.44 ±1.69^a	119.22 ± 1.65^a	0.0001
AST (IU/L)	23.09 ± 1.07^b	0.05	34.05 ± 5.98^a	27.25 ± 1.41^{ab}	0.05
ALT (IU/L)	17.82 ± 0.88^b	0.0001	30.06 ± 2.75^a	25.17 ± 1.45^a	0.0001
Urea (mg/dL)	25.01 ± 1.32	0.84 NS	25.93 ± 1.56	26.21 ± 1.64	0.84 NS
Creatinine (mg/dl)	0.665 ± 0.02^b	0.0001	0.759 ± 0.02^a	0.759 ± 0.02^a	0.0001
Albumin in urine*	-	0.19 NS	460.50 ± 47.06	381.66 ± 35.43	0.19 NS
Hemoglobin (g/dL)	12.68 ± 0.19^a	0.0001	11.69 ± 0.19^b	12.02 ± 0.21^b	0.0001
Platelets counts × 10^9 L	287.60 ± 11.23^a	0.0006	182.83 ± 10.48^b	204.90 ± 10.70^b	0.0006
Elabela (pg/mL)	18.36 ± 0.43^a	0.002	11.05 ± 0.22^b	7.61 ± 0.19^c	0.002

[a,b,c]The *P* value represents the difference among the three groups. To show which group has the highest difference, we use letters[a,b] and[c] if the three groups have no difference between then the letter used is the same. While if there is a difference among the three groups, the group that has the highest difference got the letter a and so downward.

BMI: Body mass index; BP: Blood pressure; AST: Aspartate aminotransferase; ALT: Alanine transaminase.

Table 2 Pearson correlation of elabela *vs* all study participants' cases (*n* = 90)

Variable	Pearson correlation	*P* value
BMI (kg/m^2)	-0.090	0.4200
Gestational age (wk)	0.440	< 0.0001
Systolic BP (mmHg)	-0.800	< 0.0001
Diastolic BP (mmHg)	-0.640	< 0.0001
Mean arterial BP	-0.700	< 0.0001
AST (IU/L)	-0.110	0.2000
ALT (IU/L)	0.200	< 0.0030
Urea (mg/dL)	0.004	0.9700
Creatinine (mg/dL)	-0.310	< 0.0030
Albumin in urine	0.160	0.2000
Hemoglobin (g/dL)	0.290	< 0.0040
Platelets count (× 10^9/L)	0.480	< 0.0001

MI: Body mass index; BP: Blood pressure; AST: Aspartate aminotransferase; ALT: Alanine transaminase.

Table 3 Analysis of covariance

Variable	F-ratio	*P* value
Body mass index	0.120	0.74
Gestational age	0.990	0.32
Mean arterial pressure	0.001	0.97
Platelets count	0.020	0.65

Elabela was taken as independent factor versus the study parameters taken as dependent factors; none of the factors had an impact on serum elabela.

Table 4 Demonstrating the odds ratio, 95% confidence interval and respective *P* value for serum elabela in early, late-onset pre-eclampsia cases, and healthy controls with regard to serum elabela less 25 centiles

Groups	Odds ratio	95%CI	*P* value
Early-onset PE	5.21	1.28 to 21.24	0.02
Late-onset PE	1.80	0.39 to 8.32	0.45
Controls	Reference group		

PE: Preeclampsia; 95%CI: 95% confidence interval.

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