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ORIGINAL ARTICLE

ELABELA as a Predictive Biomarker in Pre-Eclampsia: A Comparative Study of Early-Onset and Late-Onset Variants

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Abstract

Background: Significant maternal and perinatal morbidity is associated with pre-eclampsia (PE), a multisystem hypertension disease of pregnancy. The endogenous ligand for the apelin receptor (APJ) and 32-amino acid peptide hormone ELABELA (ELA) is essential for both placental development and cardiovascular homeostasis. Serum ELABELA is assessed in this study as a predictive biomarker that distinguishes between early-onset and late-onset pre-eclampsia. **Methods:** Over the course of a year, from January 2022 to January 2023, an analytical cross-sectional study was carried out at Madras Medical College in Chennai. Ninety individuals were recruited: thirty with early-onset PE (EoPE, <34 weeks), thirty with late-onset PE (LoPE, ≥34 weeks), and thirty normotensive pregnant women (controls). Sandwich ELISA was used to measure serum ELABELA. Additional parameters were total protein, random blood glucose, liver function tests, and renal function tests. SPSS v27.0 was used for statistical analysis, and the Kruskal-Wallis and Spearman correlation tests were used ($p < 0.05$ was deemed significant). **Results:** EoPE (7.0 ± 0.584 pg/mL) and LoPE (11.5 ± 0.290 pg/mL) had significantly lower mean serum ELABELA than controls (18.0 ± 0.585 pg/mL) ($p = <0.001$). Serum creatinine ($r = –0.695$) and urea ($r = –0.447$) showed significant negative associations with ELABELA, while total protein ($r = +0.557$) showed a significant positive relationship.
Conclusion: Serum ELABELA is downregulated in both pre-eclampsia phenotypes, with early-onset illness exhibiting a more pronounced suppression. These findings suggest that ELABELA is a promising circulating biomarker that may aid in the prediction and phenotypic categorisation of pre-eclampsia, warranting further evaluation in longitudinal studies.

Keywords: Pre-eclampsia, ELABELA, Apelin receptor, Biomarker, Early-onset pre-eclampsia, Late-onset pre-eclampsia, Hypertensive disorders of pregnancy

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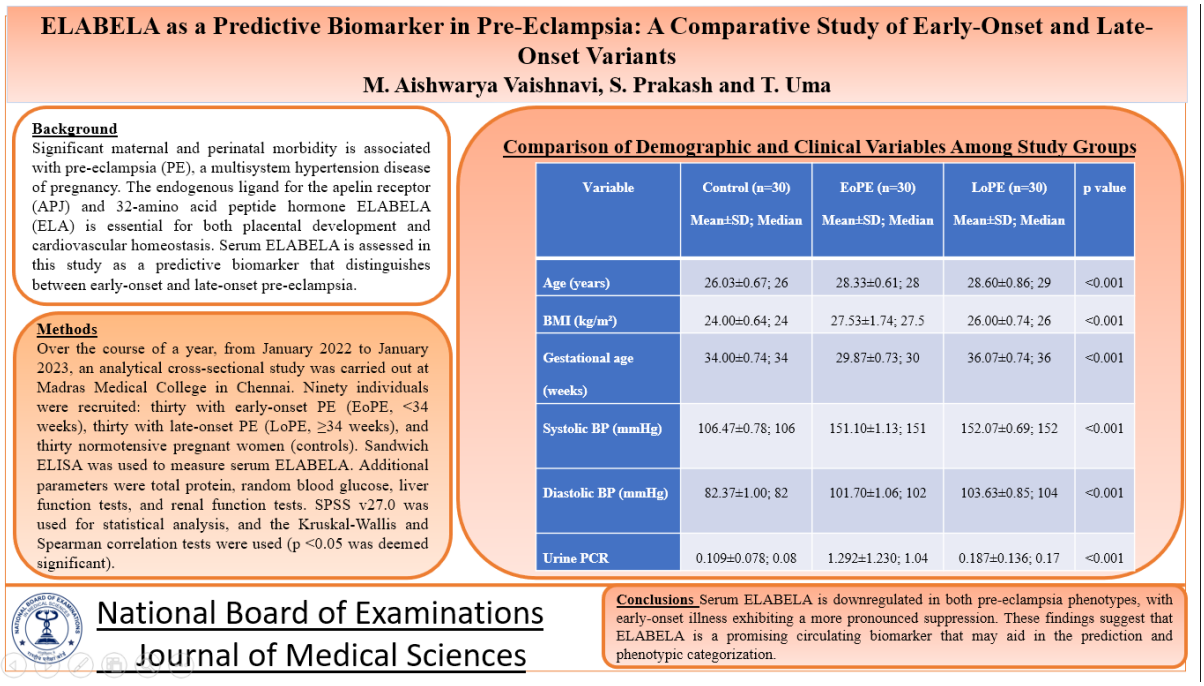
Graphical Abstract



Introduction

A pregnancy-specific condition known as pre-eclampsia (PE) is characterised by new-onset hypertension (≥140/90 mmHg) after 20 weeks of gestation, together with uteroplacental insufficiency or maternal organ dysfunction. It continues to be a major cause of maternal and perinatal morbidity and mortality, accounting for 14% of maternal deaths worldwide, and complicates roughly 2–7% of pregnancies internationally [1]. The urgent need for trustworthy prognostic biomarkers and a better comprehension of its pathogenesis is highlighted by the fact that, despite significant advancements in perinatal care, the only effective treatment is still delivery [2].

According to the two-stage concept of PE, the failure of spiral artery remodelling and deficient trophoblast invasion cause placental hypoperfusion (stage 1), which in turn causes systemic maternal endothelial dysfunction (stage 2). The pathophysiology, severity, and prognosis of early-onset (EoPE; delivery before 34 weeks) and late-onset (LoPE; delivery at or after 34 weeks) variants of PE differ significantly. LoPE is more often linked to maternal metabolic and cardiovascular comorbidities; EoPE is characterised by severe placental malperfusion, foetal development restriction, and increased cardiovascular risk in later life [3].

The 32-amino acid peptide hormone ELABELA (ELA), also known as Apela or Toddler, serves as an endogenous ligand for the G protein-coupled apelin receptor (APJ). Villous cytotrophoblasts and syncytiotrophoblasts express ELA, which has angiogenic, anti-apoptotic, vasodilatory, and cardiorenal regulatory effects. Binding of ELA to APJ activates downstream PI3K/Akt-eNOS signalling, promoting nitric oxide generation, trophoblast invasion, and endothelial function, while disruption of this axis is linked to increased

oxidative stress and impaired vascular homeostasis [18]. Exogenous ELA injection reverses the PE-like phenotype that ELA-knockout animals develop, which includes hypertension, proteinuria, and glomerular endotheliosis. This suggests that ELA plays a crucial protective function in preserving maternal-placental vascular homeostasis [4-6].

Human data on ELA in PE is still scarce and occasionally contradictory. In order to establish ELABELA as a phenotype-specific predictive biomarker in PE, the current study was planned to detect serum ELABELA levels in EoPE, LoPE, and normotensive controls and to assess its correlations with recognised biochemical indicators.

Materials and Methods

Study Design and Setting

The Institute of Biochemistry and the Institute of Obstetrics and Gynaecology, Madras Medical College, and Rajiv Gandhi Government General Hospital, Chennai, were the sites of this one-year (January 2022–January 2023) analytical cross-sectional hospital-based study. Before the event began, the Institutional Ethics Committee gave its approval, and each participant provided signed informed consent.

Study Population and Grouping

Ninety pregnant women between the ages of twenty and forty were divided into three groups of thirty: Pre-eclampsia with gestational age less than 34 weeks is classified as Group A (EoPE); pre-eclampsia with gestational age greater than 34 weeks is classified as Group B (LoPE); Pregnant women with normotension who were matched for gestational age and maternal age made up Group C (Control).

The ISSHP criteria (new-onset hypertension ≥140/90 mmHg after 20 weeks with proteinuria or organ failure) were used to diagnose PE [7]. Only women with singleton pregnancies were included in the study. Pre-existing chronic hypertension, diabetes mellitus, hyperuricaemia, renal illness, cardiovascular disease, and multiple (twin or higher-order) pregnancies were among the exclusion criteria. A formal a priori sample size calculation was not performed; a convenience sample of 30 participants per group was recruited over the one-year study period, a group size comparable to that used in other analytical studies of ELABELA in early- and late-onset pre-eclampsia [8].

Sample Collection and Laboratory Analysis

Under aseptic conditions, five millilitres of fasting venous blood were drawn from the antecubital vein. Centrifugation was used to separate the serum (3000 RPM, 15 minutes). For ELABELA estimate, one millilitre of serum was kept at -20°C. On the same day, routine biochemical measures were examined. To estimate the protein-creatinine ratio (PCR), spot urine was collected.

A commercially available sandwich ELISA kit (optical density read at 450 nm; standard curve range 100–3200 pg/mL) was used to quantify serum ELABELA. Random blood glucose (Hexokinase), urea (urease-GLDH kinetic method), creatinine (kinetic Jaffé method, IDMS-traceable), uric acid (uricase-PAP), AST and ALT (modified IFCC method), and total protein (Biuret method) were among the additional assays. Urine creatinine was measured

using the Jaffé method and urine protein using the sulphosalicylic acid method.

Statistical Analysis

Data were analysed using SPSS version 27.0. Results are expressed as mean ± SD and median. Between-group comparisons were performed using the Kruskal-Wallis test. Spearman rank correlation was used to assess relationships between serum ELABELA and biochemical variables. A p-value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

There was a statistically significant age difference across the groups, with the mean age of participants being 28.33 years in EoPE, 28.60 years in LoPE, and 26.03 years in controls (p=<0.001). EoPE had the highest mean BMI (27.53 kg/m^2), followed by LoPE (26.00 kg/m2) and controls (24.00 kg/m2) (p = <0.001). For EoPE and LoPE, the mean gestational age was 29.87 and 36.07 weeks, respectively (p = <0.001). Key clinical and demographic factors are summarised in Table 1.

Table 1. Comparison of Demographic and Clinical Variables Among Study Groups

Variable	Control (n=30) Mean±SD; Median	EoPE (n=30) Mean±SD; Median	LoPE (n=30) Mean±SD; Median	p value
Age (years)	26.03±0.67; 26	28.33±0.61; 28	28.60±0.86; 29	<0.001
BMI (kg/m²)	24.00±0.64; 24	27.53±1.74; 27.5	26.00±0.74; 26	<0.001
Gestational age (weeks)	34.00±0.74; 34	29.87±0.73; 30	36.07±0.74; 36	<0.001
Systolic BP (mmHg)	106.47±0.78; 106	151.10±1.13; 151	152.07±0.69; 152	<0.001
Diastolic BP (mmHg)	82.37±1.00; 82	101.70±1.06; 102	103.63±0.85; 104	<0.001
Urine PCR	0.109±0.078; 0.08	1.292±1.230; 1.04	0.187±0.136; 0.17	<0.001

EoPE = Early-onset pre-eclampsia; LoPE = Late-onset pre-eclampsia; BP = blood pressure; PCR = protein-creatinine ratio. Kruskal-Wallis test.

Biochemical Parameters

Mean random blood glucose was 92.73 mg/dL in EoPE and 107.40 mg/dL in LoPE compared to 87.60 mg/dL in controls (p=<0.001). Liver enzymes (AST and ALT) were considerably higher in both PE groups: in EoPE, AST was 26.57 IU/L and ALT was 24.87 IU/L; in LoPE, AST was 34.47 IU/L and ALT was 30.20 IU/L, compared to 23.53 IU/L and 16.60 IU/L respectively in controls (p=<0.001). Serum urea and creatinine were within normal limits across

all groups, while statistically significant inter-group differences were found. Total protein was considerably reduced in EoPE (5.20 g/dL) compared to controls (6.75 g/dL) and LoPE (6.81 g/dL) (p=<0.001). Table 2 provides the biochemical data.

Table 2. Comparison of Biochemical Parameters Among Study Groups

Parameter	Control	EoPE	LoPE	p value
Random blood glucose (mg/dL)	87.60±4.87	92.73±4.32	107.40±11.92	<0.001
AST (IU/L)	23.53±0.97	26.57±0.86	34.47±2.62	<0.001
ALT (IU/L)	16.60±0.50	24.87±0.73	30.20±1.30	<0.001
Urea (mg/dL)	25.20±0.55	26.00±0.64	25.47±0.94	<0.001
Creatinine (mg/dL)	0.64±0.03	0.75±0.01	0.75±0.02	<0.001
Total protein (g/dL)	6.75±0.13	5.20±0.36	6.81±0.12	<0.001

Values are Mean±SD. Kruskal-Wallis test. EoPE = Early-onset pre-eclampsia; LoPE = Late-onset pre-eclampsia.

Serum ELABELA Levels

In comparison to controls, serum ELABELA was considerably downregulated in both PE groups. In EoPE, LoPE, and controls, the mean serum ELABELA concentration was 7.0 ± 0.584 pg/mL (median 7), 11.5 ± 0.290 pg/mL (median 11.6), and 18.0 ± 0.585 pg/mL (median 18) (p=<0.001). A gradient of suppression with more severe placental illness was indicated by the decreased ELABELA levels in EoPE compared to LoPE (Table 3).

Table 3. Comparison of Serum ELABELA Among Study Groups

Variable	Control (n=30)	EoPE (n=30)	LoPE (n=30)	p value
Serum ELABELA (pg/mL) Mean ± SD; Median	18.0 ± 0.585; 18	7.0 ± 0.584; 7	11.5 ± 0.290; 11.6	<0.001

Kruskal-Wallis test. EoPE = Early-onset pre-eclampsia; LoPE = Late-onset pre-eclampsia.

Correlation of Serum ELABELA with Biochemical Parameters

Serum ELABELA showed a medium negative correlation with urea (r = –0.447, p <0.001) and a significant large negative correlation with creatinine (r = –0.695, p <0.001), according to Spearman correlation analysis. The whole correlation matrix is shown in Table 4.

Table 4. Spearman Correlation of Serum ELABELA with Biochemical Variables (n=90)

Biochemical Variable	Correlation Coefficient (r)	p value
Serum creatinine	–0.695	<0.001
Serum urea	–0.447	<0.001
Total protein	+0.557	<0.001

Correlation significant at 0.01 level (2-tailed).

Discussion

Serum ELABELA is markedly downregulated in both early-onset and late-onset pre-eclampsia, with the degree of suppression being more noticeable in EoPE, according to this study. These results support and add to the increasing amount of data linking the ELA-APJ axis to the pathophysiology of pregnancy-related hypertension diseases.

Placental angiogenesis, trophoblast invasion, nitric oxide-mediated vasodilatation, and cardiorenal fluid balance are all significantly influenced by the ELA-APJ system. Through paracrine effects on foetal endothelial cells and systemic effects on maternal vasculature, ELA—which is mostly expressed in villous cytotrophoblasts and syncytiotrophoblasts—promotes spiral artery remodelling and placental perfusion. Proteinuria, glomerular endotheliosis, and systemic hypertension are PE-like characteristics that appear in ELA-knockout mice and are reversible with exogenous ELA injection [6].

The different pathophysiology of the two phenotypes is consistent with our observation that EoPE had lower ELABELA than LoPE. Early placental malperfusion and more severe placental insufficiency, when disruption of ELA-mediated trophoblast invasion and angiogenesis would be most prominent, are the main causes of EoPE, and these differences are compounded by distinct patterns of innate immune activation reported between early- and late-onset disease [9]. According to Panaitescu et al., EoPE had lower ELABELA plasma concentrations than LoPE, which is in line with the higher cardiovascular impairment seen in early-onset illness [10]. This phenotype-specific gradient is corroborated by Amer Ali et al., who reported significantly lower serum Elabela in EoPE than in LoPE and healthy controls, with a cut-off value showing high sensitivity and specificity for distinguishing EoPE [8]. Zhou et al. similarly found reduced ELA levels, together with decreased placental ELA and APJ expression, in late-onset PE, and demonstrated in vitro that ELA promotes trophoblast invasion and proliferation through APJ signalling [11]. Yang et al., using an independent cohort and an immunochromatographic assay, confirmed markedly lower serum ELABELA in late-onset PE compared with normotensive pregnancy [12]. Khan et al. reported a parallel reduction in both apelin and ELABELA in preeclamptic women, suggesting that suppression of the wider apelinergic (apelin-ELA-APJ) axis, rather

than ELABELA alone, may accompany the disorder [13]. Most recently, Wang et al. showed that placental ELA was specifically reduced in early-onset preeclampsia and that silencing ELA impaired trophoblast invasion and migration via the MEK/ERK signalling pathway, providing direct mechanistic support for a phenotype-specific role of ELA in EoPE [14].

These findings are, however, not universal. A systematic review of the human apelinergic axis in preeclampsia by Georgiadou et al. similarly concluded that circulating ELABELA findings in early-onset disease are inconsistent across studies and that late-onset findings remain inconclusive [15]. Ma et al. measured first-trimester (10–14 week) serum ELA in a nested case-control cohort and found levels statistically unchanged between women who later developed gestational hypertension or PE and matched controls [16]. Similarly, Ozgen et al. reported no significant difference in first-trimester ELA between women who subsequently developed late-onset PE and those who remained normotensive [17].

A plausible explanation for this discrepancy is the timing of sampling relative to disease onset: ELABELA suppression may be a downstream consequence of established placental malperfusion and syncytiotrophoblast stress rather than an early antecedent change detectable before clinical disease is manifest. Consistent with this interpretation, studies reporting reduced ELABELA, including the present one, sampled at or after clinical diagnosis of PE, whereas the studies reporting unchanged levels sampled in the first trimester, well before disease onset. Differences in assay methodology (in-house ELISA kits with differing epitope specificity and reference ranges) and population characteristics may also contribute to the discrepant findings, and this should be considered when comparing absolute ELABELA concentrations across studies.

The well-documented glomerular endotheliosis brought on by sFLT1-mediated VEGF antagonism is consistent with the substantial negative association of ELABELA with serum creatinine ($r = –0.695$) and urea ($r = –0.447$), which indicates contemporaneous decline of renal function in pre-eclampsia. Although these correlations reached statistical significance, urea and creatinine values remained within normal clinical reference ranges across all groups; the observed differences are therefore of limited clinical importance and are best interpreted as a subclinical biochemical trend accompanying ELABELA suppression rather than evidence of overt renal impairment. On the other hand, the hypoproteinemia seen in EoPE—possibly as a result of increased urine protein loss and hemodilution—may be reflected in the positive association with total protein ($r = +0.557$), which reflects ELABELA suppression in this group.

Mechanistically, experimental evidence indicates that lower ELA levels may weaken APJ signalling, which can lead to decreased PI3K/Akt-eNOS activity, reduced trophoblast invasion, increased reactive oxygen species (consistent with the broader role of apelin/APJ disruption in vascular oxidative stress [18], impaired nitric oxide generation, and placental hypoxia, all of which are hallmarks of pre-eclampsia. As the present study is cross-sectional in design, it can demonstrate association but not causation; the observed correlations should not be interpreted as

evidence that ELABELA suppression directly causes these downstream changes in this cohort, and the intensity and phenotype of placental injury may, at most, be reflected in rather than caused by the degree of ELA suppression. Longitudinal studies with serial sampling are required to establish temporality and causal direction.

A further point relevant to prediction is the graded pattern seen across the three groups in this study: serum ELABELA fell progressively from controls (18.0 pg/mL) to LoPE (11.5 pg/mL) to EoPE (7.0 pg/mL) (Table 3), tracking the transition from normotensive pregnancy to increasingly severe disease. If this decline also occurs sequentially within the same pregnancy as it moves from a normotensive state toward pre-eclampsia—something only a longitudinal, serially-sampled design can confirm—a falling ELABELA trajectory, rather than a single threshold value, could serve as an antenatal warning sign that pre-eclampsia is developing. This would be consistent with the cut-off-based approach already demonstrated by Amer Ali et al., who showed that a low serum Elabela value predicted EoPE with 96.7% sensitivity and 93.3% specificity (8). These findings suggest that serum ELABELA may have a function in PE as a phenotype-stratifying biomarker. ELABELA may be useful in characterising the degree of vascular and placental damage throughout the PE spectrum, in contrast to sFLT1/PGF, which was mainly developed for early-onset illness prediction and ruling out PE [19]. Before clinical translation, however, validation in larger prospective, multi-centric cohorts with serial measures throughout gestational ages is crucial, alongside evaluation of whether ELABELA-informed risk stratification can meaningfully strengthen existing preventive strategies for pre-eclampsia [20].

Conclusion

In comparison to normotensive pregnancy, serum ELABELA is markedly suppressed in both early-onset and late-onset pre-eclampsia, with the early-onset phenotype showing the largest suppression. ELABELA's integration into the pathophysiological network of PE is seen in its correlation pattern with renal and metabolic markers. These findings support ELABELA as a promising circulating biomarker for the prediction and phenotypic categorisation of pre-eclampsia, though longitudinal studies are required to confirm its predictive value, as a causal or predictive role cannot be firmly established from a cross-sectional design. To ascertain its clinical relevance, more prospective, longitudinal trials with serial ELABELA readings, bigger sample sizes, and first-trimester screening cohorts are necessary.

Limitations

The cross-sectional design of this study prevents temporal assessment of ELABELA throughout gestation; the sample size is small (n=90); figures showing correlations could not be included in this manuscript; and the study was carried out at a single tertiary center in South India, which may limit generalisability.

Statements and Declarations

Ethics Approval

Ethical approval received from the Institutional Ethics Committee of Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

Informed Consent

Written informed consent was obtained from all participants.

Funding

No external funding was received for this study.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contributions

MAV Design of the study, literature search, data acquisition, manuscript writing and review. SP Literature search, Data analysis, Manuscript review and editing. TU Conceptualisation, manuscript review and editing. MAV acted as the corresponding author for this study.

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