Original Article

The Value of Serum Elabela in Preeclamptic Women with and without Fetal Growth Restriction at 34 Weeks of Pregnancy: A Case–Control Study

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Abstract

Background: Reliable screening methods for fetal growth restriction (FGR) are crucial to improve maternal and neonatal outcomes. Preeclampsia (PE) is a specific pregnancy ailment that contributes to FGR. Elabela (Ela), a newly discovered adipokine, was correlated with PE. **Objective:** As a marker of PE, we aimed to examine Ela's role in PE women with and without FGR as a possible screening biomarker at 34 weeks of gestation. **Materials and Methods:** A case–control study started from March 2022 to December 2022 recruited gestational age and body-indexed matched pregnant at 34 weeks into two groups. Healthy controls (55/110) and PE cases (55/110), were further stratified into (15/55) FGR-PE and (40/55) PE-without FGR. *Demographics* (systolic and diastolic blood pressure and body mass index), *biochemical* (creatinine, urea, uric acid, urinalysis, alanine transaminase, and aspartate transaminase), *hematological* (hemoglobin and platelets), and *ultrasonic parameters* [gestational age, fetal weight, umbilical artery pulsatility index (PI), and amniotic fluid index] were compared for both. Maternal serum Ela was checked by an enzyme-linked immunosorbent assay kit. **Results:** Serum Ela was significantly low in FGR-PE (10.02 ± 1.63) cases, followed by PE (11.77 ± 1.02) and healthy controls (17.58 ± 2.72), $P < 0.001$. Ela was significantly inversely correlated with systolic and diastolic blood pressures (r = -0.41, -0.50), respectively; moreover, it was positively and significantly linked to fetal weight and umbilical artery PI (r = 0.42, 0.35), respectively. **Conclusion:** Strong and significant correlations of serum Ela with FGR markers at high sensitivity 87% and specificity82%, $P < 0.001$ in PE moms make it a reliable screening for FGR in PE cases. Future studies are warranted for possible therapeutic and prognostic applications in practice.

Keywords: Fetal growth restriction, fetal weight, preeclampsia, pulsatility index, serum Elabela

Introduction

Screening preeclamptic mothers for fetal growth restriction (FGR) is the highest priority due to the possibility of adverse outcomes for both mother and child.[1] FGR is the condition when the embryo does not grow normally to reach its genetic potential, resulting in a smaller-than-expected birth weight reference established for corresponding gestational weeks.[2]

Preeclampsia (PE) is a complication of pregnancy characterized by elevated blood pressure and organ injury, typically occurring after 20 weeks of gestation. Numerous factors contribute to the pathogenesis of FGR; the primary etiology is placental insufficiency, which is characterized by reduced blood flow in both the uteroplacental and umbilical cord.[3,4]

FGR is one of the PE-related complications; earlier screening of a growth-retarded fetus is crucial because it enables closer monitoring and timely interventions that may improve maternal outcomes by reducing eclamptic fits

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and operative intervention and fetal outcomes, reduction of stillbirth, neonatal morbidity, and long-term developmental delay.[5,6] Numerous screening methods have been advocated to screen for FGR, including *Physical screening* via serial ultrasonic examination and/or Doppler study.[7]

The biochemical screening, which involves testing maternal biomarkers, provided a more rapid FGR diagnosis, but inconsistency in test duration, low predictive values, and a lack of accuracy hampered them.[8,9] The precision of detecting FGR in PE cases can be improved by *combining multiple screening techniques*, such as ultrasound measurements and maternal serum markers, but it has the drawbacks of posing overdiagnosis concerns.[10]

Heazell *et al.*[11] metanalysis discussed that maternal biomarkers show promise in distinguishing fetuses that are most likely to end with stillbirth, especially among high-risk women, which emphasizes the importance of patient risk stratification that permits appropriate care and tailored management as frequent surveillance, specialized tests, and even early terminations.

Elabela (Ela), alternatively referred to as Toddler, is a hormone that exhibits binding affinity toward the apelin receptor when coupled with G-protein. Ela is present within the adult's heart, blood vessels lining endothelial, and during the embryonic development of mice and frogs.[12] The Ela–apelin receptor (APJ) axis has recently been implicated in vasculogenesis and embryonic angiogenesis.[13]

Ela was present in the human placenta, specifically in the cytotrophoblasts and syncytiotrophoblasts. Ela could enhance trophoblast invasiveness into the uterine wall, thereby contributing to its advantageous effects on the promotion of a successful pregnancy and the early growth of the placenta.[14]

Studies discussed that Ela-deficient rats exhibit a reduction in the size of the placenta-exchange area and an overall reduction of placental size compared with control mice, which provides evidence for the involvement of Ela in supporting placenta angiogenesis.[15] In the context of PE, Ela was found to be a marker of PE, and some researchers have examined its role as a marker of FGR in PE cases.[16] However, their results were inconsistent.[17-19]

Since FGR and PE had many shared pathophysiological mechanisms in common, we proposed that Ela could serve as an FGR biomarker in FGR–PE mothers. This study was designed to verify Ela's role as a marker of FGR in confirmed Iraqi PE cases at 34 weeks of pregnancy to explore its performance in practice.

Materials and Methods

An observational case–control study included pregnant women attending Al-Yarmouk Hospital, Baghdad, Iraq, from March 2022 to December 2022. The study aims and objectives were explained, and written consent was taken from all before participation in the study.

The ethics committee of Mustansiriyah University College of Medicine Baghdad, Iraq, gave the study approval, IRB:161, dated (22/8/2023). The Declaration of Helsinki was followed in all methods. We enrolled participants that were age and body mass matched.

The inclusion criteria were age range, [18-35], primigravidae, certain dates confirmed by early dating ultrasound/and reliable dating with a viable normal fetus.

An exclusion was made to participants who were obese, had uncertain dates, or had twins or congenitally abnormal babies. PE cases those with a history of hypertension, gestational diabetes, thyroid disease, or renal and liver disease are excluded. Those who were on aspirin or steroids or had incomplete data were all omitted.

In the end, we had 110 participants that were eligible for inclusion, grouped into

1. Healthy controls (55/110).
2. PE cases (55/110) were further subdivided into (40/55) PE cases without FGR and (15/45) FGR that superimposed PE (FGR–PE). PE was defined according to NICE guidelines; 2018.[20] Via ultrasound examination, an estimation was made of fetal weight; as for the FGR, it was defined based on Delphi's conscience.[21]

Study workflow

Participants who met the study inclusion criteria had a detailed clinical history taken; a thorough general and obstetrical examination was done, including systolic and diastolic blood pressures, body mass index, fundal height estimation, and fetal lie. Following a one-night fast, 10 mm of blood was aspirated from each expectant participant to estimate Ela levels. The collected specimens were centrifuged, preserved at 80°C, and analyzed with a human Ela enzyme-linked immunosorbent assay (ELISA) reagent (catalog number: 201-12-8569, Shanghai Sunred Biological Technology, Shanghai, China).

On the same day of clinical examination, biochemical variables [Creatinine, urea, uric acid, alanine transaminase (ALT), and aspartate transaminase (AST)], a complete urinalysis for protein urea, and a complete blood count (hemoglobin and platelets) were recorded. In the ultrasound (US) department, formal obstetrical US and Doppler studies [gestational age, fetal weight, umbilical artery pulsatility index (PI), and amniotic fluid index] were done for all. FGR was screened for by the same experienced sonographer based on Delphi's conscience to reduce interobserver bias.[21]

All the study methods and sampling were described in Figure 1 study flow chart.

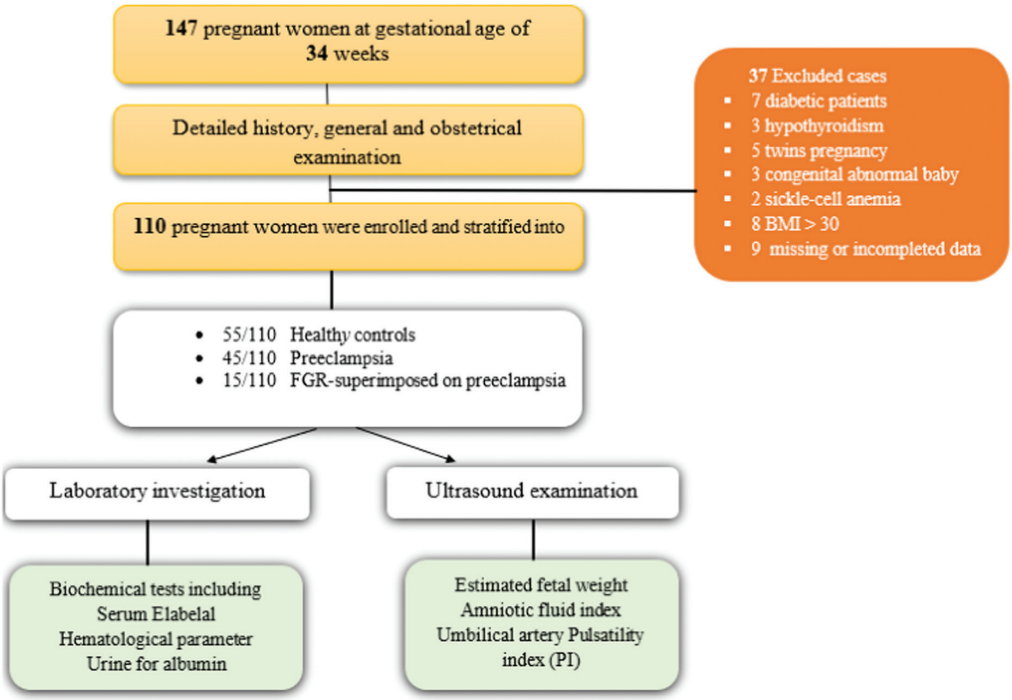

Figure 1: The study flowchart

Statistics

The study normality was checked by the D'Agostino–Pearson test. One-way analysis of variance (ANOVA) was used to compare the primary demographic criteria, which were expressed as means and standard deviations. Pearson's correlation test measured the association strength between serum Ela versus the study parameters. The receiver operator characteristic curve calculated the Ela critical value that distinguished FGR–PE from PE cases with associated sensitivity, specificity, and respected *P* value. All tests were done by Med Calc; a *P* value < 0.05 was set as statistically significant for all tests.

Results

A case–control study recruited 110 participants who were gestational age and body mass index (BMI) matched is given in Table 1. The study's primary criteria were shown. Statistically significant differences were seen regarding systolic diastolic blood pressure, hemoglobin, creatinine, urea, uric acid, alanine transaminase, and aspartate transaminase. Platelets were significantly lower in PE cases. Regarding ultrasonic variable fetal weight, umbilical artery PI, and amniotic fluid index were significantly lower in the PE cases. Serum Ela levels were significantly lower in FGR–PE versus PE cases and healthy controls (10.02 ± 1.63) versus (11.77 ± 1.02) versus (17.58 ± 2.72); *P* < 0.001, respectively, as shown in Figure 2.

Table 2 describes the Pearson's correlation between serum Ela versus the study parameters with respective *P* value. The correlation analysis signifies a statistically significant

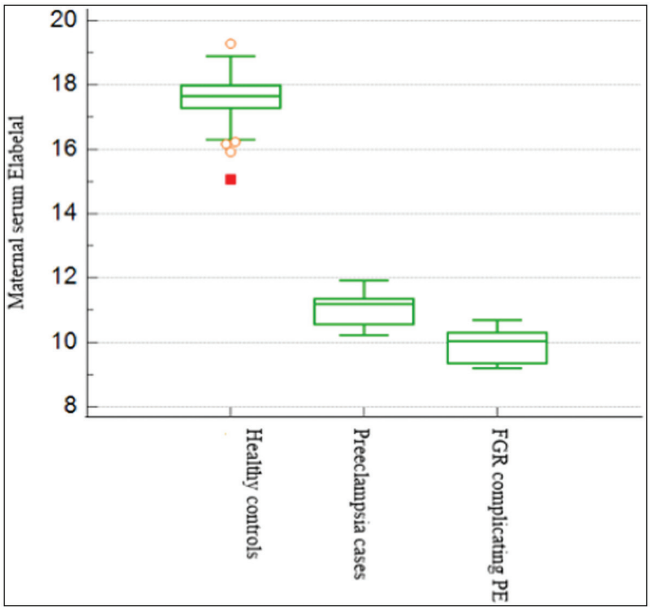

Figure 2: Serum Elabela levels in the studied groups

correlation between serum Ela levels versus systolic and diastolic blood pressures, platelet counts, fetal weight, and umbilical artery PI as *r* = (-0.41, -0.50, 0.37, 0.42, and 0.35) with significant *P* values of 0.002, 0.0001, 0.006, 0.002, and 0.0001), respectively. The rest of the tested parameters were insignificantly linked to serum Ela (creatinine, urea, uric acid, ALT, AST, and amniotic fluid index). Figure 3 shows the receiver operating characteristic curve (ROC) curve that calculated the Ela criterion levels at <10.5 with respective sensitivity 87.5%

Table 1: The primary demographic criteria of the study participants with respective *P* value

Parameters	Healthy controls ($n = 55$)	Preeclampsia ($n = 40$)	PE complicated by FGR ($n = 15$)	*P* value
Maternal age (years)	28.62 ± 4.75	27.35 ± 4.93	26.26 ± 6.64	0.67
Systolic BP (mmHg)	11.66 ± 0.41	16.44 ± 1.16	18.46 ± 1.55	**<0.001**
Diastolic BP (mmHg)	7.63 ± 0.42	10.60 ± 0.67	11.80 ± 0.88	**<0.001**
Hemoglobin (g/dL)	12.62 ± 17.10	11.30 ± 1.28	11.75 ± 0.86	0.387
Platelets ($\times 10^3/mm^3$)	249.52 ± 22.66	179.30 ± 43.94	142.86 ± 22.88	**<0.001**
Creatinine (mg/dL)	0.56 ± 0.06	0.64 ± 0.13	0.73 ± 0.05	**<0.001**
Urea (mg/dL)	17.24 ± 2.19	22.37 ± 7.47	28.86 ± 9.61	**<0.001**
Uric acid (µmol/L)	4.12 ± 0.45	6.41 ± 0.57	6.42 ± 0.59	**<0.001**
ALT (IU/L)	17.11 ± 2.23	26.09 ± 11.30	32.66 ± 7.74	**<0.001**
AST (IU/L)	16.20 ± 1.47	26.29 ± 12.41	27.73 ± 6.38	**<0.001**
Albumin in urine (mg/L)	—	234.74 ± 28.56	253.86 ± 33.98	**0.047**
Ultrasonic estimation of fetal weight (kg)	2368.64 ± 74.81	2090.72 ± 88.02	1912.26 ± 151.63	**<0.001**
Umbilical artery PI	1.19 ± 0.10	1.06 ± 0.12	0.85 ± 0.14	**<0.001**
Amniotic fluid index cm)	13.17 ± 1.56	7.06 ± 1.25	6.79 ± 0.45	**<0.001**
Serum Elabela (ng/mL)	17.58 ± 2.72	11.77 ± 1.02	10.02 ± 1.63	**<0.001**

All data are shown as means ± standard deviations. BP: blood pressure, ALT: alanine transaminase, AST: aspartate transaminase, PI: pulsatility index
All statistically significant values where $P < 0.05$ were marked as bold

Table 2: Describes Pearson's correlation between serum Elabela versus the study parameters with respective *P* values

Serum Elabela versus study parameters ($n = 55$)	Correlation coefficient	*P* value
Systolic BP (mmHg)	-0.41	**0.002**
Diastolic BP (mmHg)	-0.50	**0.0001**
Platelet ($\times 10^3/mm^3$)	0.37	**0.006**
Creatinine (mg/dL)	-0.26	0.05
Urea (mg/dL)	-0.27	0.06
Uric acid (µmol/L)	0.17	0.20
ALT (IU/L)	-0.08	0.58
AST (IU/L)	-0.02	0.91
Albumin in urine (mg/L)	-0.03	0.053
Fetal weight (kg)	0.42	**0.002**
Umbilical artery PI	0.35	**0.0001**
Amniotic fluid index (cm)	0.01	0.93

BP: blood pressure, ALT: alanine transaminase, AST: aspartate transaminase, PI: pulsatility index
All statistically significant values where $P < 0.05$ were marked as bold

and specificity 82.1%; area under the curve of 0.92 and *P* 0.001 in discriminating PE cases complicated with fetal growth restriction.

Discussion

Maternal serum Ela level is significantly low in FGR-PE versus PE cases and healthy controls. Ela correlated positively and strongly with fetal weight and umbilical artery PI. The analysis showed a strong inverse correlation between systolic and diastolic blood pressures versus serum Ela, consistent with earlier published reports that suggested Ela played a key role in blood pressure regulation.[22,23]

At the molecular level, Ela links to APJ and inhibits angiotensin II's ability to constrict blood vessels by lowering FoxM1 expression and angiotensin-converting enzymes, thereby lowering systemic pressure, which clearly explains the current study results.[24]

PE cases exhibited statistically significant differences regarding serum levels of creatinine, urea, and uric acid; moreover, Ela was inversely correlated with serum creatinine and urea. These results are in line with Ma *et al.*[22] Their study highlighted Ela's role as a reliable marker for kidney performance among PE women at 35–37 weeks of pregnancy; moreover, Ela was significantly linked with PE severity. Another study corroborated a significant decrease in Ela concentration in women with early-onset PE cases compared with healthy pregnant.[25]

Deniz *et al.*[16] declared a significant decrease in Ela level that was positively associated with PE severity. Low levels were also found in the infants' blood, signifying Ela's role in babies with low birth weights. Their study examined Ela

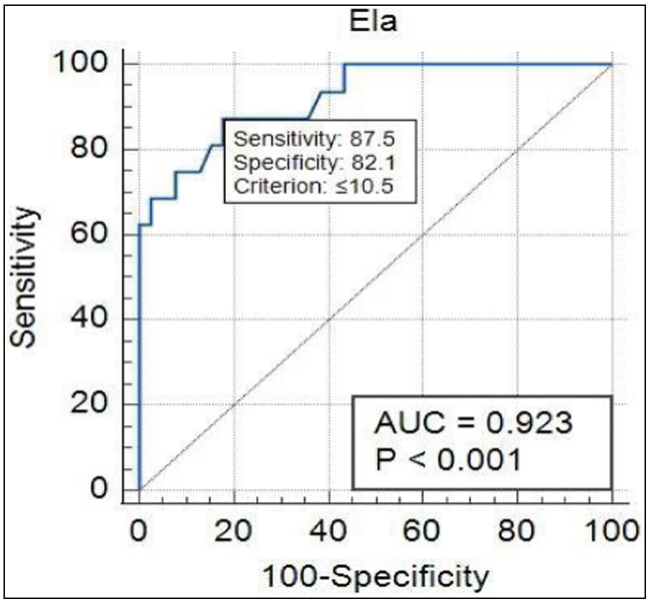

Figure 3: The ROC curve shows the criterion value of serum Elabela associated with the highest sensitivity and specificity in discriminating preeclampsia cases complicated with fetal growth restriction

levels in PE cases at 36 weeks versus healthy pregnancies at 38 weeks of gestation with respective concentrations among the newborns.[16]

Similarly, Ho *et al.*[15] report confirms a relationship between low birth weight and Ela levels. The current study showed a meaningful reduction of serum Ela levels in mothers with FGR versus PE and healthy controls.

In line with our results, Alkan and Karaküçük showed a significantly low Ela level in PE cases versus healthy controls in a case–control study. Ela was significantly correlated to newborn weight and gestational age. The authors proposed a therapeutic role for Ela in FGR cases.[17]

Behram, *et al.*[18] confirmed a significant decrease in Ela concentration in FGR mothers versus healthy pregnant at 30 weeks. They enrolled FGR cases in non-PE moms and discussed a positive link with the newborn birth weight.[18] Chng *et al.*[26], Wang *et al.*,[27] and Nardozza *et al*.[28] studies confirm a correlation between reduced Ela levels and FGR among neonates delivered to PE moms.

Some of the studies delivered contradicting results concerning Ela concentration in PE and FGR. Pritchard *et al.*[29] showed no differences regarding Ela levels in a case–control study that recruited PE cases and matched controls below 34 weeks. Another study found significantly higher Ela levels than healthy controls in late-onset PE cases. However, they did not correlate Ela levels with newborn babies' weight, which was significantly low in PE cases.[30]

Amer Ali *et al.*[25] showed significantly high Ela levels among healthy controls versus low levels in PE cases. The study recommended Ela as a marker for differentiating early and late-onset PE. Yener *et al.*[19] detected significantly high Ela serum concentrations in pregnancies complicated by FGR compared with healthy controls. Their case–control study recruited non-PE cases diagnosed with FGR at a gestational age of (36.4 ± 1.3) weeks.[19]

First, the controversy in literature may be attributed to different gestational ages at sampling time, as Ela levels differ by the gestational weeks.[22,25] Second, implementing different FGR diagnostic criteria.[19] Third, Ela is susceptible to rapid degradation by protease, which explains inconsistent findings if samples are not collected and preserved correctly or if different commercial kits are used.[31,32]

Ela has paracrine actions on fetal endothelial cells, facilitating normal placental angiogenesis essential for adequate perfusion of nutrients and oxygen to the developing baby; Ela deficiency hinders fetal growth manifested as FGR and low birth weight. Additionally, Ela is transported into the maternal bloodstream to modulate cardiovascular and renal function by activating vasodilatory pathways.[15] Sintesits discussed that decreased Ela levels aggravate PE severity, poor placental angiogenesis, endothelial dysfunction and placental ischemia, impaired renal function, and insufficient cardiovascular system (CVS) vasodilation among PE women.[22,30,33]

The current study confirms Ela's strong links to newborns' birth weight and umbilical artery PI. The ROC curve estimated the Ela cutoff value that distinguished PE–FGR complicated pregnancy from PE cases with high sensitivity and specificity, $P < 0.001$, and a reliable area under the curve of 0.9.

Many biomarkers exist with different performing abilities. Ela is unique because it is closely linked to FGR pathophysiology among PE[15-17] and non-PE cases,[18,26,27], suggesting its intimate link to growth restriction pathogenesis.

Furthermore, Ela's level is not static; it showed different gestational age levels, allowing earlier intervention regardless of the gestational age taken.[25,34,35] Targeting Ela holds promising therapeutic avenues in FGR management,[17,36] and these roles may also expand beyond PE and FGR into other pregnancy complications, including gestational diabetes mellitus and abortion.[37-40]

Being a single-center study that included a relatively small sampling size[41] was the study limitation. We could not extend the study period for more because Ela is susceptible to rapid degradation by protease, so if the samples were preserved for a long time, the test results may be hampered.[42] Indeed, the coronavirus disease 2019 laid its shadow on many work aspects; although its peak has declined, yet as a tertiary hospital, we were still facing

lots of referral cases from the periphery.[43,44] Larger studies examining the long-term implications of Ela levels with maternal and neonatal outcomes are needed to unravel this unique biomarker's more diagnostic and prognostic role.

Conclusion

Maternal circulating levels of Ela were significantly lower in pregnancies complicated with FGR versus healthy pregnant women at 34 weeks. In addition, newborns' birth weight and Doppler's PI were positively correlated with maternal serum Ela levels.

Ela's close intimacy to the pathophysiology of FGR in PE and non-PE with high reliability makes it an appealing target for therapeutic intervention. Furthermore, studies are recommended to explore prognostic and long-term implications of maternal serum Ela on maternal and neonatal outcomes.

Author contributions

EAA, AF, SKA, WN, MAKK, and ACP contributed to the conception and design of the study and analysis. EAA and AF drafted the initial manuscript. EAA, AF, SKA, and WN critically revised the manuscript. All authors reviewed, provided final approval, and agreed to all aspects of work integrity and accuracy.

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Ethical committee

The ethics committee of Mustansiriyah University College of Medicine gave the study approval, IRB:161, dated 22/8/2023.

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Conflicts of interest

There are no conflicts of interest.

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