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Is ELABELA a reliable biomarker for hypertensive disorders of pregnancy?

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ABSTRACT

Objective: We aimed to examine the ELABELA levels at different stages of pregnancy among normotensive controls and women with hypertensive disorders of pregnancy (HDP).
Study design: A total of 336 blood samples of 169 women were collected from pre-pregnancy, the first, second, and third trimesters. Women were divided into the following six groups: 1) non-pregnant healthy women; 2) healthy pregnant controls; 3) chronic hypertension; 4) gestational hypertension; 5) preeclampsia; and 6) preeclampsia superimposed on chronic hypertension. ELABELA plasma concentrations were measured by human ELA Elisa Kit (Peninsula Laboratories International, Inc. USA). Kruskal-Wallis test was used to test whether ELABELA level in each type of HDP differed from that in gestational week-matched normotensive controls.
Main outcome measures: Hypertensive disorders of pregnancy.
Results: In the first trimester, patients with gestational hypertension had higher ELABELA level than gestational week-matched normotensive controls [median (ng/ml): 31.9, (IQR (ng/ml): 16.3, 47.6) vs. 19.7 (13.7, 23.2), p = 0.03]. In the second trimester, the levels were 49.2 (32.2, 69.1) vs 24.0 (13.0, 32.6) (p = 0.002), respectively. The level for gestational hypertensive women in the third trimester did not differ significantly from that of normotensive women [43.8 (30.8, 62.7) vs 25.0 (12.3, 74.0), p = 0.82]. The ELABELA levels were similar between preeclamptic women and normotensive controls throughout pregnancy.
Conclusions: Maternal blood ELABELA levels in the first and second trimesters were elevated in women who developed gestational hypertension late in pregnancy, but the ELABELA level bears no significant relationship with preeclampsia during any stage of pregnancy.

1. Introduction

Preeclampsia is one of the most common pregnancy-related complications and greatly contributes to maternal and neonatal morbidity [1]. However, the pathophysiology of preeclampsia has not been fully elucidated, leading to difficulties with the identification of related biomarkers and hence treatment strategies. Low-dose aspirin treatment in high risk women during early pregnancy is now recommended by the American College of Obstetrics and Gynecologists (ACOG) for the prevention of preeclampsia [2]. This reinforces the need for early identification of high-risk women with the objective of implementing targeted interventions.

Currently, the most well-established biomarkers of preeclampsia are circulating placental growth factors (PlGF), soluble fms-like tyrosinekinase-1 (sFlt-1), placental protein 13 (PP13), pregnancy-associated plasma protein-A, and soluble endoglin (sENG) [3]. However, antiangiogenic biomarkers may not be suitable biomarkers for detect preeclampsia in the first trimester. For example, the anti-angiogenic factor sFlt-1 is constant in the first trimester [3]. Also, a recent study reported that the pattern of biomarkers in the first trimester vary among high-risk women who later developed preeclampsia later [3]. The different profiles of biomarkers is probably due to the fact that preeclampsia results from multiple pathophysiological pathways [4]. It is well recognized that one single biomarker is not likely to accurately

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predict preeclampsia [3]. New biomarkers in early pregnancy that can enhance the prediction power of preeclampsia are desired. Recently, Ho et al. reported that knockout of ELABELA, a novel endogenous ligand of the Apelin receptor, caused preeclampsia-like syndromes in pregnant mice, including hypertension and proteinuria, and administration of ELABELA to those mice attenuated these clinical characteristics [5]. This finding highlights a new pathway for preeclampsia and possible novel therapeutic strategies.

ELABELA may serve as a promising biomarker for preeclampsia because of its molecular characteristics and functions. ELABELA is a newly identified circulating peptide hormone which can function in paracrine and endocrine manners [6]. Its expression is restricted to a few organs including the kidney and placenta in the adult humans [7]. Animal studies and *in vitro* studies have shown that ELABELA may play a key role in fetal and placental angiogenesis, and the migration and invasiveness of trophoblast cell [5]. Also, ELABELA has been reported to have a protective effect against cardiovascular and renal failure. ELABELA preserved cellular architecture in the kidney [8] and exogenous administration reduced blood pressure and increased cardiac contractility and output in rates with pulmonary arteries hypertension [9]. Therefore, ELABELA deficiency may contribute to both placental ischemia and maternal kidney/endothelial dysfunction which manifest as either gestational hypertension or preeclampsia in pregnant women. In early life, studies have shown that ELABELA plays a role in embryogenesis and cardiac formation; ELABELA is protective against kidney injury, and reduces blood pressure in pulmonary arterial hypertension rats [9,10]. ELABELA was detectable prior to implantation of human blastocysts, and its related activities, such as renewal of embryonic stem cells, embryogenesis, and cardiac formation [7]. Therefore, it is possible that ELABELA is synthesized and secreted to maternal circulation earlier than placental angiogenesis-related factors such as PlGF and VEGF [7], as indicated in the study by Ho et al. [5].

We initially hypothesized that the maternal circulating level of ELABELA may be lower in pregnancies complicated with hypertension than normotensive pregnancies. Surprisingly, the results from our pilot study were to the contrary – women with preeclampsia had significantly higher levels of ELABELA than healthy controls. In addition, two recent studies in pregnant women found that ELABELA concentrations in preeclamptic women were not lower compared to controls [7,12]; however, this was examined at the end of the second trimester and the third trimesters when hypertension and proteinuria could be already present. To further our understanding of ELABELA, we refocused our research questions to include: What is the dynamic change in the blood levels of ELABELA during human pregnancy? Is the blood level of ELABELA during early pregnancy associated with pregnancies complicated with hypertension which is not restricted to preeclampsia? Can ELABELA be a promising biomarker for preeclampsia?

To answer these questions, we examined: (1) the longitudinal changes in maternal circulation ELABELA level from the first to the third trimester in healthy pregnant women; (2) whether ELABELA levels in maternal circulation differ between women with hypertensive disorders of pregnancy (HDP) and women without HDP.

2. Materials and methods

2.1. Population and study design

This is a nested case-control study using data and blood samples from the Shanghai Birth Cohort [13]. Briefly, six university-affiliated teaching hospitals and one district maternal and child health care hospital participated in the prospective cohort study from 2013 to 2016. Women who came for preconception care or prenatal care and planned to give birth at the participating hospitals were invited to participate in this study. Women were informed of the purpose of the study and their right to withdraw from the study at any time and for any reason. A written consent was obtained from each participant. The current study was a secondary analysis of data from the Shanghai Birth Cohort, and deidentified data and blood samples were used, therefore, this current study was exempt from institutional review board approval accordingly.

The following women were eligible to participate: ≥20 years old, married, at least one person of the couple being a registered Shanghai resident, and no intention to move out of Shanghai in the next two years. Women were interviewed by trained research staff for socio-demographic information and anthropometric measures. Ethical approval was obtained from the Ethics committee of the Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China (reference XHEC-C-2013-001, dated 7 January 2013). A total of 4127 pregnant women were included in the study. Inclusion criteria of the non-pregnant and pregnant controls were as follows: normal blood pressure, normal renal function, non-diabetic, and having matched gestation weeks with HDP cases when blood samples were drawn. As ELABELA is the homolog of the endogenous ligand apelin [9], which is associated with regulation of insulin sensitivity [14], women with preexisting and gestational diabetes mellitus were excluded.

2.2. Outcome variables

Clinical conditions were defined as follows [15]: (1) chronic hypertension: hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) before pregnancy or prior to 20 gestational weeks; (2) gestational hypertension: hypertension after 20 gestational weeks and being normotensive within 12 weeks postpartum; (3) preeclampsia: new onset of hypertension after 20 gestational weeks accompanied by one or more of the following conditions, including proteinuria (> 300 mg/day), liver disease, renal insufficiency, neurological problems, hematological disturbances, and fetal growth restriction; (4) preeclampsia superimposed on chronic hypertension: new signs of preeclampsia in women with chronic hypertension.

The normotensive controls and HDP cases were divided into six groups: (1) non-pregnant healthy women with a proven history of a normal pregnancy; (2) healthy pregnant controls; (3) chronic hypertension; (4) gestational hypertension; (5) preeclampsia; (6) preeclampsia superimposed on chronic hypertension. A total of 20 non-pregnant healthy women were chosen. Table 1 presents the sample size and gestational weeks at blood draw (range) of the pregnant controls and HDP cases. Information on age at last menstruation, pre-pregnancy BMI, birth weight, and parity was presented in Supplementary tables (S1-S3).

2.3. ELABELA measures

Venous blood samples were drawn at the enrollment and follow-up visits and processed with centrifuge at 400 rpm for 10 min immediately after collection. Serum and plasma samples were stored at −80 °C until

Table 1
Sample size and gestational weeks at blood draw.

	1st trimester	2nd trimester	3rd trimester
	Sample size/gestational weeks (range)		
Healthy pregnant controls	20/(12, 16)	20/(22, 26)	20/(31, 36)
Chronic hypertension	20/(12, 18)	15/(22, 29)	19/(32, 39)
Gestational hypertension	31/(11, 17)	32/(20, 28)	31/(30, 41)
Preeclampsia	29/(11, 19)	27/(23, 28)	31/(31, 37)
Preeclampsia superimposed on chronic hypertension	10/(12, 19)	4/(22, 26)	7/(32, 38)
*P value	0.96	0.38	0.73

* P values were based on Kruskal-Wallis test of comparing median of gestational weeks between different groups.

use. The human ELA Elisa Kit (Peninsula Laboratories International, Inc. USA) was used to measure plasma levels of ELABELA in duplicate. For 334 of 336 plasma samples tested, the coefficients of variation (CV) were below 10%; they were 13% and 21% for two samples.

2.4. Statistical analysis

Medians (inter-quartile ranges) were used to describe subject characteristics and ELABELA concentration. As ELABELA concentration was not normally distributed, the Kruskal-Wallis test was used to examine whether there were statistically significant differences in the median of ELABELA concentration or clinical characteristics among the controls and groups of women with chronic hypertension, gestational hypertension, preeclampsia, and preeclampsia superimposed on chronic hypertension. Multinomial logit regression was used to examine the association between the ELABELA concentration and subtypes of HDP, adjusting for maternal age, gestational weeks at blood collection, pre-pregnancy body mass index (BMI), and parity. Statistical analysis was conducted using Stata V.13.0 and R.

3. Results

We first compared non-pregnant normal women and normotensive pregnant women with regard to baseline characteristics and ELABELA level. Table 2 shows that compared with non-pregnant women, healthy pregnant women were a little younger and had a slightly higher median concentration of ELABELA (19.7 ng/ml vs. 13.9 ng/ml, P = 0.037). After we controlled for maternal age, the difference between non-pregnant and first-trimester levels became smaller and the p value did not reach statistical significance. The corresponding values were 20.7 ng/ml vs. 15.0 ng/ml, p = 0.13).

A longitudinal analysis revealed that ELABELA plasma concentration slightly increased from the first trimester [median (IQR): 19.7 ng/ml (13.7, 23.2 ng/ml)] to the second [24.0 ng/ml (13.0, 34.4)] and third trimesters [25.0 ng/ml (12.3, 74.0 ng/ml)] among the 20 normotensive controls (Fig. 1). While the difference in median did not reach statistical significance, the variation increased substantially.

As seen in Fig. 2, patients with gestational hypertension had higher ELABELA plasma concentrations than normal pregnant controls [median: 31.9 ng/ml, IQR: (16.3, 47.6 ng/ml) vs. median: 19.7 ng/ml (13.7, 23.2 ng/ml), p = 0.03] in the first trimester. There were no statistically significant differences in ELABELA plasma concentration between normal pregnant controls and chronic hypertension [42.3 ng/ml (13.0, 101.6 ng/ml)], preeclampsia [28.6 ng/ml (9.3, 44.1 ng/ml)], or preeclampsia superimposed on chronic hypertension [34.4 ng/ml (12.0, 88.4 ng/ml)].

Patients with chronic hypertension had higher second trimester ELABELA plasma concentrations than gestational-age-matched healthy pregnant controls [40.0 ng/ml (28.6, 55.5 ng/ml) vs. 24.0 ng/ml (13.0, 32.6 ng/ml), p = 0.034] (Fig. 3). Similarly, patients with gestational hypertension had higher ELABELA concentrations than the controls [49.2 ng/ml (32.2, 69.1 ng/ml) vs. 24.0 ng/ml (13.0, 32.6 ng/ml), p = 0.002]. However, there were no statistically significant differences in ELABELA concentration between the normal pregnancy group and preeclamptic patients [30.3 ng/ml (17.5, 49.8 ng/ml)] or patients with preeclampsia superimposed on chronic hypertension [87.5 ng/ml (42.1, 132.5 ng/ml)].

There were no statistically significant differences in ELABELA concentration among women with normal pregnancy [25.0 ng/ml (12.3, 74.0 ng/ml)], chronic hypertension [38.1 ng/ml (10.9, 83.2 ng/ml)], gestational hypertension [43.8 ng/ml (30.8, 62.7 ng/ml)], preeclampsia [41.8 ng/ml (20.1, 55.2 ng/ml)] and preeclampsia superimposed on chronic hypertension [11.2 ng/ml (5.3, 26.5 ng/ml)] in the third trimester (Fig. 4).

As seen in Table 3, after adjusting for maternal age, pre-pregnant BMI, and parity, gestational hypertension was positively associated with log-transformed ELABELA concentration in the first and second trimesters (AOR 1.99, 95% CI 1.01–3.92; 3.30, 1.44–7.56, respectively) but not in the third trimester. No consistent associations were observed in other subtypes of HDP.

We initially separated the mild and severe preeclampsia groups for our analyses but did not find any significant differences in ELABELA levels between these two subtypes of HDP in any trimester. Thus, we combined them together in the final analyses.

4. Discussion

In this study, we detected the peptide of ELABELA in the blood of non-pregnant healthy subjects. This result confirmed that ELABELA is constitutively present in circulation rather than a pregnancy-induced hormone, as suggested by a previous study [9]. Our study also found that pregnant women appeared to have higher ELABELA plasma concentrations than non-pregnant women, a finding that was expected because ELABELA produced by the embryo and placental trophoblasts contribute to the maternal circulation levels, but the difference was modest.

ELABELA level in maternal plasma samples were examined across different periods of pregnancy. Compared with the control group, the gestational hypertension group had higher ELABELA level in the first trimester, when gestational hypertension had not been diagnosed. Information on hypertensive disorders of pregnancy was collected from health record, thus information bias due to misclassification of cases and controls is unlikely.

However, this study may be underpowered and a larger sample size may be desired. The variance of ELABELA level was larger in the second and third trimester than in the first trimester, which requires a larger sample size to better detect the association between ELABELA level and the subtypes of HDP. In addition, given that pre-pregnancy BMI was positively associated with each subtype of HDP with adjusted odds ratios ranging from 1.14 to 1.37, and had a weak negative association with blood ELABELA level in the first and third trimesters, but a slight positive association with ELABELA level in the second trimester, and logistic regression may not have fully adjusted for the confounding effects of BMI. The magnitude of the associations between ELABELA level and each subtype of HDP may have been slightly underestimated in the first and third trimesters and overestimated in the second trimester.

This study is the first study to examine ELABELA plasma

Table 2
Clinical characteristics of non-pregnant women and pregnant healthy women.

	Non-pregnant controls (n = 20)	Pregnant controls (n = 20)	[#]P value
Primipara (N (%))	NA	16 (20%)	NA
Maternal age (years), median (IQR)	32.5 (29.8, 5.0)	28.5 (26.0, 31.0)	0.004
Prepregnancy BMI (kg/m^2), median (IQR)	20.7 (20.2, 22.5)	20.8 (19.9, 22.2)	0.9
ELABELA (ng/ml), median (IQR)	13.9 (10.6, 18.5)	19.7 (13.7, 23.2)[*]	0.037
ELABELA (ng/ml), mean (after controlling for age)	15.0	20.7[*]	0.13

[#] P values were from Mann-Whitney U tests or *t* test.
[*] In the first trimester.

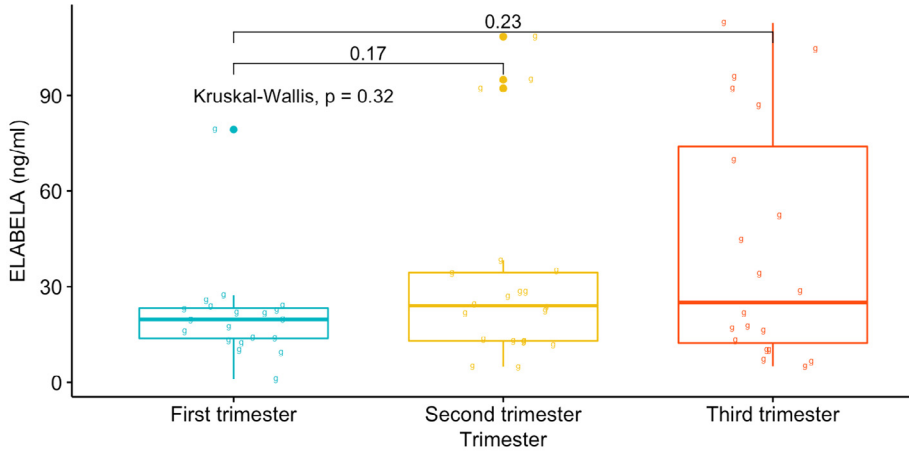

Fig. 1. ELABELA plasma concentrations in 20 women with normal pregnancies.

concentration longitudinally during pregnancy. Among women with a normal pregnancy, ELABELA concentration increases slightly from the first trimester to the second and third trimesters, but the differences did not reach statistical significance. The variation was much larger in the third trimester than in the first and second trimesters and the longitudinal changes of ELABELA throughout pregnancy are also significantly variable. The mechanisms underlying these between-individual variations are not clear and warrant future studies. It is of note that the ELABELA concentration of normotensive pregnant controls in this study (median ~20 ng/ml) was similar to that in a UK study (20.5 ng/ml) [12].

The longitudinal changes in ELABELA levels during pregnancy observed in this study are different from those in the animal study by Ho et al., which reported that the serum level of ELABELA peaked at mid-gestation with a concentration of approximately 100 pg/ml [5]. The discrepancies in ELABELA levels and dynamic changes during pregnancy suggest that the regulation and function of ELABELA during pregnancy may differ between humans and rodents.

Our study is also the first one to examine the association between maternal circulation levels of ELABELA in the early stages of pregnancy and each subtype of HDP. We found that in the first trimester, compared to women with a normal pregnancy, women with any subtype of HDP had a higher ELABELA concentration. Due to relatively small sample size, significance was only found between the gestational hypertension group and the controls. Similar results were found in the second trimester. These results were consistent with two previous studies, both of which found that preeclampsia women did not have lower levels of ELABELA in late pregnancy than normotensive controls [7,12]. In fact, Panaitescu et al. reported that ELABELA plasma levels are higher in patients with late-onset preeclampsia compared to gestational-age-matched controls with a normal pregnancy or women with early-onset preeclampsia [11]. These results contrast the finding by Ho et al. that suggests the deficiency of ELABELA causes preeclampsia [5].

Comparing and contrasting these results provide insight into the ELABELA axis during human pregnancy. First, women that develop gestational hypertension including late-onset preeclampsia may have vulnerable cardiovascular systems and suboptimal endothelial function. The observed elevated blood levels of ELABELA in these pregnant women might be due to renal compensation and/or endothelial stimulation as a protective mechanism. It has been shown in animal studies that ELABELA can induce vasodilation and increase cardiac contractility, ejection fraction, and cardiac output [9,10,16–18]. These protective effects are mediated either through the apelin receptor or angiotensin-converting enzyme and pathogenic angiotensin II signaling. These studies provide evidence to support a cardiovascular protective effect of ELABELA. ELABELA also exerts protective effects against kidney injury and on cultured renal cells through anti-inflammatory, antiapoptotic, and antifibrotic actions [19].

Renal compensation has been observed in many physiological functions, including glucose release regulation in hypoglycemia type 2 diabetes patients and plasma PH regulation in acidotic animals [20,21]. The protective effects of ELABELA also may explain our observation of its increased blood levels from the first to the third trimester while cardiac output increases to 50% above pre-pregnancy levels by

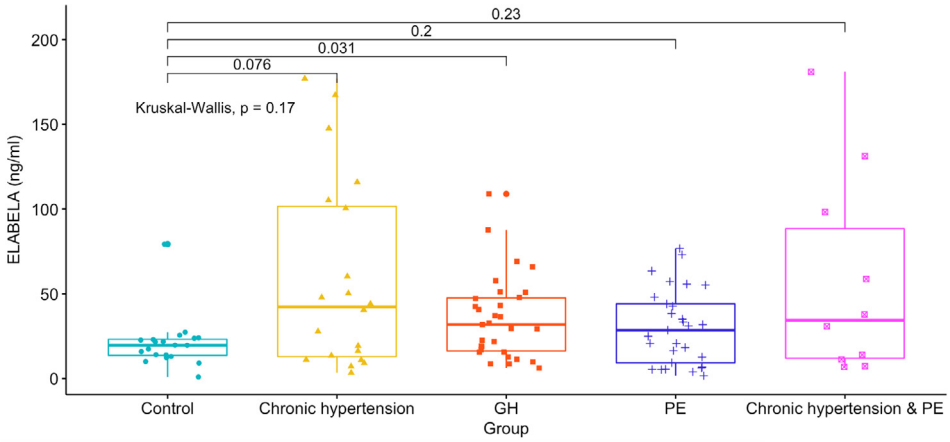

Fig. 2. First trimester ELABELA concentrations in controls and women with hypertensive disorders of pregnancy (HDP). Abbreviations: GH, gestational hypertension; PE, preeclampsia.

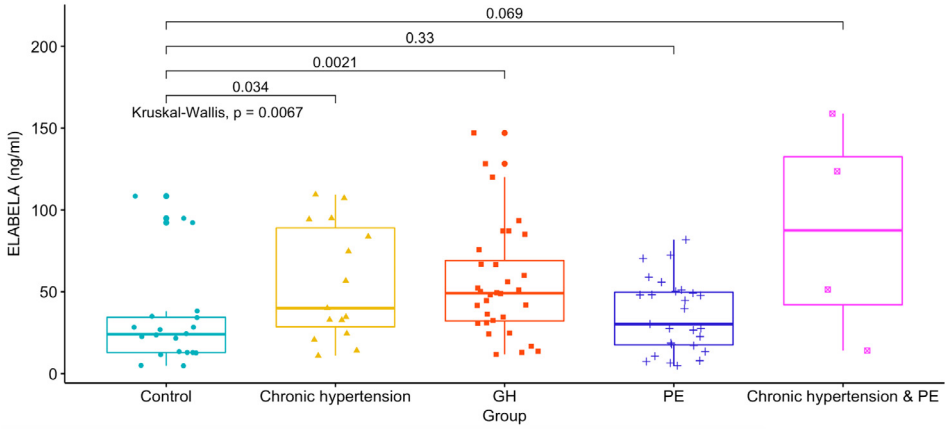

Fig. 3. Second trimester ELABELA concentrations in controls and women with hypertensive disorders of pregnancy (HDP). Abbreviations: GH, gestational hypertension; PE, preeclampsia.

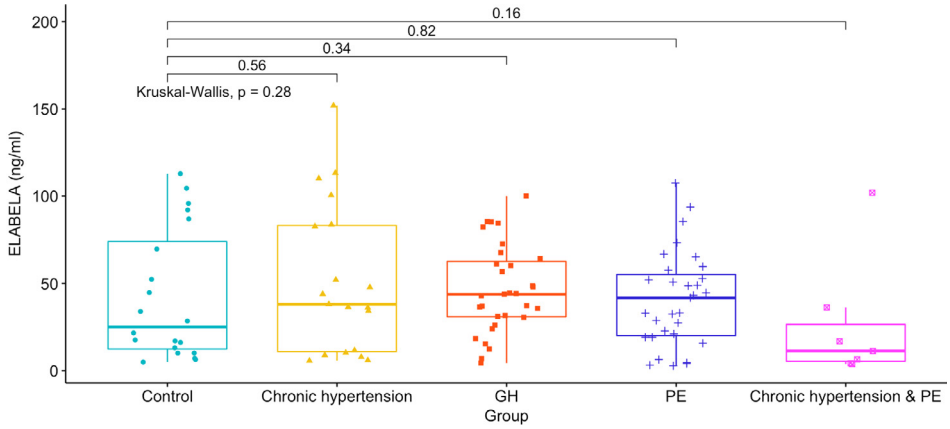

Fig. 4. Third trimester ELABELA concentrations in controls and women with hypertensive disorders of pregnancy (HDP). Abbreviations: GH, gestational hypertension; PE, preeclampsia.

Table 3
The association between log-transformed ELABELA concentration and hypertensive disorders of pregnancy.

Group	First trimester	Second trimester	Third trimester
	Log (ELABELA) (#OR,95% CI)		
Healthy pregnant control	1.0	1.0	1.0
Chronic hypertension	1.72 (0.78, 3.78)	2.53 (0.91, 6.99)	1.41 (0.69, 2.88)
Gestational hypertension	1.99 (1.01, 3.92)	3.30 (1.44, 7.56)	1.62 (0.85, 3.09)
Preeclampsia	1.28 (0.67, 2.45)	1.33 (0.61, 2.91)	1.18 (0.64, 2.20)
Chronic hypertension & preeclampsia	1.42 (0.55, 3.66)	6.59 (1.05, 41.5)	0.64 (0.26, 1.60)

Adjusting for maternal age, pre-pregnancy BMI, and parity.

16–20 weeks of gestation and remains elevated until term [22]. However, the knockout of ELABELA might undermine the renal compensation and endothelial stimulation in mice. In addition, the regulation of ELABELA during pregnancy in humans may differ from that in mice as the placenta has extremely high evolutionary diversity among species [23]; whether the mouse model is sufficient for human placenta and pregnancy research has been greatly debated [24]. Many aspects of human placentation and pregnancy can only be understood through experiments on human cells and tissues in combination with epidemiological research in humans. Due to the inaccessible placental tissues from early pregnancies and the limited human placental cell lines, well designed molecular epidemiology studies are valuable in understanding ELABELA functions during pregnancy.

Finally, we did not find differences in ELABELA plasma concentrations between women with severe preeclampsia and those with a normotensive pregnancy. No differences in ELABELA blood levels were also observed in another study when comparing women with early onset preeclampsia and normotensive pregnancy [12]. Severe preeclampsia and early onset preeclampsia are believed to be secondary features of a primary placenta disorder. These results indicate that the ELABELA plasma levels in severe or early onset preeclampsia women or in pregnant women in general more likely reflect the mixed maternal and placental contributions. And it seems unlikely that ELABELA can serve as a biomarker for preeclampsia. However, previous studies and our study do not provide the levels of ELABELA and its receptors in the uterine environment including amniotic fluid, fetus, and placentas. In some cases, even though the level of a peptide hormone is not changed, its molecular functions can be dys-regulated through its receptors [25]. Thus, it is possible that women with placenta originated pregnancy complications have altered expression of either ELABELA or ELABELA

receptors at the placental level. In addition, a recent study demonstrated a negative association between serum ELABELA concentration and blood pressure in patients with type 2 diabetes [26]. This further indicates the complexity of ELABELA regulation and function, and the potential discrepancy between pregnant and non-pregnant individuals.

5. Conclusion

Taken together, this study demonstrated the modestly elevated blood levels of ELABELA in pregnant women and the continuous slight increase during pregnancy. ELABELA plasma concentration in the first and second trimesters was positively associated with gestational hypertension, but not mild nor severe preeclampsia. Thus, ELABELA is unlikely to serve as a reliable biomarker for preeclampsia.

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Disclosure of interest

The authors report no conflicts of interest.

Author contributions

RH significantly contributed to the study design, completed the data analysis, and wrote the article. JZ significantly contributed to the study design, completed the data analysis, and wrote the article. LZ significantly contributed to interpretation of the data, critically revised the article, and approved the final version. XlH significantly contributed to interpretation of the data, critically revised the article, and approved the final version. WpY significantly contributed to interpretation of the data, critically revised the article, and approved the final version. CC significantly contributed to interpretation of the data, critically revised the article, and approved the final version. Kun Sun significantly contributed to interpretation of the data, critically revised the article, and approved the final version. WyW significantly contributed to interpretation of the data, critically revised the article, and approved the final version. LpF conceived the study design, significantly contributed to data analysis and interpretation of the data, critically revised article, and approved the final version. JZ conceived the study design, significantly contributed to data analysis and interpretation of the data, critically revised article, and approved the final version.

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Disclosures

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.06.007.

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