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ARTICLE

Increased plasma fatty acid binding protein 4 concentration at the first prenatal visit and its relevance to preeclampsia

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Abstract

Preeclampsia affects 2–8% of all pregnancies, and it is associated with significant perinatal mortality and morbidities including preterm birth and small for gestational age. We examined whether plasma fatty acid binding protein 4 (FABP4) concentrations are associated with risk of later preeclampsia development. From March 2015 to May 2016, serum FABP4 was measured in 1486 women in early pregnancy. The relationship between the levels of FABP4 and preeclampsia were evaluated using univariate and multivariate regression analysis. The median plasma concentration of FABP4 at the first prenatal visit was significantly higher in women in whom preeclampsia developed later compared with those in whom it did not ($P < 0.001$). For each 1 unit increase in FABP4 plasma concentration, the unadjusted and adjusted risk of preeclampsia increased by 8% (odds ratio (OR): 1.08; 95% confidence interval [CI]: 1.05–1.12) and 4% (1.04; 95% CI: 1.02–1.07), respectively. The addition of FABP4 to established risk factors significantly improved net reclassification improvement. Increased FABP4 at the first prenatal visit of gestation independently predicted preeclampsia and significantly improved reclassification and discrimination. This information is important to guide public health efforts in preeclampsia prevention.

Introduction

The most common classifications of hypertensive disorders of pregnancy consist of chronic hypertension, gestational hypertension, preeclampsia, and superimposed preeclampsia [1]. Preeclampsia is a pregnancy-specific, multisystem condition that is defined by new-onset hypertension and either proteinuria or end-organ dysfunction at 20 weeks of gestation or later [2]. Preeclampsia affects 2–8% of all pregnancies, and it is associated with significant perinatal mortality [3] and morbidities including preterm birth and small for gestational age [4]. Worldwide, approximately 76,000 pregnant women die each year from preeclampsia and related hypertensive disorder [5]. The origins of preeclampsia likely lie in abnormal placental development, which induces oxidative stress and maternal systemic inflammation that lead to the clinical symptoms seen in preeclampsia [6].

The fatty acid binding protein (FABP) family consists of intracellular lipid carriers that participate in regulating lipid transport and metabolism, and serum FABPs have been considered specific markers of tissue injury [7]. In humans, FABP4 circulates at concentrations of 10–50 ng/ml, comparable to or higher than that of most adipokines, and its level was elevated in obese subjects and correlated with body mass index (BMI), waist circumference, insulin resistance, dyslipidemia, and hypertension in healthy subjects [7]. Previous studies have suggested that FABP4 was associated with adiposity [8], metabolic syndrome (MS) [9], atherosclerosis [10], and stroke [11].

FABP4 shows potential as a novel biomarker for preeclampsia prediction in women with type 1 diabetes [3]. In the non-pregnant and pregnant state, FABP4 is associated with the following known preeclampsia risk factors: obesity [8], hypertension [12], and diabetes [13, 14]. However, there have been no studies on FABP4 in Chinese women with preeclampsia. Thus, we hypothesize that serum FABP4 concentrations at the first prenatal visit are associated with the development of preeclampsia in pregnant women. In this

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study of 1486 Chinese pregnant women, we assess the value of FABP4 concentrations at the first prenatal visit to predict preeclampsia.

Patients and methods

From March 2015 to May 2016, consecutive women (age ≥18 years old) who were admitted to the First Affiliated Hospital of Zhengzhou University, China, were included. We recruited singleton pregnancies at the first prenatal visit of gestation; women were to be without a history of childbirth. Pregnant women with pre-gestational diabetes and hypertension, pregnant women diagnosed with alcohol abuse or renal failure at the first prenatal visit, and pregnant women who terminated their pregnancy during follow-up were excluded from the study. This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. All participants were informed of the study protocol, and their written informed consents were obtained before inclusion.

We recorded maternal pregnancy characteristics including maternal age, pre-pregnancy BMI (self-reported weight (kg) divided by height (m^2)), ethnicity, marital status (unmarried, married), smoking status (yes, no), gravidity, gestational weeks at admission, and family history of hypertension at the first prenatal visit. We also obtained additional information from medical records, including severe anemia during the pregnancy, psychological stress during pregnancy, gestational diabetes mellitus (GDM), urinary tract infection and fibroids during pregnancy, newborn birth weight, BMI, and gestational age at delivery. Gestational age was determined according to the date of the last menstrual period and was confirmed by ultrasound reports in the first trimester. A delivery summary of gestational age, maternal BMI at delivery, and birth weight was recorded by obstetricians. Obesity has been more precisely defined by the National Institutes of Health (the NIH) as a BMI of 30 and above [15].

Preeclampsia, the primary endpoint, was defined using international guidelines [16]. We applied the international criteria to define preeclampsia as the presence of hypertension (systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg on two occasions at least 6 h apart after 20 weeks of gestation with detectable proteinuria of ≥0.3 g/24 h or >1 by urine dipstick in previously normotensive women [17]. According to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria, severe preeclampsia was diagnosed if at least one of the following symptoms appeared: SBP ≥160 mmHg; DBP ≥110 mmHg; any evidence of other organ damage including proteinuria of ≥3 g/24 h or 3+ by urine dipstick, oliguria, pulmonary edema, liver dysfunction, thrombocytopenia, or central nervous system disturbance (altered vision, headache).

Pregnant women were tested for fasting plasma FABP4 at their first prenatal visit using a venous blood sample collected after at least 8 h of fasting. The gestational age at sampling was recorded. The plasma concentration of FABP4 was batch analyzed and blind to preeclampsia status using a commercially available ELISA assay from R & D Systems (Minneapolis, MN). In our study, the lower detection limit for FABP4 was 3.0 ng/ml, and the detection range was 3–120 ng/ml. Inter-assay and intra-assay coefficients of variation were all less than 8%. Routine blood biomarkers such as C-reactive protein (CRP) and fasting plasma glucose (FPG) were tested using standard detection methods.

Statistical analysis

Variables are summarized as the mean (standard deviation; SD), median (Interquartile range: IQR), or *n* (%) per category; groups have been compared using the χ^2 or Mann–Whitney test (Student's *t*-test) as appropriate and using logistic regression analyses to adjust for multiple different variables. Incidence density 95% confidence intervals (CI) were calculated using the Poisson distribution.

The relationship between levels of FABP4 and preeclampsia were evaluated using univariate and multivariate regression analysis. We used crude models and multivariate models adjusted for all significant predictors to report odds ratios (ORs). For multivariate analyses, categorical variables included maternal age, gravidity, ethnicity, pre-pregnancy BMI, gestational age at sampling, smoking status, marital status, severe anemia during the pregnancy, family history of hypertension, psychological stress during pregnancy, GDM, urinary tract infection and fibroids during pregnancy, newborn birth weight, BMI and gestational age at delivery, FPG, CRP, and FABP4. For a more detailed exploration of the relationship between FABP4 and preeclampsia, we also used multivariate analysis models to estimate adjusted OR and 95% CIs of preeclampsia for FABP4 quartiles (with the lowest quartile as reference). Second, receiver operating characteristic (ROC) curves were used to test the overall prediction accuracy of FABP4 and other markers to diagnose preeclampsia, and the results were reported as the area under the curve (AUC). Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices were calculated to determine the clinical utility of the addition of FABP4 to established risk factors and the ability of FABP4 to improve preeclampsia prediction [18]. All statistical analysis was performed with SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA)

and the ROCR package (version 1.0-2). Statistical significance was defined as $P < 0.05$.

Results

In this study, from 1752 screened women (at admission), 1636 women (age ≥18 years old) with singleton pregnancy and without a history of childbirth were identified and included. During the study process, 41 decided to withdraw, 15 blood samples were lost, 63 were lost to follow-up or transferred hospitals, and 31 terminated their pregnancy, leaving 1486 individuals for this analysis. However, these 1486 patients were similar in terms of baseline characteristics (age ($P = 0.37$), BMI ($P = 0.55$), and gestational weeks at admission ($P = 0.31$)) compared to the overall cohort. Blood from women at their first prenatal visit was available for 1486 women, among whom preeclampsia developed in 61 (4.1%; 95% CI: 3.1–5.1%). In those women, 17 (1.1%) were defined as severe preeclampsia. The median gestational age at blood sample collected was 10 (IQR, 8–12) weeks. The median serum concentration of FABP4 was 15.8 (IQR, 11.4–25.1) ng/ml (Fig. 1). The maternal and clinical characteristics of women with and without preeclampsia are presented in Table 1. Women who developed preeclampsia had a greater BMI at admission and were more likely to have a family history of hypertension, severe anemia, and psychological stress during pregnancy (Table 1). They also had more urinary tract infections and fibroids during pregnancy as well as higher levels of FPG and CRP. Interestingly, obese women were more likely to develop preeclampsia than women without obesity (21.3% vs. 10.9%, $P = 0.012$).

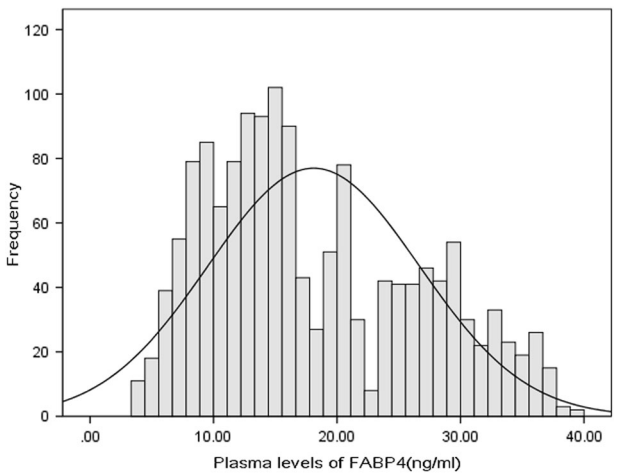

Fig. 1 Histogram of FABP4 at the first prenatal visit. FABP4 fatty acid binding protein 4

The preeclampsia distribution across the FABP4 quartiles ranged between 1.3% (first quartile) and 7.5% (fourth quartile) (Fig. 2). The median serum concentration of FABP4 at the first prenatal visit was significantly higher among women in whom preeclampsia developed later compared with those in whom it did not (24.8 [IQR: 15.9–31.2] ng/ml vs. 15.6 [IQR 11.2–24.6] ng/ml; $Z = 5.353$, $P < 0.001$) (Fig. 3).

In univariate logistic regression analysis, we calculated the OR of the FABP4 level in predicting preeclampsia compared with other risk factors. For each 1 unit increase in plasma concentration of FABP4, the unadjusted and adjusted risk of preeclampsia increased by 8% (OR 1.08 [95% CI: 1.05–1.12], $P < 0.001$) and 4% (OR 1.04 [95% CI: 1.02–1.07], $P = 0.015$), respectively (Table 2). In multivariate analyses, severe anemia during pregnancy (OR: 3.17; 95% CI: 2.12–4.75), family history of hypertension (3.58 (2.30–5.56)), psychological stress during pregnancy (2.73(1.80–4.14)), GDM (2.39 (1.56–3.79)), obesity status (1.96 (1.18–3.25)), and urinary tract infection during pregnancy (2.58 (1.76–3.79)) remained significant preeclampsia predictors. In multivariate models comparing the second, third, and fourth quartiles against the first (Q1) quartile of FABP4 (Table 2), concentrations of FABP4 in Q3 and Q4 were associated with later preeclampsia development and increased the risk of preeclampsia by 121% (OR: 2.21; 95%CI: 1.09–4.18) and 205% (3.05; 1.43–7.75), respectively. The independent association of FABP4 with preeclampsia was confirmed using the likelihood ratio test ($P = 0.027$). In a multivariate model using the fourth quartile of FABP4 vs. quartiles 1 through 3 together with the clinical variables, the marker displayed prognostic information (preeclampsia: OR for FABP4 fourth quartile, 2.07 [95% CI: 1.06–3.98; $P = 0.009$]). We also calculated the OR of the FABP4 level in predicting severe preeclampsia compared with other risk factors. For each 1 unit increase in FABP plasma concentration, the unadjusted and adjusted risk of severe preeclampsia increased by 15% (OR 1.15 [95% CI: 1.08–1.27], $P < 0.001$) and 9% (1.09 [1.04–1.16], $P = 0.004$), respectively.

Based on the ROC analysis, the optimal cutoff value of FABP4 levels as an indicator for preeclampsia screening was estimated to be 21.3 ng/ml, which yielded a sensitivity of 67.3% and a specificity of 74.4%, with the AUC at 0.71 (95% CI, 0.65–0.76) (Fig. 4). Furthermore, plasma levels of FABP4 ≥21.3 ng/ml were considered an indicator to predict preeclampsia, and the positive predictive value (PPV) and negative predictive value (NPV) were 63.9% and 73.7%, respectively. The diagnostic accordance rate was 73.3%.

With an AUC of 0.71, FABP4 showed a significantly greater discriminatory ability to predict preeclampsia compared with CRP (AUC, 0.60; 95% CI: 0.57–0.68; $P < 0.001$), FPG (AUC, 0.55; 95% CI: 0.50–0.61; $P < 0.001$), BMI (AUC, 0.57; 95% CI: 0.52–0.62; $P < 0.001$), family

Table 1 Maternal and clinical characteristics of women with and without preeclampsia

Characteristic[a]	ALL	Women with preeclampsia[b]	Without preeclampsia
N	1486	61	1425
Maternal race/ethnicity—Han, *n* (%)	1288 (86.7)	54 (88.5)	1234 (86.6)
Maternal age, median (IQR), years	28.0 (24.5–31.5)	28.4 (24.6–31.7)	28.0 (24.5–31.4)
Gravidity, mean (SD)	2.1 (1.2)	2.1 (1.3)	2.1 (1.2)
Pre-pregnancy BMI, median (IQR), kg/m^2	22.5 (21.2–24.1)	23.9 (22.2–27.5)**	22.4 (21.0–24.0)
Obesity status, *n* (%)	168 (11.3)	13 (21.3)**	155 (10.9)
Marital status—Married, *n* (%)	1376 (92.6)	45 (73.8)*	1331 (93.4)
Smoking during pregnancy, *n* (%)	278 (18.7)	13 (21.3)	265 (18.6)
Gestational age of blood sample, median (IQR), years	10 (8–12)	11 (9–13)	10 (8–12)
Severe anemia during pregnancy, *n* (%)	128 (8.6)	17 (27.9)*	111 (7.8)
Family history of hypertension, *n* (%)	159 (10.7)	19 (31.1)*	140 (9.8)
Psychological stress during pregnancy, *n* (%)	172 (11.6)	18 (29.5)*	154 (10.8)
GDM, *n* (%)	183 (12.3)	17 (27.9)*	166 (11.6)
Urinary tract infection during pregnancy, *n* (%)	201 (13.5)	20 (32.8)*	181 (12.7)
Fibroids during pregnancy, *n* (%)	121 (8.1)	10 (16.4)**	111 (7.8)
Birth weight, mean (SD), g	3235 (945)	2680 (796)*	3240 (949)
BMI at delivery, median (IQR), kg/m^2	28.1 (26.5–30.8)	29.4 (28.2–31.6)*	27.9 (26.4–30.8)
GA at delivery, median(IQR), weeks	38.5 (37.0–39.5)	36.5 (35.0–37.5)*	38.5 (37.0–39.6)
Laboratory test, median (IQR)			
CRP, mg/l	6 (3–9)	10 (6–15)*	6 (3–9)
FPG, mmol/l	4.55 (4.18–5.63)	5.15 (4.55–6.14)*	4.52 (4.17–5.61)
FABP4, ng/ml	15.8 (11.4–25.1)	24.8 (15.9–31.2)*	15.6 (11.2–24.6)

GDM gestational diabetes mellitus, *BMI* body mass index, *CRP* C-reactive protein, *FPG* fasting plasma glucose, *FABP4* fatty acid binding protein 4

**P* value <0.001; ***P* value <0.05

[a]Data are median (interquartile range), mean (standard deviation), or *n* (%)

[b]*P* value tested by χ^2 or Mann–Whitney test (Student's *t*-test). Compared with the women without preeclampsia

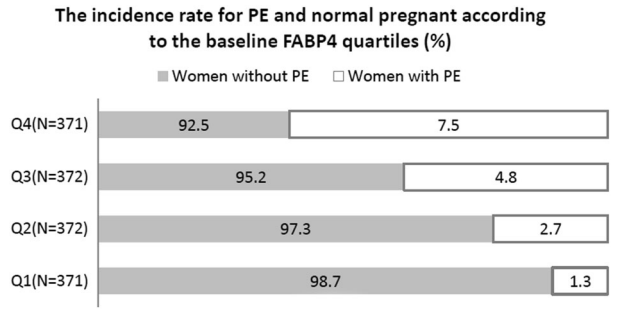

Fig. 2 The incidence rate for PE according to the baseline FABP4 quartiles. Plasma levels of FABP4 in Quartile 1 (<11.4 ng/ml), Quartile 2 (11.4–15.8 ng/ml), Quartile 3 (15.8–25.1 ng/ml), and Quartile 4 (>25.1 ng/ml). PE preeclampsia, FABP4 fatty acid binding protein 4

history of hypertension (AUC, 0.63; 95% CI: 0.59–0.69; $P = 0.001$), and psychological stress during pregnancy (AUC, 0.61; 95% CI, 0.56–0.67; $P < 0.001$). When FABP4 was added to the model containing established risk factors, the AUC was 0.77. A significant difference in the AUC between the established risk factors alone and the addition of FABP4 concentrations was observed (difference, 0.02 [95% CI: 0.01–0.03]; $P = 0.04$) (Table 3). The NRI statistic showed that the addition of FABP4 to a model with established risk factors significantly increased the correct reclassification of preeclampsia ($P < 0.001$). The IDI statistic found that the FABP4 level significantly increased discrimination between women with preeclampsia and without preeclampsia ($P = 0.03$).

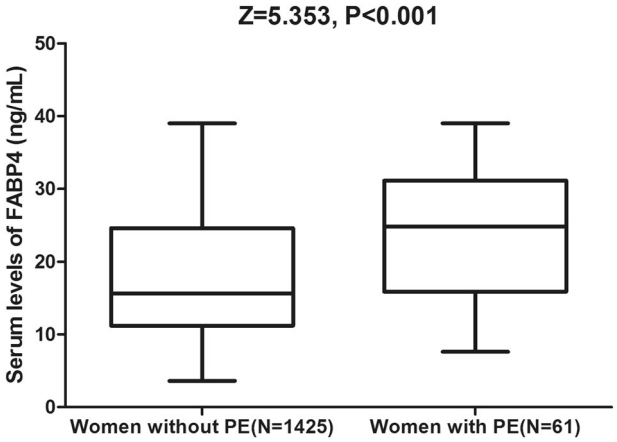

Fig. 3 Distribution of FABP4 in women with PE and without PE. Horizontal lines represent medians and inter-quartile ranges (IQR). *P* values refer to Mann–Whitney *U* tests for differences between groups. PE preeclampsia, FABP4 fatty acid binding protein 4

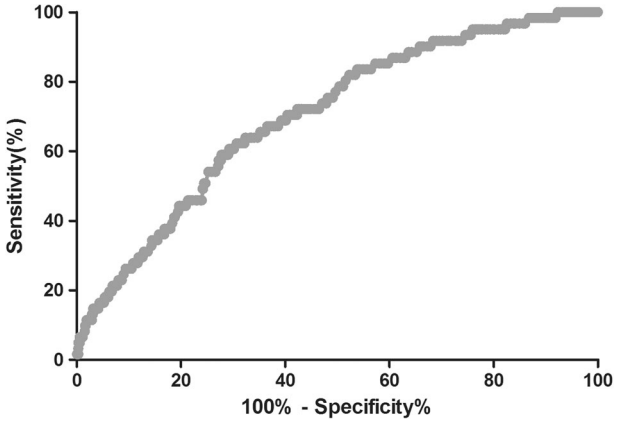

Fig. 4 Receiver operating characteristic (ROC) curves were utilized to evaluate the accuracy of plasma FABP4 levels in predicting PE. PE preeclampsia, FABP4 fatty acid binding protein 4

Table 2 Logistic regression model for serum FABP4 concentrations using preeclampsia as the dependent variables

FABP4, ng/ml	Crude OR (95% CI)	Multivariable adjusted [a]
Decrease per unit	1.08 (1.05–1.12)	1.04 (1.02–1.07)
Quartile 1 (<11.4)	Reference	1.00
Quartile 2 (11.4–15.8)	2.02 (0.68–5.97)	1.18 (0.47–4.13)
Quartile 3 (15.9–25.1)	3.72 (1.37–10.13)	2.21 (1.09–4.18)
Quartile 4 (>25.1)	5.98 (2.28–15.68)	3.05 (1.43–7.75)

[a]Adjusted for maternal age, gravidity, ethnicity, pre-pregnancy BMI, gestational age at sampling, smoking, marital status, severe anemia during pregnancy, family history of hypertension, psychological stress during pregnancy, GDM, urinary tract infection and fibroids during pregnancy, newborn birth weight, BMI and gestational age at delivery, FPG, CRP, and FABP4 quartiles

OR odds ratio, *CI* confidence interval, *GDM* gestational diabetes mellitus, *BMI* body mass index, *CRP* C-reactive protein, *FPG* fasting plasma glucose, *FABP4* fatty acid binding protein 4

Discussion

Preeclampsia is a common condition of pregnancy, marked by the onset of hypertension and proteinuria [19]. This is the first study to date to both assess the concentration of FABP4 at the first prenatal visit of gestation in relation to the development of preeclampsia and to investigate its clinical utility in Chinese pregnant women. The FABP4 level remained significantly associated with preeclampsia after controlling for established risk factors. The fourth quartile of FABP4 levels proved prognostic, and the adjusted risk of preeclampsia for women in this group increased by 107% (OR = 2.07 [95% CI: 1.06–3.98], $P = 0.009$). The FABP4 level, when added to a model with established risk factors, did significantly increase the AUC ($P = 0.04$). Furthermore, the NRI and IDI, which are proposed as superior methods to determine the clinical utility of a biomarker, showed that the FABP4 level, in addition to clinical risk factors, improved the prediction of preeclampsia. These data suggest that future targeted lifestyle interventions and more frequent medical interventions should be emphasized for women with FABP4 levels in the fourth quartile.

The value of maternal serum biomarkers, such as angiopoietin-2, and uterine artery Doppler [20], leptin [21], Follistatin-like-3 [22], and afamin [23] in the prediction of preeclampsia have been suggested in previous studies. In this study, maternal FABP4 concentrations at the first prenatal visit were significantly higher in women in whom preeclampsia developed later compared with those in whom it did not. Previous studies have also measured FABP4 levels prior to the onset of preeclampsia. In line with our findings, Scifres et al. [24] reported significantly elevated FABP4 levels before 13 weeks and at 26 weeks of gestation in women without diabetes in whom preeclampsia developed later. Similarly, another study found that FABP4 was significantly elevated in early pregnancy and the second trimester in women in whom preeclampsia developed later [3].

Severe preeclampsia occurs in 1–2% of all pregnancies, and it is often associated with higher risks of adverse pregnancy outcomes [25, 26]. A previous study suggested that 1.92% of nulliparous women developed preeclampsia, and the prevalence of mild or severe preeclampsia was 1.42% or 0.49%, respectively [27]. Similarly, in this study, we found that the prevalence of mild and severe preeclampsia was 3.0% and 1.1%, respectively.

The causes of preeclampsia are still unclear, although many risk factors for developing preeclampsia have been suggested, including first pregnancy, multiple pregnancies, maternal age, maternal and paternal ethnicity, obesity, a history of preeclampsia, and a prolonged interval between pregnancies [27]. Some risk factors, including antiphospholipid antibody syndrome, prior pre-eclampsia, chronic

Table 3 Serum FABP4 concentrations at admission prediction of preeclampsia with AUROC

Preeclampsia	AUROC				NRI(P)	IDI (*P*)
	FABP4	Risk factors [a]	Risk factors with FABP4 [a]	Incremental area (*P*)[b]		
At admission	0.71	0.75	0.77	0.02 (0.04)	0.45 (<0.01)	0.03 (0.03)

BMI body mass index, *CRP* C-reactive protein, *FPG* fasting plasma glucose, *FABP4* fatty acid binding protein 4

[a]Established risk factors including: maternal age, gravidity, ethnicity, pre-pregnancy BMI, gestational age at sampling, smoking, marital status, severe anemia during the pregnancy, family history of hypertension, psychological stress during pregnancy, GDM, urinary tract infection and fibroids during pregnancy, newborn birth weight, BMI and gestational age at delivery, and blood levels of FPG and CRP

[b]Comparison of AUROCs: established risk factors without FABP4 levels vs. established risk factors with FABP4 levels

hypertension, pre-gestational diabetes, and BMI >30, were also strongly associated with a high rate of preeclampsia [19]. Furthermore, chronic hypertension, obesity, severe anemia [28], GDM, urinary tract infection and fibroids during pregnancy [29], and psychological stress during pregnancy [30] have also been suggested as risk factors for preeclampsia. In this study, we also found that severe anemia during pregnancy, family history of hypertension, psychological stress during pregnancy, GDM, obesity status, and urinary tract infection during pregnancy remained significant preeclampsia predictors.

In multivariate models, FABP4 remained associated with preeclampsia when adjusted for the above factors. Some other mechanisms may explain the observed association between FABP4 level and risk of preeclampsia. First, elevated FABP4 levels increase the risks of obesity-related metabolic disorders and hypertension [31]. As an adipokine, FABP4 is also closely associated with hypertension. Ota et al. observed that serum FABP4 levels were significantly higher in non-treated essential hypertensives than in normotensives, and after adjustment for age, sex, and adiposity, FABP4 was an independent predictor of mean arterial pressure [32]. Second, the role of FABP4 in the pathogenesis of hypertension might be that FABP4 induces the transformation of the insulin-mediated endothelial nitric oxide synthase (eNOS) pathway, thus reducing NO production and endothelial dysfunction [33]. Third, one study found that serum FABP4 concentration was associated with insulin resistance [13]. Emerging evidence suggests that diabetes is associated with pulmonary hypertension and that diabetes modifies the course of pulmonary hypertension [34]. Lastly, Yan et al. [35] concluded that the increase in placental FABP4 expression in preeclampsia may affect the function of trophoblasts, and this increase may have a role in the pathogenesis of preeclampsia.

Major strengths of this study were that we used plasma samples collected before the onset of symptoms, which is important to establish temporality. In addition, women with essential hypertension or any existing renal disease were included, making our study more representative of the typical population. There were several limitations of our study. First, it was cross-sectional; therefore, this study could not reflect on the cause–effect relationship between FABP4 and preeclampsia. Second, the sample size was not sufficiently large. In addition, we acknowledge that while having a population mainly composed of Han Chinese women may be a strength for data homogeneity, this may also be viewed as a limit with regard to extending conclusions to other populations. Third, FABP4 levels were determined by a single measurement during the early stage of pregnancy. However, Shangguan et al. [36] reported increased third trimester FABP4 levels in women with preeclampsia compared with healthy pregnant and non-pregnant women, suggesting no effect of pregnancy on FABP4 levels.

Conclusions

The present study is the first report showing that increased FABP4 level at the first prenatal visit of gestation independently predicted preeclampsia and significantly improved reclassification and discrimination. These findings further develop our understanding of the role of FABP4 in preeclampsia. This information is important to guide public health efforts in preeclampsia prevention.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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