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Retinol Binding Protein 4 – A Novel Association with Early-Onset Preeclampsia

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Abstract

Objective—Dysregulation of maternal circulating adipokines has been implicated in several "great obstetrical syndromes" including preeclampsia (PE), small-for-gestational age (SGA) neonate and fetal death (FD). It has been suggested that adipokines provide a molecular link between metabolic derangements and inflammatory response in complicated pregnancies. Retinol binding protein 4 (RBP4), a novel adipokine, plays a role in obesity-related disorders, as well as in the regulation of the immune response. The aim of this study was to determine whether there are changes in maternal plasma concentrations of RBP4 in patients with PE and in those with an SGA neonate or FD.

Study design—This cross-sectional study included patients in the following groups: 1) normal pregnancy (n=134); 2) PE (n=104); 3) SGA neonate (n=28); and 4) FD (n=37). Maternal plasma RBP4 concentrations were determined by ELISA. Non-parametric statistics were used for analysis.

Results—1) The median maternal plasma RBP4 concentration was higher among patients with PE than in those with a normal pregnancy (p=0.03); 2) The median maternal plasma RBP4 concentrations of patients with preterm PE (<37 weeks) was higher than that of those with term PE (p=0.017) and than that of those with a normal pregnancy (p=0.002); 3) The median maternal plasma RBP4 concentration did not differ significantly between patients with a normal pregnancy and those with an SGA neonate or with an FD; 4) Among normal pregnant women, the maternal plasma RBP4 concentrations did not correlate with pre-pregnancy body mass index, gestational age at blood sampling and neonatal birthweight.

Conclusions—1) Preeclampsia, but not pregnancy with an SGA neonate or an FD, is associated with a higher median maternal plasma concentration of RBP4 than normal pregnancy; 2) Preterm PE, and specifically early-onset PE, is associated with higher median RBP4 concentrations in maternal plasma compared to term PE. These findings suggest a role for RBP4 in the pathogenesis of preterm PE, but not in SGA and FD.

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Keywords

Adipokines; fetal death (FD); fetal demise; intrauterine fetal death (IUFD); pregnancy; RBP4; small-for-gestational age (SGA) neonate

Introduction

Preeclampsia is a leading cause of maternal and perinatal mortality and morbidity[27,61,106, 110], and together with small-for-gestational age (SGA) neonate and fetal death are part of the "great obstetrical syndromes"[102]. Consistent with the syndromic nature, of these conditions, several mechanism of disease have been associated with their clinical manifestations, such as an anti-angiogenic state[16,17,30,31,[38],[57],[59],[60],65,103,122,126], abnormal physiologic transformation of the spiral arteries[14,15,26,83,91], chronic uteroplacental ischemia[12,41, 85,100,108], increased trophoblast apoptosis/necrosis[51] and endothelial cell dysfunction [22,36,92,97,99,119]. Notably, preeclampsia, SGA and fetal death have all been associated with maternal metabolic complications such as obesity[23,29,109,110,129], insulin resistance [34,52,115,131] and dyslipidemia [42,128]. In addition, these women have an increased risk of metabolic syndrome-related morbidity[20,39,44,111] and mortality[49,53,113] later in life.

Adipokines are a family of biologically active adipocyte-derived cytokines/hormones, such as leptin, adiponectin, visfatin and resistin, as well as tumor necrosis factor (TNF), interleukin (IL)-6, IL-1 and monocyte chemotactic protein-1 (MCP-1)[120]. Adipokines have been implicated in the physiology and pathophysiology of glucose homeostasis, providing a link between obesity, insulin resistance and type 2 diabetes mellitus (DM)[120]. In addition, adipocytokines play a role in the pathophysiology of inflammatory disorders such as asthma [43], inflammatory bowel disease[6,123], rheumatoid arthritis[10,105] and obesity[32,121, 132,133]. Alterations in circulating concentrations of adipokines such as leptin, adiponectin, visfatin and TNF-α have been associated with the pathogenesis of preeclampsia[24,25,45,64, 81,86,95], SGA[70,75] and fetal death[89], as well as other complications of pregnancy [58, 68,69,71-[74],[76]-[80],82,87,88,125].

Retinol binding protein 4 (RBP4), previously thought to be only a specific carrier for retinol and be produced mainly by the liver, has recently[132] been added to the rapidly expanding family of adipokines. RBP4 is suggested to have a role in obesity-induced insulin resistance and, like other adipokines, increased circulating RBP4 concentrations have been reported in patients with diabetes[132] as well as in those destine to develop overt diabetes[21,40]. Thus, lowering RBP4 concentrations has been suggested as a potential therapeutic target in type 2 DM[40,118,132]. Furthermore, RBP4 may play a role in inflammation[5,134]. Indeed, in non-diabetic human subjects, RBP4 gene expression was found to be strongly associated with inflammatory markers of adipose tissue such as CD68 and MCP-1[134].

Currently, there is only one report[117] of RBP4 concentrations in patients with preeclampsia which found no association between maternal circulating concentrations of RBP4 and preeclampsia. Moreover, there is no data regarding changes in circulating RBP4 in patients with SGA or fetal death. The aim of this study was to determine whether maternal plasma concentration of RBP4 is associated with preeclampsia, delivery of an SGA neonate or a fetal death.

Materials and methods

Study groups and inclusion criteria

A retrospective cross-sectional study was conducted comprising women in the following groups: 1) normal pregnant women (n=134); 2) patients with preeclampsia (n=104); 3) pregnant women without preeclampsia or hypertension who delivered an SGA neonate (n=28); and 4) patients without preeclampsia or hypertension who had a fetal death (n=37). Women with multiple pregnancies or fetuses with congenital and/or chromosomal anomalies were excluded.

Samples and data were retrieved from our bank of biological samples and clinical databases. Many of these samples have previously been used to study the biology of inflammation, hemostasis, and angiogenesis regulation in normal pregnant women and those with pregnancy complications.

All participants provided written informed consent prior to the collection of maternal blood. The collection of maternal blood and its use for research purposes was approved by the Institutional Review Boards of the Sotero del Rio Hospital (Chile), Wayne State University (Detroit, Michigan, USA) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD/NIH/DHHS).

Clinical Definitions

Women with a normal pregnancy were defined as those without medical, obstetrical, or surgical complications at the time of the study and who subsequently delivered at term (>37 weeks of gestation) an appropriate-for-gestational age infant[3], without neonatal complications. Preeclampsia was defined as the onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two occasions, 4 hours to 1 week apart) after 20 weeks of gestation with proteinuria (≥300 mg in a 24 hour urine collection or at least one dipstick measurement ≥2+)[1]. Severe preeclampsia was diagnosed according to the criteria proposed by the American College of Obstetricians and Gynecologists (ACOG) committee [1]. Preterm preeclampsia was defined as the development of preeclampsia before 37 completed weeks of gestation. Patients with preeclampsia were further classified as either having early-onset (<32 weeks), or late-onset (≥32 weeks) disease according to the gestational age at which preeclampsia was diagnosed. SGA was defined as birthweight below the 10th percentile[3]. Women with a fetal death included those with a singleton pregnancy and fetal death diagnosed after 20 weeks of gestation. Fetal death was determined by absence of heart motion on ultrasound examination. The body mass index (BMI) was calculated using the formula: weight (kg)/height (m^2). The study population was classified according to the pre-pregnancy BMI into two groups: normal weight (BMI <25 $kg/m^{2)}$ and overweight/obese (BMI ≥25 kg/m^2) women[2].

Sample collection and determination of RBP4 in maternal plasma

Maternal blood samples were obtained once from each woman at the time of diagnosis and collected in vials containing ethylenediaminetetraacetic acid. The samples were then centrifuged at 1300 × g for 10 minutes at 4°C and the obtained plasma was stored at -80°C until assayed. Maternal plasma concentration of RBP4 was determined by sensitive enzyme-linked immunoassays (Millipore Corporation, St. Charles, MO, USA). The RBP4 immunoassay was validated for human plasma in our laboratory, prior to the conduction of this study. Immunoassays were carried out according to the manufacturer's recommendations. The calculated inter- and intra-assay coefficients of variation for RBP4 immunoassays in our laboratory were 5% and 5.1%, respectively. The sensitivity was calculated to be 0.10 ng/mL.

Statistical analysis

Normality of the data was tested using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Since maternal plasma RBP4 concentrations were not normally distributed, Kruskal–Wallis test with post-hoc analysis by Mann-Whitney U test were used for comparisons of continuous variables. Comparison of proportions was performed using Chi-square or Fisher's exact tests. Correlations between RBP4 concentrations and pre-pregnancy BMI and gestational age at blood sampling were examined using Spearman's rank correlation test. A *p*-value <0.05 was considered statistically significant. Analysis was performed with SPSS, version 14 (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics of women with a normal pregnancy, preeclampsia, an SGA neonate and a fetal death are listed in Table 1. Compared to women with a normal pregnancy, patients with preeclampsia had a higher rate of nulliparity, women with an SGA neonate were more likely to smoke and to have a lower pre-pregnancy BMI, and those with a fetal death had a lower median gestational age at blood sampling. All three groups had a lower median gestational age at delivery and a lower median neonatal birthweight than women with a normal pregnancy.

Maternal plasma RBP4 concentration in normal pregnancy

Retinol binding protein 4 was detected in the maternal plasma of all subjects included in this study. Among women with a normal pregnancy outcome, maternal plasma RBP4 concentration did not correlated with pre-pregnancy BMI (Spearman's rho -0.64, p=0.6), gestational age at blood sampling (Spearman's rho -0.038, p=0.7) or neonatal birthweight (Spearman's rho -0.032, p=0.8). In addition, the median maternal plasma RBP4 concentration did not differ significantly between women with a normal BMI and overweigh/obese women (median 9025.5 ng/mL, IQR 7681.9-10811 vs. 9023.4 ng/mL, IQR 7272.0-10506.7, respectively; p=0.8). Similarly, there was no significant difference between women who smoked and those who did not (8102.5 ng/mL, IQR 7090.3-10332.8 vs. 9168.8 ng/mL, IQR 7602.9-10245.9, respectively; p=0.3).

Maternal plasma RBP4 concentration in patients with preeclampsia

The median maternal plasma RBP4 concentration was higher in women with preeclampsia than in those with a normal pregnancy outcome (9769.3 ng/mL vs. 9080.9 ng/mL, p=0.03; Figure 1). In patients with preeclampsia, the maternal plasma RBP4 concentrations correlated with gestational age at blood sampling (Spearman's rho -0.34, p<0.001) and neonatal birthweight (Spearman's rho -0.31, p=0.01, but not with pre-pregnancy BMI (Spearman's rho -0.03, p=0.77). The median maternal plasma RBP4 concentration did not differ significantly between women with a normal BMI and overweight/obese women with preeclampsia (9888.4 ng/mL vs. 9932.2 ng/mL, respectively; p=0.9).

RBP4 in preterm preeclampsia (<37 week's gestation)

Among patients with preeclampsia, 37% (39/104) had preterm preeclampsia. The median maternal plasma RBP4 concentration of these women was higher than in those with preeclampsia at term (10257.6 ng/mL vs. 9018.3 ng/mL, p=0.017; Figure 2). Similarly, patients with preterm preeclampsia had a higher median RBP4 concentration than women with a normal pregnancy outcome (10257.6 ng/mL vs. 9080.9 ng/mL, p=0.002; Figure 2). There was no significant difference in the median maternal plasma RBP4 concentration between women with term preeclampsia and those with a normal pregnancy (p=0.8, Figure 2).

RBP4 in early-onset preeclampsia (<32 week's gestation)

Early-onset preeclampsia (<32 weeks' gestation) was diagnosed in 27% (28/104) of patients with preeclampsia. The demographic and clinical characteristics of women with early and late-onset preeclampsia (≥32 weeks' gestation) are displayed in Table 2. The median maternal plasma RBP4 concentration of women with early-onset preeclampsia was higher than in those diagnosed with preeclampsia at ≥32 weeks of gestation (11427 ng/mL vs. 9260.0 ng/mL, p<0.001; Figure 3), as well as than in women with a normal pregnancy (11427 ng/mL, vs. 9080.9 ng/mL, p<0.001; Figure 3). In contrast, the median maternal plasma RBP4 concentration did not differ significantly between patients with preeclampsia diagnosed ≥32 weeks of gestation and normal pregnant women (p=0.8).

RBP4 in severe preeclampsia and preeclampsia with an SGA neonate

Among patients with preeclampsia, 80% (83/104) had severe preeclampsia, and 49% (51/104) delivered an SGA neonate. There was no significant difference in the median maternal plasma concentration of RBP4 between patients with severe preeclampsia and those with mild preeclampsia (9810.9 ng/mL, IQR 7816.1-11715.7 vs. 9724.7 ng/mL, IQR 7699.4-11754.2, respectively; p=0.7). Similarly, the median maternal plasma RBP4 concentration did not differ significantly between patients with preeclampsia with or without an SGA neonate (9721.6 ng/mL, IQR 8249.3-12393.2 vs. 9837.5 ng/mL, IQR 7603.4-11698.4, respectively; p=0.6).

Maternal plasma RBP4 in patients with an SGA neonate or a fetal death

Among normotensive women with an SGA neonate, 82% (23/28) had a neonate with a birthweight <5th centile for gestational age. The median maternal plasma concentration of RBP4 was not significantly different between women with an SGA neonate and those with a normal pregnancy outcome (8831.3 ng/mL vs. 9080.9 ng/mL, respectively; p=0.6; Figure 1). There was no significant difference in the median maternal plasma RBP4 concentration of women with severe SGA (<5th centile for gestational age) and those whose neonates weighed between the 5th and <10th centiles for gestational age (8938.3 ng/mL, IQR 7112.6-10328.8 vs. 7818.0 ng/mL, IQR 7079.7-9833.9, respectively; p=0.5)

Similarly, the median maternal plasma RBP4 concentrations did not differ significantly between women with a fetal death and those with a normal pregnancy outcome (8877.3 ng/mL vs. 9080.9 ng/mL, respectively; p=0.7; Figure 1).

Discussion

Principal findings of the study

1) Patients with preeclampsia had a higher median maternal plasma concentration of RBP4 than women with a normal pregnancy; 2) Early-onset preeclampsia (<32 weeks) is associated with a higher median maternal plasma RBP4 concentration than late-onset preeclampsia; 3) The median maternal plasma RBP4 concentrations of women with an SGA neonate or fetal death did not differ significantly from normal pregnant women.

RBP4 - a novel adipokine—Retinol binding protein[55] belongs to the lipocalin family and is a specific carrier of retinol from the liver to peripheral tissues. RBP4 is a plasma protein [101], while RBP1, RBP2[28], RBP5 and RBP7 are cellular proteins, and RBP3 is the interstitial form[62].

Although RBP is mainly synthesized by the liver[93], subsequent studies demonstrated that it is also produced by adipocytes[66,84]. Only recently, RBP4 has been characterized as a novel adipokine when its role in the pathogenesis of insulin resistance has been proposed[132]. RBP4, similar to other adipokines [11,58,63,77-79,86-88,112,120,121,132,133],has also been linked to

inflammation[5,134]. Gene expression of RBP4 was found to be strongly associated with inflammatory markers (i.e., CD68 and MCP-1) of adipose tissue in non-diabetic human subjects[134]. In children, RBP4 concentrations correlated not only with indices of obesity and insulin resistance but also with inflammatory factors such as C-reactive protein and IL-6[5].

RBP4 concentration during normal gestation—Among women with a normal pregnancy, there was no correlation between RBP4 concentrations and maternal age, gestational age at blood sampling, pre-pregnancy BMI and neonatal birthweight. In addition, there was no difference in the median RBP4 concentrations between normal weight and overweight/obese patients, as well as between healthy pregnant women who smoked and those who did not.

Our findings are in agreement with a recent report by Stepan et al[117] in which RBP4 was not associated with gestational age at blood sampling, gestational age at delivery and neonatal birthweight. The authors also reported a lack of correlation between RBP4 and markers of adiposity (BMI, leptin), insulin resistance (fasting glucose, fasting insulin, HOMA-IR and adiponectin) and lipid metabolism (cholesterol, triglycerides)[117]. Similarly, no change in circulating RBP with increasing gestational age was reported[7,19,35,37]. The results of our study demonstrate lack of correlation over a wide range of gestational age (20-42 weeks' gestation) and that there is no difference in RBP4 concentrations between normal weight and overweight/obese pregnant women.

RBP4 concentration is elevated in preterm preeclampsia but not in term preeclampsia—The finding that the median maternal plasma concentration of RBP4 is higher in patients with preeclampsia than in women with a normal pregnancy outcome is novel. Moreover, among patients with preeclampsia, but not in normal pregnant women, the RBP4 concentrations had a significantly negative correlation with gestational age at blood collection (at the time of diagnosis of preeclampsia). Thus, the earlier the diagnosis, the higher was the maternal plasma RBP4 concentrations. This is pertinent since the timing of the diagnosis of preeclampsia is an important index of severity. The finding that preeclampsia is associated with higher circulating RBP4 concentrations is in agreement with a recent study by Atkinson et al[4].in which a proteomic approach was used to identify novel biomarkers for preeclampsia. The authors found RBP4 to be differentially up-regulated (2.1 fold-change) in the serum of patients with preeclampsia compared to matched healthy pregnant women[4].

Our results are in disagreement with the study reported by Stepan et al[117] regarding RBP4 concentrations in maternal circulation The authors found no significant differences in the mean maternal serum RBP4 concentration between patients with preeclampsia (n=16) compared to normotensive controls (n=20) admitted to the hospital for other obstetrical complications [117]. This apparent contradiction can be explained by differences in sample size, study population and inclusion criteria for the control group. In addition, the authors[117] did not differentiate between term and preterm preeclampsia. The relatively large sample size of our study allowed us to identify higher concentrations of circulating RBP4 in patients with early-onset preeclampsia.

Why is early-onset preeclampsia associated with elevated maternal RBP4 concentrations?—The cross-sectional nature of our study does not allow us to discern a cause-effect relationship between elevated maternal plasma RBP4 concentrations and preeclampsia; however, several suggestions for this findinf can be raised:

1. An activation of the immune response has been implicated as a cause of endothelial cell dysfunction and preeclampsia [36,97,99]. Adhesion molecules play a central role in the adherence of leukocytes to endothelial cells and the subsequent migration of

white blood cells into perivascular tissue and have been implicated in the pathophysiology of preeclampsia[18]. A recent study[90] in adults with newly diagnosed type 2 DM reported a positive correlation between RBP4 and soluble adhesion molecules such as sICAM-1 and sE-selectin. It was suggested that RBP4 might be responsible for up-regulating endothelial adhesion molecules and the development of vascular complications in type 2 DM[8,56]. Furthermore, RBP4 inhibits insulin action in endothelial cells, leading to impaired NO-dependent vasodilation[127]. Thus, the increased maternal plasma RBP4 concentration in patients with preeclampsia may be an additional marker of endothelial dysfunction [90].

2. Several hallmarks of the metabolic syndrome, which includes abdominal obesity, high level of triglycerides, low level of high-density lipoprotein, cholesterol, high blood pressure, and high fasting glucose are well established risk factors for preeclampsia [29,34,42,48,[50],[52],54,110,115,131]. Similar to the metabolic syndrome, preeclampsia is emerging as a risk factor for cardiovascular complications later in life[9,33,44,96, 111,113,114,130]. Importantly, Bellami et al[9] reported in a recent meta-analysis that women who had preterm preeclampsia had the greatest risk of future cardiovascular disease, and this was higher than those who had severe preeclampsia, supporting the concept that timing of onset of preeclampsia more accurately reflects the severity of the maternal cardiovascular phenotype[9]. Elevated circulating RBP4 concentration has been linked to insulin resistance[21,40,132], a core component of the metabolic syndrome. Moreover, it has been associated with a subclinical cardiovascular disease in the elderly[47]. Thus, the elevated RBP4 concentration found in patients with early-onset preeclampsia may be a marker for a subclinical metabolic syndrome, which is reflected by the greater risk of cardiovascular complications in later life observed in these women compared to those with term preeclampsia[9].

3. Serum RBP4 concentration has been shown to be elevated in patients with impaired kidney function[94,104]. In addition, it has been suggested that the increased RBP concentration observed in patients with type 2 DM may be due to impaired kidney function rather than the diabetic state itself[46,67]. During normal pregnancy, the urinary excretion of RBP is greater than in the non-pregnant state, and increases from the first to the second and third trimester[7,35]. It is possible that the impaired renal function that accompanies preeclampsia, especially in its more severe form, may lead to decreased glomerular filtration rate and decreased excretion of RBP4 in urine. In our study, a significantly higher proportion of patients with early-onset preeclampsia (<32 weeks) had a urine dipstick measurement ≥3+ protein compared to those diagnosed with preeclampsia later in pregnancy (86% [24/28] vs. 64% [49/76], p=0.03)

4. The lack of correlation between circulating RBP4 concentrations and obesity-related parameters demonstrated in our study and those of others[117,124], leads to the suggestion that the liver, rather than adipose tissue, may be involved in regulating the circulating RBP4 concentration[13]. It may be that the differences in the RBP4 concentration between normal pregnant women and those with early-onset preeclampsia are related to liver dysfunction. Hepatic fat accumulation has been demonstrated to increase RBP4[107,116] and a positive association between alanine aminotransferase and RBP4 concentrations has been recently suggested[98]. In our study, there was a trend toward a higher rate of elevated liver function tests (aspartate aminotransferase >70 IU/L) in patients with early-onset preeclampsia than in those with preeclampsia later in pregnancy (23% [6/23] vs. 11% [8/73], respectively; p=0.1).

RBP4 concentrations in maternal blood are not associated with SGA or fetal death

Although preeclampsia, SGA and fetal death share several common mechanisms of disease, we did not find an association between circulating maternal RBP4 and pregnancies complicated by an SGA infant or a fetal death. These findings suggest that RBP4 does not play a role in the pathophysiology of these obstetrical syndromes among normotensive pregnant women. The elevated concentrations of RBP4 found only in patients with early-onset preeclampsia could be explained by different mechanisms of disease distinguishing this complication from SGA or fetal death. While the clinical manifestations of preeclampsia involve mainly the maternal compartment, SGA and fetal death are primarily a consequence of a fetal disease. Thus, the increased circulating RBP4 concentrations in preeclampsia may reflect an exaggerated maternal inflammatory response, a subclinical metabolic syndrome or other aspects of disease such as renal or liver dysfunction associated with preeclampsia.

In conclusion, we were able to demonstrate, for the first time, an association between higher maternal circulating RBP4 concentration and preeclampsia, specifically among patients with early-onset preeclampsia. Such an association was not evident among normotensive pregnant women with either an SGA neonate or a fetal death. Further studies are needed in order to elucidate the relationship between maternal circulating RBP4 concentration and preeclampsia.

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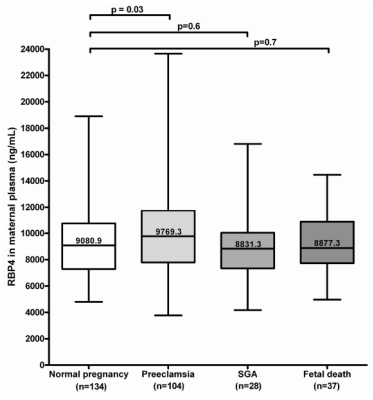

Figure 1. Box and whisker plot of the comparison of the median plasma RBP4 concentrations of women with a normal pregnancy and those with preeclampsia, SGA or fetal death

The median maternal plasma concentration of RBP4 was higher in patients with preeclampsia than in those with a normal pregnancy (9769.3 ng/mL, interquartile range (IQR) 7780.2-11732.8 vs. 9080.9 ng/mL, IQR 7284.4-10741.3, p=0.03). The median maternal plasma concentration of RBP4 was not significantly different between patients with a normal pregnancy (9080.9 ng/mL, IQR 7284.4-10741.3), those with an SGA neonate (8831.3 ng/mL, IQR 7223.9-10056.1, p=0.6) and pregnant women with a fetal death (8877.3 ng/mL, IQR 7730.4-10878.9, p=0.7).

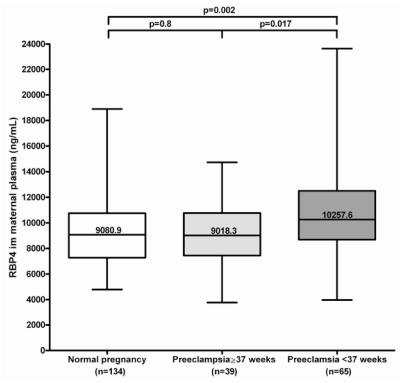

Figure 2. Box and whisker plot of the comparison of the median maternal plasma RBP4 concentration of patients with preterm (<37 weeks gestation) and term preeclampsia

The median maternal plasma RBP4 concentration of patients with preterm preeclampsia was higher than in women with a normal pregnancy (10257.6 ng/mL, IQR 8690.4-12500.4 vs. 9080.9 ng/mL, IQR 7284.4-10741.3, p=0.002), as wells as than those with term preeclampsia (9018.3 ng/mL, IQR 7451.4-10768.7, p=0.017). The median RBP4 concentration in maternal plasma did not differ significantly between normal pregnant women and those with term preeclampsia (p=0.8).

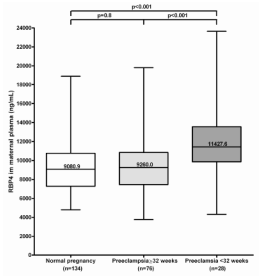

Figure 3. Box and whisker plot of the comparison of the median maternal plasma RBP4 concentration of patients with earl-onset preeclampsia (<32 weeks gestation) and those with preeclampsia diagnosed ≥32 weeks' gestation

The median maternal plasma RBP4 concentration of patients with early-onset preeclampsia was higher than in women with a normal pregnancy (11427 ng/mL, IQR 9852.9-13560.0 vs. 9080.9 ng/mL, IQR 7284.4-10741.3, p<0.001) and than those with preeclampsia diagnosed ≥32 weeks' gestation (9260.0 ng/mL, IQR 7456.0-10880.9, p<0.001). The median RBP4 concentration in maternal plasma did not differ significantly between normal pregnant women and those with preeclampsia diagnosed ≥32 weeks' gestation (p=0.8).

Table 1

Demographic and clinical characteristics of the study population.

	Normal Pregnancy (n=134)	PE (n=104)	p[1]	SGA (n=28)	p[2]	Fetal Death (n=37)	p[3]
Maternal age (years)	25 (21-29)	23.5 (20-29)	NS	23 (20-28.5)	NS	27 (25-29.5)	NS
Ethnicity, African American	79.5 (105/132)	81.7 (85)	NS	89.3 (25)	NS	88.9 (32/36)	NS
Smoking	17.4 (23/132)	13.5 (14)	NS	42.9 (12)	0.005	32.4 (12)	NS
Nulliparity	27.6 (37)	62.5 (65)	<0.001	46.4 (13)	NS	29.7 (11)	NS
Pre-pregnancy BMI (kg/m^2)	26.4 (22.6-33.1)	26.6 (23.5-30.0)	NS	23.1 (18.5-28.8)	0.027	27.9 (24.9-32.9)	NS
Gestational age at blood sampling (weeks)	37.6 (31.1-39.1)	36.0 (31.6-38.5)	NS	37.4 (34.7-38.4)	NS	31 (26.9-36.6)	0.002
Gestational age at delivery (weeks)	39.3 (38.7-40.2)	36 (32.3-38.6)	<0.001	37.6 (36.3-38.4)	<0.001	31 (27.4-36.7)	<0.001
Sample storage time (years)	7.7 (6.8-8.1)	7.5 (6.8-8.0)	NS	7.3 (6.6-7.6)	NS	7.5 (6.8-7.9)	NS
Birth weight (g)	3342 (3100-3629	2195 (1480-2815)	<0.001	2240 (1897-2470)	<0.001	1417 (779-2263)	<0.001

Values are expressed as median (interquartile range) or % (number);

PE – preeclampsia; SGA – Small-for-gestational age; BMI – Body Mass Index; NS - Not significant;

p[1] – between preeclampsia and normal pregnancy

p[2] – between SGA and normal pregnancy

p[3] – between fetal death and normal pregnancy

Table 2

Demographic and clinical characteristics of patients with early-onset preeclampsia and those with preeclampsia diagnosed ≥ 32 weeks of gestation.

	Gestational age at diagnosis of preeclampsia		
	< 32 weeks (n=28)	**≥32 weeks (n=76)**	**p**
Maternal age (years)	24.5 (20-31.7)	23.5 (19-27.7)	NS
Ethnicity, African American	67.9 (19)	86.8 (66)	NS
Smoking	10.7 (3)	16.9 (11)	NS
Nulliparity	67.9 (19)	60.5 (46)	NS
Pre-pregnancy BMI (kg/m^2)	26.8 (23.5-29.7)	26.6 (23.1-30.1)	NS
Gestational age at blood sampling (weeks)	29.5 (27.5-30.5)	37.2 (34.6-39)	<0.001
Gestational age at delivery (weeks)	30.1 (27.7-31.7)	37.3 (35.1-39)	<0.001
Sample storage time (years)	7.4 (7.1-7.9)	7.5 (6.7-8.1)	NS
Birth weight (g)	1150 (775-1370)	2590 (2025-2995)	<0.001

Values are expressed as median (interquartile range) or % (number);

BMI – Body Mass Index; NS - Not significant;