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Evidence of Endothelial Dysfunction in Preeclampsia and Risk of Adverse Pregnancy Outcome

Robert W. Powers, PhD, **Janet M. Catov, PhD**, **Lisa M. Bodnar, PhD**, **Marcia J. Gallaher, BS**, **Kristine Y. Lain, MD**, and **James M. Roberts, MD**
Magee-Womens Research Institute, Pittsburgh, Pennsylvania (RWP, JMC, LMB, MJG, JMR); Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (RWP, LMB, JMR); Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania (JMC, LMB, JMR); and Department of Obstetrics and Gynecology, University of Kentucky, Lexington (KYL)

Abstract

The purpose of this study is to investigate whether endothelial dysfunction, as assessed by elevated cellular fibronectin (cFN), in women with preeclampsia is associated with an increased risk of preterm and/or small-for-gestational-age (SGA) births. Maternal plasma cFN was measured by enzyme-linked immunosorbent assay in samples collected at admission to delivery in 605 normotensive women, 171 women with transient hypertension, and 187 women with preeclampsia. Logistic regression was used to estimate the risk for preterm delivery, SGA, or both. Elevated cFN in women with preeclampsia was associated with an increased risk of both preterm and SGA births (odds ratio, 3.0; confidence interval [CI], 1.0-8.7) compared with women with preeclampsia without elevated cFN. The risk of preterm birth was 14.7-fold higher (CI, 8.1-26.7) and the risk of SGA was 6.8-fold higher (CI, 3.5-13.1) in women with preeclampsia, hyperuricemia, and elevated cFN compared with normotensive women. Elevated cFN is prevalent among women with preeclampsia and identifies women at increased risk of preterm delivery and SGA.

Keywords

Preeclampsia; pregnancy; cellular fibronectin; small for gestational age; preterm delivery

Hypertensive disorders of pregnancy are associated with an increased risk of maternal and fetal morbidity and mortality. Among hypertensive disorders of pregnancy, preeclampsia, clinically diagnosed by gestational hypertension and proteinuria after the 20th week of gestation, is the leading cause of maternal and fetal morbidity and mortality, accounting for as much as 15% of preterm deliveries and 25% of cases of small-for-gestational-age (SGA) infants.[1-3] The clinical criteria of gestational hypertension and proteinuria are the hallmarks for identifying women with the syndrome; however, these clinical criteria have been shown to be poor predictors of adverse maternal or perinatal outcome.[4] We have previously reported that the presence of maternal hyperuricemia is associated with an increased risk of preterm delivery and SGA in women with gestational hypertension, proteinuria, or both.[5]

Endothelial dysfunction is accepted to be a central pathophysiological feature of preeclampsia leading to altered vascular reactivity and loss of vascular integrity.[6-10] Endothelial dysfunction has been evaluated by direct measurement of vascular function and changes in circulating

Address correspondence to: Robert W. Powers, PhD, Magee-Womens Research Institute, 204 Craft Ave, Room 620, Pittsburgh, PA 15213. E-mail: E-mail: rsirwp@mwri.magee.edu.

markers. Cellular fibronectin (cFN), an isoform of fibronectin synthesized locally by endothelial cells in response to tissue injury, has been reported in several studies to be elevated in women with preeclampsia.[11-16] The objective of this study is to investigate whether endothelial dysfunction, as assessed by elevated cFN, in pregnancies with and without preeclampsia identifies women at increased risk of preterm or SGA births.

Materials and Methods

Study Population

We evaluated data acquired from 1997 to 2002 as part of an ongoing study of preeclampsia at Magee-Womens Hospital, Pittsburgh, Pennsylvania, approved by the Institutional Review Board, and informed consent was obtained from all participants. Eligibility criteria were nulliparous women with singleton gestations and no obstetric or medical problems. Sociodemographic and clinical data were ascertained by a structured interview at entry to the study and medical chart abstraction after delivery.

For this nested case-control study, we randomly selected 605 normotensive women and all women who developed gestational hypertension in the cohort with available blood specimens (n = 358). The measurement of cFN is sensitive to multiple freeze-thaw cycles (>3 times), and only EDTA plasma samples can be used for this measure. The samples used in this study were not constrained by selection criteria other than availability of an appropriate EDTA plasma sample that had not been subjected to multiple freeze-thaw cycles (all samples were frozen and thawed 2 times).

Gestational hypertension was defined as systolic blood pressure persistently ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg for the first time after 20 weeks of gestation. In this study, we determined blood pressure as the average of the last 5 blood pressures obtained in semi-Fowlers position after hospital admission for delivery but before medications or clinical perturbations that would alter blood pressure. Preeclampsia (n = 187) was defined by the research criteria recommended by the National High Blood Pressure Education Program[17]: gestational hypertension, proteinuria, and return of all abnormalities to normal by 12 weeks postpartum. Proteinuria was the excretion of ≥300 mg of protein in 24 hours, ≥2+ protein on voided urine sample, ≥1+ protein on catheterized urine specimen, or a protein-creatinine ratio of ≥0.3. Transient hypertension (n = 171) was defined as gestational hypertension without proteinuria. To compare to our previous results, we also identified the presence of hyperuricemia as serum or plasma uric acid concentrations ≥1 standard deviation above normal for gestational age.[18] Plasma uric acid was measured as previously described.[19] All normotensive and hypertensive participants were tested for proteinuria.

Human cFN Quantitation

Maternal plasma cFN was quantified by an enzyme-linked immunosorbent assay specific for the ED-A domain of human cFN, as described previously.[12] In brief, plasma concentrations of cFN were determined by calculating from the linear equation of a standard curve derived from purified human cFN (Upstate Biotechnology, Lake Placid, NY). Standards and samples were diluted in a phosphate-buffered saline, 2% bovine serum albumin buffer. The optimal dilution of each sample was predetermined to provide values in the middle of the standard curve, usually 1 to 50 or 1 to 100 dilutions. A quality control sample was assayed with each microtiter plate. The coefficient of variation between runs was 7%. Elevated cFN was defined as the highest quartile of cFN (>25.53 μg/mL) among normotensive women without hyperuricemia (n = 417).

Preterm delivery was defined as fewer than 37 completed weeks of gestation. Gestational age–specific birth weight centiles were based on data from Magee-Womens Hospital adjusted for sex and race. SGA was defined as birth weight ≤10th centile corrected for gestational age, race, and sex. Maternal race and smoking status were self-reported at enrollment. Prepregnancy body mass index (BMI; weight [kg]/height [m^2]) was based on measured height and maternal self-report of prepregnancy weight at the initial visit, as previously described.[20] Maternal venous EDTA plasma samples were collected upon admission to the hospital for delivery. Samples were stored at −70°C for later analysis.

Statistical Analysis

Data are presented as the mean ± standard deviation or median and interquartile range (IQR). The χ^2 test for homogeneity and 1-way analysis of variance were used to test for differences in categorical and continuous maternal characteristics, respectively. cFN was not normally distributed (Shapiro-Wilk test, $P < .01$), so median concentrations were compared using the Wilcoxon rank sum test, and the relationship with continuous variables was evaluated using Spearman correlation coefficients. Outcomes were preterm birth and SGA infants. We also identified infants who were both preterm and SGA to describe severity. Logistic regression was used to estimate the risk for preterm delivery and/or SGA, after adjustment for BMI, smoking, and hyperuricemia. Separate models were built for each group (normotensive, transient hypertension, and preeclampsia) to estimate the risk associated with elevated cFN compared with the referent of women without elevated cFN. We then modeled the risk of preterm birth or SGA associated with combinations of hypertension, proteinuria, hyperuricemia, and elevated cFN, compared with the referent of normotensive women without these conditions. Adjusted linear regression models were used to estimate the effect of elevated cFN on gestational age at delivery and birth weight centile, independent of hypertension, proteinuria, hyperuricemia, smoking, and BMI. Statistical significance was accepted as $P < .05$ or the 95% confidence interval (CI) of the odds ratio not crossing 1.

Results

Cellular Fibronectin Is Elevated in Preeclampsia

Demographic characteristics of the 3 groups of study participants are shown in Table 1. The maternal plasma concentration of cFN were significantly elevated in women with preeclampsia (30.4; IQR, 18.2-43.2 μg/mL) compared with both normotensive pregnant women (17.3; IQR, 11.9-26.5 μg/mL) and women with transient hypertension of pregnancy (17.3; IQR, 12.2-29.1 μg/mL; $P < .01$). Women with preeclampsia were more likely to be categorized with elevated cFN (the highest quartile of cFN in normotensive pregnant women, >25.53 μg/mL, 59.4%) compared with both normotensive pregnant women (27.1%) and women with transient hypertension of pregnancy (29.2%, $P < .01$). cFN was higher in white women compared with black women (19.0 [IQR, 13.2-32.2 μg/mL] vs 15.8 [IQR, 11.0-24.0 μg/mL]; $P < .01$) and higher in nonsmokers compared with smokers (20.1 [IQR, 13.1-31.5 μg/mL] vs 16.5 [IQR, 11.6-25.5 μg/mL]; $P < .01$). cFN increased modestly as maternal age increased ($r = 0.20$, $P < .01$), and cFN concentrations were similarly correlated with serum uric acid ($r = 0.25$, $P < .01$). There was no relationship between maternal prepregnancy BMI and cFN concentrations ($r = 0.004$, $P = .90$).

Elevated cFN, Preterm Birth, and SGA

We investigated whether the presence of elevated cFN was associated with a higher prevalence of adverse pregnancy outcomes: preterm birth (<37 weeks), delivery of an SGA infant, or delivery of infants both preterm and SGA. Normotensive women with elevated cFN did not have a higher risk of any adverse outcomes compared with normotensive women without elevated cFN after adjustment for smoking, BMI, and hyperuricemia (Table 2). Similarly, the

presence of elevated cFN among women with transient hypertension posed no significant additional risk. While the risk of preterm birth and SGA tended to be higher among women with preeclampsia and elevated cFN, after adjustment for hyperuricemia, the risk was statistically significantly elevated only for the most severe outcome, delivery of an infant both preterm and SGA.

We previously reported that the presence of elevated maternal serum uric acid is associated with a significant increased risk of preterm birth and SGA in women with gestational hypertension, proteinuria, or both.[5] Therefore, we estimated the additional risk associated with elevated cFN in the presence of preeclampsia with hyperuricemia. When restricted to women with preeclampsia and hyperuricemia, the risk of SGA increased 2.9-fold (95% CI, 1.0-8.0) among women who also had elevated cFN. In addition, the risk of delivery of an infant both preterm and SGA increased 4.2-fold (95% CI, 1.2-14.3) among this group. Overall, elevated cFN or elevated uric acid were quite common in subjects with preeclampsia (80.1% of preeclampsia subjects). In addition, elevated cFN and hyperuricemia often occurred together in women with preeclampsia (42.5% of preeclampsia subjects).

We evaluated the risk of preterm birth or SGA associated with all combinations of hypertension, proteinuria, hyperuricemia, and elevated cFN compared with the referent group of women without any of these conditions. Women with preeclampsia, hyperuricemia, and elevated cFN (HPUC) had the highest prevalence of preterm birth (58.2%) and SGA (30.4%; Table 3). The risk of preterm birth in this group was 14.7 times higher compared with normotensive women, and the risk of SGA was 6.8 times higher. In addition, gestational age at delivery and birth weight centile for HPUC women were also significantly lower than that of normotensive women (Table 4). In comparison, women with clinically recognizable preeclampsia but without hyperuricemia or elevated cFN did not have a higher adjusted risk of preterm birth or SGA (Table 3). Conversely, women with preeclampsia and elevated cFN but without hyperuricemia delivered infants who were, on average, 14% smaller for gestational age ($P = .01$) compared with the referent group (Table 4). Similar to our previous observation, women with preeclampsia and hyperuricemia but without elevated cFN (HPU) evidenced a significantly higher adjusted risk of both preterm delivery and SGA (Table 3).

Discussion

These data indicate that endothelial dysfunction is common among women with preeclampsia. Women with elevated cFN in the presence of preeclampsia are more likely to deliver infants born preterm and SGA compared with women with preeclampsia without evidence of endothelial dysfunction. In addition, elevated cFN in preeclampsia with hyperuricemia, a condition previously demonstrated to be associated with an increased risk of preterm delivery and SGA,[5] is associated with a further increased risk of SGA or preterm delivery with SGA. These data indicate that evidence of endothelial dysfunction, as determined by elevated cFN, identifies women with preeclampsia who are at a particularly increased risk of adverse outcomes.

The increased incidence of preterm birth in this study is an indication of severity of the preeclampsia syndrome, and the births were, for the most part, medically indicated and induced preterm births (88%). Since care providers had no knowledge of cFN results, it did not influence the outcome. It is also possible that the spontaneous preterm births are related to preeclampsia. In a prior study, we showed that women with preeclampsia in a first pregnancy have an excess of preterm birth in their next normal pregnancy.[21] In keeping with this, elevated cFN in an otherwise normotensive uncomplicated pregnancy is not associated with an increased risk of preterm delivery or SGA. These data support the hypothesis that markers associated with the pathophysiology of the syndrome provide insight into the clinical outcome.

It is well known that hypertensive disorders of pregnancy are associated with increased maternal and fetal morbidity and mortality, including preterm delivery and SGA infants, and that the maternal syndrome preeclampsia contributes significantly to these adverse clinical outcomes. However, previous studies have reported that the clinical symptoms that identify women with preeclampsia, gestational hypertension and proteinuria, are poor indicators of adverse pregnancy outcome.[4] Conversely, it would seem logical that markers associated with the pathophysiology of preeclampsia may be more valuable in identifying women at increased risk of adverse pregnancy outcome. Endothelial dysfunction is accepted to be central to the pathophysiology of preeclampsia, and evidence of endothelial dysfunction has been reported in many studies of preeclampsia patients and is assessed by several methods, including elevated cFN.[11-16,22-25] Cellular fibronectin normally makes up less than 1% to 2% of the total fibronectin present in plasma, and importantly, cFN is synthesized by endothelial cells in response to cellular injury or stress.[26,27]

Several studies have reported that the presence of circulating markers of endothelial dysfunction including soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), E-selectin, plasma fibronectin, and cellular fibronectin are elevated in patients with preeclampsia and/or are associated with an increased risk of developing preeclampsia.[11-13,16,26,28-36] Specifically, with regard to cFN, a study published by Chavarria et al[11] in 2002 reported that maternal plasma cFN concentrations rose as pregnancy advanced, elevated cFN was present as early as 12 weeks of gestation in women who later developed preeclampsia, and elevated cFN was associated with an increased risk of developing preeclampsia (odds ratio, 16.1). Thus, endothelial dysfunction is present very early in pregnancy in women who later develop preeclampsia and identifies individuals at increased risk. In contrast, despite the relevance of endothelial dysfunction to the pathophysiology of preeclampsia, few studies have investigated the relationship between markers of endothelial dysfunction and the severity of preeclampsia or pregnancy outcomes. Djurovic et al[29] published that maternal concentrations of soluble vascular cell adhesion molecule 1 (sVCAM-1) were significantly elevated in both mild and severe preeclampsia and further elevated in preeclampsia with SGA infants. Similarly, Kim et al[32] reported that sVCAM-1, sICAM-1, and E-selectin were elevated in women with preeclampsia and that sVCAM-1 concentrations were further elevated in severe patients. Our results demonstrate that evidence of endothelial dysfunction in women with preeclampsia is associated with increased risk of SGA as well as preterm birth with SGA. In contrast, women with preeclampsia but without hyperuricemia or elevated cFN did not show evidence of an increased risk of preterm birth or SGA.

There are clear limitations in this study. The first is that the gestational age at sample collection and measurement of cFN was late in pregnancy and after women had already manifested the clinical symptoms of preeclampsia. However, this limitation is tempered by the fact that other studies have already demonstrated that cFN is significantly elevated in early pregnancy, weeks before the clinical onset of preeclampsia, compared with women who go on to have an uncomplicated pregnancy.[11,24] Another limitation is the relatively small sample size, particularly in certain subgroups (ie, hypertension and elevated cFN or hyperuricemia). In addition, there are too few participants in this study to adequately address preterm delivery of less than 34 weeks or SGA less than the third centile. However, despite this limitation, this study still has many more participants overall compared with most other studies investigating circulating markers of endothelial dysfunction, and despite relatively few participants in certain subgroups, trends or statistically significant differences in the risk of SGA and/or preterm delivery were still observed. Finally, the women in this study are low-risk nulliparious patients, and it is unknown how these data may relate to high-risk groups such as those with chronic hypertension, diabetes, or multifetal gestation.

Conclusion

We have observed that elevated cFN is common in women with preeclampsia. Among women with clinically evident preeclampsia, elevated cFN is associated with an increased risk of SGA births as well as delivery of infants both preterm and SGA. Our results also raise the provocative possibility that preeclampsia without elevated cFN or hyperuricemia is not associated with an increased risk of preterm or SGA births, but this warrants further study. In addition, elevated cFN in normotensive pregnant women is also not associated with an increased risk of adverse pregnancy outcomes. These data suggest that a central component of the pathophysiology of preeclampsia, endothelial dysfunction, may provide additional insight into the clinical outcome of this syndrome.

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Table 1

Maternal and Newborn Demographics by Hypertensive Status[a]

	Normotensive Pregnancy (n = 605)	Transient Hypertension of Pregnancy (n = 171)	Preeclampsia (n = 187)	*P*[b]
Maternal age, y	23.9 ± 5.6	24.5 ± 5.7	26.8 ± 5.9	<.01
Maternal prepregnancy body mass index, kg/m^2	25.1 ± 6.1	26.9 ± 6.6	27.5 ± 6.7	<.01
Race, % black	29.1	29.4	19.1	.02
Smoking, %	32.5	20.0	20.2	<.01
Average blood pressure before 20 weeks of gestation, mm Hg	112.7 ± 7.7/68.8 ± 5.6	117.7 ± 8.6/71.7 ± 6.5	118.1 ± 9.8/72.6 ± 7.1	<.01
Average blood pressure at delivery, mm Hg	119.4 ± 9.7/72.0 ± 7.0	148.0 ± 11.1/86.3 ± 7.4	156.4 ± 13.6/92.0 ± 9.5	<.01
Gestational age at delivery (range), wk	39.0 ± 2.2 (22.4-42.4)	38.7 ± 1.8 (32.1-43.1)	36.2 ± 3.6 (25.4-41.8)	<.01
Infant birth weight, g	3299 ± 592	3181 ± 638	2508 ± 928	<.01
Infant birth weight centile, %	50.5 ± 28.2	45.8 ± 30.3	37.3 ± 29.0	<.01
Maternal plasma uric acid at delivery, mg/dL	4.9 ± 1.3	5.1 ± 1.2	5.7 ± 1.3	<.01
Median maternal plasma cellular fibronectin (range), μg/mL[c]	17.3 (11.9-26.5)	17.3 (12.2-29.1)	30.4 (18.2-43.2)	<.01

[a] Data are presented as the mean ± SD or percentage, unless otherwise indicated.

[b] Overall χ^2 or analysis of variance comparing the 3 groups.

[c] Median (interquartile range), compared using Wilcoxon rank sum.

Table 2

Risk of Preterm Delivery and SGA in Women With Elevated cFN

	Preterm Delivery (<37 wk)			SGA (<10th Centile)			Preterm and SGA		
	%	Crude OR	Adjusted OR[a] (95% CI)	%	Crude OR	Adjusted OR[a] (95% CI)	%	Crude OR	Adjusted OR[a] (95% CI)
Model 1									
Normotensive (n = 436)	7.5	1.0	1.0	7.5	1.0	1.0	—	—	—
Normotensive and elevated cFN (n = 169)	6.5	0.6 (0.3-1.4)	0.7 (0.3-1.5)	9.2	1.2 (0.6-2.3)	1.3 (0.7-2.5)	—	—	—
Model 2									
Transient hypertension (n = 119)	9.2	1.0	1.0	9.0	1.0	1.0	2.5	1.0	1.0
Transient hypertension and elevated cFN (n = 52)	13.5	1.6 (0.6-4.3)	0.9 (0.3-2.8)	17.7	1.2 (0.5-3.2)	1.2 (0.4-3.6)	5.8	1.6 (0.5-4.8)	1.1 (0.3-3.8)
Model 3									
Preeclampsia (n = 79)	27.9	1.0	1.0	14.3	1.0	1.0	7.6	1.0	1.0
Preeclampsia and elevated cFN (n = 108)	46.3	2.1 (1.2-3.5)	1.8 (0.9-3.6)	26.4	2.1 (1.1-4.1)	2.1 (0.9-4.6)	18.5	3.1 (1.3-7.5)	3.0 (1.0-8.7)
Model 4									
Preeclampsia and hyperuricemia (n = 42)	42.9	1.0	1.0	16.7	1.0	1.0	9.5	1.0	1.0
Preeclampsia, hyperuricemia, and elevated cFN (n = 79)	58.2	1.5 (0.8-3.0)	2.0 (0.9-4.3)	30.4	2.5 (1.1-6.0)	2.9 (1.0-8.0)	24.1	3.2 (1.2-9.0)	4.2 (1.2-14.8)

Abbreviations: cFN, cellular fibronectin; CI, confidence interval; OR, odds ratio; SGA, small for gestational age.

[a]Adjusted for prepregnancy body mass index and smoking; models 1, 2, and 3 were additionally adjusted for hyperuricemia.

Table 3

Risk of Preterm Delivery and SGA With Elevated cFN and Hyperuricemia

			Risk of Preterm Delivery (<37 wk)			Risk of SGA (<10th Centile)		
	Group	n	Unadjusted Prevalence	Adjusted OR[a]	95% CI	Unadjusted Prevalence	Adjusted OR[a]	95% CI
Normotensive	N	316	7.9	1.0	Referent	7.0	1.0	Referent
Elevated cFN	C	102	2.9	0.3	0.1-1.1	11.5	1.7	0.8-3.4
Hyperuricemia	U	126	5.6	0.6	0.3-1.4	8.7	1.1	0.5-2.3
Hyperuricemia and elevated cFN	UC	61	9.8	1.2	0.5-2.9	4.9	0.8	0.2-2.6
Hypertension only	H	83	3.6	0.4	0.1-1.3	10.8	1.3	0.6-3.3
Hypertension and elevated cFN	HC	21	9.5	1.0	0.2-4.4	9.5	1.3	0.3-6.1
Hypertension and hyperuricemia	HU	36	22.2	3.1	1.3-7.5	19.4	3.4	1.3-8.7
Hypertension, hyperuricemia, elevated cFN	HUC	31	16.1	2.0	0.7-5.6	19.4	2.7	0.9-7.8
Preeclampsia	HP	37	10.8	1.3	0.4-3.9	16.2	2.0	0.7-5.8
Preeclampsia and elevated cFN	HPC	28	13.8	1.7	0.5-5.2	13.8	2.7	0.9-8.6
Preeclampsia and hyperuricemia	HPU	42	42.9	8.0	3.8-16.4	16.7	2.7	1.1-6.7
Preeclampsia, hyperuricemia, and elevated cFN	HPUC	80	58.2	14.7	8.1-26.7	30.4	6.8	3.5-13.1

Abbreviations: cFN, cellular fibronectin; CI, confidence interval; OR, odds ratio; SGA, small for gestational age.

[a]Adjusted for prepregnancy body mass index and smoking.

Table 4

Relation Between Elevated Cellular Fibronectin (cFN) and Hyperuricemia and Length of Gestation and Birth Weight Centile

			Gestational Age at Delivery			Birth Weight Centile		
	Group	n	Unadjusted Gestational Age at Delivery[a]	Adjusted Coefficient[b]	*P*	Unadjusted Birth Weight Centile[a]	Adjusted Coefficient[b]	*P*
Normotensive	N	316	38.9 (2.5)	Referent		49.5 (27.6)	Referent	
Elevated cFN	C	102	39.2 (1.3)	0.43	.11	51.5 (29.6)	0.84	.77
Hyperuricemia	U	126	39.2 (1.7)	0.40	.11	51.8 (28.3)	2.46	.41
Hyperuricemia and elevated cFN	UC	61	38.6 (1.7)	–0.19	.57	52.8 (29.6)	0.91	.82
Hypertension only	H	83	39.1 (1.3)	0.23	.44	48.3 (30.5)	–4.30	.22
Hypertension and elevated cFN	HC	21	39.0 (1.6)	0.15	.79	45.1 (29.4)	–5.27	.39
Hypertension and hyperuricemia	HU	36	38.2 (2.2)	–0.69	.10	40.5 (31.8)	–12.49	.01
Hypertension, hyperuricemia, elevated cFN	HUC	31	38.3 (2.3)	–0.43	.34	45.9 (32.4)	–5.54	.30
Preeclampsia	HP	37	38.2 (2.0)	–0.62	.14	48.0 (32.6)	–3.44	.48
Preeclampsia and elevated cFN	HPC	28	38.1 (2.1)	–0.80	.09	39.6 (28.9)	–14.14	.01
Preeclampsia and hyperuricemia	HPU	42	36.0 (4.1)	–2.88	<.01	36.4 (28.9)	–15.13	<.01
Preeclampsia, hyperuricemia, and elevated cFN	HPUC	80	34.8 (3.8)	–4.03	<.01	31.4 (27.2)	–21.43	<.01

[a] Mean (SD).

[b] Adjusted for prepregnancy body mass index and smoking. Each coefficient represents the change in the gestational age at delivery (weeks) or birth weight centile associated with having gestational hypertension, proteinuria, hyperuricemia, and/or elevated cFN compared with normotensive women.