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Follistatin-Like 3 Across Gestation in Preeclampsia and Uncomplicated Pregnancies Among Lean and Obese Women

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Abstract

The purpose of this study was to examine circulating maternal follistatin-like 3 (FSTL-3) by gestational age and obesity in pregnancy and preeclampsia. FSTL-3 was quantified in maternal plasma collected in each trimester from prepregnancy body mass index-determined groups: 15 lean and 24 obese controls and 20 obese women who developed preeclampsia. Repeated measures mixed models and logistic regression were conducted ($P \leq .05$). FSTL-3 was not related to maternal adiposity. FSTL-3 changed across pregnancy in lean controls and obese preeclampsia but not in obese controls. FSTL-3 was higher in preeclampsia in the second trimester compared to lean controls and in the third trimester compared to both control groups. Elevated FSTL-3 at mid-gestation was associated with an increased odds of preeclampsia (odds ratio 3.15; 95% confidence interval 1.19-8.36; $P = .02$). Elevated FSTL-3 concentrations were attributable to preeclampsia and were associated with increased likelihood of later developing preeclampsia, suggesting further study as a biomarker prior to clinically evident disease.

Keywords

FSTL3, FSTL-3, preeclampsia, obesity, adiposity

Introduction

Preeclampsia is a serious complication affecting 4% to 8% of all pregnancies and remains a leading cause of maternal and perinatal mortality worldwide.[1,2,3] The severe consequences of preeclampsia and lack of precise understanding of pathogenesis previously led us to conduct a global gene expression microarray study with the goal of discovering new, unbiased candidates involved in early aberrant placentation.[4] Trophoblast and decidua specimens were obtained from residual material of clinically indicated chorionic villus sampling at an average of 11 weeks gestation in women who later developed preeclampsia or had uncomplicated pregnancy outcomes.[4] A novel panel of 36 genes was associated with preeclampsia in the tissues at the time when impaired placentation occurred.

One of the candidates was follistatin-like 3 (*FSTL3*).[4] This messenger RNA (mRNA) was downregulated and this was corroborated by quantitative polymerase chain reaction.[5] *FSTL3* encodes a secreted glycoprotein that inhibits the actions of proteins in the transforming growth factor β (TGF-β) family.[6-10] Signaling in associated pathways affects proliferation, differentiation, migration, and apoptosis of several different cell types. During placentation, various endometrial TGF-β proteins display pleiotropic effects in modulating trophoblast invasion,[11] and first-trimester trophoblasts express TGF-β3.[12] Loss of *FSTL3* in animals has been reported to increase insulin sensitivity and is associated with increased subcutaneous body fat, reduced visceral fat, and binds myostatin, a TGF-β protein, which normally reduces muscle mass.[13-15] *FSTL3* knockout mice are reported to develop hypertension by 9 months of age.[15]

Follistatin-like 3 has been shown to be most highly expressed by the placenta, followed by testes, heart, and pancreas in ranked comparison with 18 other human tissues.[6] Ciarmela et al localized the expression of *FSTL3* to trophoblast, decidua, and fetal membranes in the first and third trimesters

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of human pregnancy.[16] The most intense staining for FSTL-3 protein was detected in the walls of decidual and placental blood vessels. These cells and tissues are involved in early abnormal placentation in preeclampsia.[17,18] In addition, FSTL-3 protein is measurable in the first-trimester maternal circulation[19,20] and elevated in women with clinically evident preeclampsia compared to normal pregnancies.[21,22]

FSTL-3 concentrations have not been investigated across human gestation. Based on the downregulated *FSTL3* gene expression data,[4,5] we hypothesized that maternal circulating concentrations of FSTL-3 would be lower in the first trimester among women who subsequently develop preeclampsia compared to uncomplicated pregnancies and that concentrations would increase with gestational age in women who develop preeclampsia.[21,22] We also hypothesized that FSTL-3 concentrations would be higher in obese women across gestation because expression of *FSTL3* in adipocyte is increased in obese animals compared to those with normal body weight.[14] We predicted that circulating FSTL-3 would be associated with adipose distribution in women. This was an exploratory aim since *FSTL3* knockout mice exhibit lower visceral fat[13-15]; however, higher visceral fat in women's first trimester is associated with an increased risk of developing preeclampsia.[23] Moreover, our prior study of obesity and proinflammatory cytokine tumor necrosis factor-alpha in preeclampsia led us to suggest that adipose distribution, rather than body mass index (BMI), might be a better indicator of inflammation and glucose metabolism in pregnancy.[24]

Methods

Study Population

This was nested case–control study from the ongoing Prenatal Exposures and Preeclampsia Prevention (PEPP) investigation of preeclampsia at the University of Pittsburgh, Magee-Womens Hospital and Magee-Womens Research Institute. The study was approved by the University of Pittsburgh institutional review board and informed consent was obtained from all participants. The purpose of the third program project, PEPP3, from which this study's groups were drawn, was to investigate differences between obese pregnant women who develop preeclampsia compared to similarly obese women who do not develop preeclampsia. The PEPP3 was designed to investigate the underlying biological mechanisms of obesity that contribute to the development of preeclampsia. Controls were recruited from the same clinic population as the obese patients and were selected contemporaneously. For every 5 obese individuals recruited, 1 lean control was selected. This limited number of lean pregnant women (N = 100) were recruited only for the purpose of providing a "comparison group" in order to give context to the investigation of obese women who develop preeclampsia compared to obese women with uncomplicated pregnancies and to provide a reference for changes or differences that normally occur among lean pregnant women. The sample size is too small to provide a meaningful cohort of lean women with preeclampsia. Of 100 lean pregnant women, approximately 3 to 5 might be expected to develop preeclampsia. It was decided that this would represent too few patients for a lean preeclampsia group.

Participants were recruited to the study at the time of presentation to Magee-Womens Hospital for prenatal care. All participants were healthy women without known medical complications. The medical records of participants were juried regarding pregnancy outcome by a group of physician and research investigators. Control groups for our study were designated as normal uncomplicated pregnancies in lean (N = 15) and obese (N = 24) groups, and cases consisted of obese women who developed preeclampsia (N = 20). Obesity was defined as prepregnancy BMI of $\geq$30 kg/m^2. Lean women were defined as prepregnancy BMI of $\leq$25 kg/m^2. Preeclampsia was defined by research criteria recommended by the National High Blood Pressure Education Program.[25] Preeclampsia was diagnosed by gestational hypertension and proteinuria beginning after the 20th week of pregnancy and resolution of these abnormalities postpartum. Gestational hypertension was defined as an absolute blood pressure $\geq$140 mm Hg systolic and/or $\geq$90 mm Hg diastolic. Proteinuria was defined as $\geq$300 mg per 24-hour urine collection, $\geq$2+ protein on voided urine sample, $\geq$1+ protein on catheterized urine specimen, or a protein–creatinine ratio of $\geq$0.3.

With the sample size of 59 women, a medium effect size of 0.22 can be detected with 0.80 power at a 2-tailed significance level of .05 when fitting repeated measures models based on 3 groups and 3 measurement occasions.

Blood Samples

Maternal venous EDTA plasma samples were collected at initial study enrollment (mean 9.8 weeks $\pm$ 3.1 standard deviation [SD]), at mid-pregnancy (19.9 weeks $\pm$ 1.6), and in the third trimester (34.8 weeks $\pm$ 1.6). Samples were stored at –80°C for later analysis.

Quantitation of FSTL-3

Maternal plasma FSTL-3 concentrations were determined using a DuoSet enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems (DY1288, Minneapolis, Minnesota) according to the manufacturer's instructions. This ELISA has been validated by the company. Specifically, the intra- and interassay coefficient of variation of the ELISA is between 1.7% and 3.4% and 4.6% and 6.1%, respectively. Spike and recovery analysis was acceptable with an average recovery of 96% (85%-105%) for plasma. The FSTL-3 ELISA is sensitive with a reported sensitivity of 8.5 pg/mL compared to measured concentrations of FSTL3 between 3.1 and 133.4 ng/mL in plasma from pregnant women. The ELISA was successfully tested for linearity in multiple sample types. Finally, the ELISA was extensively tested for specificity and potential cross-reactivity and found to have no significant cross-reactivity or interference with the following recombinant human molecules:

activin C, activin RIA/ALK-2, activin RIIA, activin RIIB, ADAM12, ALK-1, BAMBI/NMA, BMP-1/PCP, BMP-2, BMP-3, BMP-3b/GDF-10, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8b, BMP-10, BMP-15, BMPR-IA/ALK-3, BMPR-IB/ALK-6, BMPR-II, Cripto, DAN, Endoglin/CD105, Fibronectin, Follistatin 288, Follistatin 300, Follistatin 315, Lefty A, Inhibin A, Inhibin B, LAP (TGF-β1), MIS/AMH, Osteoactivin/GPNMB, TGF-α, TGF-β1, TGF-β1.2, TGF-β2, TGF-β3, TGF-β RII, and TGF-β RIII. No specificity and cross-reactivity were found with additional mouse, rat, and other recombinant molecules or other natural proteins.

All plasma samples were analyzed in duplicate and laboratory personnel were unaware of the pregnancy outcome at the time of analysis. In general, samples were diluted 1 to 8 in order for samples to fall within the linear and measurable range of the assay's standard curve. The sensitivity of the assay was 0.15 ng/mL. The interassay variability was less than 10%.

Adiposity Measures

Bioelectrical impedance analysis (BIA) was measured to determine body composition at each visit using the RJL Systems BIA Quantum IV (RJL System, Clinton Twp, Michigan). Each participant was instructed to remove her right shoe and sock and then lie supine with her arms away from her body. Two electrodes were placed on the right hand, one on the wrist and one on the first joint of the middle finger. Two electrodes were placed on the right foot, one on the ankle and the other on the base of the second toe. Direct measures of resistance (R), reactance (Xc), and impedance (I) were recorded. Hematocrit was measured by centrifugation of whole blood in glass capillary tubes and measured red cell volume. Fat mass, percentage of body fat, and body water were calculated using published formulas specific for pregnancy.[26,27] Changes in fat mass and percentage of fat mass were calculated by determining differences between trimesters 2 and 1, 3 and 2, and 3 and 1. Maternal height, weight, hip circumference, and abdominal circumference were determined by standard clinical measures. Waist to hip ratio (WHR) was calculated using measurements conducted at study enrollment in the first trimester before the gravid uterus had begun to change the contour of the participant's mid-abdomen.[28] The body adiposity index was calculated using the formula from Bergman et al[29] (hip circumference)/(height)$^{1.5}$ − 18.

Statistical Analysis

Descriptive statistics including means and SD for continuous variables and frequency distribution for categorical variables were initially determined to describe the clinical and demographic characteristics of the participants for each group. Mean differences among the study groups with continuous variables were compared using 1-way analysis of variance or Kruskal-Wallis test. Group comparisons using categorical data were evaluated using either the chi-square test or the Fisher exact test.

The average values of duplicate measurements were calculated. Because of the skewed distribution of FSTL-3, log transformation was used to reduce the variation and achieve normality for further analysis. Given that FSTL-3 concentrations were measured in the same participants at each trimester's visit, respectively, repeated measures mixed models were developed. This approach allowed full use of all the available data. The longitudinal relationship of each adiposity measure in each study group was examined. The difference in FSTL-3 concentrations among the 3 groups over time while adjusting for relevant covariates was tested. In the multivariate model, the interaction between group, time, parity, race, and WHR were explored. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina) and significance was set at $P < .05$.

Results

The clinical and demographic characteristics of the study participants are presented in Table 1. Average blood pressure before 20 weeks and maternal BMI were significantly elevated among obese women and were not different between obese women who did and did not develop preeclampsia. Women who developed preeclampsia delivered earlier than either group of uncomplicated pregnant women. There were no differences between the 3 groups in gestational age by study visit in each trimester. There were also no differences in maternal age, race/ethnicity, smoking, birth weight, or birth weight centile among the study groups.

Adiposity indices, fat mass, and percentage of body fat calculated from longitudinal BIA measurements are presented in Table 2. The body adiposity index and WHR are based on measurements determined only in the first trimester. By design, fat mass, percentage of body fat and first visit adiposity index, and WHR were greater in the obese groups compared to lean controls. The WHR was the only adiposity measure that was significantly different between obese women who later developed preeclampsia compared to lean women with uncomplicated pregnancies. There was no difference in WHR between the control groups.

The maternal plasma concentrations of FSTL-3 among the study groups in each trimester are presented as medians and ranges to demonstrate the skewed distribution of the raw data (Table 3). Transformed data in repeated measures models indicated that FSTL-3 concentrations were not affected by prepregnancy BMI ($P = .09$), body adiposity index ($P = .11$), WHR ($P = .78$), fat mass ($P = .60$), change in fat mass ($P = .18$), percentage of fat ($P = .79$), or change in percentage of fat ($P = .29$).

Modeling demonstrated that FSTL-3 concentrations differed in a group by time interaction adjusted for parity, race, and WHR ($P = .05$; Figure 1). The relationship of FSTL-3 concentration with gestational age was different among the 3 groups.

Within group FSTL-3 concentrations by gestational age: in the lean control group, maternal plasma FSTL-3 levels were significantly lower at visit 2 compared to the first and third visits which were not different (Figure 1). Concentrations of FSTL-3 did not change

Table 1. Clinical and Demographic Characteristics of the Study Groups.

Factor	Lean Control (N = 15)	Obese Control (N = 24)	Obese Preeclampsia (N = 20)	*P* Value
Maternal age (mean years ± SD)	23.5 (5.3)	23.7 (3.0)	24.4 (4.9)	.54
Gestational age at sample collection (mean weeks ± SD)				
Visit 1	10.4 (3.1)	10.2 (3.2)	9.0 (2.9)	.27
Visit 2	20.4 (1.8)	19.5 (1.1)	20.2 (2.1)	.35
Visit 3	34.8 (0.6)	35.0 (1.3)	34.6 (2.3)	.46
Gestational age at delivery (mean weeks ± SD)	40.1 (1.2)	39.7 (2.1)	37.9 (2.8)[a]	.005
Parity (N, %)				.003
Primiparous	15 (100.0)	23 (95.8)	13 (65.0)	
Multiparous	0 (0.0)	1 (4.2)	7 (35.0)[a]	
Race/ethnicity (N, %)				.35
Black and other	9 (60.0)	13 (51.2)	15 (75.0)	
White	6 (40.0)	11 (45.8)	5 (25.0)	
Smoking (N, %)	5 (33.0)	10 (42.0)	8 (40.0)	.79
BMI, kg/m^2; visit 1 (mean ± SD)	23.3 (2.4)	38.2 (7.0)[a]	37.5 (7.2)[a]	.0001
Average blood pressure before 20 weeks gestation (mean mm Hg ± SD)	106.9 (6.0)/63.80 (4.9)	116.3 (6.5)[a]/69.3 (3.8)[a]	117.4 (4.9)[a]/72.6 (5.0)[a]	.0001
Average blood pressure in labor (mean mm Hg ± SD)	121.1 (7.7)/70.8 (8.0)	124.5 (8.5)/71.2 (6.5)	148.0 (7.7)[a]/89.8 (7.9)[a]	.0001
Birth weight (mean grams ± SD)	3413.3 (425.1)	3316.2 (585.8)	3035.3 (845.6)	.23
Birth weight centile (mean grams ± SD)	54.4 (26.6)	53.8 (28.9)	47.9 (35.6)	.21

Abbreviations: BMI, body mass index; SD, standard deviation.
[a] Statistical significance of Bonferroni post hoc test when group is compared with lean control group ($P < .05$).

Table 2. Adiposity indices.

Measure by Time	Lean Control (N = 15), Mean ± SD	Obese Control (N = 24), Mean ± SD	Obese Preeclampsia (N = 20), Mean ± SD
% fat			
Visit 1	27.3 ± 6.97	43.7 ± 5.61[a]	46.3 ± 5.62[a]
Visit 2	29.8 ± 6.41	44.2 ± 4.83[a]	45.6 ± 6.21[a]
Visit 3	33.4 ± 5.40	45.3 ± 6.13[a]	44.1 ± 6.06[a]
Fat mass, lbs			
Visit 1	37.5 ± 13.1	99.6 ± 31.9[a]	104.5 ± 31.3[a]
Visit 2	43.7 ± 13.3	101.7 ± 25.6[a]	105.3 ± 34.1[a]
Visit 3	55.0 ± 13.7	114.6 ± 31.5[a]	111.3 ± 29.0[a]
Average waist circumference, cm; Visit 1	30.4 ± 2.56	41.4 ± 5.65[a]	43.2 ± 6.15[a]
Average hip circumference, cm; visit 1	37.2 ± 3.66	49.2 ± 5.48[a]	48.2 ± 4.68[a]
WHR	0.8 ± 0.1	0.84 ± 0.1	0.90 ± 0.1[a]
Body adiposity index; visit 1	28.2 ± 3.9	41.8 ± 6.6[a]	40.9 ± 6.6[a]

Abbreviations: SD, standard deviation; WHR, waist to hip ratio.
[a] Statistical significance of Bonferroni post-hoc test when group is compared with lean control group ($P < .05$).

Table 3. Maternal Plasma FSTL-3 Concentrations in ng/mL.

Time	Lean Control (N = 15), Median (Range)	Obese Control (N = 24), Median (Range)	Obese Preeclampsia (N = 20), Median (Range)
Visit 1	24.4 (3.10-45.1)	18.2 (7.44-74.9)	22.6 (7.23-59.8)
Visit 2	10.1 (4.24-50.5)	18.0 (6.69-124.3)	26.5 (15.0-67.9)[a]
Visit 3	26.4 (10.3-53.4)	21.3 (10.8-78.7)	49.5 (9.27-133.4)[a]

Abbreviation: FSTL-3, follistatin-like 3.
[a] Statistical significance of Bonferroni post hoc test when group is compared with lean control group ($P < .05$).

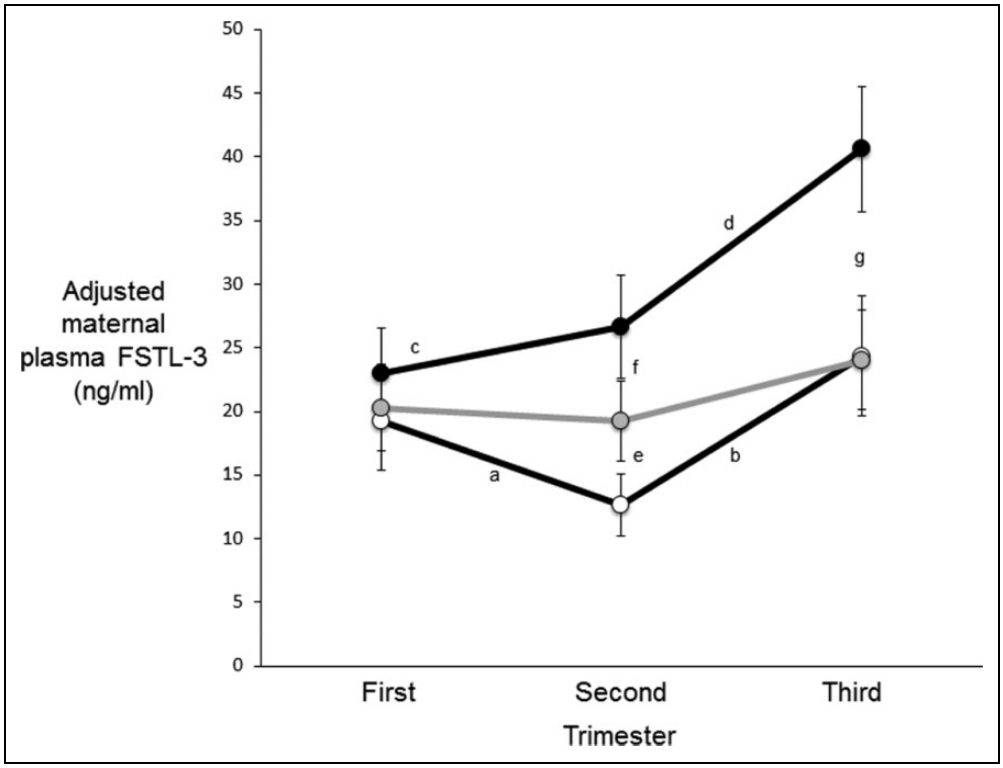

Figure 1. Adjusted mean FSTL-3 concentrations in group by time interaction. Average maternal FSTL-3 concentrations adjusted for parity, race, and WHR. Delta method was used to calculate the standard error of FSTL-3 at the original scale. Data are adjusted for mean ± SE. Open circles = lean controls, gray circles = obese controls, and closed circles = obese patients with preeclampsia . Significant differences were found in (a) lean controls between first and second trimesters ($P = .01$); (b) lean controls between second and third trimesters ($P = .0001$); (c) obese patients with preeclampsia between first and third trimesters ($P = .0002$); (d) obese patients with preeclampsia between second and third trimesters ($P = .007$); (e) lean and obese controls in the second trimester ($P = .04$); (f) lean controls and obese patients with preeclampsia in the second trimester ($P = .001$); and (g) obese patients with preeclampsia and lean controls ($P = .02$) and patients versus obese controls ($P = .01$) in the third trimester. FSTL indicates follistatin-like 3; SE, standard error of the mean; WHR, waist to hip ratio .

across gestation in the obese controls. The change in maternal FSTL-3 levels in the obese women who developed preeclampsia indicates that the highest values were in the third visit, which was significant compared to both visits 1 and 2, and there was no difference in FSTL-3 levels between the first 2 visits.

FSTL-3 concentrations between groups at each trimester: FSTL-3 concentrations were similar in all groups at the first visit (Figure 1). At the second visit, obese women who developed preeclampsia had higher FSTL-3 concentrations compared to lean controls but not obese controls. In addition, the levels of FSTL-3 in the obese controls were higher than that of lean controls. At the third visit, the levels of FSTL-3 were significantly higher in the obese women who developed preeclampsia compared to both the lean and the obese controls which did not differ.

Logistic regression of FSTL-3 concentrations in the second trimester indicated that elevated FSTL-3 concentrations were associated with a significant odds of developing preeclampsia (3.15; 95% confidence interval 1.19-8.36; $P = .02$).

Discussion

Our study demonstrated within and between group differences in maternal FSTL-3 concentrations across gestation in lean and obese women with uncomplicated pregnancies and in obese women with preeclampsia. The pattern of circulating FSTL-3 concentrations across gestation was distinct in each group of women and these patterns differed among the study groups (Figure 1). Major findings were that maternal plasma FSTL-3 was not associated with measures of fat mass or fat distribution in pregnancy; FSTL-3 concentrations were not lower in the first trimester of women who later developed preeclampsia; elevated FSTL-3 in the second trimester was associated with increased odds of developing preeclampsia; and plasma FSTL-3 was higher in the third trimester women with preeclampsia. Importantly, we determined concentrations of FSTL-3 in each trimester of uncomplicated human pregnancy.

Our hypothesis that FSTL-3 would be lower in the first trimester in women who later developed preeclampsia compared to controls was not satisfied because no differences occurred at the 10-week visit among the BMI-determined study groups. Our prior first trimester data of lower *FSTL3* mRNA,[4,5] the known role of follistatin extracellular matrix proteins to bind

and modify growth and differentiation factors through paracrine and autocrine activity[11,30] and the localization of FSTL-3 to walls of decidual and placental blood vessels[16] are consistent with a role of FSTL-3 in vascular remodeling of vessels perfusing the intervillus space. However, this did not translate into different circulating concentrations of FSTL-3 at 10 weeks gestation, the time at which we measured reduced placental mRNA.[4,5] Similar first trimester FSTL-3 concentrations decreasing toward the second trimester were found by others in normal pregnancy.[20] These data suggest minimal secretion of this protein from this site at this gestational age or that perhaps sites of production other than the placenta are more relevant to circulating FSTL-3 at this time. Decidua,[16] adipocytes,[15] cardiovascular tissue, and pancreas[6] are all potential contributors to circulating FSTL-3 protein levels.

The increased circulating concentration of FSTL-3 across gestation in women who subsequently developed preeclampsia is consistent with the finding that *FSTL3* mRNA is increased in primary human trophoblasts cultured under hypoxic conditions.[31] Between 10 and 20 weeks gestation, remodeling of placental bed spiral arteries increases oxygenation of the placenta, a process that does not take place normally in preeclampsia[17,18] and results in hypoxia and endoplasmic reticulum and oxidative stress.[32,33] Women with elevated FSTL-3 at mid-gestation had over 3-fold odds of developing preeclampsia. The well-established covariates, primiparity and race, which increase the odds of preeclampsia,[34,35] did not affect the group by time interaction in circulating FSTL-3. Rising concentrations of FSTL-3 over the course of pregnancy could be a cause or an effect of the syndrome, interacting with decreased insulin sensitivity or higher insulin resistance in preeclampsia[36] and/or the effects of hypoxia.[31] Inflammation related to insulin resistance or hypoxia induces activin A cytokine pathways that interact to increase *FSTL3* transcription via the SMAD proteins.[21,37,38] The results of the current study are consistent with others who found increased placental gene expression and higher serum FSTL-3 in the third trimester of normal weight women with preeclampsia.[21,22,39] Hu and colleagues[39] determined that increased placental *FSTL3* expression at term was the main source of FSTL-3 in maternal blood at that gestational age.

Circulating FSTL-3 was reduced between the first and second trimesters in lean but not in obese pregnant women and was increased in obese women with or without preeclampsia (Figure 1). This is likely related to metabolic differences with obesity, which have been shown to be associated with FSTL-3 in knockout mice studies.[13-15] Our data do not support that this difference is simply fat mass or fat distribution in women. Circulating lipids, measures of insulin sensitivity versus resistance, and adipocyte function might be better indicators of fat metabolism than the body composition measures of adiposity.[9,10,13-15,40] Other pathways affected by metabolic disturbances associated with obesity, such as adipokines, inflammation, and oxidative stress, also need to be investigated in relation to FSTL-3 in pregnancy and preeclampsia.

The role of FSTL-3 in pregnancy is not known although our data are consistent with an inverse relationship of FSTL-3 to insulin sensitivity. FSTL-3 antagonizes TGFβ family members myostatin and activin, which regulate fat and muscle mass as well as glucose tolerance and insulin sensitivity.[9,10,13-15] In our study, FSTL-3 was increased with obesity and advancing gestation, a setting in which insulin sensitivity is reduced.[41] The nadir of FSTL-3 in mid-gestation in lean women is consistent with reports of increasing insulin sensitivity until mid-gestation, which then converts to insulin resistance.[42-44] How FSTL-3 affects hypertension in human pregnancy remains to be determined. The hypertension in *FSTL3* knockout mice resulted from increased left ventricular end-systolic pressure and increased systolic arterial pressure compared to wild-type littermates.[15] These functional changes were explained by FSTL-3 inhibition of the protective actions of activin A on cardiomyocytes.[45]

Our study was novel in evaluating several measures of adiposity across gestation in preeclampsia and control groups based on prepregnancy BMI including BIA and the body adiposity index as an estimate of percentage of body fat.[29] Assessments of body composition using BIA parameters had been conducted in gestational hypertension (GH) and preeclampsia in the third trimester.[46,47] Fat mass was higher in GH than in normal pregnancy or preeclampsia, but the latter 2 groups did not differ in fat mass at that gestational age.[46] This contrasted with our findings that obese women had higher fat mass across gestation compared to lean women and supports the appraisal of Levario that their analysis may have been confounded by the fact that GH was diagnosed later in gestation than preeclampsia.[46] Consideration of the lean muscle mass compartment could provide further information for FSTL-3 concentrations in pregnancy.[47] Any future study will be faced with the challenges of obtaining adequately fasted participants at each research encounter as was a limitation in the current study. Additional information stands to be gained by including lean women with preeclampsia, in order to identify the variance in FSTL-3 concentrations based on BMI-defined study groups.

Conclusions

Clinically, elevated FSTL-3 concentrations were attributable to preeclampsia and at mid-gestation indicated a 3-fold increased risk of preeclampsia. Further study of FSTL-3 as a biomarker of preeclampsia before onset of the clinical signs of hypertension and proteinuria is indicated. The results of this study do not differentiate cause and effect; however, additional studies are needed to delineate covariates and the role of FSTL-3 in pregnancy and preeclampsia.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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