OBSTETRICS

The association of body mass index with serum angiogenic markers in normal and abnormal pregnancies

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OBJECTIVE: Because obesity is a risk factor for placental dysfunction, we hypothesized that maternal body mass index (BMI) would be associated with alterations in serum angiogenic markers.

STUDY DESIGN: We included 2399 singleton pregnancies with and without placental dysfunction in a prospective longitudinal cohort study of angiogenic markers. We modeled the relationship between categorical and continuous BMI, soluble fms-like tyrosine kinase-1 (sFlt-1), and placental growth factor (PlGF) over gestation, stratified by pregnancy outcome.

RESULTS: In women with normal pregnancies, a higher BMI was associated with lower sFlt-1 values across gestation ($P < .0001$), lower PlGF in the second and third trimesters ($P < .0001$), and lower rate of change in PlGF ($P < .0001$). Similar relationships were seen between maternal BMI, sFlt-1 ($P < .0001$), and PlGF ($P = .0005$) in women with clinically evident placental dysfunction.

CONCLUSION: The sFlt-1 value is inversely associated with maternal BMI. The pattern of change in PlGF is also dependent on maternal BMI, indicating that obese women may have abnormalities in angiogenesis near term.

Key words: angiogenic markers, obesity, placenta, preeclampsia, soluble fms-like tyrosine kinase-1

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Nearly 25% of women have a body mass index (BMI) in the obese range ($\geq$30 kg/m^2) prior to pregnancy.[1] Maternal obesity is associated with abnormal placental function clinically apparent as preeclampsia,[2,3] clinically unrecognized intrauterine growth restriction,[4,5] placental abruption, and potentially stillbirth.[6,7] The mechanisms underlying the association between maternal obesity and ischemic placental disease are not well understood; however, there is a large body of literature on nonpregnant individuals to support that obesity, like preeclampsia, is a state of systemic inflammation characterized by endothelial dysfunction and abnormalities in angiogenesis.[8-10] When taken together, these associations suggest the possibility that maternal obesity is associated with endothelial damage leading to abnormal placental function.

An evolving literature has linked the development of placental dysfunction with the expression of abnormal quantities of placental angiogenic proteins. In animal models, abnormal uteroplacental blood flow is associated with an increase in the antiangiogenic protein, soluble fms-like tyrosine kinase-1 (sFlt-1), which binds and antagonizes both placental growth factor (PlGF) and vascular endothelial growth factor.[11] Although the analyses were limited by sample size, observational data from the Calcium for Preeclampsia Prevention trial suggested that the ratio of sFlt-1 to PlGF increases several weeks before the onset of clinical disease in women destined to develop preeclampsia.[12]

In vitro, the adipokine visfatin alters the expression of vascular endothelial growth factor, providing a potential link between obesity and altered angiogenesis at the maternal-fetal interface.[13] In vivo data connecting maternal obesity with altered placental angiogenesis are limited, however. Although some have attempted to examine the associations between maternal obesity and alterations

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TABLE 1
Participant characteristics, by BMI category

Characteristic	First trimester BMI, kg/m^2 <25 (n = 1292)	25 to <30 (n = 584)	≥30 (n = 523)	Total (n = 2399)	*P* value
Age, mean (SD)	31.3 (5.4)	30.9 (6.2)	30.4 (5.7)	31.0 (5.7)	.005
Race/ethnicity					< .0001
Caucasian, n, %	865 (67.0%)	319 (54.6%)	220 (42.1%)	1404 (58.5%)	
African American, n, %	172 (13.3%)	146 (25.0%)	214 (40.9%)	532 (22.2%)	
Hispanic, n, %	98 (7.6%)	61 (10.5%)	69 (13.2%)	228 (9.5%)	
Asian, n, %	110 (8.5%)	31 (5.3%)	6 (1.2%)	147 (6.1%)	
Other or missing, n, %	47 (3.6%)	27 (4.6%)	14 (2.7%)	88 (3.7%)	
BMI at baseline, kg/m^2, mean (SD)	22.0 (1.9)	27.1 (1.4)	35.9 (5.7)	26.3 (6.3)	< .0001
Nulliparous, n, %	424 (32.8%)	156 (26.7%)	105 (20.1%)	685 (28.6%)	< .0001
Current smoker, n, %	31 (2.4%)	17 (2.9%)	28 (5.4%)	76 (3.2%)	.005
History of diabetes, n, %	15 (1.2%)	7 (1.2%)	25 (4.8%)	47 (2.0%)	< .0001
History of hypertension, n, %	24 (1.9%)	24 (4.1%)	52 (9.9%)	100 (4.2%)	< .0001
Gestational diabetes, n, %	35 (2.7%)	20 (3.4%)	51 (9.8%)	106 (4.4%)	< .0001
GA at delivery, mean (SD)	39.0 (1.7)	38.9 (1.8)	38.6 (2.1)	38.9 (1.8)	.004
Birthweight, g, mean (SD)	3278 (520)	3311 (532)	3301 (635)	3292 (550)	.12
Placental ischemic disease, n, %[a]	137 (10.6%)	77 (13.2%)	107 (20.5%)	321 (13.4%)	< .0001
SGA, n, %	89 (6.9%)	34 (5.8%)	37 (7.1%)	161 (6.7%)	.63
Preeclampsia, n, %	51 (4.0%)	45 (7.7%)	86 (16.4%)	182 (7.6%)	< .0001
Abruption, n, %[b]	7 (0.5%)	6 (1.0%)	2 (0.4%)	15 (0.6%)	.34

BMI, body mass index; *GA*, gestational age; *SGA*, small for gestational age.

[a] Patient may have more than 1 of SGA, preeclampsia, and abruption; [b] Compared with Fisher exact test.

Zera. BMI and angiogenic markers. Am J Obstet Gynecol 2014.

of serum angiogenic markers in preeclamptic pregnancies, their conclusions are limited by small sample size, homogenous population, and a narrow range of maternal BMI.[14,15] Furthermore, factors affecting angiogenic markers in normal pregnancies are not well understood.

We hypothesize that maternal obesity is associated with abnormalities in placental angiogenesis. We therefore investigated the effect of maternal BMI on serum angiogenic markers in normal pregnancies and those affected by clinical placental dysfunction.

Materials and Methods

Study population

This study is a secondary analysis of data from a prospective longitudinal cohort study designed to evaluate the utility of sFlt-1 and PlGF as markers for the diagnosis of preeclampsia.[16] Women were recruited from 3 urban academic medical centers in Boston, MA, and Philadelphia, PA, from 2006 to 2008. Participants were eligible for enrollment if the estimated gestational age was 15 weeks or less, they were at least 18 years old, and they were able to provide informed consent and had no more than 3 fetuses. For this analysis, we excluded women missing first-trimester BMI (n = 41) as well as those who did not have serum samples at 3 or more study visits (n = 53). Of the remaining 2544 women, we excluded 143 with multiple gestations and 2 with stillbirths, leaving 2399 participants in the final analysis.

We considered women with preeclampsia, placental abruption, or delivery of a small-for-gestational-age infant to have clinical placental dysfunction.[17] Preeclampsia was defined as systolic blood pressure elevation of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg after 20 weeks' gestation, in association with proteinuria, either spot urine protein/creatinine ratio of greater than 0.20 or at least 300 mg or 24 hours[16,18]; each case was reviewed by a consensus committee of site primary investigators (K.-H.L., S.I.P., or T.F.M.). The diagnosis of placental abruption was based on clinician diagnosis at the time of delivery and was abstracted from the medical record by trained reviewers. We defined small for gestational age as a birthweight less than the 10th percentile (z-score less than −1.28) by published sex-specific growth curves.