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Maternal Serum Leptin During Pregnancy and Infant Birth Weight: the Influence of Maternal Overweight and Obesity

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Abstract

Few studies have examined whether the distinct metabolic patterns found in obese and non-obese pregnant women may have different effects on the growing fetus. Our objective was to estimate the influence of longitudinal variation in maternal serum leptin levels on variation in infant birth weight in overweight/obese versus normal weight women. In a prospective cohort of 286 gravidas, we measured maternal weight and serum leptin levels at 6–10,10–14,16–20, 22–26, and 32–36 weeks gestation. Effects of leptin levels on infant birth weight adjusted for gestational age at delivery (aBW) were analyzed using a linear regression model that accounted for the relationship of time-varying predictors to the log transformed leptin concentrations. Overweight/obese and normal weight gravidas exhibit different relationships of aBW to maternal serum leptin and its rate of change across pregnancy. For normal weight women, aBW is not associated with either the magnitude of the logarithm of the leptin concentration nor with its rate of change in either the first or second half of pregnancy. Conversely, for overweight/obese women, we find that an increase in the rate of change in maternal serum leptin in the second half of pregnancy is significantly associated with a decrease in aBW. We find that this effect is distinct from that of maternal weight. Differences in the effect of maternal serum leptin on fetal growth between overweight/obese and normal weight women suggest metabolic and physiologic heterogeneity between these groups. Such differences may be involved in the long-term physiologic effects of the obese intrauterine environment on the health of the offspring.

INTRODUCTION

Maternal obesity influences a number of metabolic and physiologic factors that can affect the course of pregnancy, fetal development, and health of the offspring later in life[1]. There is growing evidence that the effects of obesity on pregnancy may be associated with metabolic

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DISCLOSURE

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dysregulation and disruption of the normal feedback systems that maintain metabolic homeostasis leading to the development of many of the pathological conditions associated with obesity [2–4], The earliest effects of these metabolic changes are seen in the fetal growth trajectory[5]. However, there are few descriptions of how these metabolic changes influence the course of pregnancy and affect fetal growth.

The adipokine leptin plays a particularly important role in the regulation of maternal energy metabolism during pregnancy[6–8]. Serum leptin levels are generally thought to be related to adipose tissue mass and are correlated with body fat mass and BMI in both non-pregnant[9] and pregnant adults[10, 11]. However, the regulation of maternal leptin during pregnancy is complex[8]. Serum leptin concentrations nearly double during the course of a normal pregnancy[10, 12, 13]; production and regulation by non-adipose tissue, such as the placenta, are thought to contribute to this increase[8, 14, 15]. Such changes are likely involved in optimizing the availability of substrates necessary for fetal growth, particularly by mobilizing maternal fat stores[8].

We have recently shown that overweight/obese pregnant women exhibit distinct patterns in the relationship between gestational weight gain and levels of leptin when compared to normal weight women [11]. Overweight/obese gravidas did not show the progressive increases in leptin production per unit of body mass that were seen in normal weight women. The metabolic factors that result in such differences in the leptin profile may also result in different effects of leptin on fetal growth, beyond that expected from just a difference in levels. Previous studies of maternal leptin concentration during pregnancy have not consistently shown a relationship with fetal growth[16–21]. However, few studies have examined whether the distinct metabolic patterns found in overweight/obese women may be accompanied by qualitatively different effects of leptin on the growing fetus.

The goal of this study was to estimate the influence of variation in maternal serum leptin levels during pregnancy on variation in infant birth weight in women with overweight/obese pre-pregnancy BMI (≥25.0) and normal pre-pregnancy BMI <25.0). We specifically monitored these women at multiple time points across gestation in order to gain insight into the influence of the trajectory of leptin across pregnancy on infant birth weight.

METHODS

Study Sample

We recruited 332 participants in a prospective cohort study of pregnant women at the University of Michigan Health System. The Institutional Review Board of the University of Michigan Medical School approved the study protocols. Eligible participants were 18 to 45 years of age, between 6 and 10 weeks gestation with a singleton pregnancy, and intended to deliver at the study hospital. Informed consent was obtained at the initial visit. Data and laboratory samples were collected at five time points during pregnancy: 6–10, 10–14, 16–20, 22–26, and 32–36 weeks gestation. At each time point, we obtained data from a brief interview, maternal anthropometric measurements, fetal ultrasound measurements, and a maternal blood draw. The major reason for attrition was early first trimester fetal loss (~10% of recruits). Fewer women had a multiple gestation or were lost to follow-up. Data analyses

were carried out on the cohort of 286 participants who completed the study and delivered a live infant. Less than 1% of women were excluded from any particular analysis because of missing data.

Data Collection and Variables

Baseline maternal demographic and health characteristics were collected by questionnaire upon entry into the study and by subsequent review of medical records. Changes in maternal health characteristics were assessed at each subsequent time point. Standing height was measured using a stadiometer. Weight was measured at each time point in light street clothes, without shoes, on a calibrated electronic scale (Scale-tronix, Inc., White Plains, New York). Maternal pre-pregnancy weight was collected by self-report at the initial visit. Pre-pregnancy BMI was calculated using height and pre-pregnancy weight (BMI = kg/m^2), and categorized into two levels using World Health Organization (WHO) cutoff points as normal weight ($<25.0\ kg/m^2$) and overweight/obese ($\geq 25.0\ kg/m^2$), based on the most recent recommendations of the Institute of Medicine[22].

For all analyses, the maternal weight at each study visit was corrected by subtracting the estimated fetal weight determined by ultrasound biometry using the method of Hadlock [23]. Since the weight of the fetus comprises a significant percentage of gestational weight gain, use of total weight gain overestimates correlation between mother and infant. When one variable is a sum containing a second variable in a comparison, a spurious increase in association results, called “part-whole bias”[24, 25]. The inflated correlation between birth weight and total maternal weight gain is a classic example. One strategy to address this issue is to use net maternal weight gain calculated by subtracting the estimated fetal weight from maternal weight to remove artificial structural biases from the association between birth weight and maternal weight gain. As such, this correction was done to minimize part-whole correlations between predictor and outcome variables[24, 25].

At each time point, maternal serum was collected using a standard serum separator tube (BD, Franklin Lakes, NJ), aliquotted, and stored at −80°C for analysis. Serum leptin concentration was measured using a standard commercial radioimmunoassay kit (Linco Research, St. Charles, MO). This kit is a double-antibody radioimmunoassay using a ^{125}I-human leptin tracer, a rabbit anti-human leptin serum as the first antibody, and a goat anti-rabbit gamma globulin -PEG complex as the second antibody. A purified recombinant human leptin is used as standard. The limit of sensitivity for the assay is 0.5 ng/ml. The interassay coefficient of variation is 6.4% at 3.5 ng/ml and 6.0% at 23.5 ng/ml. These assays were performed in the Chemistry Laboratory of the Michigan Diabetes Research and Training Center. Natural log-transformed values of maternal serum leptin serum concentrations were analyzed to account for deviations from the normal distribution and to improve model fit.

Infant variables, including date of delivery, birth weight (BW), and sex were collected at delivery. An ultrasound estimate of gestational age (GA) was determined by early first trimester ultrasound. Since BW varies significantly with GA, the BW was regressed onto GA. The residual values from each fit were added to the mean BW and used to represent the

GA-adjusted BW (aBW). The aBW was then used as the dependent variable for modeling of the relationship of aBW to maternal serum leptin as described below.

Statistical Analysis

All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). Univariate regression models were used to describe the demographic characteristics of the study sample and tested the hypothesis of homogeneity of the means between BMI categories. The Fisher exact test was used to assess statistical significance of categorical variables; the t-test was used for continuous variables. All analyses were stratified on maternal pre-pregnancy BMI as noted above. A p-value of <0.05 was considered significant.

We used an established analytic approach to estimate the effect of repeated measures across time (including maternal weight and log transformed maternal serum leptin levels) on an outcome (aBW) measured at one time point using the following model [26]:

$$E(aBW)=\beta' +(\beta_0)X_0+(\beta_{02})X_{02}+(\beta_{24})X_{24}+\sum_j(\beta_j)C_j+\varepsilon \quad (1)$$

In this equation X_0 is the baseline measure (6–10 weeks gestation) of the repeated measure; X_{02} is the rate of change of the measure during the first half of pregnancy (between baseline [0] and second follow up [2]) defined as $X_{02} = (X_2 - X_0)/(GA_2 - GA_0)$, where GA is the gestational age in weeks at time of measurement; and X_{24} is the rate of change of the measure in the second half of pregnancy (between second follow up [2] and fourth follow up [4]). As described elsewhere[26], the coefficient for X_0 (β_0) defines the effect of increasing the measure level by one unit at *any* study visit. This coefficient describes, for example, the effect of uniformly shifting the trajectory upward across all study visits resulting in a cumulative effect on aBW. The coefficients for X_{02} (β_{02}) and X_{24} (β_{24}) define how variation in the *rate* of weight gain in each visit interval may affect variation in aBW. The rightmost summation defines the contribution of other maternal covariates (C_j) to the expected value of aBW.

RESULTS

Table 1 presents the sociodemographic and health characteristics of the 286 participants and their newborns who completed the study. Characteristics are stratified on maternal pre-pregnancy BMI categorized as normal weight (<25.0 kg/m^2) and overweight/obese (≥ 25.0 kg/m^2). While our sample is very homogeneous with regard to measures of socioeconomic status and race, there is considerable variation in pre-pregnancy BMI. Our sample was equally distributed into the two BMI subgroups. Importantly, there were only a small number of women with pregestational and/or gestational diabetes (n=23) and very few cases of hypertension (n=4). Cases of hypertension were similarly distributed between the BMI groups, there were more cases of diabetes in the overweight/obese group. There are significant demographic differences in women with non-overweight BMIs compared to those with overweight/obese BMIs; however, our results adjust for the sociodemographic covariates that are significantly different between the strata. As expected, the infants of

overweight/obese mothers have a significantly higher birth weight than infants of normal weight mothers (Table 1).

Table 2 shows the mean maternal serum leptin concentration at each study visit. At every time point, the logarithm of the leptin concentration for women with overweight/obese BMIs was significantly higher than the corresponding values for their non-overweight counterparts ($p<0.001$). We have previously shown that leptin concentration significantly increased with advancing gestation in both strata[11]. However, the rate at which leptin levels increased across gestation was significantly lower for women with overweight/obese BMIs[11].

Table 3 first shows the relationship between variation in aBW and variation in the maternal weight trajectory using Equation 1 for each BMI stratum. We find that the effects of maternal weight and weight gain are different for overweight/obese women compared to their normal weight peers. For normal weight women, aBW is associated with the magnitude of maternal weight at any time point (given by the coefficient for X_0), as well as the rate of weight gain in the second half of pregnancy (given by the coefficient for X_{24}). Variation in aBW is not associated with the rate of change in maternal weight in the first (X_{02}) half of pregnancy for the normal weight group. In contrast, for overweight/obese women, the association between aBW and the magnitude of maternal weight is significantly smaller than that for their normal weight counterparts. Thus a 1 kg increase in the magnitude of maternal weight at any time point is associated with a 17.1 g increase in aBW (95% CI: 7.3, 26.8) in the normal weight stratum, but associated with only a 5.4 g increase in aBW (95% CI: 0.4, 10.4) in the obese/overweight stratum. Moreover, for overweight/obese women, there is no significant relationship between variation in aBW and the rate of change in maternal weight in either the first (X_{02}) or second (X_{24}) half of pregnancy. In testing for effect modification by BMI group, we found a statistically significant interaction for baseline maternal weight and BMI group on aBW ($p<0.01$), but not for the variables representing changes in maternal weight during the first half or second half of pregnancy. We also repeated these analyses excluding those individuals with hypertension and diabetes and found very similar parameter estimates with no changes in level of statistical significance.

Table 3 also shows the relationship between variation in aBW and variation in the trajectory of the logarithm of maternal leptin concentration for each BMI stratum. We find that the effects of serum leptin concentration and its rate of change across pregnancy are different for the two strata. However, the effects of leptin are qualitatively different than those found for maternal weight. For normal weight women, aBW was not significantly associated with the magnitude of the logarithm of the maternal leptin concentration (X_0) or its rate of change (X_{02} or X_{24}). In contrast, for overweight/obese women, aBW is associated with the magnitude of the logarithm of maternal serum leptin (X_0). However, in testing for effect modification by BMI group, there was not a statistically significant interaction between BMI stratum and the magnitude of leptin concentration on aBW. We also find that an increase in the rate of change in the logarithm of maternal serum leptin in the second half of pregnancy (X_{24}) is significantly associated with a decrease in aBW for overweight/obese, but not normal weight, women. Moreover, testing for the significance of this difference by BMI group, we find a statistically significant interaction between the effect of BMI stratum and rate of change of leptin in the second half of pregnancy on aBW ($p<0.05$). In analyses

excluding women with hypertension and diabetes, results were similar; there was a slight reduction in the effect of baseline leptin concentration on aBW for overweight/obese women, which is then no longer statistically significant.

DISCUSSION

There is growing evidence that the regulation and effects of metabolic systems in overweight and obese individuals is substantially different from their normal weight counterparts [2–4, 27]. However, there have been few descriptions of how these metabolic differences may influence the physiologic changes of pregnancy and their effects on the developing fetus. Our prospective population-based cohort study is meant to address these issues. We have recently shown that overweight/obese women have qualitatively different leptin profiles across pregnancy when compared to their normal weight counterparts[11]. Specifically, we found that the maternal leptin per body weight increased significantly across pregnancy for normal weight women, while it actually decreased significantly for overweight/obese women. These results suggest that overweight/obese women produce progressively lower amounts of leptin per unit mass of adipose or placental tissue as pregnancy progresses. Our current analyses build on this prior work.

In contrast to prior cross-sectional studies [17, 28–31], our study documented maternal weight and leptin levels at multiple time-points starting in early pregnancy, and analyzed their effects across a continuum of birth weight. As a result, we were able to model the relationship between birth weight and the timing and pattern of both maternal weight and leptin levels across pregnancy. Our analyses demonstrate the relationship between infant birth weight and the trajectory of both maternal weight and serum leptin concentration across pregnancy differs between overweight/obese and normal weight women. However, the effects of leptin are qualitatively different than those found for maternal weight in each stratum.

As expected, overweight/obese women in our sample had significantly larger infants than their normal weight peers. However, variation in the magnitude of maternal weight across pregnancy had a smaller effect on aBW in overweight/obese women; aBW was associated with the rate of weight gain in the second half of pregnancy (X_{24}) for the normal weight group only. Our findings in the normal weight women are similar to those from prior large population based cohorts that suggest the importance of maternal weight gain in late pregnancy [22, 32]. However, our results for overweight/obese women suggest that these women may enter pregnancy with sufficient or even surplus fat stores for the maintenance of pregnancy and that changes in maternal weight during pregnancy beyond a threshold level do not significantly affect birth weight.

The relationship of birth weight to maternal serum leptin concentration stands in contrast to its relationship to maternal weight in the different strata. First, we found that variation in infant birth weight was not significantly associated with the magnitude of maternal serum leptin level in either overweight/obese or normal weight women. However, as noted above, variation in the magnitude of maternal weight and its rate of change in late pregnancy was significantly associated with infant birth weight in both subgroups, although the effect is

significantly smaller in overweight/obese women. Therefore, the differences in the relationship of variation of aBW to variation in the rate of change of leptin cannot simply arise from differences in effect of variation in maternal weight between the two subgroups. Rather, this finding may suggest heterogeneity in the effects of other leptin-related physiologic factors that influence the maternal-fetal relationship across pregnancy in the different BMI groups.

Second, we found that an increase in the rate of change in maternal serum leptin in the second half of pregnancy is associated with a significant reduction in birth weight only in overweight/obese gravidas. As noted above, there is no concomitant relationship between infant birth weight and rate of maternal weight gain in our sample. We speculate that the differences in the effect of the leptin trajectory in the two strata may be related to late-pregnancy placental changes associated with maternal obesity. In previous studies, hyperleptinemia has been shown to adversely placental function and reduce placental uptake of amino acids in obese women, but not in normal weight women[33]. Thus, one possibility is that late pregnancy changes in leptin levels may have different effects on birth weight through different effects on nutrient transport in the two groups.

Alternatively, maternal obesity and hyperleptinemia have been associated with other markers of placental insufficiency and dysfunction[34, 35]. Leptin derived from the placenta may have an important role in the control of placental growth and function, which impacts fetal growth and development[36]. Accordingly, prior human studies have shown that second trimester placental expression of leptin is lower than normal in pregnancies complicated by fetal growth restriction[31]. In wild-type pregnant mice, administration of exogenous leptin decreases placental leptin content and leads to reductions in placental and fetal weights[37]. Thus, chronically elevated serum leptin derived from adipose tissue in obese/overweight women may suppress the late pregnancy expression of placental leptin needed for placental development and fetal growth. This model is consistent with our prior finding that overweight/obese gravidas do not show the progressive increases in leptin production per unit of body mass that are seen in normal weight women, possibly due to reduced placental production [11].

The effect of maternal obesity on the developing fetus is mediated by a complex set of metabolic and physiologic systems[38, 39]. Although there is emerging evidence that the regulation of these systems may differ among subgroups of women with different body mass indices[2–4, 11, 27, 40], there are currently few studies that investigate how the effects of these systems on the developing fetus may differ between these groups. In this work, we have shown that the effect of maternal serum leptin on fetal growth differs between overweight/obese and normal weight women. We postulate that such differences may be involved in the long-term physiologic effects of the obese intrauterine environment that influence the offspring's later risk of chronic disease. However, future studies to elucidate the details of such mechanisms will be needed. Appreciating the heterogeneous effects of physiologic factors that influence the maternal-fetal relationship in different subgroups may ultimately lead to novel interventions to prevent the consequences of maternal obesity on the offspring.

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Table 1

Sociodemographic and health characteristics of the study sample.

	All Participants N (%)	Nonoverweight BMI < 25.0 kg/m^2 N (%)	Overweight/Obese BMI ≥ 25.0 kg/m^2 N (%)
Sample size	286	143 (50.0)	143 (50.0)
Race*			
White	233 (81.5)	120 (83.9)	113 (79.0)
African-American	18 (6.3)	4 (2.8)	14 (9.8)
Asian	18 (6.3)	12 (8.4)	6 (4.2)
Other	15 (5.2)	5 (3.5)	10 (7.0)
Missing	2 (0.7)	2 (1.4)	--
Ethnicity			
Non-Hispanic	273 (95.5)	139 (97.2)	134 (93.7)
Hispanic	13 (4.5)	4 (2.8)	9 (6.3)
Maternal Age			
≤ 30	111 (38.8)	53 (37.1)	58 (40.6)
> 30	175 (61.2)	90 (62.9)	85 (59.4)
Parity*			
Nulliparous	101 (35.3)	59 (41.3)	42 (29.4)
Multiparous	185 (64.7)	84 (58.7)	101 (70.6)
Marital Status			
Married	245 (85.7)	127 (88.8)	118 (82.5)
Not Married	41 (14.3)	16 (11.2)	25 (17.5)
Highest Educational Level Completed**			
College or less	161 (56.3)	67 (46.8)	94 (65.7)
Post-Graduate	125 (43.7)	76 (53.2)	49 (34.3)
Income*			
≤ $80,000 per year	136 (47.5)	57 (39.9)	79 (55.2)
> $80,000 per year	140 (49.0)	81 (56.6)	59 (41.3)
Missing	10 (3.5)	5 (3.5)	5 (3.5)
Insurance			
Private Insurance	245 (85.7)	126 (88.1)	119 (83.2)
Medicaid/Medicare	36 (12.6)	16 (11.2)	20 (14.0)
Missing	5 (1.7)	1 (0.7)	4 (2.8)
Smoking			
Not During Pregnancy	256 (89.5)	126 (88.1)	130 (90.9)
During Pregnancy	24 (8.4)	13 (9.1)	11 (7.7)
Missing	6 (2.1)	4 (2.8)	2 (1.4)
Hypertension			
Yes	4 (1.4)	1 (0.72)	3 (2.2)
No	273 (98.6)	137 (99.3)	136 (97.8)
Diabetes*			

	All Participants N (%)	Nonoverweight BMI < 25.0 kg/m^2 N (%)	Overweight/Obese BMI ≥ 25.0 kg/m^2 N (%)
Yes	24 (8.7)	6 (4.4)	18 (13.0)
No	253 (91.3)	132 (95.7)	121 (87.1)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Birth weight (grams)***	3421.9 (508.3)	3318.2 (531.9)	3524.9 (463.2)
Gestational age (weeks)	39.1 (1.9)	39.1 (1.9)	39.1 (1.8)

* P < 0.05; Statistical significance of difference between low and high BMI groups

** P < 0.01; Statistical significance of difference between low and high BMI groups.

*** P<0.001; Statistical significance of difference between low and high BMI groups.

Table 2

The geometric mean maternal serum leptin concentration measured across gestation*.

Visit Number	Gestational Age	Leptin Concentration (ng/mL)	
		Normal Weight	Overweight/Obese
		Geometric Mean (95% CI)	Geometric Mean (95% CI)
0	6–10 weeks	13.5 (12.2, 14.9)	30.0 (27.1, 33.1)
1	10–14 weeks	14.9 (13.5, 16.4)	33.1 (30.0, 33.1)
2	16–20 weeks	16.4 (14.9, 18.2)	33.1 (30.0, 36.6)
3	22–26 weeks	20.1 (18.2, 22.2)	36.6 (33.1, 40.4)
4	32–36 weeks	20.1 (18.2, 22.2)	33.1 (30.0, 36.6)

* At each visit, the logarithm of the leptin concentration is statistically significantly different by obesity status (t-test; $p<0.0001$). Log transformed values were used for testing differences, but estimates provided in the table were back-transformed.

Table 3

The relationship of infant birth weight to the magnitude and rate of change of maternal weight and the logarithm of serum leptin concentration measured across gestation†.

	X_0	X_{02}	X_{24}
	β (95% CI)	β (95% CI)	β (95% CI)
Corrected Maternal Weight			
Normal Weight	17.1** (7.3, 26.8)	−67.3 (−422.4, 287.7)	477.6* (51.3, 904.0)
Overweight/Obese	5.4* (0.4, 10.4)	19.1 (−259.8, 298.0)	164.2 (−259.0, 587.5)
Maternal Serum Leptin			
Normal Weight	77.2 (−70.8, 225.3)	−23.4 (−2082.7, 2036.0)	−346.1 (−3467.7, 2775.6)
Overweight/Obese	159.8 (−4.9, 324.6)	−1037.8 (−3654.7, 1579.0)	−5329.8* (−8664.73, −1994.8)

* $p \leq 0.05$

** $p \leq 0.001$

† The analyses represent multivariable linear regression models showing the regression coefficients (β) and the 95% confidence interval (CI) for the relationship (Equation 1) of aBW (grams) to the corrected maternal weight in kg (see Methods) and natural logarithm of the maternal serum leptin concentration (ln [ng/mL]). The values in this table represent the conditional effect of variation in the rate (either ln [kg]/week or ln [ng/mL]/week) of the predictors across visit intervals (the coefficients for X_{02} and X_{24} in equation 1) on variation in aBW in the context of variation on the magnitude of the predictor at ANY visit (the coefficient for X_0). Results were adjusted for the following maternal covariates: race, parity, education, income.