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Mid-pregnancy maternal leptin levels, birthweight for gestational age and preterm delivery

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Summary

Objective—Maternal blood leptin levels are positively associated with adiposity. Recent studies suggest that leptin is also abundantly produced by the placenta and may function as a regulator of fetal growth. Our goal was to examine mid-pregnancy levels of leptin in maternal blood in relation to birthweight for gestational age (BW/GA) and timing of delivery after accounting for maternal pre-pregnancy body mass index (prepreg-BMI) and pregnancy complications.

Patients—Data were from 1,304 sub-cohort mother/infant pairs who participated in the Pregnancy Outcomes and Community Health (POUCH) Study (1998–2004).

Measurements—Leptin levels, measured at 16–27 weeks' gestation, were log-transformed. Geometric mean (GMean) leptin levels were estimated by weighted linear regression with gestational age at blood draw as a covariate. GMean was re-transformed to the original scale for reporting.

Results—Using the GMeans leptin in mothers of term appropriate-for-gestational age (AGA) neonates as the referent (25.2 μg/L), we observed lower levels in mothers of preterm AGA (21.9 μg/L), term small-for-gestational age (SGA) (20.3 μg/L), and preterm SGA neonates (21.7 μg/L). Results were largely unchanged after adjustment for prepreg-BMI. Leptin levels were higher in mothers who delivered large-for-gestational age (LGA) neonates, both preterm (33.6 μg/L) and term (29.1 μg/L), but the GMeans were markedly attenuated after adjustment for prepreg-BMI.

Conclusion—The association between BW/GA and maternal leptin levels after adjustment for prepreg-BMI may represent: 1) a residual effect of maternal adiposity that is not fully captured by BMI; and/or 2) variation in placental leptin levels entering the maternal circulation. In conclusion, mid-pregnancy maternal blood leptin levels may be an early indicator of fetal growth status.

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CONFLICT OF INTEREST:
None

Introduction

Leptin, widely known as an adipose-tissue secreted protein, is involved in many metabolic and hormonal regulation pathways in humans (1, 2). Under normal physiological conditions, leptin primarily regulates energy balance and is produced predominantly by adipose tissues (3). During pregnancy, leptin is abundantly produced by the placenta with 95% being secreted into the maternal circulation. (4, 5) Leptin levels rise substantially during pregnancy with low levels seen in the first trimester, a peak in the second, and a plateau in the third trimester. (6) Higher levels have been observed with increasing maternal adiposity. (7, 8) Studies suggest that leptin affects physiologic processes such as glucose metabolism, and immune system responses, and may have a role in reproduction by influencing implantation, angiogenesis, and fetal growth. (2, 8, 9)

A larger body of research has focused on leptin and pregnancy complications such as gestational diabetes (GDM) and preeclampsia (PE). (10, 11) In GDM, placental leptin appears to be up-regulated. (12) One study reported that preterm pre-eclampsia but not intrauterine growth restriction (IUGR) was associated with increased placental expression of leptin. (13) Others have found that amniotic fluid leptin levels (14) were higher in association with pre-eclampsia, and higher placental leptin levels were linked to both pre-eclampsia and a greater resistance index of the umbilical artery. (4) These studies, along with animal models that show higher maternal blood leptin levels following vessel occlusion (descending aorta and ovarian), (15) all point to greater placental leptin production in response to decreased placental perfusion.

The majority of studies to date have examined leptin levels at the time of parturition in mother and/or infant (16), or have measured maternal leptin levels during the first trimester. (17, 18) In these studies relations between leptin levels and birthweight for gestational age (BW/GA) were inconsistent, though studies of umbilical cord blood leptin levels and BW/GA tended to report a positive correlation. (16, 19) Only a few investigators have evaluated mid-pregnancy leptin levels in association with BW/GA or timing of delivery, and again results have varied. (7, 20, 21) Studies of leptin in relation to timing of delivery are especially scarce. Among twin pregnancies, higher leptin levels in amniotic fluid sampled during the second trimester were associated with lower gestational age at delivery. (22)

Large epidemiological studies have not thoroughly investigated maternal leptin levels while simultaneously considering BW/GA, timing of delivery and pregnancy complications. Based on previous studies, we hypothesized that leptin levels would be higher among pregnant women with increased body mass index (BMI) and/or maternal complications such as hypertensive disorders and gestational diabetes. Our first aim was to examine associations between mid-pregnancy maternal serum leptin levels and both BW/GA and timing of delivery (i.e. term vs. preterm) in models with and without the inclusion of maternal pre-pregnancy BMI. Our second aim was to re-examine these associations after removing woman with hypertensive disorders or gestational diabetes.

Methods

Sample

The study sample came from the Pregnancy Outcomes and Community Health (POUCH) Study designed to investigate pathways to preterm delivery (PTD) as well as other adverse pregnancy outcomes. The study received institutional review board approval at Michigan State University, Michigan Department of Community Health, and nine community hospitals. Eligibility criteria for the POUCH Study cohort included: 16th–27th week of pregnancy, maternal serum alpha-fetoprotein (MSAFP) screening, prenatal care at one of 52 clinics in 5 Michigan Communities during September 8, 1998 through June 15, 2004, singleton pregnancy with no known chromosomal abnormality or birth defect, maternal age ≥ 15 years, no pre-pregnancy diabetes mellitus, and proficiency in English. Women who met the eligibility criteria and expressed interest in the study constituted the 'sampling frame'. Those who had normal MSAFP levels were stratified by race/ethnicity and randomly sampled into the cohort. In addition, all interested women with unexplained high MSAFP levels of ≥2 MoM (multiples of the median) were invited to participate because this prenatal screening biomarker has been consistently linked to risk of PTD. Of the 3038 women recruited into the cohort, 3019 were followed (99%) through to delivery. Overall 7% of the cohort had high MSAFP levels compared with the typical 3–5% in the screened population. In cohort analyses, after sampling weights are applied, women with elevated MSAFP account for only 3–5% of the cohort, typical of any unselected pregnancy cohort. Thus, the POUCH Study cohort can be thought of as a survey sample intended to represent the original sampling frame. At enrollment (16–27 weeks' gestation) cohort women met with a study nurse, signed consent forms, completed in-person interviews and self-administered questionnaires, and had biological samples collected.

In order to conserve resources, some costly data elements (e.g. placental examinations, medical record abstraction, assays in stored biologic samples) were obtained from only a sub-sample of POUCH Study participants, referred to as the sub-cohort. The sub-cohort of 1,371 women was assembled by using a random stratified sampling design, sampling from among the cohort, and again oversampling from certain strata. There were eight sampling strata defined by race/ethnicity (African American, non-African American), MSAFP levels (high, normal), and pregnancy outcome (preterm, term). The sub-cohort included 100% of cohort women who delivered preterm (n=335) and 100% of women who delivered at term with high MSAFP (n= 165). In the remaining strata of women with normal MSAFP and term deliveries, the study sampled 72 % of African Americans (n=422) and 23% of non-African Americans (n=449). The final sample for the current investigation consisted of 1,304 sub-cohort women with complete information on maternal serum leptin levels and infant BW/GA.

Pregnancy Outcomes

Birthweight data were abstracted from medical records. Gestational age was calculated based on the last menstrual period unless it disagreed with ultrasound results (majority conducted at < 22 weeks) by greater than 2 weeks, in which case the ultrasound results were given preference. The birthweight for gestational age (BW/GA) variable was based on a

birthweight z-score (BWZ) (23) and consisted of three categories: between the 10^{th} and 90^{th} percentiles BWZ was considered appropriate-for-gestational age (AGA); $\leq 10^{th}$ percentile BWZ was considered small-for-gestational age (SGA); and $\geq 90^{th}$ percentile BMZ was considered large-for-gestational age (LGA). Timing of delivery was categorized as term (≥37 weeks' gestation) and preterm (<37 weeks' gestation) delivery.

Leptin levels

Leptin was measured in maternal serum collected at enrollment using a commercial RIA kit purchased from Linco Research, Inc. (HL-81K). The samples were incubated with ^{125}I-leptin and leptin antibody overnight. The sample was centrifuged after incubating with a cold precipitating agent. The supernatant was decanted and pellets were counted. The lower limit of detection was 0.5 μg/L. The intra-assay and inter-assay coefficient of variation were 6.6±0.8% and 5.5±0.9%, respectively.

Pregnancy complications

Hypertension was defined by diastolic blood pressure (DBP)≥90 mm Hg or systolic blood pressure (SBP) ≥ 140 mm Hg or use of anti-hypertensive medications. If onset of hypertension was ≤20 weeks' gestation it was considered chronic (CHTN). Gestational hypertension (GHTN) was defined as hypertension on 2 different days with onset after 20 weeks' gestation but before active labor. PE included women with GHTN plus one of the following as evidence of proteinuria in the absence of genitourinary infection: a) ≥ 300mg protein/24 hour urine collection or 2+ protein on urine dipstick once after 20 weeks gestation, b) 1+ protein on two occasions after 20 weeks, or c) proteinuria present before 20 weeks, but levels increased after 20 weeks. When blood pressure data were not completely recorded, a few PE cases were ascertained based on physician diagnosis in prenatal records. PE also included diagnosis of PE superimposed over CHTN. GDM was considered present if a woman met any of the following criteria: failed the glucose tolerance test (GTT) for 1 hour and 3 hours, 1hr GTT> 10.545 mmol/Land GDM diagnosis by physician, 1hr GTT> 10.454 mmol/Land fasting glucose> 5.2725 nmol/L, or no laboratory values but GDM diagnosis listed in the medical records.

Covariates

Information on maternal characteristics was obtained through questionnaires administered at enrollment. Maternal age was grouped as <20 years, 20–30 years, and ≥30 years of age. We categorized self-reported maternal race into four groups: non-Hispanic white, African-American, Hispanic, and others. Maternal education level was divided as <12 years, 12 years, and ≥12 years. Maternal parity was dichotomized as primiparous and multiparous. Mother's Medicaid Insurance enrollment served as a proxy for socio-economic status. Smoking status at enrollment was modeled as yes or no. Self-reported maternal pre-pregnancy weight and height were used to calculate body mass index (prepreg-BMI). Prepreg-BMI and gestational age at blood draw (time of enrollment) both showed a positive linear trend with leptin levels and were therefore treated as continuous measures in the analyses.

Statistical analysis

As noted above, the POUCH cohort and sub-cohort were constructed by probability sampling from the original sampling frame. Sampling weights were used in all analyses to produce results that are generalizable to the sampling frame and maintain correct standard errors for hypothesis testing and confidence intervals. SAS 9.2 SURVEY procedures incorporated strata and weights into the analyses (SAS Institute, Inc, Cary, NC). Leptin values were log-transformed to normalize the distribution and included as the dependent variable in weighted linear regression models with gestational week of blood collection as a covariate. GMean (GMean) leptin values were obtained from these models and re-transformed to the original scale for reporting. We first examined GMean leptin levels in relation to maternal characteristics and pregnancy complications, i.e. hypertensive disorders and GDM. The linear regression models were constructed with and without maternal pre-pregnancy BMI as a covariate. Next, we included pregnancy outcomes and found evidence of an interaction (p-value=0.056) between timing of deliver (term versus preterm) and BW/GA in relation to leptin levels. As a result we created a 6-level variable for pregnancy outcome, Term-AGA (referent), Preterm-AGA, Term-SGA, Preterm-SGA, Term-LGA, and Preterm-LGA and used it in the subsequent analyses. A GMean leptin level was calculated for each of the six categories, first with gestational week at blood collection as a covariate and then after adding the covariate pre-pregnancy BMI. Finally, we assessed GMean leptin levels for the 6-level pregnancy outcome variable after removing women with hypertensive disorders and GDM to examine the extent to which the associations between pregnancy outcome and leptin levels were explained by these pregnancy complications.

Results

In the study sample, weighted percentages showed that over two thirds of POUCH Study participants were under 30 years of age, about one quarter were African-American, greater than half had ≥12 years of education, and just under a half were enrolled in the Medicaid Insurance plan (Table 1). As expected, maternal blood leptin levels were highest in obese women and lowest in underweight women (Table 1). The GMean leptin level in each of the ‘non-normal’ BMI categories was significantly different from that in the group of women with normal BMI ($p<0.001$). Only one other maternal characteristic, age at study entry, was significantly associated with leptin levels. However, maternal age did not remain significant in multivariable models and did not change the estimates for the effects of other variables in the models.

Just under 10% of women had some form of hypertensive disorder during the pregnancy (Table 2). Women with GHTN, PE, and CHTN had higher GMean leptin levels than women with no hypertension disorders, though with CHTN the difference was not statistically significant. The GMean leptin level in women with GDM was significantly higher than that in women without GDM. After including pre-pregnancy maternal BMI as a covariate, the GMean leptin level remained significantly elevated in association with GHTN but was no longer associated with PE, CHTN and GDM.

For the 6-level pregnancy outcome variable, the Term-AGA referent category accounted for approximately 70% of deliveries after applying sampling weights. Women in this group had

an GMean leptin level of 25.2 μg/L (Table 3). Lower GMean leptin levels were observed in three categories, women who delivered Preterm-SGA (21.7 μg/L), Preterm-AGA (21.9 μg/L) and Term-SGA (20.3 μg/L). For the Preterm-SGA, the GMeans was not statistically significantly different from that of the Term-AGA referent, but this may be explained by the relatively smaller sample size in the Preterm-SGA category (n=20). A significantly higher GMean leptin level was noted in two other categories, women who delivered Preterm-LGA (33.6 μg/L) and Term-LGA (29.1 μg/L). After controlling for maternal pre-pregnancy BMI, differences in the GMean leptin levels were slightly attenuated and the comparison between the referent Term-AGA and Term-LGA was no longer statistically significant. Further, after removal of women with any hypertension disorder or with GDM the GMean leptin level was noticeably attenuated in the Preterm-SGA group, but in all other groups GMeans were relatively stable and comparisons with the referent group did not change. Similar results were obtained after removing only women with PE (data not shown).

In other results not detailed here, removal of under-weight mothers from our analysis had little impact. When we looked within BW/GA categories (AGA, SGA, LGA) and compared GMean leptin for preterm and term group within the categories, we found a statistically significant difference in the AGA group only (p=0.003).

Discussion

We found lower maternal leptin levels in blood sampled at mid-pregnancy among women who delivered SGA infants either term or preterm, though a small sample size limited inferences about this latter group. In addition, delivery of a preterm AGA infant was associated with lower maternal leptin levels. These findings persisted after adjusting for mother's pre-pregnancy BMI and after removal of women with complications such as hypertensive disorders or GDM. By contrast the higher maternal leptin levels observed in mothers of LGA infants was significantly attenuated in models that incorporated pre-pregnancy BMI, particularly for mothers of term LGA infants.

Overall, findings from studies of maternal leptin levels and SGA infants have been inconsistent. Some have reported no significant association; (18, 19, 21, 24) one of the reasons for this observation could be the small number of SGA infants relative to our sample size. Other researchers have observed higher maternal leptin levels in association with an SGA infant. (8, 20, 25) Most of these latter studies examined only term births and maternal leptin levels were measured close to or at the time of delivery. Often it was not clear whether women with pregnancy complications were excluded, and sample sizes tended to be small. Results from two studies were similar to our finding of lower leptin levels in mothers who delivered SGA infants, preterm or term. One of the studies gathered repeated measures of maternal leptin levels across pregnancy and excluded women with pre-eclampsia. (7) The other measured maternal leptin levels during the first trimester. (17)

In uncomplicated pregnancies maternal leptin levels increase by 2–3 fold over the course of pregnancy. (6) The placenta produces leptin (26) which is thought to support placental growth and create a maternal leptin resistance environment so that mothers maintain a positive energy state. (1) During pregnancy the free leptin form remains constant whereas

the bound form of leptin is increased. (27) This is in contrast to the condition of obesity during the non-pregnant state in which free leptin increases and levels of soluble leptin receptor remain constant. (28) The biological pathways linking maternal blood leptin levels and fetal growth need further investigation. One hypothesis is that the combination of a small or compromised placenta and poor fetal growth is accompanied by lower levels of leptin in maternal blood. In the unique situation of preeclampsia, placentas compensate and put out excess leptin resulting in higher maternal blood levels, but fetal growth may still be impaired. (7) A decrease in maternal vascular expansion (less hemodilution) associated with preeclampsia (29) might also contribute to observing higher maternal blood leptin levels. After adjusting for pre-pregnancy BMI we found that maternal leptin levels remained elevated in women with PE and in women with GHTN, the group with the highest leptin levels. In pregnancies complicated by hypertensive disorders, total placental production of leptin may not be altered but less is directed to the fetus and therefore a larger percentage enters the maternal circulation.

We also found lower mid-pregnancy leptin levels in mothers who delivered preterm AGA infants. While this may reflect underlying pathology related to early delivery, there are other possible explanations. The BW/GA cut-points that defined AGA were obtained by using percentiles from a livebirth referent population. (23) Given the same GA, preterm livebirths are, on average, smaller than fetuses who are still in-utero. (30) Thus among preterm the lower bounds of the AGA might include some who are SGA but classified as AGA. Based on these explanations it may be that maternal leptin levels are primarily related to BW/GA and there is minimal additional relation to prematurity.

On the other extreme of BW/GA, two studies examined maternal leptin levels in relation to delivery of an LGA infant, and both found no significant association after adjusting for maternal pre-pregnancy weight. (20, 31) One measured leptin levels at delivery with a sample size of only 17 women delivering LGA infants. (31) The other categorized leptin levels and therefore had limited statistical power. (20) The association we observed between higher maternal leptin levels and delivery of an LGA infant was attenuated by inclusion of maternal pre-pregnancy BMI, but still significant for the preterm LGA. Blood leptin level is closely linked to BMI and strongly correlated with body fat in non-pregnant populations. (32) But the correlation is reduced in pregnant women, most likely due to the placental contribution of leptin to the maternal circulation. We found a moderate to strong correlation ($r=0.62$) between maternal leptin level and pre-pregnancy BMI in our data which agrees with that reported by other studies of pregnant women. (7) In non-pregnant populations high blood leptin levels are associated with insulin-resistance (33), and this may be one mechanism that links leptin levels and delivery of larger babies. (20) After removing women with GDM or hypertensive disorders and adjusting for maternal prepreg-BMI, the persistent association between higher maternal leptin levels and preterm LGA in our data may mark a group with underlying elements of the metabolic syndrome without progression to GDM.

To our knowledge, this is the largest prospective study of relations between mid-pregnancy leptin levels and adverse pregnancy outcomes including prematurity. The large sample size allowed us to detect an interaction between BW/GA and timing of delivery and to assess leptin levels in groups defined by these two pregnancy outcomes. In addition, the POUCH

Study cohort included a socioeconomically diverse group of women who were representative of those delivering in the study communities, thereby enhancing the potential for generalizability. Careful medical record abstraction enabled the identification of pregnancy complications such as hypertensive disorders and GDM, to better understand their influence in leptin-pregnancy outcome associations.

Our reliance on a single measure of maternal leptin levels in pregnancy was a clear limitation. If maternal blood leptin levels reflect placental leptin production, as suggested by others (1, 7, 25), monitoring leptin across pregnancy might provide additional clues about placental function and its relation to fetal growth. A dilemma for any study of leptin levels in pregnancy is the problem of maternal anthropometrics. As a means of adjusting for adiposity, BMI is imperfect and there is an opportunity for residual confounding. Conversely, leptin derived from maternal adipocytes, or maternal weight-related leptin resistance may be in the pathway to pregnancy outcome. Leptin produced by the placenta will be diluted in maternal circulation according to maternal size, and thus adjustment for maternal BMI would be indicated. Because of these challenges, we presented results with and without maternal prepreg-BMI in the models, but all these caveats must be considered. In addition, it is likely that leptin is part of a larger network of biomarkers which together may mediate or mark pregnancy outcomes. Therefore one must be cautious in assigning a causal role to any single biomarker.

In conclusion, our study findings suggest that a careful evaluation of maternal leptin levels and pregnancy outcome should include both measures of infant size and timing of delivery, to understand the implications of potential interactions. Relations between leptin levels and pregnancy outcome are not fully explained by maternal BMI or by complications often associated with high BMI such as GDM and hypertensive disorders. These results point to a potentially intriguing role of mid-pregnancy placental leptin as marker and/or mediator in fetal growth. Our future direction will include an examination of maternal leptin levels in conjunction with placental pathologic findings within the POUCH Study.

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Table 1

Weighted frequencies of maternal characteristics and their associated geometric means (GMeans) leptin levels (n=1,304)

Maternal characteristics	N	Wt %	GMeans[a] (μg/L)	95% CI
Age				
<20 (Ref)	229	14.7	23.2	[21.4, 25.2]
20–30	737	57.1	25.8	[24.6, 27.0] **
>=30	338	28.2	24.0	[22.5, 25.7]
Race				
Non-Hispanic white (Ref)	671	65.7	25.2	[24.1, 26.3]
African American	535	24.6	24.6	[23.3, 25.9]
Hispanic	58	5.2	25.8	[21.8, 30.4]
Others	40	4.4	22.5	[18.4, 27.4]
Education				
<12 years (Ref)	297	19	24.1	[22.3, 26.0]
12 years	370	27.2	26.6	[24.9, 28.4]
>12 years	637	53.8	24.4	[23.3, 25.6]
Parity				
Primiparous (Ref)	546	41.3	24.8	[23.4, 26.2]
Multiparous	757	58.7	25.0	[23.9, 26.1]
Smoking				
No (Ref)	938	72.6	25.1	[24.1, 26.1]
Yes	366	27.4	24.4	[22.9, 26.1]
Medicaid status				
No (Ref)	565	50.9	24.6	[23.4, 25.9]
Yes	737	49.1	25.2	[24.0, 26.5]
Gestational age Enrollment (weeks)				
15–<20 (Ref)	213	15.7	24.0	[21.9, 26.4]
20–<25	915	71.1	24.9	[23.9, 25.9]
25–<28	176	13.2	26.2	[23.8, 28.7]
Pre-pregnancy BMI				
Underweight (<18.5)	61	3.8	12.4	[10.6, 14.4] ****
Normal (18.5–24.9) (Ref)	585	46.9	19.2	[18.3, 20.1]
Overweight (25.0–29.9)	289	22.9	29.2	[27.7, 30.7] ****
Obese (>=30)	369	26.3	38.4	[36.6, 40.2] ****

[a] Adjusted for gestational week at blood collection

** p-value < 0.05;

**** p-value <0.0001

Table 2

Weighted geometric means (GMeans) leptin levels in relation to pregnancy complications (n=1,304)

Pregnancy complications	N	Wt%	Model 1[a]		Model 2[b]	
			GMeans (μg/L)	95% CI	GMeans (μg/L)	95% CI
Hypertension/PE						
None (Ref)	1162	90.3	24.3	[23.4, 25.2]	24.7	[23.9, 25.4]
GHTN	54	4.1	35.2	[32.0, 38.6] ****	30.4	[27.0, 34.2] **
PE	44	2.6	29.7	[24.7, 35.9] **	26.7	[23.2, 30.7]
CHTN	44	2.9	28.2	[24.4, 32.6]	23.7	[21.2, 26.6]
Gestational Diabetes						
No (Ref)	1239	94.5	24.5	[23.7, 25.5]	24.9	[24.2, 25.6]
Yes	65	5.5	32.0	[28.5, 36.0] ****	24.6	[22.1, 27.5]

[a] Adjusted for gestational week at blood collection

[b] Adjusted for gestational week at blood collection and maternal pre-pregnancy BMI

** p-value < 0.05;

**** p-value <0.0001

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Table 3

Weighted geometric means (GMeans) leptin levels in relation to pregnancy outcome

Pregnancy outcome	N	Wt %	Model 1[a] (n=1,304)			Model 2[b] (n=1,304)			Model 3[c] (n=1,108)			
			GMeans (μg/L)	95% CI	p-value	GMeans (μg/L)	95% CI	p-value	N	GMeans (μg/L)	95% CI	p-value
Term - AGA	765	69.4	25.2	[24.7, 26.8]	REF	25.3	[24.5, 26.2]	REF	670	25.1	[24.2, 26.0]	REF
Preterm - AGA	258	8.6	21.9	[21.5, 25.0]	0.00**	22.7	[21.3, 24.2]	0.00**	204	22.0	[20.5, 23.6]	0.00**
Term – SGA	121	8.8	20.3	[18.0, 22.7]	0.00**	21.8	[20.0, 23.7]	0.00**	106	22.3	[20.3, 24.5]	0.02**
Preterm - SGA	20	0.7	21.7	[15.3, 30.8]	0.41	22.8	[17.2, 30.3]	0.48	11	18.5	[12.2, 28.1]	0.16
Term - LGA	99	11.1	29.1	[26.2, 32.2]	0.01**	26.5	[24.3, 28.9]	0.32	85	26.5	[24.1, 29.1]	0.29
Preterm - LGA	41	1.4	33.6	[27.8, 40.5]	0.00**	29.8	[25.4, 34.7]	0.05**	32	30.5	[25.3, 36.8]	0.05**

[a] Adjusted for gestational week at blood collection

[b] Adjusted for final gestational week at blood collection and maternal pre-pregnancy BMI

[c] Adjusted for final gestational week at blood collection and maternal pre-pregnancy BMI, removing all hypertensive orders (gestational hypertension, PE, chronic hypertension) and GDM

** p-value < 0.05

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