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Pre-pregnancy obesity and maternal circadian cortisol regulation: Moderation by gestational weight gain

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Over half of women of childbearing age are overweight or obese (Vahratian, 2009). Given the adverse consequences of maternal excessive gestational weight on perinatal health outcomes (Cogswell, Perry, Schieve, & Dietz, 2001; Mann, McDermott, Hardin, Pan, & Zhang, 2013; Siega-Riz, 2012; Van Lieshout, Taylor, & Boyle, 2011) and offspring risk of cardiometabolic and neurobehavioral deficits through adulthood, this represents a major public health concern (Baeten, Bukusi, & Lambe, 2001; Sen et. al, 2012; Siega-Riz, & Laraia, 2006). Given these notable health consequences, the Institute of Medicine (IOM) recommends limiting gestational weight gain in obese women to 4.99–9.07kg (Rasmussen & Yaktine, 2009), though 60% of these women gain in excess of this recommendation (Rasmussen & Yaktine, 2009). This is particularly concerning given that the coupling of maternal pre-pregnancy obesity with excessive gestational weight gain may result in additional risk for fetal overgrowth (Jensen et al., 2005), poor pregnancy outcomes (Black, Sacks, Xiang, & Lawrence, 2013), and both maternal and offspring long-term obesity and cardiovascular disease (Jensen et al., 2005; Reynolds, 2013; Siega-Riz et al., 2006). Although these studies highlight the additive risk of pre-pregnancy obesity and excessive gestational weight gain on maternal and offspring outcomes, few studies have examined mechanisms underlying these relations. However, relatively new literature supports the role of stress hormones.

During typical, healthy pregnancies, daily maternal stress hormone release changes, relative to non-pregnant women (Jansson et al., 2008). In particular, cortisol awakening responses

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Conflicts of Interest

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(cortisol peak between awakening and approximately 30 minute post-awakening) and maternal stress reactivity decline as pregnancy progresses (Entringer et al., 2010; Obel et al., 2005). Blunting of the cortisol awakening response is thought to protect against maternal and fetal morbidity associated with excessive prenatal glucocorticoid exposure (Ching-Yu & Pickler, 2010; Stroud et al., 2014). Elevated cortisol may also be associated with excessive maternal weight, given that glucocorticoids decrease basal metabolic rate (Heiman et al., 1997). However, maternal fat cells inhibit reciprocal negative relations between elevated cortisol and decreased metabolism by releasing leptin hormone, which inhibits the hypothalamic-pituitary-adrenal response to stress (Sen et al., 2012). This response, however, is altered in obese women. In particular, obesity leads to the development of leptin hormone resistance, which results in elevated circulating cortisol (Sen et al., 2012), which has been linked to poorer appetite control (Heiman et al., 1997). In fact, in non-pregnant samples, obesity-related disruptions in circadian cortisol have been supported. These disruptions were manifested as attenuated cortisol awakening responses (Abraham, Rubino, Sinaii, Ramsey, & Nieman, 2013; Champaneri et al., 2013) as well as less pronounced decreases in evening cortisol levels (Farag et al., 2008; Sedaghat, Rabiei, & Rastmanesh, 2012). These flatter circadian trajectories, in which cortisol stays elevated longer throughout the day, may account for hypercortisolism in obese samples (Farag et al., 2008).

Given support for links among obesity, weight gain, and dysregulation of circadian cortisol, in the current study, we investigated circadian cortisol levels over the second and third trimesters in obese and non-obese pregnant women. Our first aim was to investigate the influence of pre-pregnancy obesity versus normal weight on daily circadian cortisol at 24 ± 4 and 35 ± 1 weeks gestation. Given the previous studies of non-pregnant samples documenting the effects of obesity on elevated circulating glucocorticoids, we predicted that women who were obese prior to pregnancy would have the greatest daily cortisol output, manifested as a flatter daily cortisol rhythm (i.e., higher baseline values, attenuated awakening response, and higher evening values). Our second aim was to explore the interaction among maternal pre-pregnancy obesity, gestational weight gain, and circadian cortisol. Based on preliminary studies suggesting leptin resistance associated with obesity and reciprocal relations between maternal cortisol and gestational weight gain, we predicted that for obese women, greater gestational weight gain would be associated with greater daily cortisol release, manifested as a flatter daily cortisol rhythm.

Materials and Methods

Participants

Participants were recruited as part of a larger study (Behavior and Mood in Mothers and Behavior in Infants; BAMBI) of maternal depression in relation to fetal/infant development. Recruitment took place in health centers, obstetrical offices, and hospitals in the Providence, Rhode Island region. Two-hundred and fifteen participants were enrolled. Following enrollment, four participants declined participation over the course of the study. After removing participants with missing pre-pregnancy weight data, there were a total of 173 participants within the current sample, who are described in Table 1. None of the participants utilized in data analyses had been diagnosed with an endocrine disease (e.g.,

Diabetes Mellitus, Hypo/Hyperglycemia, and Hypo/Hyperthyroidism), thus eliminating such disorders as potential confounds.

Procedure/Materials

The current study was approved by the Women and Infants Hospital and Lifespan Hospitals' Institutional Review Boards. Following an initial telephone screen for exclusion criteria, the first (24±4 weeks) session included study review, consent, and interviews regarding participant demographics and health/weight history, including participant-reported most recent pre-pregnancy weight. Participants were given detailed instructions and tubes for circadian saliva collection for three days at awakening, 30 minutes post-awakening, and prior to sleep at night for both visits (i.e., 24±4 and 35±1 weeks gestation).

To increase circadian saliva collection compliance, (I) detailed written and oral instructions were provided at each visit, (II) a subsample of participants (13%) utilized Medication Event Monitoring System caps (AARDEX, Zurich, Switzerland) with robust associations between self-reported and MEMS sampling times at wake/30 minutes post ($r^2=.99-1.0$) and before bed ($r^2=.87-1.0$), (III) incentives were provided for each saliva sample, and (IV) saliva and Medication Event Monitoring System caps were obtained by study staff from participants' homes after each circadian collection. Saliva collection times were included as covariates in our subsequent analyses. Participants were instructed to avoid eating or brushing their teeth one hour prior to sampling. Upon retrieving samples, they were frozen at -80°C prior to analysis. Cortisol assays were performed using expanded range high-sensitive enzyme immunoassays (ER-HS-EIAs) completed at Dresden University. The intra-and inter-assay coefficients of variation were <8%.

Maternal pre-pregnancy BMI was calculated utilizing the following standard formula:

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2}$$
 This semi-continuous BMI variable was used for interaction analyses. Women were classified as obese (BMI ≥ 30) or not (BMI < 30; Rasmussen & Yaktine, 2009) for main effects and follow-up analyses examining direction of effects. Weight changes were calculated by subtracting pre-pregnancy weight from weight at respective visits (i.e., 24±4 and 35±1 weeks gestation). The semi-continuous variable was used for all primary analyses, while categories (i.e., above or below IOM recommendations, according to pre-pregnancy BMI) were used for follow-up analyses.

Potential covariates considered in the current sample included maternal age in years, education (percentage of participants with a high school diploma or more education), employment (percentage of participants unemployed), married (percentage), race (percentage non-white), ethnicity (percentage Hispanic), parity, household income (percentage low income defined as <\$40,000/year or approximately twice the federal poverty threshold for a family of four), and planned pregnancy (percentage), all obtained via maternal self-report at the first prenatal visit. Additionally, prenatal depression diagnoses (percentage) were captured over the course of the study via the administration of the Structured Clinical Interview for DSM-IV (SCID) and the percentage of participants with drug use (i.e., nicotine, alcohol, cannabinoids, and opiates) and major medical conditions (i.e., gallstones, oligohydramnios, generalized epilepsy, Chrone's Disease, MRSA infection,

and kidney infection with hospitalization) during pregnancy were assessed from maternal interview, medical chart review, and biochemical analyses of infant meconium (assayed for amphetamines, cannabinoids, Carboxy-THC, cocaine, codeine, hydrocodone, hydromorphone, morphine, and cotinine), respectively. Birth outcomes, including gestational age at birth, birth weight, small for gestational age (SGA; weight <10th percentile for the gestational age), large for gestational age (LGA; weight >90th percentile for gestational age), and APGAR score at 5 minutes post delivery, were collected by medical chart review following delivery.

Data Analysis

All data analyses were completed using Predictive Analytics SoftWare (PASW), version 18. At both prenatal time points (24±4 weeks and 35±1 weeks, individually), Conditional Growth Models were used to examine main (semi-continuous BMI) and interactive effects of pre-pregnancy weight (dichotomous obesity) and gestational weight gain (semi-continuous) on the circadian cortisol trajectories. Level 1 models included each cortisol collection time (awakening, 30 minutes post-awakening, and before bedtime each averaged from available data over the three collection days), while Level 2 included pre-pregnancy weight, gestational weight gain, and the interaction term. Full maximum likelihood and composite residuals for covariance structures were used to estimate all Conditional Growth Models. Follow-up repeated-measures ANOVAs were conducted to explore group differences in the direction of significant main or interactive effects of pre-pregnancy obesity (yes, no) and gestational weight gain (above or below IOM recommendations) on circadian cortisol (at awakening, 30 minutes post-awakening, and before bedtime averaged over the three collection days) identified in the growth models. The gestational weight gain variables used for follow-up tests were adjusted for pregnancy duration using IOM recommendations. In particular, it is suggested that normative weight and overweight women should gain at or below 3kg in the first trimester. While normative weight women should gain at or below 0.5kg/week in the second and third trimesters, overweight women should gain at or below 0.33kg/week in the second and third trimesters (Rasmussen & Yaktine, 2009). Obese women are recommended to gain at or below 2kg in the first trimester and at or below 0.27kg/week in the second and third trimesters (Rasmussen & Yaktine, 2009). Results from these follow-up repeated-measures ANOVAs were used to model group effects in figures, though semi-continuous variables were used in Conditional Growth Models. Cortisol collection time served as the repeated-measures variable for the ANOVAs, which were conducted separately for each prenatal time point.

Sampling distributions of residuals were examined for normality and logarithmic transformations were applied for maternal cortisol variables at the first prenatal time point (24±4 weeks gestation). No data transformations were applied at the second time point because data were normally distributed and none of the analyses simultaneously assess diurnal cortisol at both a time points. Morning cortisol samples that were collected <20 or >40 minutes apart were removed in order to assure accurate measurement of the cortisol awakening response. One-way ANOVAs and chi-square tests of association were used to examine whether potential covariates or birth outcomes differed by maternal obesity group

(see Table 1). Because no covariates were systematically related to this predictor variable, none were added in the current models.

Results

Demographic and birth outcome distributions across BMI categories can be seen in Table 1. On average, participants were 26.6 years old ($SD=5.6$ years). The diverse sample included 45% Non-Hispanic, White women (28% Hispanic, 16% Non-Hispanic Black, 4% Asian, 4% multiracial, 3% “other”). Most participants were low-income (52% <\$40,000/year), married (41%), multiparous (51%), and had unplanned pregnancies (60%). No group differences (obese, not obese) were found in maternal age, education, income, occupation, race, or ethnicity. In addition, prenatal depression did not differ by group, nor did incidence of major medical conditions or substance use, the latter of which was very rare in the current sample ($n=18$). Because no group differences were found among potential covariates, no covariates were included in analyses. Reflective of the aims of the parent study to recruit a sample of women at low-risk for adverse neonatal outcomes, babies in this sample were born at 39 weeks gestation ($SD=2$ weeks) and 3341 grams ($SD=542$ grams). 6% of babies were small for gestational age and 5% were large for gestational age. Average APGAR score at 5 minutes after delivery was 9 ($SD=1$). Birth outcomes did not significantly differ by obesity group. Maternal cortisol values for awakening ($r=.47, p<.001$), 30 minutes post-awakening ($r=.61, p<.001$), and prior to sleep ($r=.20, p=.032$) were significantly correlated at the first and second visit.

Aim I: Investigate the influence of pre-pregnancy obesity versus normal weight on daily cortisol output at 24±4 and 35±1 weeks gestation

At 24±4 and 35±1 weeks gestation (both main effects of cortisol sampling time, $p<.001$), circadian patterns in cortisol were observed and displayed the typical attenuation over pregnancy (see Figure 1). Patterns of attenuation differed by maternal weight variables; at 35±1 weeks, circadian cortisol patterns differed by pre-pregnancy obesity group (estimate=3.524, $SE=1.470, p=.018$). Examination of means patterns (see Figure 1) and follow-up Repeated-Measures ANOVAs reveal that participants who were obese prior to pregnancy ($n=38$) had higher evening cortisol than participants who were not obese prior to pregnancy ($n=107$, 28 missing cortisol data; $F(2,286)=6.57, p=.002$). No significant associations were found among pre-pregnancy obesity and cortisol at 24±4 weeks.

Aim II: Explore the interaction between maternal pre-pregnancy BMI, gestational weight gain, and circadian cortisol levels at 24±4 and 35±1 weeks gestation

The interaction among pre-pregnancy obesity, gestational weight gain, and circadian cortisol was significant (estimate=.019, $SE=.008, p=.025$) at 35±1 weeks but not at 24±4 weeks ($p>.05$). Obese pregnant women ($n=32$, 6 missing weight gain data) with excessive gestational weight gain (i.e., above 7.94kg at 35 weeks gestation; $n=22$) had higher evening cortisol levels than obese women with gestational weight gain within IOM recommendations (i.e., at or below 7.94kg at 35 weeks gestation; $n=10$; see Figure 2). In fact, the circadian pattern, largely manifested as a lack of evening nadir, but also including a somewhat blunted awakening response, is nearly absent in these women. No differences in cortisol were found

for non-obese women ($n=86$, 21 missing weight gain data) who gained above ($n=41$) or below IOM recommendations ($n=45$).

Discussion/Conclusion

Overall, pre-pregnancy obesity was associated with increased evening cortisol in late pregnancy, but not in second trimester. Associations between elevated evening cortisol and obesity also appeared to be moderated by weight gain in excess of IOM Guidelines. In particular, obese women who gained in excess of IOM guidelines had flatter trajectories of circadian cortisol. This pattern was not observed in obese women gaining weight within the IOM recommendations, and was also not observed in women who were not obese prior to pregnancy, regardless of whether they gained weight in excess of IOM recommendations.

The present study supports effects of pre-pregnancy obesity on maternal HPA regulation in addition to interactions between pre-pregnancy obesity and gestational weight gain on maternal cortisol regulation. This study also has several unique strengths, including the use of prospective, longitudinal measures of prenatal weight and cortisol. In addition, the collection of cortisol samples across multiple time points allowed the current study to model circadian variations by maternal weight. The current sample was racially, ethnically, and socioeconomically diverse, thereby supporting the external validity of findings. The careful measurement and consideration of major covariates to these potential relations also supports the internal validity of results.

Study findings complement prior literature in several important ways. First, the current study extends known relations among obesity and circadian cortisol to the prenatal period. The same circadian cortisol trajectories found in non-pregnant, obese samples were replicated in the current pregnant sample (Meena, Chandola, Brunner, & Kivimaki, 2010).). These elevations in cortisol were further moderated by excessive gestational weight gain over pregnancy. Our findings complement animal studies which suggest that this interaction is due to reciprocal relations between cortisol and weight, which are exacerbated by obesity (Heiman et al., 1997; Stroud et al., 2014). In particular, greater cortisol release reciprocally inhibits basal metabolism and appetite suppression, leading to even greater weight gain in at-risk mothers.

Our findings also complement a small number of human studies of both prenatal obesity and maternal cortisol in relation to poor offspring health outcomes. Specifically, these studies suggested that the effects of obesity on poor infant/child health outcomes may be due to a blunted HPA axis response resulting in flatter circadian cortisol trajectories over pregnancy (Abraham et al., 2013; Champaneri et al., 2013; Meena et al., 2010). Although we were not able to examine this mediation hypothesis with regard to poor infant birth outcomes because of the lack of variability and restricted range of these outcomes in the current sample, we examined relations among prenatal obesity, maternal cortisol, and both infant birth weight and gestational age at birth. None of these relations were statistically significant, which may have again been due to the fact that most infants in the current sample were relatively healthy.

The current study suggests that obese women with excessive gestational weight gain show greatest alterations in circadian cortisol and thus may be at greatest risk for poor infant/child health outcomes. Our findings support a strong need for weight management in the perinatal period. Aside from negative effects of excessive glucocorticoid exposure on maternal health, maternal hypercortisolism may lead to fetal overexposure to maternal glucocorticoids, resulting in poorer pregnancy outcomes and long-term programming of health and behavioral difficulties in offspring (Baeten et al., 2001; Cogswell et al., 2001; Sen et al., 2012; Siega-Riz, 2012; Siega-Riz & Laraia, 2006; Van Lieshout et al., 2011). These patterns in late pregnancy are especially concerning given that this is a time of rapid fetal growth and a sensitive period for maladaptive offspring growth patterns (Kivlighan, DiPietro, Costigan, & Laudenslager, 2008).

Elevated evening cortisol in obese women during third trimester may have emerged for several reasons. First, as noted previously, women's biological responses to stressors diminish over pregnancy, making the third trimester a relative period of quiescence. Thus, this time period may be most sensitive to deviations in these normative patterns of stress hyporesponsivity. Support for this hypothesis comes from literature demonstrating the negative effects of increasing gestational psychosocial stress on risk for preterm birth (Glynn, Schetter, Hobel, & Sandman, 2008). Secondly, the emergence of significant findings in late pregnancy may be due to a cumulative or growing effect of established links between maternal obesity and elevated cortisol release (Heiman et al., 1997; Stroud et al., 2014), though this hypothesis warrants further investigation. In particular, for women who are obese prior to pregnancy and therefore exhibit leptin resistance, the effects of greater cortisol release over pregnancy may lead to increased appetite, decreased metabolism, and additional gestational weight gain above and beyond what would be expected during pregnancy in a normative sample. This additional metabolic disturbance and weight may then reciprocally raise glucocorticoid concentrations, leading to a negative cycle with multiple risk pathways for the developing fetus. Obesity is also associated with other biological (e.g., sleep, inflammation, and medical comorbidities) and psychosocial factors (e.g., stigma and self-esteem/body image) that are related to stress hormones (Björntorp & Rosmond, 2000; Bose, Oliván, & Laferrère, 2010; Rogge, Greenwald, & Golden, 2004). These influences may therefore directly (e.g., inflammation may lead to activation of the HPA axis during pregnancy) or indirectly (e.g., body image issues may lead to more subjective distress and physiological stress) further contribute to excessive weight gain and prenatal risk and should also be explored in late pregnancy in future research.

Future studies should also examine interactive effects of maternal weight and altered glucocorticoid release patterns, particularly elevated evening cortisol levels during gestation, on infant health outcomes. Additionally, findings suggest that interventions combining weight and stress management, shown to be efficacious in non-pregnant samples (Foreyt & Poston, 1998), may be helpful for obese pregnant women. Given research highlighting differential effects of nutrition on cortisol based on obesity status, nutritional interventions may play a particularly useful role as part of weight management strategies. Preventive interventions may include education for obese women of child-bearing age and early assessment/treatment to reduce adverse fetal/child outcomes.

The current study had limitations that should be considered when evaluating results. First, participants were asked to retrospectively report pre-pregnancy weight. Although some error in self-report is to be expected, a robust overlap ($r=.95$) between pre-pregnancy weight from self-report and medical chart review in a large subset of the sample ($n=102$ of 173) suggests that these estimates are valid. Mothers and infants also had limited variability in health conditions due to the larger study exclusion criteria, limiting the ability to explore effects of maternal obesity, weight gain, and cortisol on infant health outcomes. Lastly, because this study was not selected to investigate maternal obesity, sample sizes were not evenly dispersed across obesity study groups.

Overall, findings further support interactions between prenatal metabolic and stress systems and highlight the importance of assessing pre-pregnancy obesity and gestational weight gain when evaluating pregnancy/offspring risk. Links among pre-pregnancy obesity and altered circadian cortisol rhythms may be moderated by excessive gestational weight gain in late pregnancy. Although not tested in the current study given the lack of adverse birth outcomes, these elevations may account for adverse offspring health outcomes seen in prior studies. Future studies should examine prenatal maternal obesity, cortisol, and weight gain in relation to maternal and offspring health. Specifically, future studies might test whether interactions between maternal obesity and excessive gestational weight gain in predicting childhood health outcomes (e.g., pre-term birth, large-for-gestational-age/macrosomia, rapid catch-up growth in pre-term infants, birth defects, or later childhood emergence of cardiometabolic or neurobehavioral deficits) are mediated by physiological mechanisms such as maternal glucocorticoid release over pregnancy. These findings would then support combined stress and weight management interventions for obese pregnant women.

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Author Contributions

Dr. Stroud designed and oversaw the larger research study, obtained funding for the larger research study, and aided in data collection and interpretation. Dr. Bublitz contributed to data collection, data cleaning/analysis, and interpretation. Dr. Aubuchon-Endsley completed final data cleaning, coding, analysis, and interpretation. All authors were involved in conceptualization and writing the paper and had final approval of the submitted and published versions. We would also like to acknowledge the contributions of all BAMBI project staff, volunteers, and participants for their many contributions.

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- Pre-pregnancy obesity, gestational weight gain, and diurnal salivary cortisol interact
- Findings were significant in a socioeconomically at-risk sample in late pregnancy
- Women obese prior to pregnancy who gained in excess of IOM guidelines had greater evening cortisol at 35 ± 1 weeks gestation
- No such patterns were found at 24 ± 4 weeks gestation, in non-obese women, or in those within IOM recommendations

Figure 1.

Evening cortisol patterns differ by pre-pregnancy obesity group in late pregnancy. *Post-hoc* analyses demonstrated that women who were obese prior to pregnancy ($n=38$) had higher evening cortisol values than women who were not obese prior to pregnancy ($n=107$) at 35 ± 1 weeks gestation. There were no significant differences in cortisol values between women who were obese prior to pregnancy ($n=33$) and women who were not obese prior to pregnancy ($n=118$) at 24 ± 4 weeks gestation.

Figure 2.

Excessive weight gain ($>7.94\text{kg}$) in women obese prior to pregnancy leads to elevated evening cortisol at 35 ± 1 weeks gestation.

The above results derived from a Repeated-Measures ANOVA suggesting that for women who were obese prior to pregnancy, excessive weight gain ($n=22$) led to elevated evening cortisol, though this pattern was not observed for obese women gaining within IOM recommendations ($n=10$). Further, there were no differences in circadian cortisol among women who were not obese prior to pregnancy, regardless of whether they gained within ($n=45$) or above IOM guidelines ($n=41$). IOM Guidelines were adjusted for 35 weeks gestation duration such that excessive weight gain was defined as $>14\text{kg}$ in women of normative weight prior to pregnancy, $>10.26\text{kg}$ in women who were overweight prior to pregnancy, and $>7.94\text{kg}$ in women who were obese prior to pregnancy.

Table 1**Maternal Demographic and Infant Characteristics by Weight Group**

	Maternal Weight Group		<i>p</i>
	Obese Prior to Pregnancy (<i>n</i> = 38)	Non-obese Prior to Pregnancy (<i>n</i> = 135)	
	Mean (<i>SD</i>)/%	Mean (<i>SD</i>)/%	
<u>Maternal Demographic & Pregnancy Variables</u>			
Age (Years)	27 (5)	27 (6)	<i>ns</i>
Education (% HS)	54%	36%	<i>ns</i>
Unemployed (%)	57%	40%	<i>ns</i>
Income (% Low)	64%	46%	<i>ns</i>
Married (%)	41%	41%	<i>ns</i>
Race (% Non-White)	54%	54%	<i>ns</i>
Ethnicity (% Hispanic)	24%	28%	<i>ns</i>
Parity (% Multiparous)	58%	50%	<i>ns</i>
Planned Pregnancy (%)	65%	53%	<i>ns</i>
Prenatal Depression (%)	42%	34%	<i>ns</i>
Drug use (%)	8%	11%	<i>ns</i>
Major Medical Condition (%)	3%	2%	<i>ns</i>
<u>Infant Characteristics</u>			
Gestational Age at Birth (weeks)	39 (3)	39.5 (2)	<i>ns</i>
Birth weight (grams)	3292 (662)	3348 (513)	<i>ns</i>
Small for Gestational Age (% yes)	6%	7%	<i>ns</i>
Large for Gestational Age (% yes)	3%	6%	<i>ns</i>
Apgar 5 minutes	9 (1)	9 (1)	<i>ns</i>

Note. Differences in obesity group were quantified for the following categories based on self-reported data from the 24±4 week session: Education (% with at least a HS diploma), Unemployed (% not currently working, not on prenatal leave), Income (% low income defined as <\$40,000/year or twice the federal poverty threshold for a family of four), Married (% in self-described category), Race (% Non-White), Ethnicity (% Hispanic), Parity (% with 1 prior, full-term birth), and Planned Pregnancy (% in self-described category). Over the course of the study, Prenatal Major Depression was assessed by SCID interview, while Drug Use (i.e., nicotine, alcohol, cannabinoids, and opiates) and Major Medical Conditions (i.e., major maternal infections or other conditions requiring hospitalization or surgery, amniotic fluid imbalance during pregnancy, or neurological impairments like epilepsy) were assessed from maternal interview, medical chart review, and biochemical analyses of infant meconium. Obesity group differences were examined based on the % of participants meeting criteria for a major depressive disorder diagnosis, major medical condition, or use of above substances during the study. Small-for-Gestational-Age was calculated based on growth curve percentiles below 10%, while Large-for-Gestational-Age was calculated based on growth curve percentiles above 90%.