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Sleep duration, napping behaviors and restless legs syndrome during pregnancy and the trajectories of ultrasonographic measures of fetal growth: findings from the NICHD Fetal Growth Studies–Singletons

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Abstract

Objectives: Given the plausible mechanisms and the lacking of empirical evidence, the study aims to investigate how gestational sleep behaviors and the development of sleep disorders, such as restless legs syndrome, influence ultrasonographic measures of fetal growth.

Methods: The study included 2,457 pregnant women from the NICHD Fetal Growth Studies - Singletons (2009-2013), who were recruited between 8-13 gestational weeks and followed up to five times during pregnancy. Women were categorized into six groups based on their total sleep hours and napping frequency. The trajectory of estimated fetal weight (EFW) from 10 – 40 weeks was derived from three ultrasonographic measures. Linear mixed effect models were applied to model the EFW in relation to self-reported sleep-napping behaviors and RLS status, adjusting for age, race and ethnicity, education, parity, pre-pregnancy body mass index category, infant sex, and prepregnancy sleep-napping behavior.

Results: From enrollment to near delivery, pregnant women's total sleep duration and nap frequency declined and RLS symptoms frequency increased generally. No significant differences in EFW were observed by sleep-napping group or by RLS status. Results remained similar in sensitivity analyses and stratified analyses by women's pre-pregnancy body mass index category (normal versus overweight/obese) or by infant sex.

Conclusions: Our data indicate that there is no association between sleep during pregnancy – assessed as total sleep duration and napping frequency, nor RLS symptoms – and fetal growth from weeks 10 to 40 in healthy pregnant women.

Keywords:

fetal weight, sleep duration, napping, restless legs syndrome, linear mixed effect models, time-varying exposures

1. Introduction

Changes in sleep behaviors occur in women during pregnancy, with significant changes being detected as early as 11 -12 weeks of gestation,[1] when increase in total sleep time, decrease of sleep efficiency, and reduction of slow wave sleep were observed compared with the prepregnant sleep characteristics. Decreased sleep quality from the second to the third trimester is a common phenomenon.[2] Self-reported daytime sleepiness was also frequent, which was reported by about a third of pregnant women.[3] In addition, a number of sleep disorders manifest during pregnancy, including restless legs syndrome (RLS). Approximately 20% of pregnant women experience RLS at any point in their pregnancy, which is much higher than a burden of 2 – 10% in the general population.[4] The incidence of RLS increase as pregnancy progresses.[5]

There are several plausible mechanisms proposed linking maternal sleep to fetal growth outcomes. Short sleep duration, sleep fragmentation, poor sleep quality may lead to a cascade of alterations in endocrine and inflammatory responses, inducing impaired glucose tolerance and insulin sensitivity,[6] which could lead to placental hypervascularization[7] and macrosomia [8]. Maternal circadian disruption has been associated with the variation in 'clock' gene expression in placenta [9] and placental methylation [10], both of which may be related to compromised placental function and a range of adverse pregnancy outcomes, including low birthweight.[11] Oxidative stress also increases with sleep disorders,[12] including RLS,[13] and, it may lead to

endothelial dysfunction [14] and ultrastructural and molecular changes in placenta that increases risk of intrauterine growth restriction.[15]

A number of observational studies have examined how sleep duration,[16-20] daytime sleepiness or napping behaviors,[18,20-24] and RLS[25] were related to birth size; however, mixed results have been reported. All of the studies have only measured birthweight, not fetal growth. The measure of birthweight or fetal size at birth with adjustment for gestational age does not reflect fetal growth trajectory. Previous data have shown how trimester-specific and anthropometric-specific measures of fetal growth perturbations are associated with postnatal growth, developmental outcomes, and health outcomes [26]; and sometimes, these measures were more closely related to disease risk than birthweight [27,28]. Fetal growth trajectory in utero is thought to be associated with various patterns of physiological function and the programming of fetal origins of adult diseases.[28] In addition, almost all of the previous studies only assessed sleep variables at one time point during pregnancy. Small observational studies with multiple measures suggested that greater variation in sleep duration over pregnancy was associated with smaller birth weight (n = 65 nulliparous mothers)[20]; however, cumulative number of RLS episodes during pregnancy was not related to the risk of low birth weight (n = 174 with RLS data)[21].

Given changes in sleep behaviors and fetal growth velocity over the course of pregnancy, longitudinal data are in great need to disentangle whether sleep behaviors and RLS throughout gestation have any impact on the trajectory of fetal growth. The current study aims to

investigate how sleep behaviors during pregnancy, assessed by total sleep hours and napping frequency, and gestational RLS, influence fetal growth trajectory. We hypothesize that short sleep duration, frequent napping, RLS incidence, and higher RLS severeness are related to sub-optimal fetal growth.

2. Participants and Methods

2.1. Study population and design

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies - Singletons was a multicenter, multiracial prospective cohort study of generally healthy pregnant women without major chronic diseases [29]. The study protocols were approved by institutional review boards at NICHD and at each participating clinical sites. The study has been registered at CLINICALTRIALS.GOV and the link to the study is: https://clinicaltrials.gov/ct2/show/NCT00912132. Between July 2009 and January 2013, 2,802 women with singleton pregnancies (18-40 years), who gave informed consent to participating in the study, were recruited from 12 US clinical centers between 8-13 weeks of gestation. Gestational dating was based on women's reported date of her last menstrual period and confirmed by the ultrasound screening at enrollment. At enrollment, a standardized survey was administered to assess information, including the demographics, socioeconomic status, reproductive history, and medical history since the current pregnancy. Participants were asked to report any diagnosed anemia since she becomes pregnant. Height and weight at enrollment were self-reported and recorded by trained study personnel.

2.2. Outcomes: Fetal growth assessment

Ultrasonographic examination was performed at enrollment visit (8 – 13 weeks) and six subsequent visits. To capture fetal growth data in almost all gestational weeks, women were randomized to one of the four ultrasonography schedules, starting at 16, 18, 20, and 22 weeks, respectively, and thereafter for up to five visits. The five visits were scheduled between 16-22 (visit 1), 24-29 (visit 2), 30-33 (visit 3), 34-37 (visit 4), and 38-41 (visit 5) gestational weeks. Fetal biometric measurements were performed consistently across sites and visits using the Voluson E8 Ultrasound System (GE Healthcare). Images were captured using the ViewPoint (GE Healthcare). Measurements were taken for humerus length (HL), femur length (FL), biparietal diameter (BPD< from the outer to the inner edge of the calvarial wall using the linear function), head circumference (HC, using the ellipse function), and abdominal circumference (AC, using the ellipse function). All participating ultrasound technicians in the study were trained and credentialed by the study's central ultrasonographic unit.[30] Intra-observer correlations were greater than 0.99 for all fetal ultrasonographic measurements. The ratio of the HC to AC (HC/AC) was calculated to assess asymmetric growth restriction. Estimated fetal weight (EFW) was derived from measures of HC, AC, and FL using the Hadlock formula.[31] EFW was treated as the primary outcome in our study and the individual measures were the secondary outcomes of the study.

2.3. Exposures

2.3.1 RLS assessment

RLS symptoms and the frequency of symptoms were assessed at enrollment and at each of the first five visits during pregnancy, as detailed elsewhere[32]. The four essential diagnostic criteria, approved by the International Restless Legs Syndrome Study Group (IRLSSG), were assessed via questionnaire to define RLS[4]. Specifically, the four criteria are: 1) urge to move the legs that is usually accompanied or caused by uncomfortable and unpleasant sensations in legs; 2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity; 3) the urge to move or unpleasant sensations are partially or totally relieved by movement; and 4) the urge to move or unpleasant sensations are worse in the evening or night than during the day. To improve specificity, we added a fifth question by asking whether leg cramps present during the urge of leg moving. Women who confirmed the presence of leg cramps were not considered to have RLS. We defined new onset of RLS as having newly developed RLS at any visit during pregnancy[32] and we excluded women who had RLS prior to this pregnancy. To determine clinical significance, we also asked the women to report the frequency of unpleasant sensations in legs and the frequency were categorized as less than once per month, 2 – 4 times per month, 2 – 5 times per week, and 6 or more times per week. The new onset RLS in pregnancy (yes/no) and frequency of RLS symptoms (categorical variable with 4 classes) were two primary exposures.

2.3.2 Sleep and napping behaviors

At enrollment, women were asked about their sleep and napping behaviors before and during pregnancy, including the total hours of actual sleep in a typical 24-hour period (≤6 hours, 7 hours, 8- 9 hours, or ≥10 hours) and nap frequency during the day or evening because of

getting sleepy (rarely or never, sometimes, or most of the times). The sleep and napping behavior questions were repeated in each of the following five visits to assess the behaviors since the last visit.

Following the previously published methods,[33] the sleep-napping behavior variable was created for the prepregnancy period, enrollment, and each follow-up visit, as <=7 hours and never/rarely; <=7 hours and sometimes/mostly; 8-9 hours never/rarely; 8-9 hours and sometimes/mostly; >=10 hours and never rarely; and >=10 hours and sometimes/mostly.

2.4. Covariate assessment

Women's demographic and socioeconomic status were assessed at enrollment via a structured questionnaire, including age, race and ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and Asian or Pacific Islander), education (high school or less, some college or associate degree, and college undergraduate degree, or post graduate degree), parity, and self-reported weight and height at enrollment. An a-priori list of variables was included in the analysis, including parity (0 or ≥1), pre-pregnancy BMI (calculated from self-reported enrollment weight and height), and infant sex (male/female).

2.5. Statistical Methods

The distribution of sample characteristics and the sleep, napping, RLS variables were summarized. Friedman test was used to study the distribution of exposure variables (i.e. the sleep, napping, and RLS variables) by visit.

To study the relationship between the exposure variables and EFW, we applied linear mixed effect models. First, an unadjusted linear mixed effect model was fit for one exposure variable at a time. For each exposure variable, the model included a random intercept for each woman (to account for the repeated and time-varying measures within women), linear and quadratic fixed effects for scaled gestational age (by subtracting the sample mean and dividing it by the sample standard deviation), the fixed effect for the exposure variable being examined and interaction terms between the scaled gestational age terms and the exposure variable. Note that the exposure variables are time varying and change for each visit. Next, an adjusted linear mixed model was constructed, which additionally included age, race and ethnicity, education, parity, pre-pregnancy BMI, infant sex, and prepregnancy sleep-napping behavior. Since the fetal growth trajectory showed no variance across both RLS presence (yes/no) and severity groups (four frequency groups), we chose to exclusively present the results related to RLS presence for the sake of brevity. To study the conditional associations of sleep-napping and RLS presence in relation to EFW, the adjusted models include both primary exposures of interest and the interactions of these exposures with the scaled gestational age. To calculate the predicted value for the mixed models, we performed bootstrapping and used the median of the bootstrapped values for the point estimate and the 95% interval was calculated using the 2.5^{th} quantile and 97.5^{th} quantile. The one-way ANOVA F test by sleep-napping behavior group and t-test by RLS presence status were conducted whether the bi-weekly predicted EFW were different. For the secondary outcomes, we repeated the adjusted models for HL, FL, BPD, HC, AC and HC/AC.

Several sensitivity analyses for EFW were performed that 1) excluded preterm births (n=150); 2) stratified women by their pre-pregnancy BMI category (normal weight vs overweight or obese); and 3) by infant sex. We also investigated whether or not birthweight differed by sleep and RLS exposures to verify findings observed in EFW trajectories. We fit a linear regression model with linear, quadratic and cubic fixed effects for scaled gestational age at delivery, the fixed effect for the exposure variable being examined and interaction terms between the scaled age at delivery terms and the exposure variable, adjusting for the same covariates included in the main analysis.

The R software (version 3.6.1, R Development Core Team) was used for all the statistical analysis with p-value = 0.05 as the significance level. To account for multiple comparisons, the Bonferroni correction was applied for all secondary outcomes by adjusting the significance level to 0.05/7 = 0.007 (i.e. to account for the seven total outcomes including the EFW and six secondary outcomes).

3. Results

Of the 2,802 eligible women, we excluded 18 women who were not eligible after enrollment and 43 women who deactivated from the study, including 29 moved, 10 who had voluntarily terminated their pregnancy, and 4 other reasons. We further excluded women who had miscarriages/stillbirths (n=27), pre-pregnancy RLS (n=84), and missing data in EFW, exposure variables, or covariates (n=173). The analytic sample included 2,457 women. The sample

characteristics were presented in **Table 1**. Women were recruited at a mean age of 28.2 years (SD: 5.5) with 26.8% of non-Hispanic white, 28.0% of non-Hispanic black, 28.6% of Hispanic, and 16.6% of Asian/Pacific Islanders. Based on pre-pregnancy BMI, 56.0% were normal weight, 27.5% overweight, and 16.5% obese. About 24.5% reported having anemia at enrollment at early pregnancy (8 – 13 weeks), 4.3% of the women were diagnosed with gestational diabetes, and 5.9% had hypertensive disorders of pregnancy.

The distribution of total sleep hour, napping frequency, the combined sleep-napping behavior, and RLS frequency differed by visit (**Table 2**, all p-values < 0.001). The proportion of pregnant women with total sleep less than 6 hours increased slightly from 16.3% at enrollment and 15.6% at visit 1 to 35.5% at visit 5, while the proportion with total sleep more than 10 hours decreased from 24.4% at enrollment to 8.5% at visit 5. About 43.4% women napped most of the time at enrollment and the proportion dropped to 18.6–23.2% in visits 1-5 (p-value < 0.001). The proportion of women who reported RLS less than once per month started at 93.7% at enrollment and decreased to around 77.8 – 81.0% in visit 2 – 5 (p-value < 0.001).

The adjusted trajectory of EFW by sleep-napping behavior (panel A) or by RLS presence (panel B) are shown in the **Figure 1** and the corresponding predicted EFWs by gestational week are presented in **Table 3** by sleep-napping group and in **Table 4** comparing the RLS absence and RLS presence groups. Overall, between 10 – 40 weeks, the estimated EFW and their 95% prediction interval overlap with each other between the sleep-napping groups and between the RLS status groups and no statistically significant differences were observed by group (all p-values > 0.84).

In 30 – 36 weeks, where the mean predicted EFWs appeared to diverge, women with 8 – 9 hours of total sleep and who rarely or never napped had the greatest mean EFW between 30 – 38 weeks of gestation, while women with more than 10 hours of total sleep and reported napping frequency of sometimes/mostly had the smallest mean EFW (figure and table 3). The difference in mean predicted EFW between the two extreme groups increased. However, the predicted EFW and their 95% prediction interval overlap with each other and the estimated difference was 18.6g (95%C (-116.7, 171.8) in week 30 and 71.6 g (95% CI (-243.9, 415.9) in week 40. (all p-values > 0.84 between 10 -40 weeks). Compared to the RLS absence group, fetus of women with gestational RLS had slightly greater, but non-significant, mean EFW (table 4, all p-values > 0.84 between 10 -40 weeks). Similarly, the adjusted trajectories of the individual fetal growth measures did not differ by sleep-napping group or by RLS presence status (**supplemental figure 1-6, supplemental table 2-13**).

Supplemental table 1 summarized the model outputs from the adjusted model in the overall sample, sample excluding preterm births, and subsamples by prepregnancy weight status and by fetus sex. Comparing to the findings in the overall sample, consistent insignificant findings were observed in all sensitivity analyses. In **Supplemental Table 14** and **Supplemental Figure 8**, we present the results of the linear regression model and the predicted value of birthweight by sleep-nap/RLS categories, respectively. No significant differences were detected for either sleep and variable or the RLS presence status (all p-values > 0.25).

4. Discussion

In this prospective cohort of 2,457 pregnant women, we observed significant changes in total sleep duration, napping behavior, and RLS presence or severity (data not shown) over the course of pregnancy. No statistical difference in fetal growth trajectory during the gestational weeks 10 – 40 were detected by sleep-napping behavior groups nor between women with or without RLS during pregnancy. Our findings added new longitudinal evidence that sleep behavior change or new onset of RLS during gestation may not have clinical consequences in fetal growth outcomes in generally healthy pregnant women.

To our knowledge, this is the first prospective study that examined in utero fetal growth curve in relation to sleep behavior and RLS during gestation, beyond sleep-disordered breathing or obstructive sleep apnea [34-36]. All prior studies only assessed birth size or evaluated small or large for gestational age based on birth weight. Short or long sleep duration were not associated with small for gestational age or large for gestational age.[37,38] Except for one study, all other studies included in a systematic review reported no significant association between RLS and birth weight, despite variations in sample size and methods used to define RLS. [25] Notably, in one large cohort of pregnant women (n = 1,563), RLS frequency assessed using the similar criteria as ours from IRLSSG during the third trimester showed no association with birth weight, aligning closely with our study findings [39]. Verified with our birth weight data, findings from our ultrasonographic measures of fetal growth provided new longitudinal evidence of a null relationship between maternal sleep or RLS with fetal growth, which is largely consistent with prior pooled analyses from the previous reviews using birth anthropometry data.

The null findings could be due to the fact that all women in this sample were relatively low-risk women without major chronic conditions, whose fetuses may have the resilience to adapt to alteration in total sleep duration, nap frequency, or RLS. A small proportion of our sample developed gestational hypertension (5.9%) or gestational diabetes (4.3%). Prior studies suggested that sleep may have indirect impact on the risk of gestational hypertension and gestational diabetes, which may impact fetal growth. Several reviews have found that extreme sleep duration, particularly short sleep duration,[37] and RLS [25,37] were individually associated with 1.4 – 5.0 times increased odds of pre-eclampsia and/or gestational hypertension and 1.3 - 1.5 times increase odds in gestational diabetes.[37] A 'U-shape' association was identified between sleep duration in the second trimester and the risk of gestational diabetes, after adjusting for confounders and napping frequencies[33]. However, gestational hypertension and diabetes may have the counteracting impacts on fetal growth. For example, we observed an adjusted association between gestational diabetes and *larger* fetal size significant between week 28 - 40 [40] and an association between severe preeclampsia and *smaller* estimated fetal weights between week 22 – 38.[41] Yet, our study did not identify differences in EFW by sleep behavior or RLS presence status. Additionally, the relationships between RLS-fetal growth trajectories did not vary by race/ethnicity (data not shown), although our study may have been underpowered. Future studies in high-risk women or women with gestational complications are needed to answer whether sleep durations and/or RLS are related to fetal growth outcomes.

Although the majority of women do not have chronic conditions at enrollment, our cohort included about 44% of with overweight or obesity. Our stratified analysis did not seem to support the differential impact between sleep behaviors and fetal growth by women's pre-pregnancy BMI category. A prior cross-sectional study observed that both short and long sleep duration were associated with elevated plasma leptin in overweight or obese women, but not among normal weight women. [42] Free plasma leptin was found inversely associated with fetal length in women with normal weight and positively associated with fetal length in pregnant women with obesity.[43] However, insufficient sleep did not seem to change the leptin/grehlin levels under experimental conditions.[44] In pregnant women, whether maternal sleep duration and RLS have any impact on adipokines requires further investigation. Sex-specific differences in fetal growth has been well-documented; however, our data did not support that there is sex-dependent impact of sleep behavior or gestational RLS on fetal growth.

Several strengths of the study should be noted. Our study has incorporated longitudinal measurements of sleep behaviors and RLS over the course of pregnancy. Fetal growth was based on ultrasonographic measures, which provided novel insights of the maternal sleep - fetal growth trajectory relationship. The exposures of interest were accounted for their time-varying nature in our models. Women's demographic and socioeconomic status and pre-pregnancy BMI were controlled for to avoid confounding. Sensitivity analyses supported the robustness of current findings. Finally, the multicenter multi-racial/ethnic pregnant-fetus cohort is unique, which allowed us to generalize our findings in low-risk pregnant women in the U.S.

There are some limitations of the current study. Maternal sleep were self-reported rather than objectively measured; therefore, may be subject to measurement errors. [45] Our findings need further verification by objective sleep measures. The specificity of RLS assessment may be low by using the 2003 RLS criteria than the updated 2014 criteria, which intends to exclude four features due to RLS-irrelevant medical or behavioral condition.[46] Information about medication use that may relieve, induce or aggravate RLS-like symptoms were not analyzed. In addition, we did not collect information about other sleep disturbances, such as obstructive sleep apnea, which was seen to be associated with low birth weight.[37] Residual confounding may exist in our study. For example, sleep-promoting medication use present in a number of pregnant women, although the proportion is likely small.[47] Some of the medications, such as benzodiazepines and hypnotic benzodiazepine receptor agonist (HBRA), are found associated with increased risk of small for gestational age and/or low birth weight[47]

We did not observe associations between gestational sleep-napping behavior, RLS symptoms, and ultrasonographical measurement of fetal growth trajectory between 10 - 40 weeks. Future studies including objective sleep measures are warranted to verify our study findings. Our study suggests that changes in total sleep hours, frequency of napping, or the onset and severity of RLS during pregnancy may not raise significant clinical concerns regarding fetal growth outcomes among generally healthy pregnant women.

CRediT author statement

Muzi Na: conceptualization, writing- original draft, writing review & editing. **Samidha S. Shetty:** methodology, formal analysis, writing review & editing, visualization. **Xiaoyue Niu:** methodology, writing review & editing, supervision. **Stefanie N. Hinkle:** writing review & editing. **Cuilin Zhang:** conceptualization, investigation, resources, writing review & editing, funding acquisition. **Xiang Gao:** conceptualization, writing review & editing, supervision

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Figure legend

Figure: Adjusted relationship between (A) sleep-napping behavior and (B) RLS presence and estimated fetal weight. Adjustment include age, race and ethnicity, education, parity, pre-pregnancy BMI, infant sex, prepregnancy sleep-napping behavior, and mutually adjusted for the other exposure variable. BMI, body mass index; RLS, restless legs syndrome.