Obstetrics

Fetal neuromaturation in late gestation is affected by maternal sleep disordered breathing and sleep disruption in pregnant women with obesity

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Abstract

Objective: Maternal sleep disordered breathing and sleep disruption have adverse effects on pregnancy outcomes through multiple potential pathophysiologic pathways. We hypothesize that disordered maternal sleep also adversely impacts the neuromaturation of the fetus.

Methods: Participants in this prospective observational study included 102 obese pregnant women (pre-pregnancy body mass index [BMI] of 30 or higher) at 36 weeks of pregnancy. Fetal neuromaturation, defined through measures of fetal heart rate variability, motor activity, and motor-cardiac coupling, was quantified through digitized fetal actocardiography during an afternoon recording. Maternal sleep measures were collected overnight through polysomnography. Data analysis focused on multiple regression, controlling for maternal BMI, blood pressure, and diabetes.

Results: Indicators of higher sleep disordered breathing were associated with delayed fetal neuromaturation and greater fetal motor activity. Less maternal sleep disruption (shorter rapid eye movement [REM] latency, more REM sleep, and/or fewer transitions) was associated with higher fetal heart rate variability and coupling-based neuromaturation.

Conclusion: Characteristics of disordered maternal sleep affect the developing fetal nervous system. It is unknown whether these results extend to populations that are not characterized by obesity. The influence of maternal sleep on the developing fetal nervous system has been understudied and may yield effects that persist beyond pregnancy.

KEYWORDS
fetal development, fetal heart rate, obesity, polysomnography, pregnancy, sleep
1 | INTRODUCTION

Maternal sleep disorders are common in pregnancy and there is significant concern about their deleterious consequences for maternal and pregnancy outcomes. There are two main categories of sleep disorders. Sleep disordered breathing refers to events, such as obstructive sleep apnea, that contribute to hypoxia. Sleep disruption refers to alterations in typical sleep architecture, and includes sleep that is characterized by frequent awakening, sleep deprivation, and changes in normal cycling through sleep stages of light, deep, and rapid eye movement (REM) sleep. Maternal sleep disordered breathing, and to a lesser extent, sleep disruption, have been linked to a number of adverse outcomes including gestational diabetes, pre-eclampsia, and preterm birth.1–3 Documentation of more direct effects on the fetus has been largely constrained to interference with fetal growth (both accelerated and restricted) based on birth weight.4 Size at birth can signal a disrupted intrauterine milieu, but is an imperfect instrument to infer functional consequences.

Evaluation of the developing fetal nervous system is necessarily by proxy and limited by access. Research predominantly relies on measures of fetal heart rate and variability, fetal motor activity, and correspondence between the two. Each changes in predictable ways that maternal sleep disordered breathing and sleep disruption will be associated with reduced coupling between fetal heart rate and motor activity.

The current prospective observational study evaluates whether maternal sleep disorders, identified using polysomnography, adversely affect neuromaturation of the near-term fetus. Given the multiple disruptions to the normative intrauterine milieu, we predict that maternal sleep disordered breathing and sleep disruption will be associated with delayed fetal neuromaturation, manifest by reduced fetal heart rate variability and motor activity, reflecting less parasympathetic innervation. Changes in fetal heart rate often co-occur with fetal movements, mediated by simultaneous activation of cardiac and somatic processes within the fetal central nervous system. This association becomes stronger as the fetus matures and the length of time between change in one and change in the other decreases.5,11,12 As a result we expect that sleep disordered breathing and sleep disruption will be associated with reduced coupling between fetal heart rate and motor activity.

Obesity is a well-known risk factor for sleep disordered breathing and, as such, is a common confounder in research in pregnant and non-pregnant adults. Obesity also poses well-identified threats to pregnancy13,14 that overlap with those of sleep disorders. Sleep disorders can be exacerbated by obesity and both can independently contribute to poor pregnancy outcomes. Maternal obesity has also been independently linked to alterations in fetal neuromaturation.15,16 Sleep disordered breathing has been identified as a contributor to the pathophysiology through which obesity exerts adverse effects on outcomes.17 In the current study, participation was limited to pregnant women with pre-pregnancy body mass indices (BMI) of 30 or higher to both control for obesity and maximize observation of maternal sleep disorders during polysomnography. In addition to BMI, common consequences of obesity—diabetes and elevated blood pressure—were evaluated as potential confounders.

2 | MATERIALS AND METHODS

Women carrying singleton fetuses were recruited from the obstetric practices of a university-based medical institution. Eligibility was restricted to non-smoking, obese women with normally progressing pregnancies and without clinical indication for polysomnography, other than maternal obesity, or use of pharmaceutical sleep aids. Fetal neuromaturation assessment was conducted in the afternoon of the overnight recording in a separate facility. The protocol was reviewed and approved by the local institutional review board and women provided written consent. In all, 108 women attended the afternoon assessment. Six women were excluded because of polysomnography refusal (one); total sleep less than 1 hour (one); and inability to collect artifact-free fetal neurobehavioral data (four), resulting in a final sample of 102 women.

Table 1 presents maternal and infant characteristics of the predominantly African American sample. Despite the degree of obesity, only 12 (11.7%) participants had been diagnosed with gestational or adult-onset diabetes mellitus and 17 (16.6%) with chronic or pregnancy-induced hypertension; most (n = 78; 76%) had neither condition, six were comorbid. With the exception of one infant delivered shortly after their study visit in the 36th week of pregnancy, all were full term (i.e. >37 weeks) and free of congenital anomalies.

Pregnant women visited a fetal assessment laboratory in mid-afternoon (mean pregnancy duration 36.3 weeks, standard deviation 0.8 weeks) and participated in 50 min of fetal monitoring in a semirecumbent position. Subsequently, women were escorted to the clinical sleep study facility, given dinner, and following lights out, polysonomography was continued through to 6:00 am the next morning (details below).

Fetal data were digitized from the output port of a Toitu MT320 (Toitu Ltd., Tokyo, Japan) fetal actocardiograph, which detects fetal heart rate and motor activity through a single wide array Doppler transducer. Post-processing included resampling, artifact detection and interpolation, and variable quantification using custom software described in depth elsewhere.12 The following measures were derived: (1) fetal heart rate variability (FHRV), the standard deviation in fetal heart rate, computed in 1-minute epochs, averaged over the recording period; (2) fetal motor activity (FACTIVE), the total value of all actograph data points per minute divided by the number of data points, averaged over the 50-min recording period; and (3) fetal neuromaturation, quantified as the coupling between fetal heart rate and
fetal movement bouts as follows: (a) coupling frequency, the proportion of time that movement bouts were associated with excursions in fetal heart rate of 5 bpm or more over baseline within +15/-5 s of movement onset (fCOUP-F), and (b) mean latency between movements and fetal heart rate change (fCOUP-L). Definitions are based on previous work\textsuperscript{11,12}; higher coupling frequency and shorter latency values are indicative of neuromaturation as they reflect tighter integration between fetal cardiac and somatic neural processes.

Pregnant women were assessed using standard polysomnography as recommended by American Academy of Sleep Medicine guidelines.\textsuperscript{18} Signals were recorded continuously (RemLogic 1.3 N7000; Natus) and subsequently non-REM and REM sleep were visually scored using electroencephalogram waveforms, ocular movements, and chin muscle tone in 30-s sequential epochs. Apneas were defined as a complete cessation of airflow lasting at least 10 s, and hypopneas as a 30% or more decrease in airflow for at least 10 s in association with oxygen desaturation of 3% or more, or an arousal.\textsuperscript{18}

Sleep disordered breathing was quantified using: (1) the apnea-hypopnea index, which reflects the number of apnea and hypopnea events per hour of sleep; (2) the mean duration of these events; and (3) the mean level of peripheral oxygen saturation during the night (SpO\textsubscript{2}). Characterization of sleep architecture and sleep disruption included: (1) percentage of total sleep time spent in deep (stage N3) non-REM sleep; (2) percentage of total sleep time in REM sleep; (3) duration from sleep onset to initial REM onset (REM latency); and (4) the number of stage transitions between adjacent epochs to or from waking to the various stages of sleep, including N1, N2, N3, or REM, and between N1, N2, N3, and REM, weighted for total sleep time.

Maternal covariates BMI and mean arterial pressure (calculated as [systolic +2(diastolic)]/3) were computed based on measurements taken during the afternoon visit. The presence/absence of diagnosed maternal diabetes was analyzed as a categorical dummy variable (yes = 1).

Statistical analysis commenced with examination of distributions. Pearson correlation coefficients were used to describe unadjusted associations. Separate multiple linear regressions were conducted for the sleep variables, with maternal covariates entered at step one, followed by fetal variables at step two (SPSS Statistics v25; IBM Corp., Armonk, NY, USA).

### RESULTS

Women were recorded for approximately 7 h overnight (mean ± standard deviation, 431 ± 50 min). Table 2 provides...
Table 3: Associations among maternal sleep measures

|                        | Apnea-hypopnea index | Event duration | SpO₂ | Deep/N3 sleep | REM sleep | Latency to REM | Transitions |
|------------------------|----------------------|----------------|------|---------------|-----------|----------------|-------------|
| Apnea-hypopnea index   | -                    | -              | 0.20*| -0.35**      | -0.07    | -0.13          | 0.32**      | 0.18        |
| Event duration         | -                    | -              | -0.07| -0.02         | 0.04     | 0.24*          | -0.14       | -0.01       |
| SpO₂                  | -                    | -              | 0.06 | 0.13          | -0.14    | -0.22          | 0.24*       | 0.32**       |
| Deep/N3 sleep         | -                    | -              | 0.04 | 0.02          | -0.53**  | -0.22*         |             |             |
| REM sleep             | -                    | -              | -0.53**| -0.22*      |           |                |             |             |
| Latency to REM        | -                    | -              | -0.35**| -0.22*      |           |                |             |             |

Abbreviations: REM, rapid eye movement; SpO₂, oxygen saturation.

*< 0.05; **< 0.001.

Descriptive statistical values for maternal sleep and fetal neuromaturation measures. Table 3 presents unadjusted correlation coefficients for sleep variables. Tables 4 and 5 present regression results controlling separately for maternal BMI, diabetes, and mean arterial pressure. As expected, a higher maternal apnea-hypopnea index was associated with lower maternal oxygenation (Table 4). The apnea-hypopnea index and duration of sleep disordered breathing events were also associated with longer latency to REM sleep, indicating that latency to REM is sensitive to sleep disordered breathing. Regression results reveal expected associations between higher BMI and markers of sleep disordered breathing (apnea-hypopnea index, SpO₂); longer sleep disordered breathing events were associated with higher daytime mean arterial pressure. Results for sleep architecture (Table 5) reveal no associations with BMI but diabetes was negatively associated with REM sleep.

Given the novelty of the data, Tables 4 and 5 include data generated from each equation and those that neared, but did not attain, significance (i.e. P < 0.10), are noted. Controlling for potential maternal confounding variables, fetuses of women with sleep disordered breathing (higher apnea-hypopnea index, lower SpO₂) were significantly more active and there was a trend association with longer event duration (Table 4). Higher apnea-hypopnea index was significantly associated with longer latencies between fetal movements and fetal heart rate change (fCOUP-L); this association was in the same direction but reached a trend level of significance for the other two sleep disordered breathing indicators. The complementary measure of fetal maturation, coupling frequency (fCOUP-F), was negatively associated with the duration of sleep disordered breathing events.

Table 5 also depicts a consistent pattern of significant or near-significant associations between daytime fetal measures and maternal sleep architecture related to REM and sleep disruption. Deep (N3) non-REM sleep was unrelated to fetal measures (not shown). However, more REM sleep and shorter REM latency were associated with more frequent fetal coupling (fCOUP-F) and lower fCOUP-L (less latency between coupled movements). Similarly, higher fHRV was also associated with more REM sleep and shorter times to initial REM onset. In contrast, more disrupted sleep, measured by the number of transitions, was significantly associated with longer fCOUP-L, and a trend towards lower fCOUP-F.

4 | Discussion

Multiple pathophysiologic pathways have been proposed that link disordered maternal sleep to the neurohormonal, inflammatory, and metabolic milieu of pregnancy. Here, using polysomnography, the reference standard for detecting sleep disordered breathing and quantifying sleep architecture and disruption, we found that maternal sleep characteristics may have repercussions for the development of the fetal nervous system. When detected, the direction of these associations was consistent with the hypothesis that higher levels of sleep disordered breathing and sleep disruption are associated with reduced fetal neuromaturation near term. These associations are based on a sample of obese women not previously diagnosed with this condition and persisted after controlling for level of obesity and its common correlates of elevated blood pressure and diabetes.

Although this study was not designed to identify the underlying pathophysiology of these associations there is no scarcity of likely suspects. Sleep disordered breathing generates a cycle of acute hypoxia and re-oxygenation, which has implications for oxygen availability to fetal tissues as well as other documented maternal consequences including oxidative stress, inflammation, vascular changes, sympathetic activation, and insulin resistance. Two studies offer conflicting results as to whether episodes of obstructive sleep apnea exert transient effects on fetal heart rate. Here we did not find associations between daytime variability in fetal heart rate and sleep disordered breathing; rather, associations were based on more subtle indicators of neural maturation represented by somatic-cardiac integration (i.e. coupling frequency and latency). Fetuses of women with more sleep disordered breathing and lower overnight oxygenation levels were significantly more active. A gradient in fetal motor activity has been documented among normal weight, overweight, and obese women near term, with more fetal motor activity in the highest weight group. In contrast, there is a report of reduced fetal motor activity in women with pre-eclampsia and that this reduction is reversible with treatment of mild, pre-existing sleep disordered breathing. Differences in methods may account for the contrasting findings.
for these discrepancies but together these reports suggest associations between maternal oxygenation and fetal activity, which require further study.

Changes in maternal sleep with advancing pregnancy include reductions in the amount of time women sleep while in bed (i.e. sleep efficiency) and less REM sleep. Among women with uncomplicated pregnancies, latency to initial REM sleep onset has been observed to decrease in late pregnancy. In contrast, in a cohort of pregnant women with sleep disordered breathing in late pregnancy and frequent apneas that caused brief periods of waking, latency to REM sleep increased and there was evidence of greater sleep disruption compared with early pregnancy. In general, empirical evidence linking sleep disruption to altered pathophysiology is less extensive than for sleep disordered breathing, but the cost of sleep deprivation to the fetus appears to be reflected in a similar way. Here, maternal sleep disruption, evidenced by reduced percentage of REM sleep, longer latency to initial REM sleep, and more sleep stage transitions during the night (but not by duration of deep/N3 sleep) was also associated with reduced neuromaturation in one or both daytime measures of neural integration. Less REM sleep was also associated with lower fetal heart rate variability, an indicator of maturation that is suggestive of lower fetal parasympathetic tone. Nevertheless, how and why maternal REM sleep in particular should exert effects on fetal development is unknown.

These conclusions rely on the assumption that sleep characteristics observed during a single night polysomnogram reflect the “typical” sleep of participants at this point in gestation and, to influence the intrauterine milieu enough to affect fetal development, for some time prior to it. Hence, maternal sleep may have been more disrupted during polysomnography than normal, and especially with respect to the onset and duration of REM sleep, which disproportionally occurs later in the night. However, this type of study limitation introduces an element of “noise” to the maternal sleep data that works against our ability to detect significant associations with fetal neuromaturation measures. It is unclear whether results extend to non-obese populations. Not all pregnant women have sleep disordered breathing, but most women experience reductions in sleep quality as pregnancy progresses. The obesogenic environment may compound effects of both on the fetus. While the strength of associations was relatively modest, the influence on the developing fetal nervous system may shift the trajectory of development with consequences that persist beyond pregnancy. If so, it suggests greater attention should be directed to detecting and ameliorating sleep disordered breathing and general sleep disruption for reasons beyond the more proximal effects on pregnancy outcomes.

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**CONFLICTS OF INTEREST**

The authors have no conflicts of interest.

**AUTHOR CONTRIBUTIONS**

JAD contributed to design, planning, conduct, data analysis, and manuscript writing; HW contributed to planning and study conduct; RSR contributed to planning, study conduct, and data analysis; JLH contributed to design, planning, and conduct; FPS contributed to planning and conduct; and GWP contributed to design, planning, conduct, and manuscript writing.

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