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Antenatal sleep quality associated with perinatal outcomes in women of advanced maternal age

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Objectives: The increasing prevalence of advanced maternal age (AMA) coupled with poor sleep quality among pregnant women makes it important to study their association with perinatal outcomes. However, little is known about the interaction of AMA and maternal antenatal sleep on perinatal outcomes. Here, we examined whether associations between AMA and perinatal outcomes are modified by antenatal sleep quality.
Participants: Data were collected from 446 women, with a singleton pregnancy and no pregnancy complications, who participated in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study.
Measurements: Participants completed the Pittsburgh Sleep Quality Index (PSQI) at 26-28 weeks gestation and had perinatal outcome data collected upon delivery. Interactions between AMA and maternal sleep quality on perinatal outcomes were investigated and where significant, analyses were further stratified by maternal age. All analyses were adjusted for maternal BMI at 26-28 weeks gestation, ethnicity, and maternal education.
Results: Neonates of mothers of AMA and poor sleep quality (PSQI score >5) had increased odds of stay in the neonatal intensive care unit (adjusted odds ratio = 3.53, 95% CI: −1.21 to 10.27) and shorter birth length (adjusted mean difference = −1.05 cm, 95% CI: −1.82 to −0.20), as compared with women of AMA and good sleep quality (PSQI score ≤5). In women <35 years, sleep quality did not associate with perinatal outcomes.
Conclusion: Poor sleep quality in women of AMA was associated with neonatal health outcomes. Improving maternal antenatal sleep may potentially improve perinatal outcomes in offspring of women of AMA.

Introduction

Pregnancy is often associated with sleep problems such as disruption of sleep and short sleep duration because of physical discomfort, anxiety, or hormonal changes.[1] Sleep quality tends to become progressively worse during late pregnancy, with decreased sleep efficiency and more frequent awakenings.[2] Sleep disturbances can also be caused by pregnancy-onset sleep-disordered breathing and restless legs syndrome, as a result of physiologic changes associated with pregnancy.[3] Poor sleep quality and short sleep duration have been previously linked to adverse perinatal outcomes such as preterm birth, odds of stillbirth and lower birth weight.[4] Both poor sleep quality and lack of sleep have been associated with a proinflammatory state as demonstrated by increased inflammatory

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cytokines.[5-9] Several studies went on to suggest causal relationship by experimentally restricting sleep and showed an increase of inflammatory mediators[10,11] In fact, women seem to be more sensitive to the inflammatory effects of poor sleep quality compared with men.[12-14] Blair et al showed that proinflammatory cytokine – interleukin 8 – mediated the association between sleep quality and gestation length amongst the African American pregnant women in the study.[15]

The prevalence of advanced maternal age (AMA) is increasing worldwide.[16-18] Although there is no universal definition for AMA, many papers classified it as 35 years and above.[17,19-23] AMA is associated with a range of pregnancy complications (eg. preclampsia and gestational diabetes),[22,23] increased perinatal morbidity and mortality,[17,20,23] increased risk of admission to neonatal intensive care unit (NICU),[20,22,23] stillbirth[17,23,24] and fetal growth restriction, and/or low birth weight.[20,23] The likelihood of requiring induction[20] or caesarean section[22] during delivery is also elevated. It is noteworthy that sleep quantity and quality also changes with age, with a decrease in sleep efficiency,[25] sleep duration and slow wave sleep as the age increases.[26,27] At the same time, prevalence of sleep disorders such as insomnia also tend to increase with age.[28] It is reported that women are more sensitive than men when it comes to age-related changes in sleep[29,30] Hence, we are interested to study if women with AMA are more susceptible to poor sleep quality, resulting in poorer perinatal outcomes. Sleep is a modifiable lifestyle factor and if found to be a moderator between AMA and poor perinatal outcomes, it can be a potential target for intervention to improve perinatal outcomes amongst mother with AMA.

As increased maternal age is a risk factor for pregnancy complications,[31-34] some studies have attributed the poorer perinatal outcomes associated with AMA to these comorbidities.[35,36] Hence, in this study, we focused on healthy women with no known pregnancy complications, to better understand moderating effect of maternal antenatal sleep between AMA and perinatal outcomes, independent of pregnancy complications. We hypothesized that poor sleep quality within healthy pregnancies of women with AMA may be associated with increased adverse perinatal outcomes.

Methods

Study population

Data were collected prospectively from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study. The methodology is described in detail in our previous work.[37] In brief, 1247 pregnant women were recruited from two major maternity hospitals in Singapore – the National University Hospital and the KK Women's and Children's hospital between June 2009 and September 2010. Women were excluded if they had a multiple pregnancy (i.e. twins; n = 10) or if they conceived by *in vitro* fertilization (n = 85). Informed written consent was obtained from each participant, with procedures approved by the National Healthcare Group Institutional Review Board (IRB) and the SingHealth Centralized IRB.

Maternal characteristics

Data on maternal age, ethnicity, and education were collected via interviewer-administered questionnaires at the recruitment visit in the first trimester of pregnancy. Information on pregnancy complications was obtained from the medical records. Maternal height and weight were measured at 26-28 weeks gestation by trained research staff, to derive body mass index (BMI).

Maternal antenatal sleep data

During the 26-28 weeks clinic visit, participants were asked to complete the Pittsburgh Sleep Quality Index (PSQI) to assess their sleep quality in the previous month. The PSQI global score was derived from the sum of seven component scores for sleep duration, sleep disturbances, sleep latency, daytime dysfunction, sleep efficiency, sleep quality, and use of sleep medications. A higher score reflects poorer sleep quality and more sleep problems. Poor sleep quality was defined as a global PSQI score of >5.[38]

Perinatal outcomes

Birth data (i.e. birth weight, birth length, head circumference), neonatal problems (e.g. jaundice and other complications like hypoglycemia and meconium aspiration), highest level of neonatal stay (i.e. normal nursery or intensive/special care) and delivery details (i.e. mode of delivery, induction) were extracted from case notes (Table 1 for list of perinatal outcomes studied).[37] Gestational age was derived from estimated due date (defined as 40 weeks) determined by ultrasound scan measurements between 7-12 weeks of gestation. Using gestation-specific and sex-specific locally derived reference ranges, birth weight was defined as small for gestational age (SGA) below the 10th percentile, appropriate for gestational age between the 10th and 90th percentiles, and large for gestational age (LGA) above the 90th percentile.

Statistical analysis

Multivariable logistic regression models were used to estimate the association of poor sleep quality (PSQI score >5) on categorical perinatal outcomes (i.e., type of labour, mode of delivery, prematurity, level of nursery care, presence of neonatal complications, and jaundice). These regression models were adjusted for AMA (defined as maternal age ≥35 years), ethnicity, maternal education, and 26-28 weeks BMI.

Separately, multivariable linear regression analyses were used to model associations of poor sleep quality (PSQI score >5) on continuous outcomes (i.e., anthropometric measures and gestational age). In each analysis, the sleep variable was considered simultaneously (i.e., in 1 step) with the following independent variables: AMA, ethnicity, maternal education, and 26-28 weeks maternal BMI.

To test our hypothesis whether antenatal sleep modifies the association of AMA on perinatal outcomes, we included a multiplicative interaction term (AMA x sleep quality) in the multivariable logistic and linear regression models. For interaction terms that were statistically significant, we further stratified our analyses by maternal age (<35 and ≥35 years). No other effect modifiers were hypothesized, and no other interactions were assessed. All analyses were run on IBM SPSS, version 24.0 (IBM, Armonk, NY, USA).

Results

Among the 1152 women who had a singleton pregnancy and conceived naturally, 271 had one or more pregnancy complications (i.e., gestational diabetes, pre-eclampsia, gestational hypertension) and were excluded from our analysis. We excluded 139 women who had no or little delivery data available (due to dropout, loss to follow-up or they delivered in other hospitals), 276 women who were not given the PSQI, and another 20 women with incomplete PSQI data. A total of 446 women were included in the analysis and their characteristics are provided in Table 1. The average age of the participants included was 30.0 ± 5.1 years, with 20.4% of the women classified as having AMA (Table 1).

Table 1
Demographic characteristics and perinatal outcomes of participants in this study

Participant characteristics	Participants (n = 446)
Maternal age (years), mean (SD)	30.0 (5.1)
Maternal age, n (%)	
< 35 years old	355 (79.6)
> 35 years old	91 (20.4)
Maternal BMI, mean (SD)	25.9 (4.4)
PSQI, n (%)	
≤ 5	255 (57.2)
> 5	191 (42.8)
Ethnicity, n (%)	
Chinese	225 (50.4)
Malay	146 (32.7)
Indian	75 (16.8)
Maternal highest education category, n (%)	
No education/primary	12 (2.6)
Secondary	108 (24.2)
Diploma/technical education	166 (37.2)
University	149 (33.4)
Postgraduate	5 (1.1)
Missing	6 (1.3)
Perinatal outcomes	
Type of labour, n (%)	
Spontaneous	283 (63.5)
Induced	117 (26.2)
Missing	46 (10.3)
Mode of delivery, n (%)	
Normal vaginal birth	331 (74.2)
Elective caesarean section	38 (8.5)
Emergency caesarean section	77 (17.3)
Neonatal complications[a], n (%)	
Yes	315 (70.6)
No	128 (28.7)
Missing	3 (0.7)
Premature, n (%)	
Yes	22 (4.9)
No	424 (95.1)
Small for gestational age (SGA), n (%)	36 (8.1)
Large for gestational age (LGA), n (%)	38 (8.5)
Highest level of neonatal stay	
Normal nursery	140 (31.4)
ICU /special care nursery	306 (68.6)
Neonatal jaundice	
No significant jaundice	394 (88.3)
Jaundice with phototherapy	43 (9.6)
Missing	9 (2.0)
Gestational age (weeks), mean (SD)	39.0 (1.2)
Birth weight (g), mean (SD)	3124 (381)
Birth length (cm), mean (SD)	48.7 (2.1)
Head circumference (cm), mean (SD)	33.4 (1.3)

SD = standard deviation; PSQI = Pittsburg Sleep Quality Index; ICU = intensive care unit.
Data are n (%) unless otherwise stated.
[a] Neonatal complications include secondary to transient tachypnoea of new born, meconium aspiration, congenital pneumonia, hypoglycaemia, congenital malformation, feeding disorders, perinatal infection, and stress.

After adjusting for covariates, initial data analysis revealed that offspring of AMA had higher birth weight, birth length, and head circumference although there was no difference in the odds of LGA (Table 2). No significant association was observed between maternal antenatal sleep quality and perinatal outcomes (Table 2). There was a significant interaction between AMA and poor sleep quality on level of neonatal stay ($p = 0.021$), birth weight ($p = 0.026$), and birth length ($p = 0.040$) (Table 2). Then, we conducted analyses on these variables with significant interaction, stratified by maternal age (Table 3). Women with both AMA and poor sleep quality had offspring who were born shorter and at higher risk of requiring special neonatal care at birth, as compared with women of AMA but with good sleep quality. Their offspring also tend to have lower birth weight, although it did not reach statistical significance ($p = 0.072$). In women younger than 35 years of age, sleep quality did not associate with any perinatal outcomes studied.

Discussion

Overall, we observed that women of AMA had babies with higher birth weight, longer birth length, and bigger head circumference. On the other hand, we did not see any significant difference in perinatal outcomes between women with and without poor sleep quality. However, poor sleep quality in women with AMA was associated with shorter birth length and a trend of lower birth weight. These anthropometric measurements may reflect *in utero* growth. Although there was no increased risk of individual neonatal complications, we observed increased odds of staying in the special care nursery or NICU in the offspring of AMA mothers with poor sleep quality, which may be a composite representation of the infants' well being and general health.

The relationships between AMA and poor perinatal outcomes such as stillbirth, early prematurity, low birth weight, caesarean section rates, and postpartum hemorrhage have been previously reported.[39,40] In our study, we did not observe higher prematurity, higher odds of SGA, or caesarean section. This could be because we excluded women with pregnancy complications, which women of AMA are at higher risk of. The associations of maternal antenatal sleep quality with poorer perinatal outcomes have also been studied, but findings are varied and inconsistent.[4] A recent meta-analysis by Warland et al.[4] summarized literature on maternal sleep (i.e., sleep disordered breathing, sleep quality, sleep duration, and sleep position) and fetal outcomes (i.e., birth weight, growth, stillbirth and prematurity). Most of the papers reviewed suggest that there is no clear association between sleep quality and birth weight and/or fetal growth,[41-45] although a few papers reported that the group with poorer sleep may have lower birth weight.[46-48] Findings with poor sleep quality and preterm birth were mixed, with some finding a significant association[46,48-51] although others did not.[42-44,52] One group even reported that women with low sleep disturbances had higher risk of preterm labour.[53] However, this study was conducted in active duty military women and may not be representative of the civilian population.

Poor sleep quality and short sleep duration have been associated with an increased inflammatory state demonstrated by increased inflammatory cytokines such as interleukin-6, tumor necrosis factor alpha and C-reactive protein.[5-9] Women, in particular, are more susceptible to increased inflammation as a result of sleep disturbances and poor sleep.[12-14] Blair et al showed that proinflammatory cytokine − interleukin 8 − was a mediator between sleep quality and gestation length amongst the African American pregnant women.[15] Increased proinflammatory state has been observed in fetal growth−restricted pregnancies.[54]

Poor sleep quality in women of AMA has been shown in our study to be related to poorer perinatal outcomes that have been linked to poorer outcomes later in life. For example, research has shown that shorter birth length is associated with a higher risk of coronary heart disease.[55] Poor sleep quality in women of AMA is also linked to increased odds of neonatal stay in the special care nursery or NICU, which is costly and exposes neonates to greater risk of iatrogenic events.

Our study is one of the first study to report the interaction of AMA and mothers' antenatal sleep quality on perinatal outcomes, in healthy women with no pregnancy complications. Additional studies are needed to test the generalizability of our findings to other populations of pregnant women. An important limitation of our study is that we did not screen women for pregnancy-onset sleep disorders

Table 2
Association of poor antenatal sleep quality and advanced maternal age on perinatal outcomes

Exposure studied with perinatal outcomes	Advanced maternal age (AMA)	Poor sleep quality (PSQI>5)	Poor sleep quality x AMA interaction
	OR[a,c] (95% CI)	OR[b,d] (95% CI)	p-value
Type of labour	0.86 (0.47 to 1.55)	0.77 (0.49 to 1.23)	0.294
Mode of delivery	1.32 (0.78 to 2.25)	1.35 (0.86 to 2.10)	0.575
Neonatal complications	1.73 (0.97 to 3.09)	1.35 (0.86 to 2.10)	0.334
Prematurity	0.78 (0.25 to 2.43)	1.17 (0.47 to 2.89)	0.997
Highest level of neonatal stay	1.37 (0.80 to 2.34)	1.15 (0.75 to 1.75)	**0.021**
Neonatal Jaundice	1.01 (0.45 to 2.26)	1.15 (0.59 to 2.22)	0.207
Small for gestational age (SGA)	0.57 (0.19 to 1.70)	1.12 (0.54 to 2.31)	0.997
Large for gestational age (LGA)	1.86 (0.88 to 3.90)	0.87 (0.43 to 1.75)	0.376
Exposure studied with perinatal outcomes	Mean difference[a,c] (95% CI)	Mean difference[b,d] (95% CI)	p-value
Gestational age (weeks)	−0.07 (−0.36 to 0.22)	−0.06 (−0.30 to 0.18)	0.173
Birth weight (g)	**113 (24 to 201)**	11 (−61 to 83)	**0.026**
Birth length (cm)	**0.7 (0.2 to 1.1)**	−0.3 (−0.6 to 0.1)	**0.040**
Head circumference (cm)	**0.4 (0.1 to 0.7)**	0.1 (−0.2 to 0.3)	0.280

[a] Adjusted for poor sleep quality, maternal BMI at 26-28 weeks gestation, ethnicity, and maternal education.
[b] Adjusted for advanced maternal age, maternal BMI at 26-28 weeks gestation, ethnicity, and maternal education.
[c] Reference to control group with maternal age <35 years.
[d] Reference to control group with good sleep quality (PSQI ≤5).

or pre-existing sleep disorders. Hence, we could not assess whether the relationship between AMA and sleep quality on perinatal health outcomes was due to the presence of sleep disorders or other causes. Finally, results for antenatal sleep quality was based on self-report. Future studies should include objective measurements of sleep using actigraphy or polysomnography.

Our study shows that poor sleep quality was associated with shorter birth length and increased likelihood of admission to a special care nursery or NICU in offspring born to mothers of AMA. Improving sleep quality may help improve perinatal outcomes amongst mothers of AMA.

Disclosure

All the authors have no potential conflict of interest to declare.

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Table 3
Association of poor maternal sleep quality with neonatal outcomes

Neonatal outcomes	Unadjusted		Adjusted [a]			
	Maternal age <35 years (n = 355)	Maternal age ≥35 years (n = 91)	Maternal age <35 years (n = 346)		Maternal age ≥ 35 years (n = 89)	
	OR[b] (95% CI)		OR[b] (95% CI)	P-value	OR (95% CI)[b]	P-value
Special neonatal care/ICU	0.98 (0.62 to 1.54)	**3.28 (1.21 to 8.91)**	0.89 (0.56 to 1.42)	0.890	**3.53 (1.21 to 10.27)**	**0.021**
	Mean difference (95% CI)		Mean difference (95% CI)[b]	P-value	Mean difference (95% CI)[b]	P-value
Birth length (cm)	−0.23 (−0.21 to 0.67)	**−1.05 (−1.88 to −0.23)**	−0.05 (−0.40 to 0.49)	0.834	**−1.01 (−1.82 to −0.20)**	**0.016**
Birth weight (g)	38 (−40 to 116)	−143 (−312 to 26)	51 (−29 to 131)	0.209	−153 (−319 to 14)	0.072

ICU = intensive care unit.
[a] Adjusted for maternal BMI at 26-28 weeks gestation, ethnicity, and maternal education.
[b] Reference to control group with good sleep quality (PSQI ≤5).

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