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Poor Sleep Quality is Associated with Preterm Birth

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Study Objectives: Preterm birth (PTB) is a major public health priority and the most common adverse pregnancy outcome. Several risk factors have been identified, but a gap in the understanding of the underlying etiology of PTB persists. Poor sleep quality is a correlate of adverse health outcomes. Therefore, we evaluated whether sleep quality during pregnancy was a clinically relevant risk factor for PTB.

Design: Observational

Measurements and Results: Participants included 166 pregnant women (mean age = 28.6 ± 5.5 years). Self-report questionnaires, including the Pittsburgh Sleep Quality Index (PSQI), were administered at 14-16, 24-26, and 30-32 weeks gestation. Logistic regression models were used to evaluate whether sleep quality was associated with preterm delivery. Poor sleep quality was a predictor of preterm birth, with the largest effects in early pregnancy (14-16 weeks) (OR: 1.25 95% CI [1.04-1.50], P = 0.02) and more modest effects in later pregnancy (30-32 weeks) (OR: 1.18 95% CI [0.98-1.42], P = 0.07). With every one-point increase on the PSQI, the odds of preterm birth increase 25% in early pregnancy and 18% in later pregnancy.

Conclusions: Poor sleep quality, in both early and late pregnancy, is associated with an increased risk of delivering preterm. Currently the specific pathway(s) through which disturbed sleep contributes to PTB are unknown. We suggest that poor sleep may contribute to increased risk for PTB both independently, as well as in conjunction with other established risk factors, such as stress.

Keywords: Preterm birth, sleep quality, pregnancy, women, stress, health, sleep

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INTRODUCTION

Sleep disturbances, a common complaint in pregnancy, can result from myriad physiological, hormonal, vascular, and metabolic changes.[1-3] In a recent poll from the National Sleep Foundation, over 79% of women reported that their sleep was different during pregnancy than at any other time; however, no distinction was made as to which aspect of sleep the women were describing.[4] Empirical studies suggest that up to 25% of pregnant women report significant sleep disturbance in the first trimester, with rates climbing to nearly 75% by the third trimester.[5,6] While it is accepted that sleep progressively worsens across the gestational period,[2,6,7] our current knowledge relies heavily on a small handful of reports with one or two assessments and a broad range of measurements.

Longitudinal assessments of sleep across pregnancy may be clinically relevant, given the overwhelming evidence that poor sleep quality—one's subjective perception that one's sleep was unrefreshing, poor or inadequate—is linked with an array of adverse health outcomes including inflammation, metabolic syndrome, insulin resistance, and type 2 diabetes,[8-10] as well as the recent hypothesis that sleep disturbance is associated with an increased risk for adverse pregnancy outcomes.[3] Indeed, emerging data indicate that poor sleep quality is associated with preeclampsia, longer time spent in labor and poor delivery outcomes (increased cesarean deliveries), postpartum depression,[11-13] and recently preterm birth (PTB).[14] PTB is a major public health priority for the U.S. and a research priority of the National Institutes of Health (NIH). It is the leading cause of infant morbidity due to increased respiratory disease, neonatal infections, and neurodevelopmental impairments, as well as infant mortality.[15] The rate of PTB in the U.S. has increased from approximately 9% to 12% in the last 25 years.[16,17] Although several risk factors have been identified, a gap in the understanding of the pathophysiology of PTB persists.

To address this, we evaluated the relation between subjective sleep quality ascertained at 14-16, 24-26, and 30-32 weeks gestation and risk of preterm delivery (< 37 weeks) in a cohort of community dwelling women. We hypothesize that poor sleep quality, particularly in early pregnancy (< 20 weeks), is associated with increased risk of delivering preterm.[3] Additionally, given that poor sleep may be one mediator of the association between psychosocial stress and adverse health outcomes,[18-22] we also explore the possibility that disrupted sleep may explain, in part, the established relation between psychosocial stress and preterm birth.[23-25]

METHODS

Participants

The current sample comprised 166 women who were recruited from a large university medical center during the first trimester of pregnancy. Initial prenatal recruitment criteria were as follows: singleton pregnancy, ≥ 18 years, English-speaking, nonsmoker, and free of medications or any condition that could dysregulate neuroendocrine function. Additional inclusion criteria for the current study were assessment of sleep at a minimum of one of the following study visits: 14-16, 24-26, and 30-32 weeks gestation. Participants provided written informed consent, and the study was approved by the U.C. Irvine Institutional Internal Review Board.

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Sleep Quality Measure

The Pittsburgh Sleep Quality Index (PSQI),[26] an 18-item questionnaire, was used to measure habitual sleep quality over the previous month. It comprises 7 subscales assessing habitual duration of sleep, nocturnal sleep disturbances, sleep latency, sleep quality, daytime dysfunction, sleep medication usage, and sleep efficiency. Each subscale has a possible score 0-3, with an overall global score 0-21. Higher scores reflect poorer sleep quality. In reports of various non-pregnant cohorts, a sensitivity of 89.6% and specificity of 86.5% and good internal consistency (Cronbach $\alpha = 0.80$) are reported when using a cutoff ≤ 5.[26,27] The PSQI and its psychometric properties have been validated in pregnant women.[28,29] We used the established cutoff > 5 to depict poor sleep quality.[26]

Determination of Gestational Length

Pregnancies were dated according to current American College of Obstetricians and Gynecologists (ACOG) guidelines[30] by comparison of last menstrual period to estimates based on early ultrasound measurements by the research nurse at the first study visit at 15 weeks' gestation. Deliveries occurring < 37 weeks were categorized as preterm, while deliveries occurring ≥ 37.0 weeks were categorized as term.

Additional Measures

Demographic variables associated with sleep and/or preterm birth were evaluated as covariates. Demographic variables included maternal age, ethnicity (Caucasian: yes or no), income (< 30,000, 30,000-60,000, and > 60,000), and education (≤ high school, technical/some college, ≥ college degree). Psychosocial variables included depressive symptoms characterized by the 9-item Center for Epidemiological Studies Depression scale (CES-D),[31] perceived stress characterized by the 10-item Perceived Stress Scale (PSS),[32] and anxiety symptoms characterized by the 20-item Spielberger Trait Anxiety Inventory (STAI).[33] These variables were evaluated as continuous measures. The sleep item was removed from the CES-D to avoid redundancy and collinearity. Medical (obstetrical) risk for preterm birth was defined as the presence of specific historical risk factors and medical conditions in the index (current) pregnancy, including previous history of preterm birth, vaginal bleeding, and pregnancy-induced hypertension. Risk conditions were determined through interview and extensive medical chart review by the research nurse. Medical risk was coded as a dichotomous variable with 1 indicating the presence of ≥ 1 condition and 0 indicating the absence of any current or historical risk conditions.[23,34]

Statistical Analysis

Demographic and clinical characteristics of the entire sample were examined with descriptive statistics. Due to the small number of women who delivered preterm and non-normal data distribution, we used Wilcoxon/Fisher exact tests and Mann-Whitney U tests to evaluate whether the baseline demographic and psychosocial measures were different between women who delivered preterm compared to women who delivered at term. Pearson correlation coefficients were run to examine relations between demographics, psychosocial variables, sleep quality, and preterm birth. Logistic regression models were run to evaluate whether sleep quality was associated with preterm delivery. According to guidelines suggested by Baron and Kenny[35] and more recently by Lockhart et al.,[36] logistic regression also was used to evaluate whether sleep quality might mediate relations between stress and preterm delivery. Lastly, we ran a post hoc analysis to explore whether the duration of poor sleep quality was associated with other identified risk factors. Analyses were run using SAS 9.0. Associations were considered significant if $P < 0.05$.

RESULTS

Demographic characteristics of the entire sample are shown in Table 1. There were 15 (9.0%) women who delivered preterm and 151 (91%) who delivered at term. The two groups did not differ in terms of age, ethnic distribution or education. However, there were significant groups differences in income categories ($P = 0.003$), thus income was included as a covariate in the logistic regression models. Women who delivered preterm reported more disrupted sleep at Time 1 (14-16 weeks) and Time 3 (30-32 weeks) (Table 2). There were no group differences at the first visit for the CES-D, the PSS, or the Spielberger anxiety questionnaire (Ps > 0.05) in this sample; therefore, they were not included in the models. However, as shown in Table 2, there were group differences at Time 3 for the PSS, the CES-D (minus the sleep item), and the STAI (Ps < 0.05). There were no group differences in prenatal obstetric risk factors; however, due to the usual associations between medical risk factors and PTB, we chose to include it in the models.

Table 3 shows a correlation matrix of sleep, psychosocial measures, and preterm birth at each time point. Sleep quality was correlated with the PSS and the Spielberger anxiety questionnaire at each time point. However, it was only correlated with the CES-D (minus the sleep item) at Time 1 (14-16 weeks).

Logistic regression models were run for each time period. At Time 1 (14-16 weeks), poorer sleep quality significantly predicted a higher probability of preterm birth after adjusting for income and the presence of medical risk factors ($\chi^2 = 5.44$, $P = 0.02$; OR 1.25 [95% CI 1.04-1.50]). At Time 3 (30-32 weeks), this was reduced to a trend ($\chi^2 = 3.21$, $P = 0.07$; OR 1.18 [95% CI 0.98-1.42]). We also tested an a priori hypothesis that sleep may be a mediator in the relationship of stress and PTB in the third trimester. Using the Baron and Kenney method, first perceived stress, then both perceived stress and sleep quality were entered in a logistic regression model. The data suggest that sleep mediates the relationship between perceived stress and PTB (Table 4). The odds ratio between stress and PTB was attenuated and became nonsignificant consistent with mediation.

We lastly explored whether the duration of poor sleep quality (0, 1, 2, or 3 times) was associated with other known risk factors which could partially explain the variable results between sleep quality and PTB. Women with poor sleep quality at more time points had higher levels of perceived stress ($\rho = 0.36$, $P = 0.0001$), depression ($\rho = 0.52$, $P < 0.0001$), and anxiety ($\rho = 0.38$, $P < 0.0001$) at Time 1 (14-16 weeks). There was also a modest relationship between the number of times poor sleep quality was reported and PTB ($\rho = 0.16$, $P = 0.095$).

DISCUSSION

Our primary aim was to evaluate whether sleep quality was associated with preterm birth. We found that poor sleep quality, in early pregnancy (14-16 weeks) and in later pregnancy

Table 1—Demographic characteristics of 166 pregnant women at 14-16 weeks gestation by delivery status and PSQI Score

	Total N = 166		Term Deliveries N = 151		Preterm Deliveries N = 15		PSQI ≤ 5 N = 84		^PSQI > 5 N = 48	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age*										
18-24	37	22.7	34	23.0	3	20.0	15	18.07	10	20.83
25-29	53	32.5	48	32.4	5	33.3	31	37.35	13	27.08
30-34	47	28.8	44	29.7	3	20.0	22	26.51	15	31.25
35+	26	16.0	22	14.9	4	26.7	15	18.07	10	20.83
Income*#										
< $30,000	40	24.5	34	23.0	6	40.0	16	19.51	14	29.17
$30,000–60,000	38	23.3	31	20.9	7	46.7	18	21.95	16	33.33
Over $60,000	85	52.2	83	56.1	2	13.3	48	58.54	18	37.50
Education*										
Primary, elementary, middle school	5	3.05	4	2.68	1	6.67	1	1.19	1	2.08
High school/or GED	23	14.02	22	14.77	1	6.67	13	15.48	7	14.58
Technical or vocational school	8	4.88	7	4.70	1	6.67	3	3.57	4	8.33
Some college but no degree	39	23.78	33	22.15	6	40.00	16	19.05	17	35.42
Associate degree	16	9.76	16	10.74	0	0.00	9	10.71	6	12.50
Bachelor's degree	44	26.83	40	26.85	4	26.67	26	30.95	9	18.75
Other graduate degree (Masters, Doctorate)	22	13.41	22	14.77	0	0.00	13	15.48	2	4.17
Certificate	7	4.27	5	3.36	2	13.33	3	3.57	2	4.17
Ethnicity**										
Non-Hispanic White	78	47.56	71	47.7	7	46.7	40	47.62	21	43.75
All others	86	52.44	78	52.3	8	53.3	44	52.38	27	56.25
Parity										
0	73	44.0	68	45.0	5	33.3	35	41.67	23	47.92
1	57	34.3	49	32.5	8	53.3	31	36.90	16	33.33
2	21	12.7	21	13.9	0	0.0	12	14.29	7	14.58
3+	15	9.0	13	8.6	2	13.4	6	7.14	2	4.17
History of Preterm Birth										
Yes	19	11.4	18	11.9	1	6.7	8	9.52	5	10.42
No	147	88.6	133	88.1	14	93.3	76	90.48	43	89.58
Prenatal Medical Risk Factors										
0	79	47.6	72	47.7	7	46.7	33	39.29	25	52.08
1-2	71	42.8	63	41.7	8	53.3	39	46.43	21	43.75
3+	16	9.6	16	10.6	0	0	12	14.28	2	4.16

*Missing data from 3 women. **Missing data from 2 women. #Wilcoxon/Fisher exact tests show differences in the income categories (P = 0.003) between women who delivered preterm vs. term. ^PSQI > 5 indicates poor sleep quality.

(30-32 weeks), was associated with an increased risk of delivering preterm. Specifically, we showed that with every one-point increase in the PSQI score in early pregnancy, the odds of preterm birth increased by 25%; in later pregnancy the odds increased by 18%. This is the first report, to our knowledge, that has evaluated sleep quality in conjunction with other established correlates as a risk factor for preterm birth, and the only one to have more than two assessments of sleep quality across pregnancy. These data provide new evidence in support of our hypothesis that disturbed sleep in early pregnancy may be a critical behavioral risk factor for adverse pregnancy outcomes.[3] It also supports the extant literature indicating that poor sleep in late pregnancy is associated with an increased risk of poor delivery outcomes.[11,12,37]

We sought to provide additional evidence as to whether poor sleep quality mediates the relationship between perceived stress and PTB.[36] Interpretations are consistent with the current literature of a bi-directional relationship between sleep and stress.[18,20,38-40] We contend that our data provide evidence that sleep quality may indeed be one mediator in the established relationship between stress and PTB.[23,41,42] Sleep is impaired by a multitude of influences ranging from financial strain[43] to stressful life events[44] to posttraumatic stress disorder.[45] Pregnancy can also be a time of increased stress.[23,46] Mounting evidence confirms that higher levels of stress are indeed associated with more disrupted sleep,[43,44,47,48] both of which are associated with immune and neuroendocrine dysregulation and increased morbidity.[19,39] Further evaluation with studies designed to test

Table 2—Sleep and psychosocial measures across pregnancy

	Time 1: 14-16 Weeks				Time 2: 24-26 Weeks				Time 3: 30-32 Weeks			
	Preterm		Term		Preterm		Term		Preterm		Term	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
PSQI Total*	7.79	4.88	4.97	2.68	6.20	3.95	5.03	2.61	7.79	4.13	5.26	2.73
PSS**	28.7	9.1	26.5	7.2	27.1	8.8	24.9	7.2	31.6	12.2	25.1	7.5
CESD#	15.9	3.2	17.1	3.3	16.6	2.7	16.5	2.7	17.8	3.7	16.6	2.9
STAI^	41.1	16.0	36.1	10.7	42.0	15.0	35.5	11.2	47.5	17.9	34.5	10.9

PSQI, Pittsburgh Sleep Quality Index; STAI, State-Trait Anxiety Inventory; PSS, Perceived Stress Scale; CES-D, Center for Epidemiologic Studies-Depression Scale with the sleep item removed. *PSQI scores were significantly different between Preterm and Term deliveries at Time 1 Mann-Whitney U test, P-value = 0.05 and Time 3 P-value = 0.03. **PSS scores were significantly different between Preterm and Term deliveries at Time 3 Mann-Whitney U test, P-value = 0.04. #CES-D scores were significantly different between Preterm and Term deliveries at Time 3 Mann-Whitney U test, P-value = 0.02. ^STAI scores were significantly different between Preterm and Term deliveries at Time 3 Mann-Whitney U test, P-value = 0.002.

Table 3—Correlation matrix of sleep, psychosocial measures, and preterm birth across pregnancy

	14-16 Weeks				24-26 Weeks				30-32 Weeks			
	PSQI	PSS	CES-D#	STAI	PSQI	PSS	CES-D	STAI	PSQI	PSS	CES-D	STAI
PSS	0.32**	–	–	–	0.43**	–	–	–	0.49**	–	–	–
CESD	−0.20*	−0.09	–	–	0.07	0.04	–	–	0.13	0.02	–	–
STAI	0.40**	0.72**	−0.09	–	0.45**	0.73**	−0.01	–	0.53**	0.75**	0.06	–
Preterm Birth^	-0.28**	−0.08	−0.11	−0.13	−0.07	−0.09	−0.02	-0.17*	-0.24**	-0.23**	−0.12	-0.31**

PSQI, Pittsburgh Sleep Quality Index; STAI, State-Trait Anxiety Inventory; PSS, Perceived Stress Scale; CES-D, Center for Epidemiologic Studies- Depression Scale. Value is minus the sleep item. *P < 0.01, **P < 0.001. ^point biserial correlations.

Table 4—Regression analyses evaluating sleep quality and perceived stress at 32 weeks gestation and whether quality of sleep mediates the relationship between perceived stress at 32 weeks' gestation and preterm birth

	β estimate	Odds Ratio	95% CI	R^2 Change
Crude Model	0.10	1.10	1.03-1.18	
Model 1				0.11
Obstetric Risk	0.20	1.22	0.60-2.50	
Income Category (> $60,000)	−1.66	0.19	0.01-0.82	
Income Category ($30,000-$60,000)	0.91	2.49	0.32-4.38	
PSS (Time 3)	0.08	1.08	1.00-1.16	
Model 2				0.12
Obstetric Risk	0.26	1.30	0.63-2.71	
Income Category (> $60,000)	−1.59	0.20	0.01-0.98	
Income Category ($30,000-$60,000)	0.91	2.49	0.33-4.85	
PSQI (Time 3)	0.09	1.10	0.89-1.36	
PSS (Time 3)	0.06	1.06	0.97-1.15	

The Crude Model represents a logistic regression in which perceived stress at 32 weeks' gestation predicts preterm birth. Model 1 was adjusted for obstetric risk (none or 1+) and income categories (< $30,000, $30,000–$60,000, and > $60,000). Model 2 was adjusted for income, obstetric risk, and for quality of sleep at 32 weeks' gestation.

mediation are required to effectively determine the direction of the relationship.

These data augment the small but growing literature regarding the link between sleep and pregnancy outcomes. The emphasis in previous studies has primarily focused on sleep disordered breathing (SDB) as a robust physiological contributor to preeclampsia and preterm birth.[49-51] SDB is associated with hypoxia and subsequent inflammation thought to contribute to gestational hypertension and preeclampsia.[51,52] However, other investigations have identified subjective measures of sleep, including sleep duration[12] and sleep quality[13,37,53] as independent risk factors for increased time spent in labor, increased rate of cesarean delivery, and postpartum depression. This report augments these previous investigations and extends the association to preterm birth.

Identification of novel risk factors might provide insights into mechanisms leading to preterm birth.[16] Although there are various pathways postulated to increase risk of PTB, growing evidence supports a role for an exaggerated inflammatory response.[54,55] We speculate that the timing and chronicity of poor sleep in pregnancy may affect different physiological pathways that may increase the vulnerability of women to subsequent infection, stress, or other psychosocial risk factors.[3,56] Sleep disturbance, whether it is poor sleep quality or short sleep duration, is associated with an exaggerated inflammatory response (i.e., higher circulating and stimulated levels of inflammatory cytokines).[6,57]

Stemming from these reports, a model describing the role of sleep and inflammation in the pathogenesis of adverse pregnancy outcomes was recently proposed, in which sleep disturbances, particularly during the first 20 weeks of pregnancy, contribute to the development of subclinical symptomatology and eventual disease via increased systemic inflammation.[3] This hypothesis is based on in vitro data, which suggest that increased levels of cytokines inhibit trophoblast invasion.[58] This would result in subsequent disruption of the remodeling of the maternal vessels of the maternal vascular bed and placenta, an abnormality present in preeclampsia, preterm birth, and pregnancies with intrauterine growth retardation. Sleep disturbances in late pregnancy, on the other hand, may directly initiate the inflammatory response associated with parturition.[59,60] Since poor sleep can initiate an inappropriate inflammatory response,[10,61] sleep may contribute to PTB by the premature activation of one or more of the normal processes associated with parturition.[59] Disturbed sleep may also augment this response in conjunction with stress, a known activator of inflammatory pathways.[25,62]

The reason for a lack of association between sleep quality at Time 2 and PTB is unclear. Although most reports indicate that sleep quality is improved during the late second trimester, the mechanisms through which this occurs are unknown. Definitive evidence is unavailable, for instance, as to whether a hormonal shift affects sleep or if simply sleep is "less" disrupted during this time, as compared to early gestation with the accretion of physiological changes or late gestation when physical size and restless legs syndrome (RLS) significantly disrupt sleep.[63] It is also plausible that RLS, a motor-sensory disorder which causes significant sleep disruption, contributes to poor sleep quality in a percentage of the women, particularly in late pregnancy. Upwards of 30% of women in the third trimester complain of RLS.[63-65] Studies to further evaluate the interactions among sleep, inflammatory markers, and delivery/pregnancy outcomes are desperately needed.

While our findings are both novel and provocative, we acknowledge several limitations that may preclude the ability to generalize to all women. Although the percentage of preterm births (9%) is consistent with expectations based on epidemiological data,[66] the relatively small number requires replication to increase confidence in the findings. We also recognize that sleep quality was the only measure of sleep available. Although sleep quality is one of the more robust correlates of adverse health outcomes in other domains,[8,13,67] additional measures of sleep, including continuity and duration, are needed to provide corroborative evidence of this relation. There are however, several strengths of the current study. First, this was a prospective study in which the pregnancies were carefully dated according to current ACOG guidelines, which increases the confidence in the outcome variable of PTB. There was also detailed medical information collected upon enrollment and throughout the study, as well as at delivery, to characterize the cohort. This allowed for evaluation of alternative explanations, including gestational hypertension and other medical risk factors, and also for investigation of the mediating role of sleep disruption in the link between psychosocial stress and preterm birth.

In summary, this study provides evidence for the first time, that poor sleep quality represents a risk for PTB. It likely co-occurs in the presence of other established risk factors, which supports the hypothesis that risk for PTB is determined by a cluster of risk factors[24] and is multifactorial.[62] What is unique and clinically relevant here is that sleep is a behavior that can be measured easily and quickly during prenatal visits. More importantly, it can be modified behaviorally with positive benefits.[68-70] Improving maternal sleep through behavioral interventions may be a relatively simple option to reduce the risk for adverse pregnancy outcomes by ameliorating the negative effects of deleterious psychosocial (i.e., depression) and biological (i.e., inflammatory) pathways.[3]

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