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24-Hour Sleep Duration in Early Gestation is Associated with Increased Markers of Inflammation Among Women with a History of Preeclampsia

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Abstract: *Background:* Sleep duration, both short and long, is recognized as a potential contributor to adverse health conditions. This study evaluated whether long sleep duration in early gestation (15 weeks) was associated with increased circulating concentrations of inflammatory cytokines across pregnancy.

Methods: Self-reported 24-hour sleep duration and blood samples were obtained concurrently at 15, 24 and 36 weeks gestation in 85 pregnant women with a history of preeclampsia. Plasma samples were assayed for the inflammatory cytokines IL-2, -6, -8, IFNγ, TNFα, GM-CSF and anti-inflammatory cytokines IL-4, -5, and -10 using Luminex technology. A ratio of pro-to-anti-inflammatory cytokines was calculated using multiples of the median (MOMs) for each relevant cytokine type to normalize the data for comparison. Data were analyzed using repeated measures mixed models.

Results: Women with long sleep (≥ 9 hours) at 15 weeks gestation had higher IL-6 concentrations throughout gestation than women who were regular sleepers ($p = .003$). No other cytokine or the ratio of pro-to-inflammatory cytokines differed between groups. No interactions of group by time were significant.

Conclusions: The tendency to sleep for more than 9 hours in early pregnancy may contribute to increased low-grade inflammation as evidenced by higher circulating concentrations of IL-6. This may initiate or augment pre-existing pathophysiology associated with adverse pregnancy outcomes. While, our data are preliminary, they direct further investigation to determine whether this association increases risk for adverse pregnancy outcomes.

Keywords: Sleep duration, pregnancy, cytokine, inflammation, preeclampsia.

INTRODUCTION

Sleep duration, both short and long, is recognized as a potential contributor to adverse health conditions including cardiovascular disease [1, 2] and Type 2 diabetes [3]. Despite the mutual recognition, most investigations have more often considered how short sleep duration contributes to adverse health outcomes [1, 4-6]. This emphasis is likely due to the long-term and continuing decline in habitual sleep duration from 8 to 6 ½ hours per night, particularly among women [7]. Long sleep duration, on the other hand, is most often assessed in association with increased psychopathologic symptoms and increased risk for mortality [8-10]. Recently some investigations have reported that long sleep (≥ 9 hours), in addition to short sleep duration, is indeed a risk factor for metabolic syndrome [11], Type 2 diabetes [12] and cardiovascular disease [3, 13]. These findings suggest that long sleep while often overlooked, is an important correlate to consider when evaluating sleep and health [8].

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Pregnant women report a host of sleep disturbances beginning in the first trimester [14-18]. Not surprisingly, many women indicate they require or obtain longer sleep duration than before they became pregnant. To date, the emphasis between pregnancy-related sleep disturbances and health has been on sleep disordered breathing (SDB) during pregnancy [19-21]. While the consequences of SDB are emerging as critically important to maternal and fetal outcomes [22-25], there is sufficient evidence that other facets of sleep, including sleep duration (either short or long) are also important to adverse pregnancy outcomes [5, 26, 27]. Among the small literature, two have focused on gestational diabetes with one considering the relationship between long sleep and gestational hypertension (GH) as well as preeclampsia [26]. GH is an important risk factor to understand as women who have GH in early pregnancy often go on to develop preeclampsia or have a small for gestational age baby. Both of these conditions are further associated with a woman delivering preterm, which also contributes to fetal morbidity [28, 29]. It is clear that additional information is needed to understand the effects of long sleep on pregnancy outcomes.

Among the myriad physiological changes that take place during pregnancy, inflammation (increases in pro-inflammatory cytokine expression) is important to consider.

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It is not only an identified pathway linking disturbed sleep and poor outcomes [30, 31], but imbalances of the cytokine milieu both in the maternal periphery as well as the feto-placental unit may be associated with the pathogenesis of adverse pregnancy outcomes [32-34]. Emerging evidence suggests that poor sleep quality and upper airway resistance during pregnancy are associated with higher levels of inflammatory markers [16, 35, 36]. *In vitro* studies indicate that inflammatory cytokines can inhibit invasion of human trophoblasts [37-39]. Furthermore, women with adverse pregnancy outcomes, such as preeclampsia, have increased concentrations of inflammatory cytokines compared to women with normal pregnancies [40, 41] however, the majority of the evidence is retrospective.

Given the indication that disturbed sleep contributes to inflammation, and the association between inflammation and adverse pregnancy outcomes, we evaluated whether long sleep duration across 24-hours in early gestation was associated with subsequent inflammation known to contribute to adverse pregnancy outcomes. To begin this preliminary look we took advantage of data collected as part of an exercise intervention study that attempted to reduce the frequency of preeclampsia in women who had this condition in a prior pregnancy. We hypothesized that those women who self-reported long sleep duration across 24-hours in early pregnancy would have higher circulating concentrations of inflammatory cytokines, as well as a higher ratio of pro- to anti-inflammatory cytokines than women with regular sleep duration. We posited that a particularly relevant time to assess increased inflammatory response in conjunction with disturbed sleep would be 14-16 weeks gestation since this is the time when inappropriate inflammation might interfere with normal remodeling of the maternal arteries supplying the intervillous space [42, 43].

MATERIALS AND METHODS

Participants

This is a secondary analysis of data from a trial evaluating the efficacy of using moderate exercise as a prophylaxis in the prevention of recurrent preeclampsia (N = 140). Inclusion criteria included a history of preeclampsia without pre-existing diabetes, essential hypertension, or multiple gestations and no limitations of physical activity. Following collection of baseline health and questionnaire data, women were randomized into a moderate walking group or control group. The current sample consists of 85 women who had sleep and cytokine data at each time point. All women were enrolled in early gestation (15 ± 2.8 weeks). Sleep and cytokine data were collected at 15, 25, and 35 weeks gestation. The Institutional Review Board at the University of Pittsburgh approved this study and all women signed informed consent.

Sleep Variables

Two sleep variables were identified. *Sleep Satisfaction* was determined through a single question that asked the degree to which a participant felt she got enough sleep (Never, Sometimes, Often or Routinely). Participants were dichotomized into NO (Never or Sometimes) or YES (Often or Routinely). *Sleep Duration* was assessed from a single question on the Paffenbarger exercise questionnaire [44]. Participants reported the number hours they spent sleeping or reclining each day (across a 24-hour period). Hence, these data likely include naps. The range was from 5-13 hours. We initially defined short sleep duration as less than 7 hours. However, there were few women (n=4) with short sleep duration (<7 hours) so data were dichotomized based on the mean (8.8 ± 1.4 hours) and median (9 hours), into regular sleepers (< 9 hours) and long sleepers (≥ 9 hours). The rationale was based on suggested practice recommendations for pregnant women [45] and that pregnant women generally report longer sleep duration, particularly when assessed over 24-hours [15, 45].

Cytokine Assays

The proinflammatory cytokines IL-2, -6, -8, IFNγ, GM-CSF, TNFα and the anti-inflammatory cytokines IL-4, -5, and -10 were measured in duplicate by Luminex technology. Luminex Multiplex Bead Immunoassays (Biosource; Invitrogen, Carlsbad, CA) are solid phase sandwich immunoassays, which are analyzed with a Luminex 100™ instrument. These specific pro- and anti-inflammatory cytokines are in this standard kit. By monitoring the spectral properties of the beads and the amount of associated R-Phycoerythrin (RPE) fluorescence, the concentration of one or more analytes can be determined. Samples were measured in duplicate. Inter-assay variation for each cytokine was as follows: IL-2 = 7.8%, IL-6 = 4.4%, IL-8 = 6.2%, IFNγ = 8.6%, GM-CSF = 5.7%, TNFα = 7.4%, IL-4 = 5.9%, IL-5 = 7.1%, IL-10 = 5.8%.

Data Management and Statistical Analysis

Means and percentages of demographic and clinical variable values were determined for descriptive purposes. Participants were dichotomized into two groups based on median sleep duration by self-report across 24-hours at 15 weeks gestation: regular sleepers (< 9 hours) and long sleepers (≥ 9 hours). The distribution of each cytokine was assessed. None of the cytokine data were normally distributed so individual cytokine values were log transformed for normalization. The pro-inflammatory group consisted of IL2, IL6, IL8, IFNγ, TNFα, and GM-CSF. The anti-inflammatory group consisted of IL4, IL5, and IL10. The pro- to anti-inflammatory ratio was calculated as the multiples of the median (MoMs) for each relevant cytokine type to normalize the data for comparison. This procedure allowed for standardization by creating comparable units as well as reducing the skewness that is apparent with cytokine data [46]. A repeated measures analysis of variance was performed using SAS Proc Mixed procedure to test for group, time and group*time interactions to examine whether long sleep duration in early pregnancy is related to changes in the means of individual cytokines and/or the ratio of pro- to anti-inflammatory cytokines across time. Models controlled for the covariates age, BMI, race, and treatment group (walking versus control). We used a more stringent p-value < .01 for main effects due to multiple comparisons.

RESULTS

Table **1** describes the maternal characteristics of the entire cohort, as well as by groups: regular (< 9 hours) and

Table 1. Maternal Characteristics at Enrollment for Entire Cohort of Women and for those who Slept < or ≥ 9 Hours (Mean (SD or percent))

	Entire Cohort (N = 85)	< 9 Hours (N = 42)	≥ 9 Hours (N = 43)	Test-Statistic (df) p-value
Demographics				
Age	30.1 (4.9)	30.2 (4.5)	30.0 (5.4)	t(83)=0.22, p=0.83
% Caucasian	84.7 (n=72)	88.1 (n=37)	81.4 (n=35)	$\chi^2(1)=0.74$, p=.39
Gravid Status (range 1-6)	2.7 (1.1)	2.7 (1.1)	2.7 (1.1)	t(83) = -.23, p =.82
Parity (range 1-6)	1.3 (.74)	1.2 (.58)	1.3 (.87)	t(81) = -.40, p = .67
Maternal Anthropometry				
BMI (kg/m^2)at enrollment	29.2 (8.7)	30.5 (9.5)	28.0 (7.7)	t(83)=1.30, p=0.20
% Normal (< 25.0)	37.7 (n=32)	35.7 (n=15)	39.5 (n=17)	$\chi^2(1)=0.13$, p=.72
Smoking Status				
% Never	62.4 (n=53)	57.1 (n=24)	67.4 (n=29)	Fisher Exact = .22
% Quit	27.1 (n=23)	26.2 (n=11)	27.9 (n=12)	
% Current smoker	10.6 (n=9)	16.7 (n=7)	4.7 (n=2)	
% Assigned to Walking Group	55.3 (n=47)	57.1 (n=24)	53.5 (n=23)	$\chi^2(1)=0.12$, p=0.74
% Assigned to Control Group	44.7 (n=38)	42.9 (n=18)	46.5 (n=20)	
% Not Satisfied with Sleep	41.2 (n=35)	47.6 (n=20)	34.9 (n=15)	$\chi^2(1)=1.42$, p=0.23

long (≥9 hours) sleepers. Participants were 30.1 ± 4.9 years, 84.7% Caucasian with a mean BMI = 29.2 ± 8.7 upon entry into the study. Nine (10.6%) women reported smoking cigarettes at enrollment. Women who slept ≥ 9 hours did not differ from those who slept <9 hours on any of the participant characteristics. In the complete cohort, approximately 41% (n = 35) indicated they were not satisfied with their sleep at 15 weeks gestation. Fig. (**1**) shows the distribution of total sleep duration at 15 weeks. Sleep duration also changed across time (data not shown).

Table **2** shows the means and standard deviations for all the cytokines evaluated. IL-2 changed across time being significantly higher at T1 than at T2 or T3 (p = .01) (Fig. **2**). Other cytokines changed but did not meet the more stringent p-value <.01. IL-6 differed by group (p = .003). It was greater in long sleepers (≥ 9 hours) compared to women who were regular sleepers (<9 hours) (Fig. **3**). There were no significant interactions. Concerning the pro- to anti-inflammatory ratio, there were no significant changes across time, group differences or a group by time interaction.

DISCUSSION

We examined the distribution of total sleep duration across a 24-hour period in sedentary pregnant women all of whom had a previous preeclamptic pregnancy. Among this sample of 85 pregnant women over half reported 9 or more hours of total sleep within a 24-hour period at 15 weeks gestation. This is consistent with the current literature [14, 15, 45]. However, sedentary women, especially obese and pregnant, are likely to have longer sleep duration than active lean pregnant women [47-49]. We found that women who reported longer sleep duration in early gestation had higher IL-6 concentrations across pregnancy compared to women with regular sleep duration. This is consistent with previous literature [16]. A time effect was also observed for IL-2. We did not, however, observe a time X group interaction. These results partially support our hypothesis that poor sleep may contribute to an exaggerated inflammatory response prior to 20 weeks gestation, which could initiate pathophysio logical changes, (i.e. cardiovascular) associated with disease

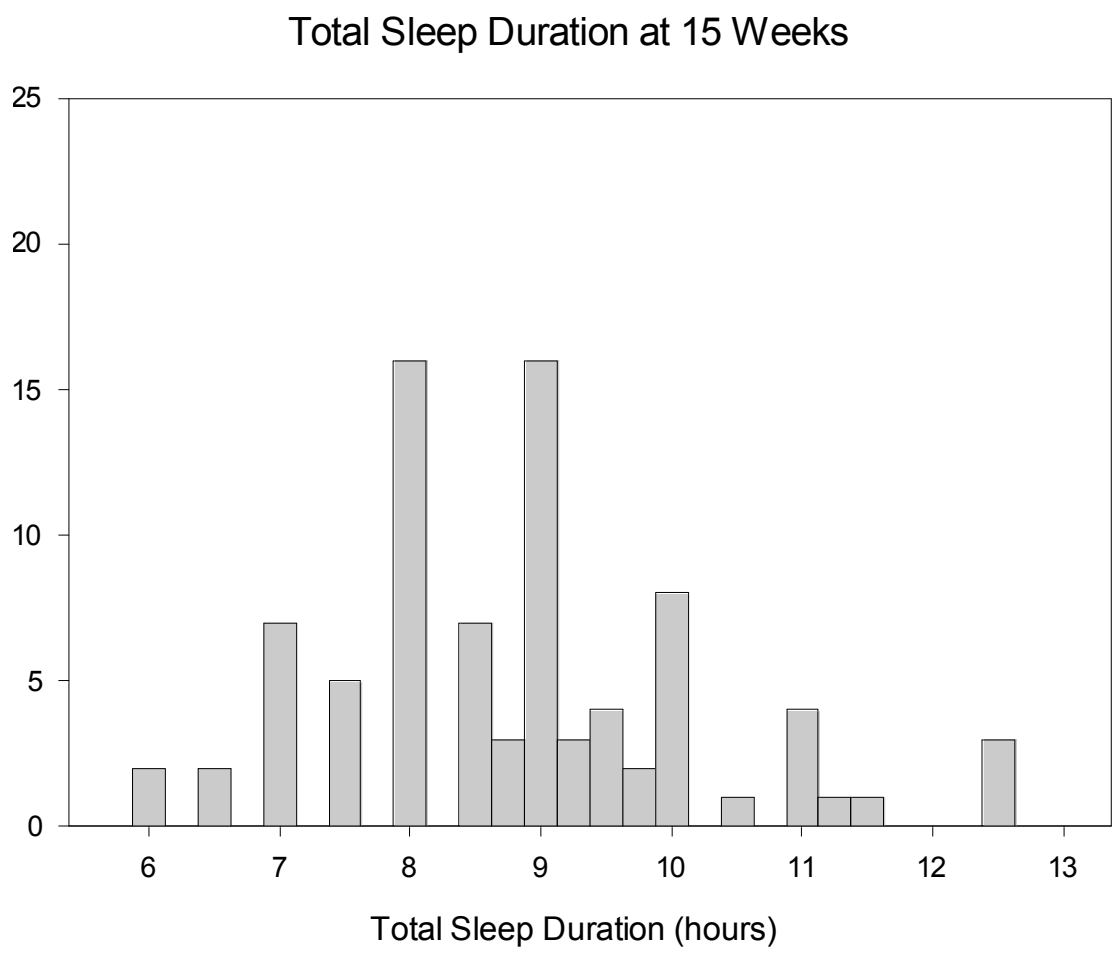

Fig. (1). Distribution of self-reported sleep duration at 15 weeks gestation.

Table 2. Cytokine Changes Over Time According to Group (Mean (STD))

	15 Weeks (T1)	24 Weeks (T2)	36 Weeks (T3)	Statistics Controlling for Age, Race, BMI and Treatment	Post Hoc [c]
Pro-inflammatory					
IL-2 (pg/ml) [a]				Grp: F(1,77)=3.33, p=0.07 Time: F(2,77)=4.50, p=0.01 Grp*Time:F(2,77)=0.29, p=0.75	T1> T2, T3
<9 hrs	96.3 (47.3)	84.0 (50.3)	91.3 (58.6)		
≥ 9 hrs	123.1 (54.3)	101.3 (53.5)	101.9 (56.0)		
Il-6 (pg/ml) [a]				Grp: F(1,76)=9.52, p=0.003 Time: F(2,76)=0.62, p=0.54 Grp*Time:F(2,76)=0.43, p=0.65	<9 hrs less than ≥9hrs
< 9 hrs	14.1 (10.8)	15.0 (11.7)	13.5 (9.4)		
≥ 9 hrs	28.3 (21.4)	25.3 (22.6)	23.3 (20.3)		
IL-8 (pg/ml) [a]				Grp:F(1,78)=4.86, p= 0.03 Time:F(2,78)=2.41, p= 0.10 Grp*Time:F(2,78)=0.42, p=0.66	
< 9 hrs	17.4 (9.0)	16.9 (11.5)	18.4 (13.9)		<9 hrs less than ≥9hrs
≥ 9 hrs	23.9 (11.4)	19.6 (10.3)	22.0 (13.1)		
IFN-γ (pg/ml) [a]				Grp: F(1,78)=1.40, p=0.24 Time: F(2,78)=3.12, p=0.0498 Grp*Time: F(2,78)=0.49, p=0.61	T1 > T2
< 9 hrs	42.4 (23.0)	38.7 (25.2)	46.0 (35.6)		
≥ 9 hrs	53.8 (26.2)	44.9 (28.7)	47.1 (29.2)		

TNF-α (pg/ml) [a]				Grp: F(1,77)=0.23, p=0.63 Time: F(2,77)=1.15, p=0.32 Grp*Time: F(2,77)=0.01, p=0.99	
< 9 hrs	30.7 (17.4)	29.0 (21.0)	33.0 (28.5)		
≥ 9 hrs	37.6 (24.1)	31.1 (21.7)	35.0 (26.1)		
GM-CSF (pg/ml) [a]				Grp: F(1,76)=1.57, p=0.22 Time: F(2,76)=0.91, p=0.41 Grp*Time: F(2,76)=0.12, p=0.88	
< 9 hrs	74.5 (54.8)	71.0 (56.3)	69.2 (80.7)		
≥ 9 hrs	107.6 (118.0)	73.9 (47.8)	87.4 (76.9)		
Anti-inflammatory				Grp: F(1,78)=3.99, p=0.049 Time: F(2,78)=3.54, p=0.034 Grp*Time: F(2,78)=0.46, p=0.63	<9 hrs less than ≥9hrs T1 > T2, T3
IL-4 (pg/ml) [a]					
< 9 hrs	63.8 (47.4)	60.3 (45.4)	53.3 (42.1)		
≥ 9 hrs	79.9 (45.8)	65.1 (39.2)	69.9 (49.3)		
IL-5 (pg/ml) [a]				Grp: F(1,77)=2.17, p=0.15 Time: F(2,77)=0.72, p=0.49 Grp*Time: F(2,77)=0.10, 0.90	
< 9 hrs	6.9 (4.1)	6.9 (5.6)	8.0 (7.0)		
≥ 9 hrs	8.7 (4.8)	8.5 (6.2)	8.2 (5.2)		
IL-10 (pg/ml) [a]				Grp: F(1,76)=3.27, p=0.07 Time: F(2,76)=0.13, p=0.88 Grp*Time: F(2,76)=0.27, p=0.76	
< 9 hrs	12.6 (9.1)	12.9 (9.0)	14.2 (16.7)		
≥ 9 hrs	17.9 (14.2)	15.7 (10.7)	18.0 (15.1)		
Ratio Pro:Anti-inflammatory MoM [b]				Grp: F(1,78)=0.45, p=0.50 Time: F(2,78)=4.34, p=0.02 Grp*Time: F(2,78)=0.80, p=0.45	T2 > T3
< 9 hrs	1.0 (0.2)	1.1 (0.4)	1.0 (0.2)		
≥ 9 hrs	1.1 (0.6)	1.2 (0.4)	1.1 (0.3)		

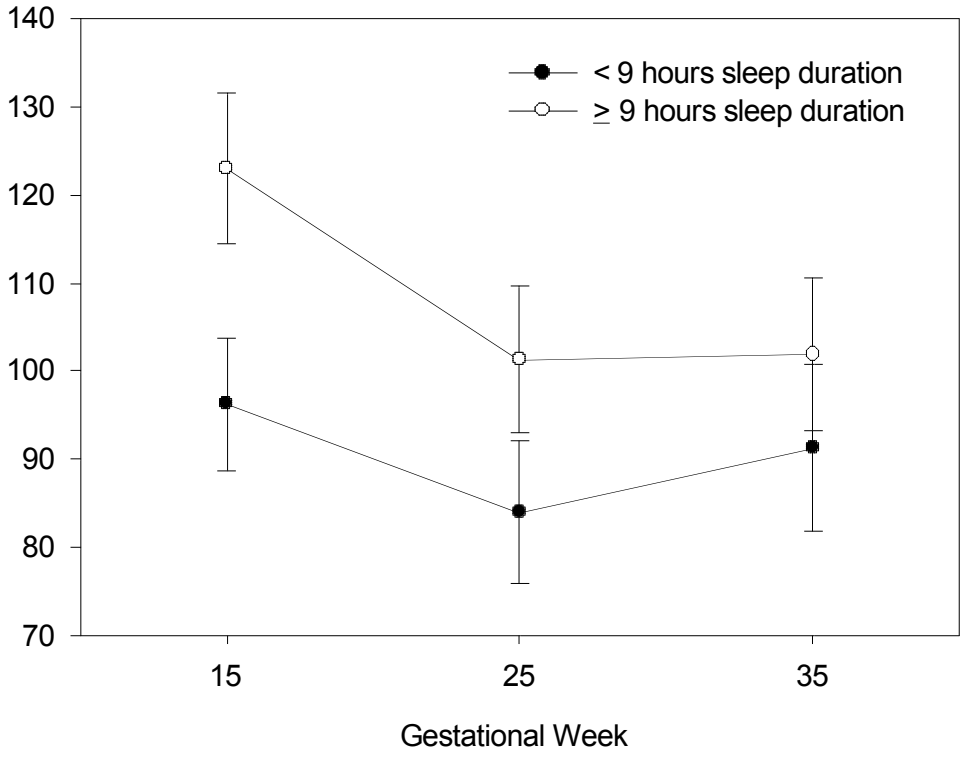

Fig. (2). Concentrations of IL-2 (pg/ml) assayed at 15, 25 and 36 weeks gestation. Women who self-reported ≥ 9 hours of sleep per night (Open circles) had higher concentrations ($p < .07$) across pregnancy compared to women who self-reported < 9 hours of sleep per night (closed circles). IL-2 values significantly dropped across pregnancy ($p < .01$). Of note: Luminex was used to assay a series of cytokines. Hence, by nature of the assay the concentrations are significantly higher compared to ELISA kits [86].

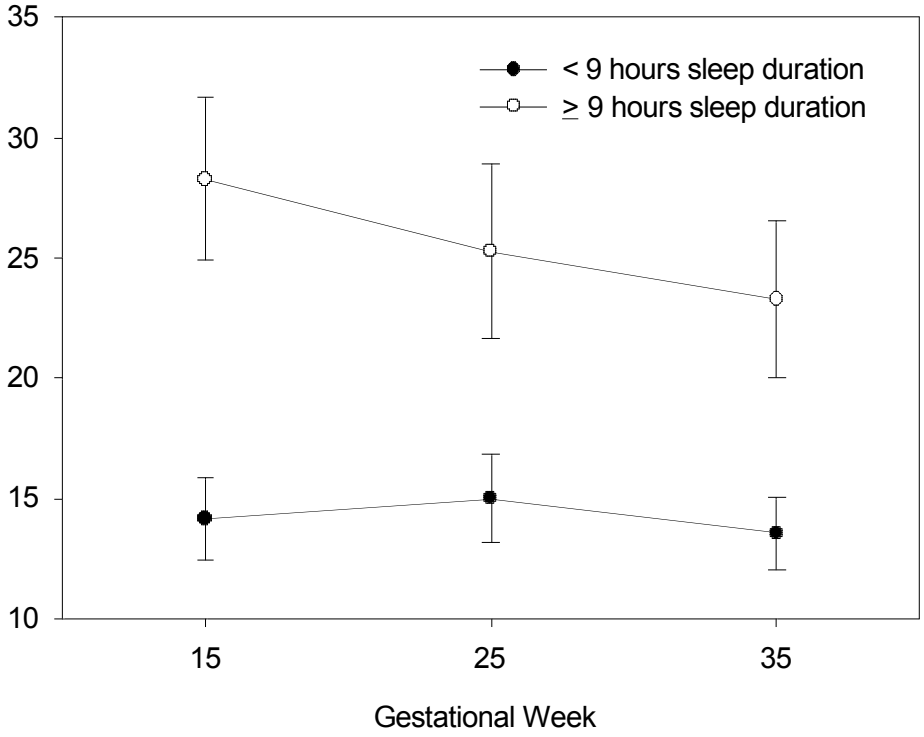

Fig. (3). Concentrations of IL-6 (pg/ml) assayed at 15, 25 and 36 weeks gestation. Women who self-reported ≥ 9 hours of sleep per night (Open circles) had higher concentrations (p = .003) across pregnancy compared to women who self-reported < 9 hours of sleep per night (closed circles). However, there was no significant change across time. Of note: Luminex was used to assay a series of cytokines. Hence, by nature of the assay, which still remain unclear, the concentrations are significantly higher compared to values obtained via ELISA [86].

development and future morbidity [50]. While long sleep duration has not historically been considered poor sleep, emerging evidence is shifting this paradigm [3, 10, 11]. Understanding the role of sleep is critical not only to pregnancy outcomes, but for future health conditions as well. Women who have had a preeclamptic pregnancy are at increased risk for future cardiovascular disease [51-53]. This risk is evidenced by increased blood pressure readings, inflammation, impaired endothelial function and dyslipidemia long after delivery [54-57]. These maternal complications can also have extensive negative consequences for the offspring who are also at increased risk for adolescent and adult onset cardiovascular disease, metabolic syndrome and diabetes [58, 59]. Further exploration of these preliminary findings is needed to facilitate interpretation as well as gauge the value of assessing pregnancy-related sleep disturbance as a potential risk factor in the development of adverse outcomes.

The effects of long sleep duration during pregnancy are not clear despite several reports, including our current data, suggesting that a large percentage of pregnant women report long sleep (≥ 9 hours). An in-depth exploration of this relationship may have significant clinical relevance for pregnancy since long sleep duration is a recognized independent predictor of hypertension [26, 60-62], a hallmark sign of preeclampsia [54, 63]. We hypothesize that the inflammatory pathway may connect long sleep duration and high blood pressure. Recent lines of data support this hypothesis. Williams et al. show an association between long sleep duration and elevated mean third-trimester blood pressures and preeclampsia risk in pregnant women [26]. We show that long sleep duration is associated with increased inflammation and the extant literature supports an association between increased inflammation and pregnancy-induced hypertension/ preeclampsia [37, 64-68]. Moreover, preeclampsia is proposed to be an endothelial cell disorder [53, 54, 69] in which cytokines are both potent stimulators and products of endothelial cells [70, 71]. Although provocative, additional studies are required to examine sleep, inflammation and outcome concomitantly in order to confirm these relationships.

The relationship between long sleep and adverse health outcomes is likely mediated by an array of correlates. Long sleepers report more depressive symptoms, they exercise less, are more often obese, they are often not married, and they are of lower socioeconomic status [8]. Unfortunately, these variables were unavailable from this cohort. We recognize this as a limitation. Relevant to the hypotheses evaluated here is that each of these correlates contribute to increased inflammation [72]. Interestingly Patel and colleagues report that other pregnancy-related sleep disorders, such as restless legs syndrome and sleep disordered breathing, also predispose to long sleep duration [10] which may compound the exaggerated inflammatory response to long sleep. Presently, it is unclear as to whether long sleep duration in pregnancy is solely an independent factor or a mediator of other established risk factors as well.

Many correlates have a bi-directional relationship with sleep. For instance, long sleep duration has been shown to predict increased weight/obesity, while increased weight/obesity has been shown to predict longer sleep duration [8]. Our cohort of women was all overweight/obese

and sedentary, and considered at high-risk for preeclampsia. This factor may also contribute to a percentage of women requiring longer sleep. Understanding the dynamics of this relationship is important since increased weight is highly correlated with increased systemic inflammation [10, 11] and preeclampsia [73, 74]. The increased levels of IL-6 are not surprising in this sample given the well established evidence that adipose tissue is a major source for IL-6 [75] and subsequent increased inflammation. However, the fact that recent evidence further demonstrates a U-shaped relationship with maternal serum IL-2 concentrations and BMI [76], as well as an increase in BMI with specific polymorphisms of the IL-4 receptor [77] suggests that sleep duration may be an additive factor in a complicated relationship. A clearer understanding is particularly important if we are to reduce the 50,000 pregnancies afflicted yearly by pregnancy-related hypertension and preeclampsia [57, 63, 78].

Although the study design was prospective, there are certain limitations to the interpretability of these findings. The primary study was not designed to evaluate the relationship between sleep and inflammatory markers. Thus, the sleep information used is a crude approximation of actual sleep habits. Despite this, our measure is similar and confirmatory of other studies of long sleep duration in women [10, 13, 26]. It does imply that more detailed sleep information is needed to fully elucidate these relationships. Specifically, the presence of snoring or sleep disordered breathing or restless legs syndrome was not ascertained in the study. It is well established that obesity is a risk factor for snoring and sleep disordered breathing [79] and inflammation [76, 80]; both of which increase the risk of adverse pregnancy outcomes [22, 24, 25]. Other psychosocial correlates, including depression and stress were also not considered. These are recognized to contribute to inflammation and adverse pregnancy outcomes [81-83]. Hence, it is likely that IL-6 may have been elevated prior to enrollment into the study. Future studies need to take these correlates into consideration. Although the assessment of nocturnal and daytime sleep is a limitation, the data are also unique. Sleep duration across 24-hours is likely to include daytime napping which is noted to be higher in pregnant women [15]. We note the small sample size is probably too small to have sufficient power, but the confidence in these preliminary findings is augmented with multiple assessments from each participant in a cohort of high-risk women. While a strength, the homogeneity of only testing women with history of preeclampsia restricts the generalizability of our findings. Furthermore, data on the interval between pregnancies was not collected. Hence, we are unable to determine when the sleep duration changed (if at all). A more heterogeneous and larger cohort is needed in order to understand these relationships better and to more accurately identify which women are most at risk. Finally, we are cognizant that the unavailability of delivery and outcome data, currently blinded as part of the primary study, precludes an evaluation of sleep, inflammation and outcome.

We had hoped that the ratio of an array of proinflammatory to anti-inflammatory markers would be a better indicator of an "inflammatory" phenotype than a single cytokine such as IL-6. However, there are limitations even though the approach we chose (for which we did not find differences) would seem a more sensitive approach to defining inflammation [84]. Using the MoMs allowed us to combine different cytokines present at different concentrations. However, not all cytokines are equipotent in their activities. It is unclear whether there are clinically relevant distinctions when the median of a proinflammatory cytokine such as IL-6 is compared to the median of an anti-inflammatory cytokine such as IL-10.

In summary, we suggest that long sleep duration early in gestation is associated with an increase in basal inflammation. This inflammation underlies a defective placentation characterized by reduced invasion of fetal extravillious trophoblast cells and reduced remodeling of maternal uteroplacental spiral arteries which initializes subsequent pathophysiology [37]. Despite the preliminary nature of these relationships, we hypothesize that in conjunction with other factors, including a history of preeclampsia/preterm birth, obesity and a sedentary lifestyle [66, 74, 85], the 25 - 40% of pregnant women with significant sleep disturbances during the first trimester may be at further increased risk for adverse outcomes. The extent to which an exaggerated inflammatory response is the biological mediating pathway requires further evaluation.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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