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How Disturbed Sleep May Be a Risk Factor for Adverse Pregnancy Outcomes A Hypothesis

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Abstract

Adverse pregnancy outcomes associated with significant maternal and infant morbidity are on the rise in Western society despite advances of medical technology. Current risk factors are insufficient to identify women at greatest risk of developing an adverse outcome. An attempt to identify novel contributors to increased risk is warranted. Sleep disturbances are frequent during pregnancy, yet are often dismissed as irrelevant. Emerging evidence indicates that sleep disturbances are associated with poor health outcomes, including cardiovascular disease. Disturbed sleep is also linked with an increased inflammatory response. Increased inflammation is proposed as a key biological pathway through which chronic disease and adverse pregnancy outcomes develop. In this paper, we propose a model and a testable hypothesis of how disturbed sleep in the first 20 weeks of pregnancy could contribute to adverse pregnancy outcomes such as preeclampsia, intrauterine growth restriction, and preterm birth via increased inflammation.

Target Audience—Obstetricians & Gynecologists, Family Physicians

Leaning Objectives—After completion of this article, the reader should be able to outline data linking sleep disturbances with an increased risk of some systemic disorders, recall characteristics of pregnancy complications which support the hypothesis that sleep disturbances may be related to these pregnancy outcomes, and summarize the likelihood and types of sleep disturbances that are common in pregnant women.

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In the United States over 1 million pregnancies each year result in adverse outcomes that increase maternal and infant morbidity (1,2). The most frequent adverse outcomes include preeclampsia, intrauterine growth restriction (IUGR), and preterm birth. Despite extensive research and the identification of multiple risk factors little progress has been made in understanding or preventing these disorders. The need to explore novel contributors to these disorders is highlighted by the fact that established risk factors identify only about 50% of women at risk for adverse outcomes (2-5). Sleep disturbances, a frequent complaint of pregnant women (6,7), are now recognized as important contributors to several disease states and we propose that sleep disturbances may be a novel contributor to adverse pregnancy outcomes.

Sleep is not merely the absence of waking. On the contrary, it is a state during which specialized physiological activities occur in the brain and throughout the body. It is an active process in which metabolism, tissue restoration, memory consolidation, and general homeostatic balance is maintained (8,9). Homeostatic and circadian influences dictate that we spend approximately one-third of our lives asleep (10). Yet, to date, the primary focus in the pathogenesis of disease has been on the role of waking factors with little attention to sleep.

Sleep disturbances are implicated in both increased morbidity and mortality. Poor sleep quality is associated with increased risk for depression (11-13) (Okun et al, in press), whereas short sleep duration is associated with increased incidence of diabetes (14,15), obesity (16,17), as well as increased all-cause mortality (18-20). Of the many disease outcomes associated with poor sleep, cardiovascular disease is of particular relevance to several pregnancy complications, such as preeclampsia, IUGR, and preterm birth. These adverse pregnancy outcomes share risk factors with cardiovascular disease and are associated with a greater risk of developing cardiovascular disease later in life (21,22). Therefore, for purposes of illustration we emphasize the consistent association of poor sleep quality and short sleep duration with increased risk of cardiovascular disease (23-27), an association that is stronger in women than men (23,26).

Disturbed sleep affects several biological pathways associated with cardiovascular morbidity, including neuroendocrine, metabolic, and inflammatory systems. One way that disturbed sleep may increase cardiovascular disease is by exacerbating well recognized cardiovascular risk factors. Importantly, many of these are also risk factors for adverse pregnancy outcomes. Two major risk factors for cardiovascular disease are obesity (16,17,28-30) and independently, increased insulin resistance (31,32). Short sleep duration and sleep disturbances are associated with increased BMI (16,17,29,33), whereas experimental sleep deprivation and poor sleep quality can increase insulin resistance (31,34).

Several risk factors for cardiovascular disease also increase adverse pregnancy outcomes. Preeclampsia and spontaneous preterm birth are increased in women with BMIs >30 (35-37), and increased insulin resistance is associated with higher rates of preeclampsia and growth restricted babies (38-40). Furthermore, these adverse pregnancy outcomes share pathophysiological features with cardiovascular disease. Increased oxidative stress, endothelial dysfunction and inflammation are implicated in the pathogenesis of cardiovascular disease and adverse pregnancy outcomes (21,22,41,42). We propose that through these common mechanisms disturbed sleep may contribute to the risk of adverse pregnancy outcomes.

We review the relevant published literature to support the hypothesis that disturbed sleep may increase adverse pregnancy outcomes. Information specifically addressing sleep disturbances and pregnancy outcomes is limited. Therefore, our goal is to use existing information on the relationship of sleep to disease, and particularly cardiovascular disease, to inform a rationale and a testable hypothesis for how disturbed sleep may increase preeclampsia, IUGR, and preterm birth.

Sleep and Pregnancy

A common perception is that sleep is markedly disturbed in pregnancy (6,7,43). Sleep disturbances are typically classified as: disturbed sleep quality, poor sleep continuity, short/long sleep duration, restless legs syndrome, and sleep disordered breathing. Sparse data are available that indicate what to expect with regards to the timing, degree, frequency, and/or severity of a specific pregnancy-related sleep disturbance. Although up to 75% of pregnant women experience some form of sleep disruption during pregnancy, the number of women who report significant sleep complaints in the first trimester is only about 25% (7).

Common Pregnancy-Related Sleep Disturbances

The subjective perception of poor sleep quality is the most commonly assessed sleep disturbance during pregnancy (7,44-46), with sleep quality typically declining as pregnancy progresses (7,47). Sleep continuity, another measure of sleep, is the degree of fragmentation in a sleep period. Several indices describe sleep continuity, including sleep latency, number of awakenings, and total minutes spent awake. Pregnancy is characterized by poor sleep continuity (7,44,45,48-50). Sleep is also assessed by evaluating the amount of sleep achieved during the night. Sleep duration varies throughout pregnancy typically decreasing by term (7, 45,47,51). Restless leg syndrome is a neurosensory disorder that typically begins in the evening and often prevents a person from falling asleep. It can contribute to poor sleep continuity and quality. It is common during pregnancy with rates reaching 27% by the third trimester (52, 53). Finally, sleep disordered breathing includes abnormalities of respiratory pattern (pauses in breathing) or the quantity of ventilation during sleep. It can greatly disturb sleep quality, continuity and duration. Sleep disordered breathing is thought to increase during pregnancy by as much as 20% (54).

Sleep and Adverse Outcomes

Data linking sleep disturbances and adverse pregnancy outcomes are limited (48,55-59). Women with preeclampsia have poorer sleep quality and continuity than women without preeclampsia (55,56), whereas shorter sleep duration in late pregnancy is associated with longer labor times and increased cesarean section rates (58). Sleep disordered breathing, and snoring, a common symptom of sleep disordered breathing, are linked with increased risk for preeclampsia, gestational hypertension, and small-for-gestational-age infants (60-62). Although these studies suggest that certain sleep disturbances are related to adverse outcomes, small sample sizes and cross-sectional designs preclude clear conclusions.

Additional Considerations

It is likely that sleep disturbances may not all have the same impact to increase adverse outcomes. Sleep quality (63-66) and sleep disordered breathing (67,68), for example, have a greater effect on the inflammatory response than sleep duration or sleep continuity. Sleep disordered breathing leads to hypoxia followed by restitution of normoxia. This well recognized pathogenic cascade leads to oxidative stress and a subsequent increase in inflammatory activation (69). It is also prudent to assert that we do not believe that sleep disturbances are an independent causal link to adverse outcomes. We propose that in conjunction with other risk factors, the risk for adverse outcomes may be increased among the 25% of pregnant women with significant sleep disturbances during the first trimester.

Inflammation as a Relevant Biological Pathway

Of the several mechanisms by which sleep alters normal physiology, augmented inflammatory activation could provide a link between disturbed sleep and adverse pregnancy outcomes. Poor

sleep quality and continuity, reduced sleep duration, and sleep disordered breathing, are all associated with augmentation of the inflammatory response as indicated by increased circulating concentrations of the proinflammatory cytokines, interleukin (IL)-6 and tumor necrosis factor (TNF)-α (70-73), and the acute phase protein, C-reactive protein (CRP) (74-76).

Inflammation is considered a component of the pathogenesis of adverse pregnancy outcomes (77-80). IL-6, TNF-α and CRP are increased with preeclampsia, (81-84), IUGR, (77,79,85), and preterm labor/birth (86-89). One mechanism by which inflammation may increase adverse pregnancy outcomes is by interfering with normal trophoblast invasion. In experimental studies, increased inflammatory cytokines, such as TNF-α, interfere with trophoblast implantation (90,91). Remodeling of the spiral arteries to increase placental perfusion requires normal trophoblast invasion (38,92,93). Failed remodeling of these vessels with associated reduced trophoblast invasion is present with preeclampsia, pregnancies complicated by IUGR and one third of the cases of preterm birth (94).

The Hypothesis

In Figure 1, we propose a model of the possible role of sleep and inflammation in the pathogenesis of adverse pregnancy outcomes. We propose that sleep disturbances during the first 20 weeks of pregnancy contribute to increased systemic inflammation. Despite the necessity of a dominant proinflammatory profile for early pregnancy success (95), based on in vitro experiments in which cytokines inhibit trophoblast invasion, it is postulated that an exacerbated inflammatory response interferes with normal trophoblast invasion. This would result in subsequent disruption of the remodeling of the maternal vessels of the maternal vascular bed, an abnormality present in preeclampsia, preterm birth, and pregnancies with IUGR (96).

We propose that “positive feedback” plays a role in the association of sleep disturbance with increased inflammation. In this regard, it is well documented that disturbed sleep (naturally occurring or induced experimentally) is associated with increased markers of inflammation (70,72,73,75,97). It is also well recognized that systemic inflammation results in a disruption of sleep (98,99). The bi-directional relationships linking disturbed sleep and inflammation may amplify their association and consequences in pregnancy.

The model also proposes that health behaviors can contribute independently to increased sleep disturbance and inflammation, and thus increase risk of adverse pregnancy outcomes. Again, relationships are bi-directional, with lifestyle choices impacting sleep parameters and vice versa. Smoking, for instance, is associated with poor sleep continuity and shorter sleep duration (100). This sleep disruption can result in anxiety, which, in turn, leads to increased smoking due to the anxiolytic properties of cigarettes (101). Alcohol use similarly disturbs sleep continuity (102) and sleep duration (103). Despite this, alcohol is frequently used as a self-remedy for sleep problems, resulting in further sleep disruption (104). In support of the proposed model, consistent evidence shows that both smoking and excessive alcohol intake are associated with increased inflammation (105,106). Similarly, obesity and its metabolic correlates, including insulin resistance, are associated with short sleep duration, often resulting from sleep disordered breathing (107). Short sleep duration can also result in weight gain, via reductions in the anorexogenic hormone, leptin, and increases in the appetite-promoting hormone, ghrelin (108,109). Furthermore, adipose tissue is a prominent producer of proinflammatory cytokines; hence, obese individuals have higher circulating levels of inflammatory markers than individuals of more normal weight (110).

A further pathway that may link sleep and inflammation is the neuroendocrine system. Several positive and negative feedback processes play a role in closely regulating hormonal and

neuronal factors that modulate inflammatory processes. The release of adrenal hormones (catecholamines) and activation of sympathetic nerves increases the production of inflammatory cytokines from activated immune organs and cells (111). In turn, catecholamines disturb sleep (112). The bi-directionality of these systems is auto-amplifying as disturbed sleep increases nocturnal sympathetic activity (113,114). Hormones from the hypothalamic-pituitary-adrenal (HPA) axis are also linked with inflammatory responses. The HPA axis regulates inflammatory responses via cortisol secretion. Cortisol ordinarily suppresses the production of proinflammatory cytokines (115,116). As part of a negative feed back loop, proinflammatory cytokines can stimulate the HPA axis to produce more cortisol (111) that shuts off the inflammatory response. However, chronic cortisol secretion results in a down-regulation of glucocorticoid receptor sensitivity that blunts cortisol's suppressive effects (115). Of interest here is that the hormones of the HPA axis are secreted in a diurnal manner paralleling the sleep-wake cycle (117). Disrupted sleep, however, can produce mild elevations in HPA axis hormones (114). Thus, sleep disturbances that accompany pregnancy may begin a cascade of effects to dysregulate this homeostatic process. Specifically, both disrupted sleep and inflammation result in chronic HPA activation, which in turn, results in decreased glucocorticoid sensitivity and prolonged/exaggerated inflammatory responses. As depicted in Figure 1, this auto-amplifying process may increase the risk of adverse pregnancy outcomes, particularly when it occurs early in gestation.

The capacity of sleep to engender these feed forward loops is because of the fact that sleep, despite its necessity for healthy survival (118,119), can be modified both by endogenous and exogenous factors. Pregnancy initiates physiological changes that affect sleep. Volume redistribution leads to nocturia and nocturnal awakenings (120). Furthermore, humans are able to voluntarily override the biological drive to sleep. The amount and quality of sleep a woman achieves is often influenced by demands of life, work, and family (121). Therefore, we suggest that altering sleep patterns, whether from pregnancy changes or "voluntarily," results in disturbed sleep that can initiate the cascade of processes outlined in Figure 1.

Beginning early in the first trimester, pregnant women report an increase in the number of awakenings and time spent awake at night (7). Although a high percentage of women report disturbed sleep, few actually experience complications. Why do some women develop adverse outcomes, whereas others do not? This raises a consideration important to most biological systems and also an important component of this or any hypothesis proposing risk factors for adverse pregnancy outcomes. Obesity, for example, is a major risk factor for preeclampsia with a 3-fold increased frequency of preeclampsia in women with a BMI >30 (35,122). However, since the usual incidence of preeclampsia is 3% to 4%, almost 90% of obese women will not develop preeclampsia. Sleep disturbances do not exist in isolation. As with obesity, if sleep disturbances are identified as a risk for adverse outcomes they may be operative only in pregnancies in which they interact with maternal or fetal factors that converge with disturbed sleep, perhaps at the level of increased inflammation, to adversely affect a particular pregnancy.

Testing the Hypothesis

The hypothesis presented is testable. There are several ways to collect sleep data. The gold standard in measuring sleep is polysomnography because it provides an objective, physiological assessment of sleep-wake patterns for an entire sleep period (123). However, this method is often cost-prohibitive as the recording time and data are restricted by expense and high participant burden. A more practical and less costly alternative is to use actigraphy and sleep diaries concurrently. An actigraph is a wrist-watch like device that is activated by movement and allows objective evaluation of behavioral sleep variables including awakenings, wake time during the night and total sleep time that may not be perceivable by the participant (124). The combination with subjective assessments of sleep (e.g., sleep diaries) allows for the

collection of data over long periods of time and at multiple time points. Other strategies can evaluate sleep disordered breathing, such as questionnaires for the woman or her bed partner asking about specific symptoms of sleep disordered breathing. Sleep disordered breathing can also be assessed objectively, but more invasively, by devices that measure ventilatory flow limitation during sleep.

To relate disturbed sleep to an exaggerated inflammatory response, ideally multiple blood samples would be obtained to determine diurnal rhythmicity of the inflammatory markers. Subject burden, particularly among pregnant women, is a concern and reduced sampling frequency may be a more realistic approach.

Our hypothesis suggests that the gestational period during which the sleep-inflammation relationship is evaluated is important. Among the few prior studies that have considered sleep as a risk factor in pregnancy outcomes, sleep was assessed after 22-weeks gestation (48,57, 58). Also as yet, no interaction between sleep disturbances and inflammatory activation on adverse outcomes has been tested. We propose that the interaction between disturbed sleep and inflammation needs to be examined before 20-weeks gestation during the stage of vascular remodeling of the vessels perfusing the placenta.

Ideally, we suggest examining this relationship in a cohort of at least 400 nulliparous women without a diagnosed psychiatric or sleep disorder. We suggest this sample size given a conservative prevalence rate of 15% in the development of either preeclampsia, IUGR, or preterm delivery. Collection of sleep data would be for three 2-week periods so that consistent sleep patterns and variability can be determined. At the conclusion of each 2-week period, blood samples, self-reported data on confounding variables, such as depression, stress, and health behaviors, and anthropomorphic data would be collected. Finally, pregnancy and delivery outcomes would be retrieved from patient medical records. The final sample of women used to test the relationship would be ascertained using a nested case-control design matching women with a complication to those with normal outcomes on various sociodemographic variables.

Summary and Conclusion

Disturbed sleep, although very common in pregnancy, has not been examined as a factor contributing to risk for adverse pregnancy outcomes. We propose a model linking sleep disturbances in early gestation to adverse pregnancy outcomes via increased inflammation. Specifically, we propose a feed forward loop between sleep disruption and inflammation during a critical period of early pregnancy when inflammation can act to inhibit the trophoblast invasion and associated remodeling of maternal blood vessels that perfuse the placenta. Assessing sleep disturbances as a risk factor for adverse outcomes could provide a target for intervention especially since sleep problems are amenable to treatment.

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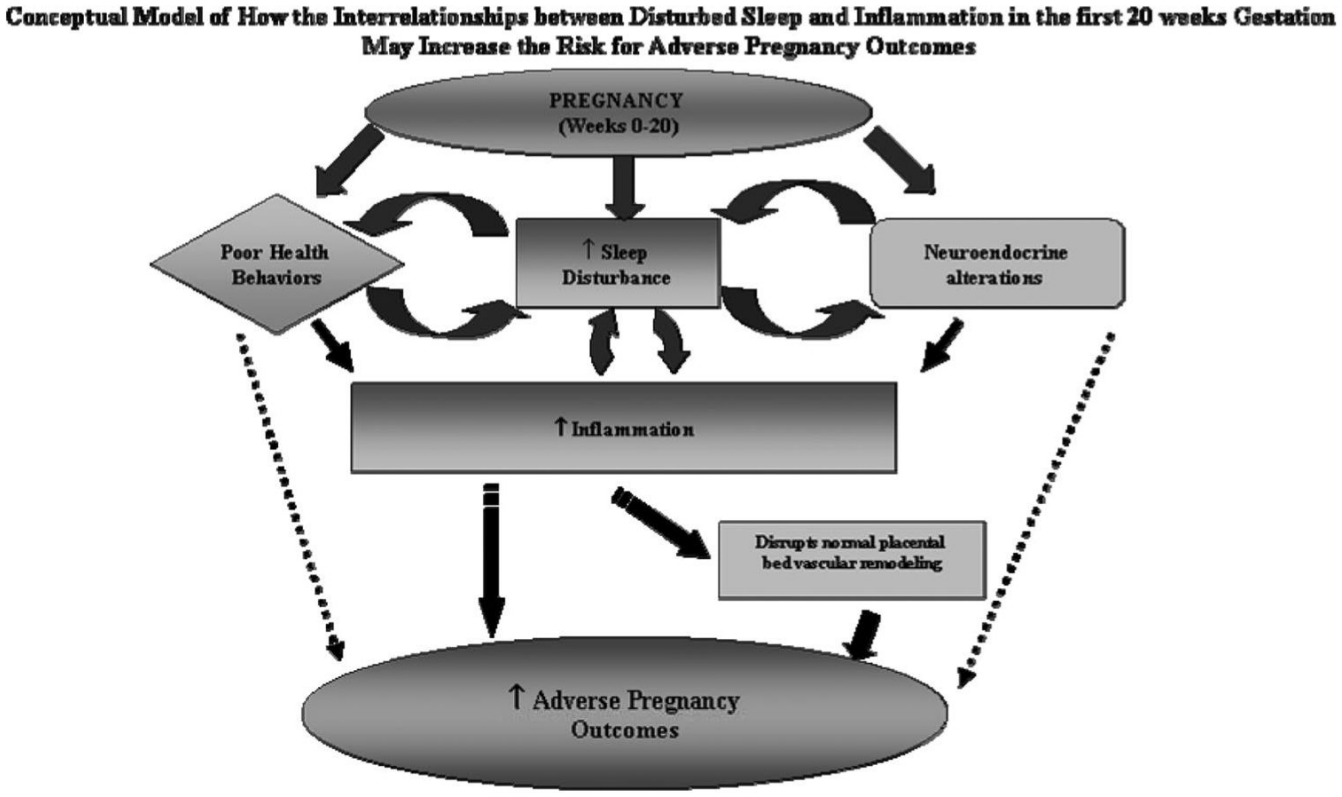

Fig. 1.

We propose that the major effects of disturbed sleep occur in the first 20 weeks of pregnancy. During this time many important physiological events take place. One of these, the profound remodeling of maternal vessels perfusing the placenta to increase placental blood flow, does not occur normally with preeclampsia, intrauterine growth restriction, and preterm birth. In vitro studies indicate that excessive inflammation inhibits trophoblastic invasion that is necessary to stimulate normal vascular remodeling (dashed solid arrows). Disturbed sleep outside of pregnancy is associated with increased inflammation. Persistent and chronic sleep disturbance early in gestation may contribute to increased inflammation. The augmented inflammatory response may be magnified via a feed forward process because animal evidence suggests that increased inflammatory cytokines disrupt sleep. Poor health behaviors, such as smoking, alcohol consumption and obesity, and neuroendocrine alterations (dotted arrows), may also contribute to sleep disruption and/or increased inflammation. Poor health behaviors are known independent moderators of sleep and inflammation. In this setting, also, there is the likelihood of a feed forward process since disturbed sleep can contribute to poor health behaviors. We posit that disturbed sleep acting through increased inflammation and poor health behaviors increase adverse pregnancy outcomes primarily by interfering with normal placental bed vascular remodeling.