Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome

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ABSTRACT

Short sleep duration, poor sleep quality, and insomnia frequently characterize sleep in pregnancy during all three trimesters. We aimed: (i) to review the clinical evidence of the association between conditions of sleep loss during pregnancy and adverse pregnancy outcomes; and (ii) to discuss the potential pathophysiological mechanisms that may be involved. A systematic search of cross-sectional, longitudinal studies using Medline, Embase, and PsychINFO, and MeSH headings and key words for conditions of sleep loss such as ‘insomnia’, ‘poor sleep quality’, ‘short sleep duration’, and ‘pregnancy outcome’ was made for papers published between January 1, 1960 and July 2013. Twenty studies met inclusion criteria for sleep loss and pregnancy outcome: seven studies on prenatal depression, three on gestational diabetes, three on hypertension, pre-eclampsia/eclampsia, six on length of labor/type of delivery, eight on preterm birth, and three on birth grow/birth weight. Two main results emerged: (i) conditions of chronic sleep loss are related to adverse pregnancy outcomes; and (ii) chronic sleep loss yields a stress-related hypothalamic–pituitary–adrenal axis and abnormal immune/inflammatory reaction, which, in turn, influences pregnancy outcome negatively. Chronic sleep loss frequently characterizes sleep throughout the course of pregnancy and may contribute to adverse pregnancy outcomes. Common pathophysiological mechanisms emerged as being related to stress system activation. We propose that in accordance to the allostatic load hypothesis, chronic sleep loss during pregnancy may also be regarded as both a result of stress and a physiological stressor per se, leading to stress ‘overload’. It may account for adverse pregnancy outcomes and somatic and mental disorders in pregnancy.

1. Introduction

Pregnancy is one of the most important periods in a woman’s life. Despite being a natural phenomenon, pregnancy is accompanied by major physiological, psychological and social changes [1,2]. Sleep disorders are among the most widespread major problems experienced in pregnancy [3–8]. In a recent poll by the National Sleep Foundation, more than 79% of women reported that their sleep had been altered during pregnancy compared to any other time [6].

Sleep restriction, short sleep duration, poor sleep quality, sleep-disordered breathing, and parasomnias have been described as widespread sleep problems during pregnancy [3,5,9–14]. The quantity and quality of sleep of pregnant women have been shown to be altered during pregnancy [3,4,13]. Previous studies have documented trimester-specific changes in sleep architecture [3–6,8–10]. Emerging evidence also indicates that sleep disturbances during pregnancy are associated with women’s poor health outcomes [15–17]. In addition, recent data indicate that sleep disturbances are associated with adverse pregnancy outcomes including intrauterine growth restriction and preterm birth [18–20].

As other sleep disorders in pregnancy such as sleep-disordered breathing, and parasomnias have already been covered in detail elsewhere [5,10,11,16,20,21], this study focuses on the available data concerning conditions of sleep loss such as short sleep duration, poor sleep quality, and insomnia with respect to the outcome.
of pregnancy. It has already been hypothesized that such sleep conditions cause serious consequences, which include depression, diabetes, and various cardiovascular dysfunctions [22–28]. The primary aim of this article is systematically to review the clinical evidence of the association of such sleep conditions and pregnancy outcome. The secondary aim is to discuss the potential pathophysiological mechanisms that may be involved in this interaction. A model of the role of chronic sleep loss in modulating stress response (allostasis) [29–31] and consequences on pregnancy outcome will be proposed.

2. Methods

2.1. Search strategy

A systematic search of Medline, Embase, and PsychINFO was performed. The initial search was conducted in November 2011 with a final search in July 2013. The search strategies used MeSH headings and keywords for ‘insomnia’, ‘poor sleep quality’, ‘short sleep duration’ or ‘sleep restriction’ and ‘pregnancy outcome’.

2.2. Inclusion and exclusion criteria

Studies were included if they: (1) involved human adult pregnant women aged >18 years; (2) were longitudinal observational, case–control, or cross-sectional studies, or meta-analyses; (3) analyzed prevalence and characteristics of disturbed sleep such as insomnia and poor sleep quality, short sleep duration and pregnancy outcome; and (4) were published between January 1, 1960 and July 2013. Studies were excluded if: (1) they did not control for confounding factors such as other sleep disorders or other comorbid disorders (i.e. other sleep disorders, sleep-disordered breathing, restless leg syndrome, depression); (2) they did not analyze data stratified by race and age; (3) they were not available in full text; or (4) they were not available in English.

3. Results

3.1. Selection of articles

Forty-one articles were retrieved, 21 of which were excluded after detailed review as they did not meet the inclusion criteria. Twenty papers were included and their data retrieved (Fig. 1).

Three studies focused on gestational diabetes (Table 2), three on hypertension, pre-eclampsia/eclampsia (Table 3), five on the length of labor/type of delivery (Table 4), five on preterm birth (Table 5) and three on fetal growth (Table 6).

3.2. Chronic sleep loss during pregnancy and adverse pregnancy outcome: clinical evidence

In the USA, more than one million pregnancies each year result in adverse outcomes that increase maternal and infant morbidity [31–36]. Even if only few investigations have focused on this issue, emerging evidence indicates that conditions of sleep loss may have a role in adverse outcomes of pregnancy. Changes in sleep pattern during pregnancy have been widely described in all three trimesters of pregnancy since 1968 [for overviews see 3–10]. Conditions of sleep loss such as short sleep duration [37–39], poor sleep quality [4,13,38–51], poor sleep efficiency with an increase in time spent awake during the night [13,42,46], and insomnia [38,52] characterize the sleep of pregnant women during the period of pregnancy. The most frequent adverse outcomes include conditions related to mother morbidity such as prenatal depression, gestational diabetes, and pre-eclampsia. In addition, abnormal duration of labor, type of delivery, intrauterine growth restriction, and preterm birth have been considered adverse pregnancy outcomes.

Prenatal depression prevalence estimates range from 10% to 25% [53–57], and it is a significant risk factor for miscarriage, preterm birth, and low birth weight[53,58–62]. Sleep disturbances are more frequent in depressed than in non-depressed women during pregnancy, especially in early gestation [57,63–65]. Although few studies have investigated the role of sleep loss in the development of depressive symptoms during pregnancy [51,66,67] (Table 1), they show that it may constitute a risk for developing...
Table 2
Sleep loss and gestational diabetes.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Study population</th>
<th>Week of gestation</th>
<th>Sleep evaluation</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qiu et al. [70]</td>
<td>Cross-sectional</td>
<td>1290 pregnant women</td>
<td>14th</td>
<td>Sleep questionnaires</td>
<td>GD risk was increased among women sleeping &lt;4 h vs 9 h/night. RR = 5.6 (1.31–23.69)</td>
</tr>
<tr>
<td>Reutrakul et al. [71]</td>
<td>Cross-sectional</td>
<td>169 pregnant women</td>
<td>2nd trimester</td>
<td>Sleep questionnaires</td>
<td>SD inversely correlated with glucose values (r = −0.21, P &lt; 0.01) Each hour of reduced sleep time was associated with a 4% increase in glucose levels SD &lt;7 h/night increases risk of developing GD</td>
</tr>
</tbody>
</table>

GD, gestational diabetes; RR, relative risk; SD, sleep duration.

Table 3
Sleep loss and hypertension, pre-eclampsia.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Study population</th>
<th>Week of gestation</th>
<th>Sleep evaluation</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekholm et al. [74]</td>
<td>Cross-sectional</td>
<td>9 women with pre-eclampsia</td>
<td>3rd trimester</td>
<td>Sleep questionnaires</td>
<td>Sleep is impaired in pre-eclamptic subjects</td>
</tr>
<tr>
<td>Edwards et al. [75]</td>
<td>Cross-sectional</td>
<td>25 pre-eclamptic women</td>
<td>3rd trimester</td>
<td>Polysomnography</td>
<td>Pre-eclamptic subjects had markedly altered sleep architecture, with a markedly increased percentage of NREM SWS Longer latency to REM sleep and reduced time spent in REM compared to normal pregnancy</td>
</tr>
<tr>
<td>Williams et al. [76]</td>
<td>Prospective cohort study</td>
<td>1272 pregnant women</td>
<td>3rd trimester</td>
<td>Sleep questionnaires</td>
<td>Sleep duration &lt;6 h/night in early pregnancy was associated with increased mean 3rd trimester blood pressure</td>
</tr>
</tbody>
</table>

REM, rapid eye movement sleep; NREM, non-REM sleep; SWS, slow wave sleep.

Table 4
Sleep loss, length of labor and type of delivery.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Study population</th>
<th>Week of gestation</th>
<th>Sleep evaluation</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al. [77]</td>
<td>Cross-sectional</td>
<td>99 multiparous women</td>
<td>3rd trimester</td>
<td>Sleep questionnaires</td>
<td>No relationship between poor sleep quality and length of labor type of delivery SD &lt;6 h; long labor increased risk of cesarean deliveries by 4.5-fold</td>
</tr>
<tr>
<td>Lee et al. [78]</td>
<td>Cross-sectional</td>
<td>131 pregnant women</td>
<td>3rd trimester</td>
<td>Sleep questionnaires</td>
<td>Poor sleep quality related to long labor cesarean deliveries</td>
</tr>
<tr>
<td>Naghi et al. [79]</td>
<td>Cross-sectional</td>
<td>88 pregnant women</td>
<td>3rd trimester</td>
<td>Sleep questionnaires</td>
<td>Sleep disorders are risk for emergency cesarean; OR, 1.57 (95% CI, 1.14–2.16)</td>
</tr>
<tr>
<td>Wangel et al. [80]</td>
<td>Population-based cohort study</td>
<td>10,662 pregnant women</td>
<td>3rd trimester</td>
<td>Sleep questionnaires</td>
<td>Poor sleep quality/short SD related to long labor cesarean delivery</td>
</tr>
<tr>
<td>Zafarghandi et al. [81]</td>
<td>Cross-sectional</td>
<td>457 pregnant women</td>
<td>3rd trimester</td>
<td>Sleep questionnaires</td>
<td>Poor sleep may contribute to risk for preterm birth</td>
</tr>
</tbody>
</table>

PSQI, Pittsburgh Sleep Quality Index; SD, sleep duration; OR, odds ratio; CI, confidence interval.

Table 5
Sleep loss and preterm birth.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Study population</th>
<th>Week of gestation</th>
<th>Sleep evaluation</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strange et al. [89]</td>
<td>Cross-sectional</td>
<td>220 pregnant women</td>
<td>2nd trimester</td>
<td>Sleep questionnaires</td>
<td>Disturbed sleep in pregnancy may be associated with preterm birth SD &lt;8 h per night is a risk factor for 1st and 2nd trimester miscarriage. OR, 3.80 (95% CI, 1.01–14.3)</td>
</tr>
<tr>
<td>Samaraweera et al. [90]</td>
<td>Case–control</td>
<td>504 controls</td>
<td>1st, 2nd trimesters</td>
<td>Sleep questionnaires</td>
<td>Poor sleep. Risk of preterm birth: 1st trimester OR, 1.25 (95% CI, 1.04–1.50) 3rd trimester OR, 1.18 (95% CI, 0.98–1.42) SD &lt;5 h per night is a risk for preterm birth OR, 2.4 (95% CI, 1.0–6.4)</td>
</tr>
<tr>
<td>Okun et al. [91]</td>
<td>Observational</td>
<td>166 pregnant women</td>
<td>1st, 2nd, 3rd trimesters</td>
<td>PSQI</td>
<td>Poor sleep may contribute to risk for preterm birth</td>
</tr>
<tr>
<td>Micheli et al. [92]</td>
<td>Prospective mother–child cohort study</td>
<td>10,662 nulliparous women</td>
<td>3rd trimester</td>
<td>Sleep questionnaires</td>
<td>Poor sleep may contribute to risk for preterm birth</td>
</tr>
<tr>
<td>Okun et al. [93]</td>
<td>Cross-sectional</td>
<td>217 pregnant women</td>
<td>20–30</td>
<td>Sleep questionnaires</td>
<td>Poor sleep may contribute to risk for preterm birth</td>
</tr>
</tbody>
</table>

PSQI, Pittsburgh Sleep Quality Index; EES, Epworth Sleepiness Scale; PSS, Perceived Stress Scale; SD, sleep duration; OR, odds ratio; CI, confidence interval.
emerging as a significant factor for developing it [87,88]. Studies evaluating the relationship between sleep loss and preterm birth [89–93] (Table 5) show that both poor sleep quality and short sleep duration may contribute to preterm birth. In addition, some research in the available literature has studied the relationship between conditions of sleep loss during pregnancy and birth growth [81,94,95] (Table 6). From these data, we may hypothesize that both mothers’ sleep duration and quality may negatively affect neonates’ Apgar score, birth weight, or gestational age. Low birth weight is a marker of suboptimal prenatal environment, which is known to exert lifelong effects on organ structure and organization of physiologic systems [96,97].

3.3. Chronic sleep loss during pregnancy and adverse pregnancy outcome: psychobiological hypotheses

Common pathophysiological mechanisms in the relationship between sleep loss and negative pregnancy outcome emerged as being related to stress system activation. Whereas previous research has shown that sleep quality and insomnia are antecedent to depressive symptoms [28,98], some authors argued that the relationship between sleep disorders and depression during pregnancy may be more complex [64–67]. Based on animal and human data, it was previously thought that an alteration of the hypothalamic–pituitary–adrenal (HPA) axis may be a potential underlying mechanism for the relationship between sleep problems and pre-natal depression [99,100]. Other authors have sustained the hypothesis that depression and disturbed sleep may be associated with increased proinflammatory system activity [101,102], and that this may be considered also during pregnancy [65,91]. Other authors have hypothesized that these mechanisms, i.e. HPA axis and proinflammatory system alterations, are also involved in the association between sleep loss and both the development of diabetes [17,103–107] and hypertension [18,27] during pregnancy. In addition, a sleep disorder-related alteration in systematic inflammation has been hypothesized as the causal mechanism in the pathogenesis of adverse pregnancy outcomes, including length of labor [18,87], type of delivery [18,87], preterm birth [18,87], and intrauterine fetal growth [18].

3.4. Chronic sleep loss during pregnancy as a determinant of stress: a proposed model

We propose that conditions of chronic sleep loss that are experienced during pregnancy may be considered both a result of stress and as a stressor per se according to the allostatic load hypothesis (Fig. 2). Conditions of stress during pregnancy may result in the activation of allostatosis, and, if the allostatic reaction occurs in a woman with both predisposing factors for insomnia and some neuroendocrine alterations, it may result in chronic sleep loss. The latter is typically associated with the chronic activation of both the inflammation and HPA axis. Given the bidirectional relationship between sleep and stress system, conditions of sleep loss may lead

antenatal depression. Gestational diabetes is also a frequently occurring medical condition during pregnancy [68] and is associated with an increased risk of complications for both mother and child [68,69]. Although only few studies have investigated the role of disturbed sleep due to glucose tolerance in pregnancy, they have found that short sleep duration may increase the risk of gestational diabetes [70,71] (Table 2).

Hypertension and pre-eclampsia also have a variable incidence ranging from 5% to 10% of pregnancies [72,73]. Pre-eclampsia and eclampsia are major causes of maternal and perinatal morbidity and mortality [72,73]. Although few studies have investigated the relationship between both sleep duration and quality with trimester-specific blood pressures and hypertensive disorders in pregnancy [74–76] (Table 3), they show that both short sleep duration and poor sleep quality may have a role in developing hypertensive disorders during pregnancy. Few studies have evaluated the relationship between sleep loss, insomnia, and length of labor [77–81] (Table 4). According to these findings, both short sleep duration and poor sleep quality may increase the risk of both labor duration and cesarean delivery.

Preterm birth is also a major health concern, accounting for 75% of perinatal mortality and more than half of long-term morbidity [82–85]. Preterm birth is hypothesized to be a multifactorially caused phenomenon [86]; indeed maternal sleep disruption is
to a vicious circle by auto-amplifying prolonged/exaggerated inflammatory responses which, in turn, may generate a state of allostatic load. We propose that in the same manner, the latter condition may account for all the different conditions of pregnancy adverse outcome related to sleep loss.

Pregnancy is a time of increased stress [108–111]. It has been hypothesized that maternal stress represents a significant cause of maternal and perinatal morbidity and mortality [31,112–115]. Psychosocial factors such as socio-economic status, work status, marital status, level of education, access to prenatal care, substance abuse, ethnicity, cultural background, and quality of relationships with partners and parents have been identified as determinants of stress during pregnancy [31].

This conceptualization of insomnia suggests the importance of the ‘3P’ model (predisposing, precipitating, and perpetuating factors) [116]. Predisposing factors are present before insomnia is manifested, and it is hypothesized that they interact with precipitating factors, i.e. stressful life events over time, to increase the risk of insomnia. Mounting evidence confirms that higher levels of stress are indeed associated with more disrupted sleep [116–122], both of which are associated with immune and neuroendocrine dysregulation and increased morbidity [22,123,124].

Within this context, sleep disorders during pregnancy may be considered a stress response to an increased level of stress in pregnancy (Fig. 2). Conditions of stress during pregnancy may result in the activation of the stress system and the allostatic. The stress system is essentially an alarm system that is activated each time a discrepancy between expectations and reality is generated. The allostatic is the adaptive response of the organism to a stressful condition, i.e. environmental or internal stimuli. It is produced by the joint activities of the central and autonomic nervous systems, the HPA axis, and the immune system [22,29]. However, if the stressful condition becomes chronic, it may produce the so-called ‘allostatic state’, characterized by an increased activity of the mediators on their target cells that leads to receptor desensitization and tissue damage, thus reflecting the situation known as ‘allostatic overload’ [22,123,124]. This may cause serious consequences, which include insomnia, depression, and various cardiovascular dysfunctions, which, in turn, could sustain the above-mentioned negative effects of sleep loss on different aspects of pregnancy (Fig. 2).

Sleep loss, due to environmental, genetic, biological, and psychosocial factors reciprocally interacting, may be considered a typical condition of allostatic load [22,29], which promotes severe physiologic, neurologic, and behavioral consequences [for review, see 22] involving increased arterial blood pressure, reduced parasympathetic tone, increased proinflammatory cytokines, and increased oxidation [22,29]. Within this framework, conditions of sleep loss have therefore been considered a neurologic and physiologic stressor per se [22,29]. In animal models, and in men and non-pregnant women, sleep loss has been associated with the development of cardiovascular disease [24,26], hypertension [27], insulin resistance and Type 2 diabetes [103–107], as well as with an increased risk for depression [28,98]. All these negative changes induced by sleep loss could sustain some negative outcome for pregnancy such as pre-eclampsia and gestational diabetes, through an allostatic ‘overload’ mechanism [23–27]. Sleep loss may affect nervous structures that play a major role in producing and maintaining allostatic load: amygdala and hippocampus interpret what is stressful and regulate responses [125,126]. It has been hypothesized that the hippocampus–amygdala alteration may represent one of the possible pathophysiological mechanisms of depression [123].

Consequences of disrupted sleep include a reduction in neurogenesis which, in turn, endangers hippocampal integrity and thereby, via HPA axis dysregulation, contributes to the pathophysiology of depression [22,29,123,124].

Within this hypothesis, perinatal depression could also be an expected outcome of sleep loss as allostatic factor. Thus, a sustained overactivation of the stress system could be a possible mechanism underlying the relationship between sleep deprivation, short sleep duration, insomnia, and negative pregnancy outcome. Because sleep plays key homeostatic functions counterbalancing the negative effects of stress, its alterations – including sleep loss and disruption – yield an overactivation of the HPA axis, of the sympathetic nervous system, and of the proinflammatory system [22].

Maternal sleep disruption could then act as a stressor per se activating the stress system. Hence, according to the allostatic load hypothesis, we propose that conditions of chronic sleep loss may also be considered as one of the psychological/physiological stressors/determinants of stress during pregnancy. It may lead to a vicious circle, inducing the occurrence of the allostatic load (Fig. 2) and thereby contribute to adverse pregnancy outcomes. Thus, a sustained overactivation of the stress system may be a mechanism underlying the relationship between sleep deprivation, short sleep duration, insomnia, and negative pregnancy outcome. Because sleep plays key homeostatic functions in counterbalancing the negative effects of stress, its alterations, including sleep loss and disruption, yield an overactivation of the HPA axis, of the sympathetic nervous system, and of the proinflammatory system [22].

In summary, we propose that conditions of chronic sleep loss experienced during pregnancy may be considered both a result of stress and a stressor per se (Fig. 2). This may account in the same frame for conditions of adverse pregnancy outcomes related to sleep loss.

4. Conclusions

Conditions of sleep loss such as short sleep duration, poor sleep quality, and increase in time spent awake during the night, frequently characterize the sleep of pregnant women during all three trimesters. Emerging evidence indicates that conditions of sleep loss in pregnancy are associated with adverse pregnancy outcome such as prenatal depression, gestational diabetes, pre-eclampsia, abnormal length of labor, cesarean delivery, alteration in fetal growth, and preterm birth. Indeed, the empirical evidence is still scarce and further rigorous studies are needed to reach definite conclusions. Potential pathophysiologic mechanisms, which various authors have described as being involved in the relationship with adverse pregnancy outcomes, include both the HPA axis and the proinflammatory system alteration. In accordance with the allostatic load conceptualization, we propose that conditions of chronic sleep loss in pregnancy may be regarded as a result of stress and as a physiological stressor per se, leading to stress ‘overload’. It may impair the HPA axis and the proinflammatory system, leading to such important negative pregnancy outcomes. This model may therefore account for all the different conditions of adverse pregnancy outcomes related to sleep loss. Thus, we propose that conditions of sleep loss should be included among the determinants of stress already identified during pregnancy (Fig. 2).

Within this framework, sleep disorders during pregnancy need to be systematically assessed and treated. Prenatal screening and intervention for relevant biopsychosocial risk factors may be useful in preventing stress-related perinatal complications and should include sleep disorders. Guidelines for pharmacological and cognitive behavioral treatments of sleep disorder need to be developed for all the sleep disorders that could contribute to conditions of sleep loss during pregnancy.
Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.02.013.

References


