Sleep Disruption and Gestational Diabetes

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Abstract: Numerous studies in non-pregnant populations have demonstrated associations between sleep disturbances and a broad range of medical conditions including type 2 diabetes. Data exploring the relationship between sleep and adverse pregnancy outcomes are now emerging. This review will summarize the literature regarding sleep duration and sleep disordered breathing during pregnancy and its potential impact on maternal glucose metabolism.

Keywords: Sleep, short sleep duration, sleep disordered breathing, pregnancy, gestational diabetes.

INTRODUCTION

Overall, women have a greater risk for sleep disorders than men, and complaints of sleep disturbance are more prevalent among women than men across the life span. Pregnancy has been associated with several alterations in sleep and a high incidence of sleep disturbances [1]. Many of the hormonal and physiological changes that occur during pregnancy have been linked to alterations in sleep. Sleep, like nutrition and exercise is an essential component of a healthy lifestyle. Numerous studies in non-pregnant populations have demonstrated associations between sleep disturbances and a broad range of medical conditions including type 2 diabetes. Data exploring the relationship between sleep and adverse pregnancy outcomes are now emerging.

The possibility that sleep abnormalities are associated with pregnancy complications is biologically plausible. First, data suggests that sleep disorders are prevalent in early pregnancy, and pregnancy itself has been linked to alterations in sleep [1-4]. Second, disturbed sleep is associated with autonomic dysfunction, inflammation, oxidative stress, metabolic dysregulation, endothelial dysfunction and inflammation [5-11]. These same pathophysiologic mechanisms have been implicated in the pathogenesis of adverse pregnancy outcomes, including gestational diabetes [12-14]. This review will summarize the literature regarding sleep disruption during pregnancy and its potential impact on maternal glucose metabolism.

SLEEP AND GLUCOSE METABOLISM IN NON-PREGNANT POPULATIONS

Studies of experimental sleep deprivation and sleep fragmentation have linked these sleep alterations with impairments in metabolic function. Spiegel et al compared measurements of carbohydrate metabolism in healthy subjects who were restricted to 4 hours in bed per night with measurements taken at the end of a sleep-recovery period. They found that glucose clearance was 40% slower in the sleep debt condition than in the sleep recovery condition [15]. In a recent study, using an experimental model of sleep fragmentation, levels of insulin sensitivity and glucose effectiveness were shown to decrease in the sleep fragmented state [16]. Similarly, epidemiologic studies have consistently demonstrated an association between shortened sleep duration and metabolic disease [17-23]. Reports from several large cohort studies suggest a relationship between sleep duration (self-reported and objectively assessed) and impaired glucose tolerance and type 2 diabetes. Data from the Sleep Heart Health Study suggest that compared to individuals sleeping 7-8 hours/night, individuals sleeping ≤ 5 hours/night or less than 6 hours/night have an adjusted odds ratio for diabetes of 2.51 and 1.66, respectively [20]. Although the greater part of the evidence points to an association between short sleep and diabetes, a few reports have also described an association between long sleep (≥ 9 hours) and diabetes risk [24, 25].

Sleep disordered breathing (SDB) has also been associated with metabolic dysfunction. SDB refers to a group of disorders characterized by abnormal respiratory patterns (e.g., apneas, hypopneas) or abnormal gas exchange (e.g., intermittent hypoxia) during sleep [26, 27]. SDB is clinically characterized by the presence of respiratory disturbances observed during a sleep study. It is most commonly diagnosed using the Apnea Hypopnea Index (AHI), a sum of the number of apneas and hypopneas that occur per hour of sleep. In adults an AHI of 0-4.9 is considered normal, with an AHI of ≥ 5 defining SDB. An AHI of 5-15 is typically considered mild SDB, 15-30 moderate SDB, and > 30 as severe SDB [26, 27]. The most common type of SDB, especially among young obese women, is obstructive sleep apnea (OSA) which is characterized by repetitive episodes of nocturnal upper airway obstruction. Mouse models of intermittent hypoxia have been developed that mimic the oxygen profile in human OSA. Data from such models have demonstrated that intermittent hypoxia can cause acute insulin resistance in...
otherwise lean, healthy mice and that it exacerbates the metabolic effects of diet-induced obesity [28, 29]. Epidemiologic data supports an association between sleep apnea and type 2 diabetes [30-33]. Cross-sectional data from the Wisconsin Sleep Cohort Study demonstrated that self-reported diabetes was three to four times more prevalent in subjects with an AHI ≥15 than in those with an AHI < 5 [32]. One large longitudinal investigation demonstrated that moderate-severe sleep apnea was an independent risk factor for incident diabetes in an Australian population-based cohort [30]. Recently, Aronsohn and colleagues looked at the impact of untreated OSA on glucose control in type 2 diabetes and found that increasing severity of OSA is associated with poorer glucose control, independent of adiposity and other confounders, with effect sizes comparable to those of widely used hypoglycemic drugs [34].

GESTATIONAL DIABETES

Maternal metabolic physiology during pregnancy, especially in the third trimester, is primarily influenced by placental hormones. These hormones affect both glucose and lipid metabolism with the goal of providing the growing fetus with an ample supply of nutrients at all times. Carbohydrate metabolism during pregnancy is directed toward supplying glucose and amino acids to the fetus, while providing extra free fatty acids, ketones, and glycerol as sources of maternal fuel [35, 36]. Physiologic changes during normal pregnancy include: hyperplasia of the insulin-secreting pancreatic beta cells, increased insulin secretion, and progressive insulin resistance. These changes result in transient maternal hyperglycemia after meals due to increasing insulin resistance and transient hypoglycemia between meals and at night due to the continuous fetal uptake. The insulin resistant state of pregnancy exists to support the demands of the growing fetus however, it can become pathological when a woman’s pancreatic function is not sufficient to overcome this new metabolic state [37].

Gestational diabetes mellitus (GDM), defined as glucose intolerance that begins or is first recognized during pregnancy, affects 1-14% of all pregnancies [38]. Almost uniformly, GDM arises from significant maternal insulin resistance. Screening for GDM is usually done by first performing a 50 gram, 1-hour oral glucose tolerance test (OGTT). If this 1-hour OGTT test is abnormal (≥ 130 or 140 mg/dL cut-off values are typically used) then a fasting 3-hour, 100 gram OGTT test is used to diagnose GDM using either the National Diabetes Data Group or Carpenter-Coustan diagnostic thresholds [38]. Gestational diabetes has been associated with an increased risk of preeclampsia, fetal macrosomia, birth trauma, and neonatal metabolic complications that often require admission to the neonatal intensive care unit (hypoglycemia, hyperbilirubinemia, hypocalcemia). There are also potential long-term consequences to infants born to mothers with GDM, such as an increased risk of developing obesity and diabetes during childhood [39]. Traditionally recognized risk factors for gestational diabetes include: advanced maternal age, obesity, family history of type 2 diabetes, membership in a racial-ethnic group with a high background rate of type 2 diabetes (e.g., Hispanic-American, African-American, Native American), and a personal history of chronic hypertension. Recently, given the emerging evidence regarding sleep, sleep disruption and metabolic dysregulation, interest has emerged in evaluating whether poor sleep during pregnancy may impact maternal glucose metabolism.

SLEEP DURATION AND GESTATIONAL DIABETES

Several investigators have now reported a positive association between self-reported short sleep duration and gestational diabetes (Table 1) [40-42]. The data suggests that women with self-reported shortened sleep durations during pregnancy have a 2-10 times greater risk of GDM. Facco et al and Qiu et al found that the risk of GDM remained even after controlling various confounding factors including body mass index (BMI) [40, 41]. In addition, Qiu et al described a curvilinear relationship between maternal habitual nightly sleep duration in early pregnancy and maternal mean 1-hour OGTT values. Mean glucose concentrations were 16.3 mg/dL higher in women who reported sleeping ≤ 4 hours per night (95% CI 1.1, 31.6), 2.3 mg/dL higher (95% CI -1.8, 6.3) for women reporting sleep durations of 5-8 hours/night and 6.3 mg/dL higher (95% CI -0.5, 13.2) for women who reported sleeping ≥ 10 hours/night, compared with those who reported sleeping on average 9 hours/night. The obvious

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population Description</th>
<th>Definition of Short Sleep Duration</th>
<th>Odds Ratio or Relative Risk (95% Confidence Intervals)</th>
<th>Adjusted Odds Ratio or Relative Risk (95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facco et al., 2010</td>
<td>189</td>
<td>Healthy nulliparous women with singleton gestations</td>
<td>&lt; 7 hours/night</td>
<td>10.6 (1.3, 85.5)</td>
<td>11.7 (1.2, 114.5)*</td>
</tr>
<tr>
<td>Qiu et al., 2010</td>
<td>1290</td>
<td>Pregnant women without pre-gestational diabetes</td>
<td>≤ 4 hours/night</td>
<td>5.56 (1.3, 23.7)</td>
<td>4.18 (0.94, 18.60)**</td>
</tr>
<tr>
<td>Reutrakul, et al., 2011</td>
<td>169</td>
<td>Healthy pregnant women</td>
<td>&lt; 7 hours/night</td>
<td>2.4 (1.0, 5.9)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*adjusted for age, race/ethnicity, BMI and snoring
**adjusted for age, race/ethnicity, and BMI
N/A= not reported
Sleep Disruption and Gestational Diabetes

Table 2. Sleep Disordered Breathing Symptoms and Gestational Diabetes Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population Description</th>
<th>SDB Symptoms</th>
<th>Odds Ratio or Relative Risk (95% Confidence Intervals or p Value)</th>
<th>Adjusted Odds Ratio or Relative Risk (95% Confidence Intervals or p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facco et al., 2010</td>
<td>189</td>
<td>Healthy nulliparous women with singleton gestations</td>
<td>Frequent snoring ≥ 3 nights/week</td>
<td>4.9 (1.3, 18.1)</td>
<td>6.9 (1.4, 33.9)*</td>
</tr>
<tr>
<td>Qiu et al., 2010</td>
<td>1,290</td>
<td>Pregnant women without pre-gestational diabetes</td>
<td>Snoring most or all of the time</td>
<td>1.86 (0.88, 3.94)</td>
<td>1.54 (0.71, 3.35)**</td>
</tr>
<tr>
<td>Bourjeily et al., 2010</td>
<td>1000</td>
<td>Women 24-48 hours postpartum</td>
<td>Frequent snoring ≥ 3 night/week, Frequent gasping/snoring ≥ 3 night/week, Frequent choking/stopping breathing ≥ 3 night/week</td>
<td>2.7 (1.7, 4.3) 3.3 (1.9, 5.6) 2.6 (1.3, 5.5)</td>
<td>2.1 (1.3, 3.4)† 2.4 (1.4, 4.3)† 2.0 (0.9, 4.3)†</td>
</tr>
<tr>
<td>Olivarez et al., 2011</td>
<td>220</td>
<td>Healthy nulliparous women with singleton gestations</td>
<td>Positive Berlin and/or Epworth Sleepiness Scale Score (≥10)</td>
<td>0.99 (0.98)</td>
<td>N/A</td>
</tr>
<tr>
<td>Reutrakul et al., 2011</td>
<td>169</td>
<td>Healthy pregnant women</td>
<td>Frequent snoring ≥ 3 nights/week</td>
<td>3.4 (1.3, 8.8)</td>
<td>N/A</td>
</tr>
<tr>
<td>O’Brien et al., 2012</td>
<td>1719</td>
<td>Pregnant women with singleton gestations ≥ 28 weeks</td>
<td>Frequent snoring ≥ 3 nights/week, Chronic (snoring both before and during pregnancy), Pregnancy-onset snoring</td>
<td>1.29(0.96, 1.74) 1.67(1.10, 2.52)</td>
<td>0.91(0.55-1.49)† 1.0 (0.72, 1.39)†</td>
</tr>
</tbody>
</table>

*adjusted for age, race/ethnicity, BMI and sleep duration
**adjusted for age, race/ethnicity, and BMI
†adjusted for age, BMI, smoking and multifetal gestation
‡adjusted for age, race/ethnicity, BMI, smoking, parity and education level
N/A= not reported

Limitation of the currently available data is the use of self-reported sleep duration as the exposure variable. Self-reports of sleep duration have a reasonable although not exact correlation with objective measures (e.g., actigraphy) of sleep, with self-report generally overestimating objectively measured sleep [43]. Prospective investigations using objective sleep measures are needed to confirm these initial findings regarding the impact of sleep duration on glucose metabolism in pregnancy.

While the majority of the literature has focused on short sleep in pregnancy, there are some data suggesting that long sleep duration can negatively impact glucose metabolism in pregnancy. Qui et al described a curvilinear relationship between habitual nightly sleep duration in early pregnancy and maternal mean-1-hour plasma glucose after a 50 gram oral glucose challenge [41]. Compared to women who reported sleeping 9 hours per night on average, mean glucose concentrations were 16.3 mg/dl (p=.04) higher for women sleep ≤ 4 hours per night and 6.3 mg/dl (p=.07) higher for women sleeping ≥ 10 hours per night.

**SLEEP DISORDERED BREATHING AND GESTATIONAL DIABETES**

Several reports have now been published regarding the relationship between sleep-disordered breathing symptoms and gestational diabetes (Table 2) [40-42, 44-46]. Several studies have reported positive associations between frequent snoring, the most common symptom of SDB, and GDM, even after controlling confounding factors, including BMI. Bourjeily et al looked at several SDB symptoms, snoring, gasping/snorting and choking/stopping breathing, and reported that when all three symptoms were combined the association with GDM was stronger than for any individual symptom (adjusted odds ratio 4.0, 95% CI 1.4, 11.1) [44]. In contrast, Olivarez et al did not find a positive association or trend between SDB and GDM, even after controlling confounding factors, including BMI [45]. However, these authors used the Berlin Questionnaire and the Epworth Sleepiness Scale as their measure of SDB. The Berlin Questionnaire and Epworth Sleepiness Scale were designed for and validated in non-pregnant, predominantly male, middle-aged and elderly populations [47, 48]. Indeed, there is some data suggesting that these tools are not as accurate in pregnancy [49, 50].

Again, as with the sleep duration, data using objective measures of SDB are limited. While investigators have demonstrated that self-reported habitual snoring correlates with objective findings on polysomnogram (PSG) [51], studies utilizing objective SDB measures are needed to accurately define the relationship between SDB and adverse pregnancy outcomes. Data regarding the effect of objectively assessed SDB on glucose metabolism in pregnancy are limited, and primarily retrospective [52, 53]. In one
conflicts of interest.

...that are specifically targeted towards pregnant women. Can lead to public health recommendations regarding sleep disturbances, and do not routinely refer or treat women who have sleep-related complaints. Additionally, this research can lead to public health recommendations regarding sleep that are specifically targeted towards pregnant women.

SUMMARY

In summary, several cohort and cross-sectional studies have examined the relationship between self-reported sleep duration and SDB symptoms and pregnancy outcomes and have found associations between shortened sleep duration, snoring and glucose metabolism in pregnancy. However, interpretation of this data is limited given the paucity of objective sleep measures, and inconsistent adjustment for confounding factors such as obesity. Further research, using objective measures of sleep duration and SDB, is needed to better understand how these sleep disturbances modify a woman’s risk of adverse pregnancy outcomes. Unlike many other adverse pregnancy outcome risk factors, sleep is potentially modifiable. If future research demonstrates that certain sleep disturbances increase the risk of adverse pregnancy outcomes such as gestational diabetes, the next step would be to design studies to determine whether screening for and treating these disorders can improve maternal and fetal outcomes. This research could lead to significant changes in clinical practice because obstetric care providers currently are not trained to screen for sleep disturbances, and do not routinely refer or treat women who have sleep-related complaints. Additionally, this research can lead to public health recommendations regarding sleep that are specifically targeted towards pregnant women.

CONFLICT OF INTEREST

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

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Declared none.

REFERENCES


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