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Sleep duration and disorders in pregnancy: implications for glucose metabolism and pregnancy outcomes

M O'Keeffe[1,2] and **M-P St-Onge**[1,2]

[1]New York Obesity Nutrition Research Center, St Luke's/Roosevelt Hospital, New York, NY, USA

[2]Institute of Human Nutrition, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Abstract

Humans have an innate requirement for sleep that is intrinsically governed by circadian and endocrine systems. More recently, reduced sleep duration has gained significant attention for its possible contribution to metabolic dysfunction. Significant evidence suggests that reduced sleep duration may elevate the risk for impaired glucose functioning, insulin resistance and type 2 diabetes. However, to date, few studies have determined the implications of reduced sleep duration with regard to glucose control during pregnancy. With the high prevalence of overweight and obesity in women of reproductive age, the occurrence of gestational diabetes mellitus (GDM) is increasing. GDM results in elevated risk of maternal and fetal complications, as well as increased risk of type 2 diabetes postpartum. Infants born to women with GDM also carry a life-long risk of obesity and type 2 diabetes. The impact of reduced sleep on glucose management during pregnancy has not yet been fully assessed and a paucity of literature currently exits. Herein, we review the association between reduced sleep and impaired carbohydrate metabolism and propose how reduced sleep during pregnancy may result in further dysfunction of the carbohydrate axis. A particular focus will be given to sleep-disordered breathing, as well as GDM-complicated pregnancies. Putative mechanisms of action by which reduced sleep may adversely affect maternal and infant outcomes are also discussed. Finally, we will outline important research questions that need to be addressed.

Keywords

sleep; sleep-disordered breathing; pregnancy; gestational diabetes

INTRODUCTION

Gestational diabetes mellitus (GDM) generally develops at approximately 24–28 weeks of gestation[1] and is classified as glucose intolerance during pregnancy. This condition is the most common pregnancy-associated disorder and affects 7% of all the US pregnancies.[1] However, variation in prevalence among ethnic and racial groups are well documented, with a greater prevalence reported among native American, Asian, Hispanic and African-American populations compared with non-Hispanic Whites.[1] During the past two decades, the prevalence of GDM has increased by 10–100% depending on race and ethnicity.[2,3] Risk

Correspondence: Dr M-P St-Onge, New York Obesity Nutrition Research Center, St Luke's/Roosevelt Hospital, 1090 Amsterdam Avenue, Suite 14D, New York, NY 10025, USA. ms2554@columbia.edu.

CONFLICT OF INTEREST

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factors for the condition include obesity, advanced maternal age and a family history of diabetes, but Asian populations are thought to possess a specific genetic predisposition for the condition.[2]

The obesity epidemic is largely responsible for the significant increase in GDM.[4] Currently in America, 32% of women of reproductive age are overweight or obese, whereas 17% have a body mass index ≥35 kg m^{-2}.[5] As a result, more women are now either overweight or obese before, and throughout, pregnancy. Comorbidities associated with GDM include maternal hypertensive disorders,[6] increased risk of cesarean delivery and birth complications, as well as elevated risk of type 2 diabetes postpartum.[1] The established comorbidities are not isolated to the expectant mother: infants born to women with GDM are more likely to suffer from macrosomia,[7] hypoglycemia and hyperbilirubinemia,[8] as well as obesity and type 2 diabetes.[9]

The rise in GDM has been paralleled by a significant decrease in sleep duration. Over the past 4 decades, sleep duration has declined by 2.3 h with Americans reporting average nightly sleep duration of 6.2 h per night.[10] Sleep durations of this length fall below adult recommendations of 7–8 h sleep per night. Recently, significant metabolic and endocrine dysfunction,[11–13] as well as increased mortality risk,[14–16] have been linked to reduced sleep. The interaction between sleep duration and glucose metabolism has been the focus of much research and it is now recognized that sleep curtailment can adversely impact glycemic control.[12,17–19] However, there is a paucity of studies examining the effects of reduced sleep duration on glucose metabolism during pregnancy. This review summarizes the available data on the interaction between sleep duration and quality on glucose metabolism, with a particular emphasis on GDM. The mechanisms by which disturbed sleep may affect glucose metabolism and pregnancy are also discussed.

Sleep and pregnancy

That sleep is altered during pregnancy has been known for quite some time[20] and preclinical studies have documented pregnancy, as well as trimester-specific, changes in sleep architecture.[21] The first trimester is commonly associated with increased daytime sleepiness,[22] as well as total sleep time.[23,24] Rising hormone levels during this period may partially account for these changes. Progesterone is known to exert soporific effects,[25] and administration of exogenous progesterone has been shown to reduce time to sleep onset and modify sleep architecture, such that more time is spent in non-rapid eye movement sleep.[26] Other changes, such as organogenesis, place an additional burden on maternal energy stores and the increase in sleep time may reflect a potential mechanism to conserve energy. Nausea, vomiting, frequent urination[20] and insomnia[27] may further disrupt sleep increasing the likelihood of daytime somnolence.

During the second trimester, sleep architecture is modified such that less time is spent in stage 3 and 4 non-rapid eye movement sleep and there is a concomitant decrease in rapid eye movement sleep.[22] Nocturia accounts for the majority of nighttime awakenings during the second trimester. Compression of the bladder, as a result of increasing uterine size, means more frequent urination.[28] Other factors such as heartburn and increasing fetal movements may further fragment sleep. By the third trimester, physical changes cause significant discomfort and can impair the ability to fall asleep, as well as maintain sleep. Backache and itching are common complaints during advanced gestation and the shortest sleep durations are commonly reported during the final trimester, despite more time spent in bed.[29]

Breathing capacity, particularly during sleep, may also be influenced by fluctuating hormone levels. Increasing levels of estrogen and progesterone induce changes in the respiratory

capacity via modifications of smooth muscle tone in the respiratory tract.[30] In addition, excess weight before pregnancy can cause additional problems, due to further compression of the thorax. Such changes in respiratory function, whether as a result of rising hormone levels or excess weight, diminish breathing capacity during sleep resulting in increased nighttime awakenings.

Short sleep duration and glucose metabolism—the evidence

Recently, disturbed sleep has been regarded as a potential pathological agent in disorders of carbohydrate metabolism. In the Sleep Heart Health Study, participants with both shorter and longer sleep durations were at elevated risk of impaired glucose tolerance and diabetes[31] and, in those with type 2 diabetes, both duration and quality of sleep were found to predict hemoglobin A1c levels.[32] National Health and Nutrition Examination Survey (NHANES) data also indicate that short sleep is associated with increased risk of impaired carbohydrate metabolism[33] and reduced sleep has been found to be an independent risk factor for incident diabetes in women.[34] However, not all studies are in agreement with this association. The Coronary Artery Risk Development in Young Adults (CARDIA) study found no association between sleep duration and diabetes risk[35] and there was no effect of sleep duration on incidence of diabetes in a large prospective study from Sweden.[36]

Despite the lack of causality offered by the observational literature, experimental data strongly supports the hypothesis that reduced sleep duration impedes euglycemia. Sleep restriction studies demonstrate reduced glucose tolerance in healthy individuals following acute periods of partial sleep deprivation. Spiegel *et al.*[12] reported significant adverse effects of short sleep (4 h per night for 6 nights) in young, healthy men compared with regular sleep (12 h sleep opportunity). Both the acute insulin response and glucose disposal rate were reduced with short sleep compared with regular sleep. Furthermore, elevated post-breakfast glucose was observed with short sleep, but not regular sleep, despite similar insulin levels, indicating significant glucose intolerance with short sleep.[12] Nedeltcheva *et al.*[37] documented decreased glucose tolerance with both oral and intravenous glucose tolerance tests following reduced (5.5 h per night for 14 days) but not regular sleep (8.5 h per night) in a group of overweight men and women. Other studies have since reported that short sleep duration also decreases insulin sensitivity compared with longer sleep.[38,39]

The collective evidence, from observational and intervention studies, indicate that moderate sleep restriction has the capacity to adversely affect glucose homeostasis. Reductions in glucose tolerance and insulin sensitivity, as a result of sleep deprivation, are of particular concern for individuals with impaired glucose functioning. However, caution should be employed when interpreting the results of these studies. To date, most of the sleep deprivation studies have not matched energy intakes between the short and regular sleep phases;[12,37] therefore, participants were in different states of energy balance during both phases. Some evidence suggests that while sleep deprivation does affect glucose and insulin action it may be dependent on energy balance.[40]

Sleep and gestational diabetes

The effect of sleep on GDM has also been investigated, albeit to a lesser degree as type 2 diabetes (Table 1). Several observational studies suggest that glycemic control may be compromised as a result of short sleep duration (< 7 h per night) in patients with GDM.[41,42] One prospective study of 189 nulliparous healthy women reported that short sleep duration (< 7 h per night) was associated with glucose intolerance during the gestational period.[41] A range of sleep questionnaires that assessed sleep duration, sleep-disordered breathing (SDB), daytime sleepiness, restless leg syndrome, insomnia and overall sleep quality were administered during the first/second trimester (6–20weeks) and repeated during the third

trimester (28–40 weeks). During the first trimester, 28% of the population reported short sleep, whereas by the third trimester this had increased to 40%. Furthermore, short sleep was associated with higher fasting glucose levels during the oral glucose tolerance test (OGTT), as well as with overt GDM even after for controlling for covariates such as age, race, prepregnancy body mass index and snoring.

Qiu *et al.*[42] also explored the association between sleep duration and GDM risk. In early pregnancy (24–28 weeks; $n = 1290$), sleep duration, as well as snoring, was assessed by interview. Sleep duration was categorized into four categories: ≤4, 5–8, 9, ≥10 and 9 h per night was taken as the reference sleep category. Compared to the reference sleep category both short (≤4 h per night) and long (≥10 h per night) sleep was positively associated with elevated glucose levels following 1 h 50 g OGTT. Short sleepers had the highest glucose levels and GDM was present in 5.3% of study participants. Women with the shortest sleep duration (≤4 h per night) had the greatest risk of developing GDM and the risk was most pronounced in overweight women.[42] These associations were independent of age and race/ethnicity. Reutrakul *et al.*[43] used four validated sleep questionnaires (Epworth sleepiness scale (ESS); Berlin questionnaire; Pittsburgh Sleep Quality Index (PSQI); and Nocturia, Nocturnal enuresis and sleep interruption questionnaire) to examine the relationship between sleep disturbance, glucose tolerance and pregnancy outcomes. Pregnant women were enrolled in the study at their scheduled OGTT (1 h 50 g glucose load) at approximately 26 weeks gestation. Of the 169 women enrolled, poor quality sleep was reported in 64% of the study population and excessive daytime sleepiness (41%) and daytime dysfunction (14%) were also reported as significant sleep complaints. In terms of glucose tolerance, 68% of women had normal OGTT results and 26% were diagnosed with GDM. A significant correlation between sleep duration and glucose levels was reported in the GDM group, such that for every hour of reduced sleep there was a 4% increase in glucose levels. Moreover, short sleep and measures of poor sleep quality (ESS, PSQI) were also found to be associated with preterm delivery and greater rate of admission to neonatal intensive care units in both GDM and non-GDM women.[43]

In addition to the possible effect of sleep duration on glucose metabolism, SDB, namely, obstructive sleep apnea, may also develop during pregnancy. Obstructive sleep apnea is characterized by repetitive episodes of upper pharyngeal obstruction resulting in decreased airflow and hypoxia. These obstructions commonly result in sleep fragmentation and nighttime awakenings. Obesity, in particular excess upper thoracic adiposity, as well as reduced upper airway volume are causative factors in the pathogenesis of obstructive sleep apnea. Due to the prevalence of overweight and obesity in women of reproductive age, obstructive sleep apnea is becoming increasingly commonplace during pregnancy, yet screening and treatment of obstructive sleep apnea are not routine.

Obstructive sleep apnea is associated with particular morbidities including hypertension, type 2 diabetes and cardiovascular disease. Both hypertension and glucose abnormalities are present during pregnancy in the form of gestational hypertension, preeclampsia and GDM. Whether obstructive sleep apnea during pregnancy can adversely affect maternal and infant outcomes has not been systematically evaluated. However, several studies report a relationship between frequent snoring, a commonly used proxy measure of obstructive sleep apnea, and impaired glucose metabolism. It should be noted that obstructive sleep apnea is commonly assessed under the umbrella term of SDB; therefore, for the purpose of this review, obstructive sleep apnea will be considered synonymous with SDB. One observational study found that 29% of the study population ($n = 169$) were at elevated risk of SDB and approximately 20% of women had a combination of elevated SDB risk coupled with short sleep (<7 h per night). Furthermore, women diagnosed with GDM were found to have scores indicative of greater risk of SDB than non-GDM women.[43] Similarly, when

Facco *et al.*[41] examined the relationship between frequent snoring (≥3 nights per weeks) with GDM risk, they found that approximately 20% of their study population were frequent snorers. Both elevated OGTT results and greater incidence of GDM was found among frequent snorers despite controlling for age, race and prepregnancy body mass index.[41] In addition, others have found an approximate twofold increased risk of GDM among patients who snored. This effect was more pronounced (6.9-fold increased risk) in overweight snorers compared with lean snorers.[42]

Mechanisms of action

Several mechanisms have been proposed to explain the relationship between sleep duration and quality, and glycemic control[44] (Figure 1). Whether the mechanisms of action differ between pregnant and non-pregnant individuals has yet to be determined. However, the slight reduction in glucose tolerance that accompanies all pregnancies[45] may result in the expectant mother being more susceptible to the adverse effects of disturbed sleep on glucose metabolism. One of the primary mechanisms by which short sleep results in impaired glucose functioning is glucose intolerance, which is defined as the inability to maintain euglycemia by metabolizing exogenous glucose via insulin-dependent and non-insulin dependent mechanisms.[46] Maintenance of euglycemia is largely dependent on pancreatic beta cells to produce sufficient insulin to ensure glucose disposal. However, in diabetes, both type 2 and gestational, insulin sensitivity is impaired and beta cells are required to increase the level of insulin required for normoglycemia. Sleep can alter the effectiveness of both glucose tolerance[12] and insulin sensitivity[38,39] and this may be mediated via slow wave sleep (SWS).[47] During sleep, particularly stage 3 and 4 SWS, brain glucose utilization is reduced.[48] Early nocturnal sleep is also accompanied by a decrease in the stress response systems (sympathetic nervous system[49] and the hypothalamic pituitary adrenal axis (HPA)[50]). There is also a concomitant reduction in circulating cortisol and epinephrine[51] and increase in growth hormone and pro-lactin.[52] The reduction in cortisol and elevation in growth hormone are particularly pronounced during SWS.[53] These processes are involved in the restorative nature of sleep and it has been shown that a reduction in total sleep time[39] or increased awakening during nocturnal sleep[54,55] result in reduction in the percent SWS.

Reduced SWS has, in non-pregnant women and men, been linked to increased risk of impaired glucose tolerance and insulin sensitivity,[47] presumably as a result of the disruption of the aforementioned hormonal axis. Furthermore, because most 'normal pregnancies', those unaffected by metabolic disorders such as GDM, are accompanied with some degree of insulin resistance,[45] a reduction in the duration or quality of sleep may increase the severity of insulin resistance and, hence, increase the risk of GDM.

Cortisol may also represent a medium through which altered sleep may disrupt glucose metabolism. However, the effect of sleep on cortisol levels currently remains unclear. Some,[11,56] though not all,[57,58] experimental studies report disruption of the circadian secretion of cortisol, together with other markers of the stress response system, with partial sleep restriction. However, other studies find no effect.[59] One factor that needs to be considered when reviewing the data is whether or not the sleep restriction intervention *per se* increases stress levels or whether the actual reduction in total sleep time induces altered cortisol secretion. If short sleep duration is responsible for disruption in cortisol levels (that is, elevated evening and night-time cortisol levels) then this may, over time, adversely affect carbohydrate metabolism[60,61] decreasing insulin sensitivity and downstream insulin signaling. In addition, obstructive sleep apnea has also been shown to affect the stress response system. Adrenocorticotrophic hormone, a marker of HPA activity, is elevated in patients with obstructive sleep apnea, and continuous positive airway pressure treatment has been shown to effectively reduce circulating hormone levels.[62] An elevation in HPA

activity, as a result of inadequate or SDB-affected sleep, can increase susceptibility to insulin resistance and impaired glucose tolerance.

Cortisol and other glucocorticoids alter glucose metabolism via several different mechanisms including decreased translocation of glucose transporter type-4 receptors to the cell surface,[63] decreasing insulin release from pancreatic β-cells,[64] impairing peripheral glucose uptake and enhancing hepatic gluconeogenesis.[65] There are also some mixed reports that cortisol levels can influence insulin receptor binding and downstream insulin signaling.[66–68] Alterations in stress markers during pregnancy may increase the likelihood of miscarriage,[69] infant developmental delays[70] and is likely to contribute to impaired glucose homeostasis in GDM-affected pregnancies.

Sleep duration may also have significant implications for the inflammatory response during pregnancy. Sleep deprivation studies suggest an increased inflammatory response when participants are sleep deprived.[71] Increased interleukin-6, tumor necrosis factor-α and C-reactive protein have been shown to be inversely associated with decreasing sleep duration,[72–74] and the presence of SDB has also been shown to induce a pro-inflammatory state.[75,76] Elevations in these cytokines can disrupt maintenance of normoglycemia by reducing insulin sensitivity and downstream insulin signaling.[77] Conditions of impaired glucose control, such as GDM, are also associated with an increased inflammatory response and elevated oxidative stress.[78]

Cytokines have a significant role during pregnancy with basal levels of certain cytokines present in the amniotic fluid throughout the gestational period.[79] During the gestational period, the expression of inflammatory mediators can be viewed as a synchronized balance between pro- and anti-inflammatory cytokines. This balance may vary with each trimester and disruption of the equilibrium between pro- and anti-inflammatory mediators can adversely affect pregnancy outcomes. As previously mentioned, sleep duration and SDB have both been linked to upregulation of a pro-inflammatory response.[72,75] More recently, sleep duration has been shown to alter the inflammatory state during pregnancy[29] and some studies have found increased incidence of preterm labor and delivery in women with SDB compared with non-apneic controls.[80,81] In addition, a pro-inflammatory state can alter insulin signaling, as well as insulin sensitivity, thereby suggesting another pathway by which sleep can impair glucose control. Moreover, a pro-inflammatory response as a result of sleep loss may increase the risk of preeclampsia,[82] a condition increasingly linked to insulin resistance.[83]

Hypoxia is another pathological hallmark of SDB. Hypoxic conditions, as a result of recurrent apneas and hypopneas, facilitate generation of reactive oxidative species resulting in increased oxidative stress[84] and a pro-inflammatory cascade.[85] During pregnancy hypoxia has been shown to reduce maternal arterial oxygen saturation giving rise to inadequate blood oxygen for the developing infant, a factor which has been implicated in fetal growth retardation[86] and fetal distress.[86] Hypoxia can also be attributed to increasing circulating pro-inflammatory cytokines,[75,87] which as previously discussed adversely affects pregnancy outcomes.

Changing hormone levels also influence sleep quality via changes in respiratory function. Both estrogen and progesterone alter the smooth muscle tone of the respiratory tract: increasing levels of estrogen induce narrowing of the upper airways resulting in constricted breathing,[88] whereas progesterone is believed to increase pharyngeal muscle tone and minute ventilation.[30] These effects are exacerbated in overweight or obese women, in whom the risk of SDB, and GDM, is elevated. Excessive adiposity leads to compression of the airways resulting in overt SDB. Although data are inconclusive, it is generally believed that

snoring affects pregnant women to a greater extent than non-pregnant women.[89,90] Several studies have examined the relationship between snoring, SDB and pregnancy and some,[91] though not all,[90] report that SDB during pregnancy may adversely affect fetal development. Moreover, the presence of SDB has been shown not only to result in metabolic abnormalities[92,93] and daytime dysfunction[94] but the repetitive nocturnal arousals also decrease the duration and quality of sleep[95] both of which are independently associated with metabolic complications.

As SDB has recently been shown to compromise glucose regulation[96] and treatment of SDB with continuous positive airway pressure has demonstrated improvements in glucose control,[97] identifying and treating SDB during pregnancy may reduce maternal and infant distress and thereby decrease the incidence of pregnancy-related complications8 attributed to hypoxia. However, rates of screening and diagnosis of SDB are low, and a recent finding illustrates the need for SDB screening, particularly in vulnerable populations such as patients with type 2 diabetes[98] and overweight or obese pregnant women.

SUMMARY

Pregnancy is associated with significant hormonal, biochemical and physical alterations. Sleep is also modified by pregnancy and trimester-specific changes. Total sleep time, particularly in the third trimester, is reduced while nocturnal awakenings are increased. Together these changes reflect a shortening of sleep duration and an increase in fragmented sleep. Both short and fragmented sleep have previously been associated with increased risk of type 2 diabetes in men and non-pregnant women. Preliminary studies examining the relationship between sleep and GDM suggest that duration and quality of sleep may also contribute to increased risk of GDM. Overweight and obese pregnant women are at elevated risk of SDB, which in non-pregnant study populations has been associated with type 2 diabetes.

Several mechanisms exist by which sleep may modulate impairment in glucose metabolism, yet no study to date has extensively examined the relationship between sleep and GDM. The complexity of the relationship between sleep and glucose metabolism is highlighted by the multiple pathways that are affected by sleep and SDB. The lack of knowledge on how these pathways are affected by sleep is an important area of research that warrants further examination. In our review of the literature, we have identified important unanswered research questions: To what extent does reduced sleep duration affect maternal and infant outcomes? Would increasing sleep duration (either by increased nocturnal sleep or daytime naps) during pregnancy reduce or perhaps prevent the metabolic impairments associated with short sleep? In addition to this, is pregnancy accompanied with specific mechanisms by which disturbed sleep can impair glycemic regulation?

Undiagnosed SDB is common and increased body weight is a primary risk factor. Given the prevalence of overweight and obesity among women of reproductive age, identification of at-risk individuals and subsequent treatment of SDB may be an important issue to consider when monitoring pregnancy, particularly high-risk pregnancies. Whether treatment of SDB can improve maternal and infant outcomes, particularly in relation to GDM, has never been examined. Drawing on the data from non-pregnant populations, partial sleep deprivation, as well as SDB, contribute to significant metabolic abnormalities and increase the risk of glucose dysregulation. These data, combined with the few available epidemiological studies in pregnant women, indicate that much work is needed to unravel the relationship between sleep and sleep-related disorders and GDM.

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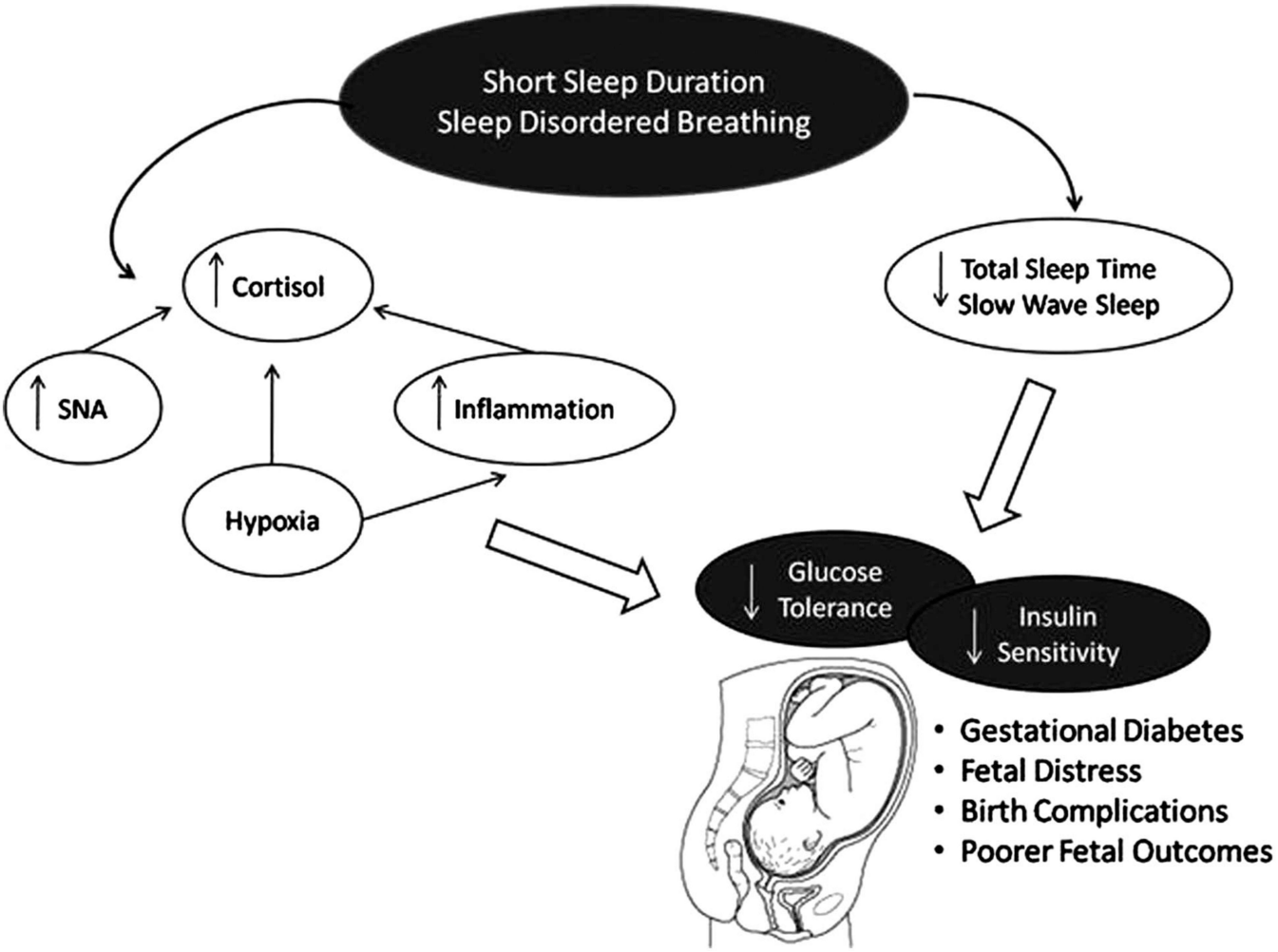

Figure 1.
Mechanisms of action via which sleep may affect carbohydrate metabolism during pregnancy.

Table 1

Studies examining the relationship between sleep and sleep-disordered breathing during pregnancy with gestational diabetes risk

Author	**Qiu *et al.*[42]**	**Facco *et al.*[41]**	**Reutrakul *et al.*[43]**
Sample size	***n* = 1290**	***n* = 189**	***n* = 169**
EGA at assessment	18 weeks	First assessment: 13.8 weeks Second assessment: 30.2 weeks	26.2 weeks
Parity	Nulliparous and multiparous	Nulliparous	Unspecified
Method of assessment	Interview	Questionnaire	Questionnaires
Measures	• Duration of sleep during pregnancy • Prepregnancy sleep duration • Frequency of snoring • OGTT results	• Duration of sleep during pregnancy • Snoring and frequency of snoring • OGTT results	• Daytime sleepiness • Snoring assessment • Sleep quality • Nocturia, nocturnal enuresis and interruption of sleep • OGTT results
Outcome	• Increased GDM risk among short sleeper (≤4 h per night) compared with regular sleeper (9 h per night) • Snoring was associated with twofold increased risk of GDM • Overweight women who slept short or snored had the greatest risk of GDM	• Short sleep duration and frequent snoring associated with elevated OGTT results • Greater incidence of GDM with both short sleep and frequent snoring	• Sleep duration was inversely related to glucose levels • Each hour of reduced sleep resulting in 4% increase in glucose levels • Increased likelihood of GDM associated with increased risk of sleep-disordered breathing • Individuals with sleep-disordered breathing, short sleep and frequent snoring had elevated risk GDM

Abbreviations: EGA, estimated gestational age; GDM, gestational diabetes; OGTT, oral glucose tolerance test.