Sleep disorders in Pregnancy: Glycaemic implications

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Abstract

Sleep is one of the essential biorhythms of the body that helps in optimum restoration of many body functions. The sleep-wake cycle is determined by the circadian centre and is responsible for the anabolic functions in the body. Infants require about 14 to 18 hours of sleep per day, which reduces gradually to about 8 hours in adults. Urbanization and evolutionary changes have altered the sleep hygiene and shortened the sleep duration. This lead to various sleep disorders like sleep disordered breathing, insomnia and narcolepsy. Sleep disorders lead to adverse cardio-metabolic consequences, including insulin resistance and hyperglycaemia. Pregnancy poses an enormous burden on the homeostasis of the women with alteration in many physiological functions. The sleep disorders during pregnancy lead to adverse foeto-maternal outcomes with long term cardiovascular implications. In this article, I review the pathophysiology of sleep disorders during pregnancy and their glycaemic implications.

Keywords: Sleep disorders, Pregnancy, Diabetes, Gestational diabetes.

Introduction

Sleep is divided into two broad types known as the rapid eye movement (REM) and non-REM (NREM) sleep. Mammals and birds are the only two species that exhibit this pattern of sleep. Human sleep is governed by the close interaction between the circadian rhythms and the endocrine system. Sleep disorders are broadly defined as the ones that affect the initiation and maintenance of sleep, disorders of sleep-wake schedule, circadian rhythm disorders, and disorders affecting the sleep stages, transitions and partial arousals in the absence of any secondary cause or substance abuse.[1] Data from non-pregnant individuals have conclusively shown that lack of sleep leads to insulin resistance and type 2 diabetes. Maternal sleep is essential for a number of physiological functions in the body that are essential to maintain a healthy growth of the foetus.

Sleep disturbances in pregnancy have been well recognized since time immemorial leading to adverse foeto-maternal consequences. The physiological changes in pregnancy could lead to sleep disruption, exacerbate the pre-existing sleep disorders and lead to de-novo sleep disorders. Pregnancy is considered as a diabetogenic state due to the elevation in hormones like human placental lactogen, cortisol and growth hormone. During pregnancy, even a minor alteration in the sleep hygiene could lead to glucose intolerance in women, who are already in a vulnerable state. Pregnant women with pre-gestational obesity have a higher incidence of sleep disorders than lean women. The relation between sleep disorders in pregnancy and diabetes has not been studied in great details and the information is often extrapolated from non-pregnant patients.[2] In this review, we cover the pathophysiological changes in pregnancy responsible for the sleep disorders and their implications on the glucose intolerance.

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Sleep and Pregnancy — Physiological alterations

Every adult human requires about 6 to 8 hours of daily sleep. Sleep has restorative function and is essential to prepare the mother to divert the energy needs to the foeto-placental unit. Pregnancy induces many changes in the hormonal, immunological, structural and functional systems that enable the safe delivery of a newborn. The state of pregnancy demands additional requirements of the mother, including the sleep duration. The increased sleep conserves more maternal energy and directs the same for the foetal nourishment and organogenesis. Increase in the duration of the sleep results in elevated levels of human chorionic gonadotropin and progesterone, which are essential for maintenance of pregnancy. High progesterone levels in the 1st trimester may exert a soporific effect.

The duration of sleep increases from the 1st to 2nd trimester, but is reduced in the 3rd trimester due to

Table-1: Common symptoms during pregnancy that affect the sleep rhythm.

Symptoms	1st trimester	2nd trimester	3rd trimester
Nocturia	++	+	+++
Heartburn	±	++	+++
Nausea, Vomiting	++++	+	-
Pruritus	-	-	+++
Foetal movements	-	±	++++
Muscle aches	-	+	++
Uterine contractions	-	±	++++

various physiological disturbances.[3] The physical symptoms observed in pregnancy that affect sleep hygiene, trimester wise are shown in Table-1. Heartburn is a common symptom in pregnancy and elevated oxytocin could lead to sleep fragmentation. After delivery, the nutritional needs of the newborn further result in sleep fragmentation, exacerbating the stress of the sleep deficit. The studies conducted in postpartum women showed that the gestational related weight gain persists in women with short sleep independent of the confounders. Preexisting disorders like asthma are exacerbated during pregnancy due to the physiological changes like nasal congestion and reduced lung compliance.

Sleep disorders in Pregnancy

The prevalence of sleep disorders increases with advancing gestational age. Previous reports suggest that 25% of pregnant women have sleep disorder in the 1st trimester, which is increased to 70% in the 3rd trimester. Sleep disorder is a broad term encompassing many individual disorders as shown in Box-1. Most of the sleep disorders are characterized by sleep deficiency with the exception of narcolepsy, which has excessive sleep. The detailed review of sleep disorders is beyond the scope of this article and the readers are requested to look up the recent articles on the subject.[4] Table-2 summarizes the risk factors and pathophysiological changes that exacerbate sleep disorders in pregnancy along with their adverse outcomes. Sleep disorders lead to adverse metabolic consequences which further perpetuate the sleep disorders leading to a self-propelled cyclical state.

Box-1: Sleep disorders in pregnancy

- Sleep disordered breathing
- Restless leg syndrome
- Leg cramps
- Insomnia
- Short sleep duration
- Narcolepsy
- Circadian rhythm disturbances

Sleep disordered breathing (SDB) encompasses a wide spectrum of symptoms ranging from snoring to obstructive sleep apnoea (OSA). SDB is prevalent in about 10% of pregnant women and is characterized by the intermittent episodes of hypopnoea and apnoea. Central sleep apnoea resulting in SDB is not reported frequently during pregnancy. Restless leg syndrome (RLS) is a disorder of unclear etiology leading to a sense of urgency to move the legs in the night time. RLS is observed in over a quarter of pregnant women and the wide variation in prevalence is due to the different diagnostic criteria employed. Leg cramps are considered as sleep related movement disorder characterized by intense, painful muscle contraction of the calf that disrupts the sleep and daytime functioning.

Insomnia and short sleep duration (SSD) are common but under-diagnosed disorders in pregnant women. Insomnia is defined as difficulty in initiation and maintenance of sleep and non-refreshing sleep with compromised daytime functioning. SSD is defined as sleep duration of less than 7 hours per night. The risk factors for SSD include nulliparity, obesity, hypertension and advanced age. All

Table-2: Pathophysiological alterations and their consequences of sleep disorders in pregnancy.

Disorder	Pregnancy related risk factors	Pathophysiological changes	Adverse outcomes
Sleep disordered breathing	• Upper airway oedema • Nasal congestion • Reduced functional residual capacity	• Reduced leptin sensitivity • Elevated leptin • Increased Ghrelin • Inflammatory markers	• Gestational hypertension • Gestational diabetes • Preterm delivery • ↑ risk of caesarean delivery • Foetal growth restriction
Restless Legs Syndrome	• Iron deficiency • Folate deficiency • Elevated oestradiol	• Reduced dopamine • Hypothalamic dopaminergic deficiency	• Gestational hypertension • Gestational diabetes
Insomnia	• All factors as noted in Table 1	• Hypothalamo-pituitary-adrenal axis dysfunction • Increased Interleukin-6 • Increased C-reactive protein	• Long labour duration • ↑ risk of caesarean delivery • Preterm delivery
Narcolepsy	• Risk of cataplexy due to labour pains	• Reduced Orexin A	• Anaemia • Glucose intolerance • ↑ risk of caesarean delivery
Circadian rhythm disorders	• Sleep disorders • Elevated prolactin • Elevated oestradiol	• Increased proinflammatory markers • Increased Reactive 02 species • Altered immunity • Circadian disturbances	• Metabolic syndrome • Early foetal loss • Preterm birth • Low birth weight infants

these disorders have been shown to be independently associated with glucose intolerance during pregnancy.[5] SSD has been linked with weight gain, glucose intolerance, preterm delivery and low birth weight infant. The condition is usually treated by the cognitive behavioural therapy, as use of the sedatives is associated with congenital anomalies.

Narcolepsy is a disorder prevalent in young females of childbearing age and is characterized by excessive daytime sleepiness, cataplexy, hypnogagic hallucinations and sleep paralysis. The disorder has limited adverse outcomes because it is associated with increased duration of sleep. Previous data suggest that both deficiency and excess of sleep are associated with increased risk of poor pregnancy outcomes. The circadian rhythms of the body are controlled by the pacemaker located in the suprachiasmatic nucleus of the hypothalamus. The data about the circadian desynchronization during pregnancy was derived from the nurses working in shift duties. Preliminary data exist regarding the effect of circadian rhythms on labour, as shown by the occurrence of spontaneous rupture of membranes mostly during night time followed by the onset of the labour in early morning.

Diagnosis and Management of Sleep Disorders

The guidelines are not clear about the risk factors, which warrant screening for sleep disorders in the pregnant women. Box-2 gives the clinical indicators that help clinicians in deciding about the evaluation. The evaluation for sleep disorders is by the use of sleep questionnaires, actigraphy and polysomnography (PSG). The well validated sleep questionnaires that are commonly used are Epworth sleepiness scale (ESS) and Pittsburgh sleep quality index (PSQI).[6] Abnormal sleepiness is denoted by ESS score greater than 10 or PSQI more than 5. Actigraphy is the recording of the body motion over a long period of time and is used to identify relative periods of rest and activity. A piezoelectric beam located in the wearable device generates a signal with every movement and is displayed known as the actigraph. PSG is the gold standard for the diagnosis of sleep disorders. PSG involves simultaneous record of multiple physiological functions of the body during the various stages of sleep. The main parameters of interest include sleep onset latency, sleep stages, sleep efficiency and the number of apnoea and hypopnoea episodes. The diagnosis and severity of OSA are based on the apnoea/hypopnoea index (AHI). An AHI score between 5 to 15 is classified as mild, up to 30 is moderate and a score of more than 30 is termed as severe OSA. However, the procedure is cumbersome limiting its wide use in the evaluation of pregnant women.

Box-2: Risk factors for sleep disorders.

- Excessive day time sleepiness
- Abnormal weight gain
- Mood disturbances and Depression
- Unexplained fatigability
- Habitual snoring
- Obese or overweight pregnant women
- Pre-existing Type 2 DM

Table-3: Commonly used drugs and their class during pregnancy.

Class of drugs	Examples	Pregnancy Category
Benzodiazepines (BZD)	Lorazepam, Flurazipam	D, X
BZD agonists	Zolpidem	C
Antidepressants	Amitryptiline, Doxepin	C
Antihistamines	Diphenhydramine	B

Box-3: Measures to improve sleep hygiene.

- Keep regular sleep schedule
- Avoid forcing or delaying the sleep
- Avoid caffeinated beverages
- Avoid alcohol
- Adjust bedroom environment
- Avoid going to bed with empty stomach
- Keep all gadgets away from the bedroom
- Pray and meditate regularly

Non-pharmacological therapy plays a vital role in the treatment of sleep disorders. The sleep hygiene measures to be followed are shown in Box-3. Cognitive behavioural therapy (CBT) is the cornerstone of the management of sleep disorders in pregnancy. This is despite the fact that there is a lack of clinical evidence demonstrating the benefit of CBT over hypnotics in sleep disorders. The use of hypnotics is limited due to the fear of teratogenicity in pregnant women. The safety data about the commonly used drugs in sleep disorders during pregnancy is given in Table-3. None of the hypnotic drugs are safe during pregnancy and lactation period. Anti-allergic drugs (Chlorpheniramine, Diphenhydramine) with sedation as their side effect are preferred.

Sleep Disorders and Glucose Intolerance — Pathophysiological links

Alterations in the quantity and the quality of sleep have been shown to have considerable effect on the carbohydrate metabolism. Previous studies have indicated, that lack of sleep predisposes an individual to metabolic dysfunction culminating into diabetes. The effects are observed on the phases of insulin release,

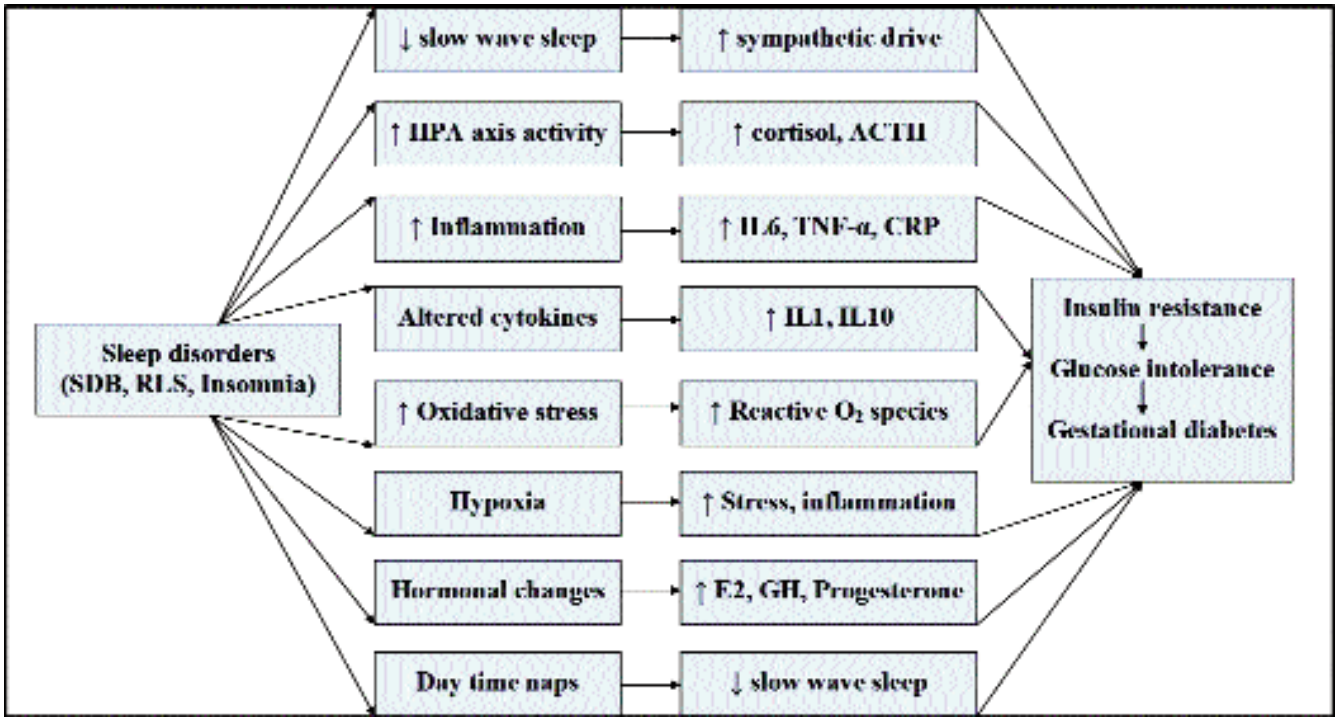

Figure: Pathophysiological links between sleep disorders and diabetes.

glucose disposal rate and disposal of carbohydrate load after a meal.[7] However, some of these studies lack specificity because of non-demarcation between the changes that are mediated by the body weight and caloric intake. Multiple mechanisms mediate the glucose intolerance due to various sleep disorders as shown in Figure.

The glucose utilization of the brain decreases during the slow wave sleep (also known as stage 3 and 4 of NREM sleep). The stress response system is subdued at this stage, with the reduced release of diabetogenic hormones like cortisol and epinephrine. However, the duration of slow wave sleep is reduced in pregnancy leading to increased release of stress hormones and activation of hypothalamo-pituitary-adrenal axis. Cortisol alters glucose metabolism by increasing hepatic gluconeogenesis, impaired insulin release and reduced peripheral glucose uptake. Disturbed sleep-wake cycle alters the fine balance between the sympathetic and parasympathetic hormones leading to the excessive release of sympathetic hormones. Excessive daytime napping also reduces the slow wave sleep in the night time, thereby, leading to insulin resistance.

Sleep deprivation induces a pro-inflammatory state with the release of tumour necrosis factor-α, C-reactive protein and interleukins 1, 6 and 10. These pro-inflammatory cytokines impair the downstream insulin signaling pathways and leads to a state of severe insulin resistance. Amniotic fluid has shown the presence of cytokines and sleep disorders tilt the balance in favour of the inflammation. Hypoxia with recurrent spells of disrupted breathing leads to oxidative stress, release of reactive oxygen species which further aggravates the inflammatory response. The reduced maternal arterial oxygen content leads to intrauterine growth retardation and delivery of small for gestational age babies.

Sleep Disorders & Gestational Diabetes Mellitus (GDM)

GDM is the most common abnormality observed in pregnancy with many adverse consequences. There is a rise in incidence of GDM, which is paralleled by fall in sleep duration. The increased prevalence of GDM is primarily driven by obesity, advanced maternal age, vitamin D deficiency, etc. GDM is important from a public health perspective because, infants born to mothers with GDM have a higher lifetime risk of diabetes and obesity. SSD has been linked with an increased risk for GDM.[8] Every 1 hour deficiency of sleep results in 4% rise of the prevalent glucose levels. GDM has been shown to be strongly associated with less (<4 hour) or more (>10 hour) duration of sleep per night. SDB complicates the metabolic milieu during pregnancy. Obesity coupled with

reduced upper airway volume could lead to OSA in pregnant women. OSA is an independent risk factor for hypertension, diabetes and many other metabolic disorders. Snoring has been proposed as a crude measure of identifying the OSA in pregnancy for the lack of PSG. Frequent or habitual snoring (> 3 nights per week) has been associated with the increased risk of GDM in pregnancy.[9] This effect is exacerbated in obese snorers but persist independent of the body weight. The treatment of SDB during pregnancy with continuous positive airway pressure (CPAP) has been shown to improve the glycaemic control and also reduce the adverse outcomes.

Future Directions

The data related to sleep disorders and maternal hyperglycaemia is scanty due to various reasons. They include lack of awareness, difficulty in formal assessment, absence of guidelines and the need to follow up with multiple specialists. Large prospective studies are required to identify the exact epidemiological association between sleep disorders and maternal diabetes and interventional studies are also required to look at the impact of these measures on diabetes improvement. Future research should include the patterns of growth and development in babies born to sleep deprived mothers to assess the long term implications of these disorders.

Conclusion

To conclude, sleep disorders during pregnancy are common and often silent. They lead to maternal hyperglycaemia and adverse gestational outcomes. Early identification and appropriate management therapies are essential to prevent the morbidity in pregnancy. Further research is required to unravel the mechanistic links between the sleep disorders and glucose metabolism independent of the confounding factors like obesity.

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