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CLINICAL REVIEW

Pathophysiological changes associated with sleep disordered breathing and supine sleep position in pregnancy

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SUMMARY

Sleep is a complex and active physiological process that if disrupted, can result in adverse outcomes both within and outside of pregnancy. Sleep disordered breathing (SDB) occurs in 10–32% of pregnancies. Substantial physiological changes occur during pregnancy that impact on maternal sleep, which typically deteriorates with advancing gestation. Pregnancy challenges maternal homeostatic regulation of many systems which effect maternal sleep, including the respiratory, cardiovascular, endocrine, and immune systems. SDB can result from varying degrees of airway compromise and potentially cause systemic hypoxia. The hypoxia may be acute, intermittent or chronic in nature with complications dependant on the duration and the gestation at which the insult occurs. It is unlikely that this effect is mediated by a singular mechanistic pathway but results from a complex cascade of events across multiple maternal organ systems. Regardless of the etiology, both SDB and supine sleep position are associated with a variety of obstetric and perinatal complications including, pre-eclampsia/eclampsia, gestational diabetes mellitus, cardiomyopathy, heart failure, fetal growth restriction, poor neonatal condition at birth, stillbirth and neuro-psychiatric problems in offspring. Both maternal sleep position and sleep disordered breathing are potentially modifiable or treatable factors that if addressed have the potential to improve maternal and fetal outcomes. This narrative review summarizes the maternal and placental pathophysiological aberrations associated with sleep disordered breathing and supine sleep position in pregnancy.

Introduction

Sleep is a complex behavioral function conserved across multiple species with deprivation or disruption resulting in a myriad of functional, cognitive, neuroendocrine and neurodegenerative impairments and potentially even death [1–3]. Pregnancy, and the evolutionary advantage that it confers to the fetus, challenges almost all maternal homeostatic mechanisms particularly the cardiovascular and respiratory systems which is of particular relevance to sleep [1,4].

Perturbations in sleep are common in pregnancy, with women often describing increased frequency of awakenings, lower overall sleep duration and higher levels of daytime sleepiness compared with pre-pregnancy patterns. Indeed there is mounting evidence showing that sleep abnormalities negatively impact obstetric and perinatal outcomes [5–11] and treatment, particularly those related to obstructive airway symptoms, ameliorates some of these complications [12–14]. Maternal sleep position has also been linked with adverse outcomes particularly stillbirth [15–18]. The mechanisms underpinning these complications are often unclear. The aim of this narrative review is to detail the pathophysiological changes affecting the respiratory, cardiovascular, endocrine, immune, inflammatory and stress response systems in pregnancy specific to maternal sleep disorders and supine sleep position and explore some of the possible pathways that influence pregnancy complications. The search methodology involved identifying relevant papers in PubMed using appropriate keywords relevant to maternal sleep and adverse pregnancy outcomes. The reference lists of these reviews were searched for key publications both inside and outside of pregnancy and key words and appropriate Mesh terms were identified to further refine the search.

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Abbreviations

AFP	alpha-fetoprotein
AHI	apnea hypopnea index
aOR	adjusted odds ratio
BMI	body mass index
CI	confidence interval
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CS	cesarean section
FRC	functional residual capacity
hCG	human chorionic gonadotropin
HPA	hypothalamic-pituitary-adrenal
NREM	non-rapid eye movement
OR	odds ratio
OSA	obstructive sleep apnea
PAPP-A	pregnancy associated plasma protein-A
PlGF	placental growth factor
REM	rapid eye movement
ROS	reactive oxygen species
SDB	sleep disordered breathing
sFlt-1	soluble fms like tyrosine kinase-1
VEGF	vascular endothelial growth factor

Sleep disordered breathing in pregnancy

Sleep disordered breathing (SDB) refers to a variety of aberrations in sleep patterns including snoring and obstructive sleep apnea (OSA) [19]. The prevalence of SDB in pregnancy is variably reported depending on the screening or diagnostic criteria used, population studied and gestation at assessment but is estimated to occur in 10–32% of pregnancies [20]. These disorders are characterized by varying degrees of maternal hypoxia as a result of partial or complete, intermittent airway obstruction or collapse, leading to fluctuations in oxygen saturation levels [21,22]. Risk factors for SDB in pregnancy include hypertension, advanced maternal age, raised body mass index (BMI) and increased neck circumference [20]. Teasing out the relationship between SDB, maternal co-morbidities and pre-existing maternal conditions can be challenging. Outside of pregnancy obesity is known to predispose to OSA [23]. Within pregnancy, BMI as opposed to pregnancy weight gain has also been correlated with SDB [20].

Changes in maternal sleep patterns during pregnancy have been well described [24] with a recent meta-analysis showing that 46% of women experience poor sleep quality during pregnancy [25]. They report frequent awakenings, shorter sleep duration, snoring as well as fatigue [26–28] with symptoms typically deteriorating over the course of pregnancy and peaking in the third trimester [27,29,30].

SDB is associated with a plethora of negative maternal, obstetric and perinatal outcomes including cardiovascular and metabolic disease, fetal growth restriction, preterm birth, low birth weight, operative delivery, low 5-min Apgar score, stillbirth and perinatal death, longer hospital stay, as well as maternal and neonatal admission to intensive care [8,9]. More recent evidence also suggests that offspring of women with high levels of daytime sleepiness have poorer executive function and increased neuropsychiatric problems in early childhood [31]. (Table 1).

Physiological changes in pregnancy and their impact on maternal sleep

Respiratory

The respiratory system is substantially transformed in pregnancy as a result of hormonal influences, alterations in airway mucosa, reduced airway dimensions as well as changes in thoracic dimensions that impact lung function. There is a 5–7 cm increase in chest circumference secondary to increases in both the anterior-posterior and transverse diameters [32]. Nasal congestion and rhinitis of pregnancy have been reported to affect almost 40% of pregnant women [33]. Susceptibility to rhinitis of pregnancy is precipitated by the increased hyperemia and mucosal edema of the respiratory tract [34] which is mediated by progesterone and estrogen [33]. Elevated progesterone levels also stimulate maternal respiratory drive resulting in a 30% increase in resting minute ventilation compared to the post-natal period [2].

Hyperemia and edema of the upper respiratory tract reduce airway dimensions which are further compromised during sleep. In an awake state, the airway is held open by the pharyngeal dilator muscles of the upper airway. However the activity of these muscles is decreased during sleep which can result in partial or total collapse of the airway further compromising airway calibre [19,35]. In addition, there is evidence to suggest that increased maternal neck circumference secondary to soft tissue edema also aggravates SDB [35–37]. The cumulative effect of the physiological changes that occur in the respiratory tract and more broadly during pregnancy often results in a perception of shortness of breath affecting approximately 75% of women even with mild exertion [2].

As gestation progresses, the growing gravid uterus increases intra-abdominal pressure causing cephalad displacement of the diaphragm thus reducing lung capacity [32]. Chest wall compliance is compromised and functional residual capacity (FRC) decreases by 10–25% [32]. FRC is further reduced with supine sleep position [2,34]. Collectively, the combination of a lowered FRC, 30% increase in oxygen consumption, 15% increase in metabolic rate and a lower overall oxygen reserve, increase maternal susceptibility to hypoxia [32] with nocturnal arterial oxygen saturation significantly lower in pregnancy. Indeed, almost one in four women spend >20% of the night with oxygen saturations <90% [38]. (Fig. 1).

Endocrine

Following implantation, the exponential rise in human chorionic gonadotropin (hCG) levels results in a concomitant rise in progesterone and estrogen from the preserved corpus luteum [4]. Progesterone not only induces sleep it also influences the time spent in either rapid eye movement (REM) or non-rapid eye movement (NREM) stages with appropriate duration of both essential to maintain wellbeing. Progesterone stimulates respiration by increasing resting minute ventilation [2] while estrogen reduces the time spent in REM sleep [2,24,36] by activating sleep-active neurons in the ventrolateral preoptic area [36]. Additionally estrogen results in over-production of secretions by the serous-mucous glands of the respiratory tract. This compounds the effect of the increased vascularity and causes more nasal congestion, mucosal edema and upper airway resistance thus increasing the susceptibility of pregnant women to upper airway obstructive symptoms and SDB [33].

Other hormones produced either by the corpus luteum or the placenta may also influence maternal sleep [36]. Relaxin is

Table 1
Complications related to Sleep Disordered Breathing.

Maternal Complications	Neonatal Complications
Gestational hypertensive conditions (including pre-eclampsia and eclampsia) [8,97,98] • Pre-eclampsia aOR 2.22 (95% CI 1.94–5.54) [8] aOR 2.5 (95% CI 2.2–2.9) [97] aOR 2.42 (95% CI 1.43–4.09) [98] • Eclampsia aOR 2.95 (95% CI 1.08–8.02) [8] aOR 5.4 (95% CI 3.3–8.9) [97] • Gestational hypertension aOR 1.67 (95% CI 1.42–1.97) [8] aOR 2.46 (95% CI 1.30–4.68) [98]	Fetal growth restriction [8,9] aOR 1.05 (95% CI 0.84–1.31) [8] OR 1.19 (95% CI 0.94–1.51) [9]
Gestational diabetes mellitus [8,97] aOR 1.51 (95% CI 1.34–1.72) [8] aOR 1.89 (95% CI 1.67–2.14) [97]	Stillbirth/perinatal death [8,9] OR 2.02 (95% CI 1.25–3.28) [9]
Cardiomyopathy [8,97] aOR 3.59 (95% CI 2.31–5.58) [8] aOR 9.01 (95% CI 7.47–10.87) [97]	Preterm birth [9,98] OR 1.86 (95% CI 10.50–2.31) [9] aOR 1.90 (95% CI 1.09–3.30) [98]
Congestive heart failure [8,97] aOR 3.63 (95% CI 2.33–5.66) [8] aOR 8.94 (95% CI 7.45–10.73) [97]	Low 5-min Apgar score OR 2.14 (95% CI 1.24–3.71) [9]
Stroke aOR 2.93 (95% CI 1.07–8.04) [97]	Neonatal nursery unit admission OR 1.90 (95% CI 1.38–2.61) [9]
Acute renal failure aOR 2.73 (95% CI 1.69–4.41) [97]	Low birth weight/small for gestational age OR 1.67 (95% CI 1.00–2.78) [9]
Pulmonary embolism and infarction aOR 4.47 (95% CI 2.25–8.88) [97]	Early childhood psychiatric problems [31]
Pulmonary edema [8,97] aOR 5.06 (95% CI 2.29–11.1) [8] aOR 7.50 (95% CI 4.63–12.15) [97]	
Congestive heart failure [8,97] aOR 8.94 (95% CI 7.45–10.73) [97]	
Peripartum hysterectomy aOR 2.26 (95% CI 1.29–3.98) [8]	
Prolonged hospital stay [8,97] aOR 1.18 (95% CI 1.05–1.32) [8] aOR 3.06 (95% CI 2.76–3.40) [97]	
Intensive care unit admission aOR 2.74 (95% CI 2.36–3.18) [8]	
Postoperative wound complications [8,9,97] aOR 1.77 (95% CI 1.24–2.54) [8] OR 3.67 (95% CI 1.82–7.40) [9] aOR 1.89 (95% CI 1.53–2.34) [97]	
Operative delivery (including assisted vaginal delivery, elective cesarean, emergency cesarean) [9,97,98] Assisted vaginal delivery OR 1.88 (95% CI 1.10–3.21) [9] Cesarean delivery OR 1.81 (95% CI 1.55–2.11) [9] aOR 1.12 (95% CI 1.01–1.23) [97] aOR 1.60 (95% CI 1.06–2.40) [98] Elective CS OR 1.38 (95% CI 1.09–1.76) [9] Emergency CS OR 1.52 (95% CI 1.20–5.29) [9]	
Maternal mortality aOR 2.58 (95% CI 2.42–11.53) [97]	

CS, cesarean section; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

produced by the corpus luteum and impacts the musculoskeletal and circulatory systems. It mediates remodeling of airway connective tissue making them more susceptible to collapse [36]. Additionally, because of its effects on the ligamentous attachments of the rib cage, it results in an increase in the thoracic subcostal angle [2] which negatively impacts breathing mechanics during pregnancy. It also functions to induce systemic maternal vasodilation resulting in fluid retention and maternal discomfort [36]. Maternal discomfort, particularly in the third trimester, has been repeatedly described as a factor that negatively impacts on sleep quality [24,39–42]. (Fig. 1).

Circulatory

There are substantial cardiovascular and hematologic changes that occur in pregnancy. Blood volume increases by 10–15% due to the erythropoietin stimulated increase in red cell production as well as an increase in plasma volume by 30–50%. The increase in red cells is not proportional to the increase in plasma volume resulting in a reduction in blood viscosity allowing increased organ perfusion [32].

The increased blood volume results in an increased preload, which in combination with a decreased afterload, as a result of the systemic maternal vasodilation, causes a 20–30% increase in stroke volume. This, in conjunction with the rise in maternal heart rate by 15–20 beats per minute, culminate in a rise in cardiac output by 30–50%. The rise in pulmonary blood flow, decreased pulmonary vascular resistance and reduced intravascular colloid osmotic pressure increases susceptibility of extravasation of fluid into the pulmonary interstitial spaces and edema [32]. In some vulnerable women, a combination of the above together with reduced airway dimensions and supine maternal position [43], can result in decreased maternal oxygen saturation and relative hypoxia [34]. Using magnetic resonance imaging, the anterior-posterior diameter of the inferior vena cava is significantly reduced in the supine position compared to the lateral decubitus position. This occurred in 60% of women in the second trimester and 72% of women in the third trimester [44]. This aortocaval compression results in a reduction in venous return and cardiac output [45].

In the non-pregnant population, OSA has been linked with systemic hypertension as well as fatal and non-fatal cardiovascular events [19]. A proposed mechanism for this is endothelial

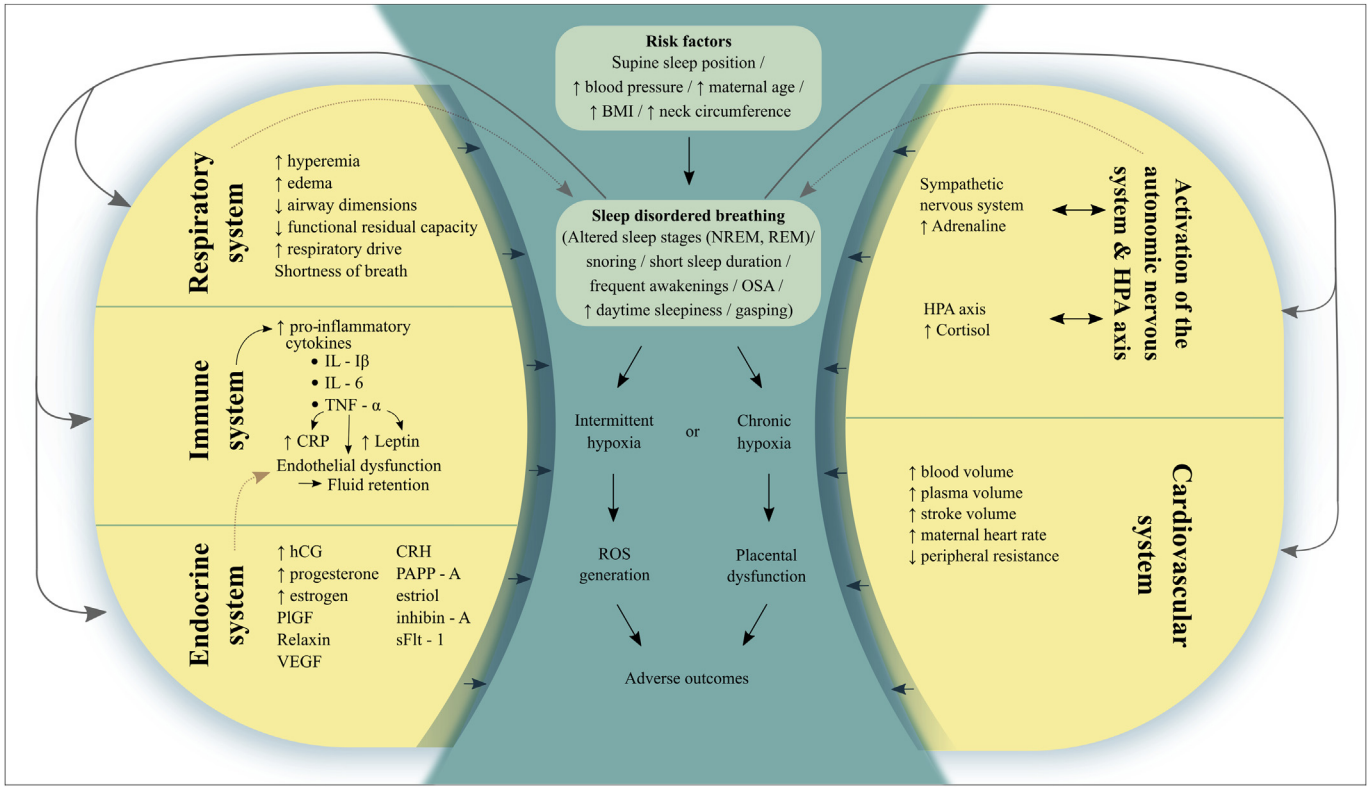

Fig. 1. Mechanisms that potentially meditate adverse outcomes in sleep disordered breathing during pregnancy. BMI, body mass index; CRH, cortiotrophin-releasing hormone; CRP, C-reactive protein; hCG, human chorionic gonadotropin; HPA, hypothalamic-pituitary-adrenal; NREM, non-rapid eye movement; OSA; obstructive sleep apnea; PAPP-A, pregnancy associated plasma protein-A; PlGF, placental growth factor; REM, rapid eye movement; ROS, reactive oxygen species; sFlt-1, soluble fms like tyrosine kinase-1; VEGF, vascular endothelital growth factor.

dysfunction. The etiology of endothelial injury has not been fully elucidated however hypoxemia and its resultant generation of reactive oxygen species (ROS) and systemic inflammation are possible mechanisms [46]. An impaired brachial artery flow-mediated vascular response has been proposed as a surrogate marker for endothelial dysfunction. One study of elderly participants found that brachial artery baseline diameter and flow-mediated dilatation was reduced in those with OSA [47]. Another study found evidence of vascular remodeling in the SDB cohort [48]. A recent study showed that in non-pregnant patients with OSA, cerebral vasodilatation in response to hypoxia was significantly reduced but this was improved with continuous positive airway pressure (CPAP) therapy [14]. (Fig. 1).

Immune, inflammatory and stress response to SDB

A vital aspect of pregnancy is the adaptation of the maternal immune system to prevent rejection of the feto-placental semi-allograft. Although it is generally accepted that for a successful pregnancy to continue to term there should be some overall attenuation of the maternal immune response there appears to be three distinct immunological phases [49]. The first stage of the immunological response is a pro-inflammatory phase and is related to the first and early second trimesters of pregnancy when implantation and development of the placenta takes place. The second phase corresponds to a period of rapid fetal growth and development when all components in the pregnancy (mother, fetus and placenta) are in immunological harmony and the predominant feature is an anti-inflammatory state. The final phase corresponds to the peripartum period when fetal development is largely complete and it has to make the transition to extrauterine life. A pro-inflammatory state recurs with influx of immune cells into the myometrium triggering uterine contractions, labor and expulsion of the fetus and placenta [49–54].

There is evidence that abnormal sleep both in the pregnant and non-pregnant state is associated with elevations in pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and other markers of inflammation including C-reactive protein (CRP) [49,55–62]. CRP is synthesized in the liver and is regulated by pro-inflammatory cytokines. It has been shown to promote atherosclerosis and thrombosis and is also associated with endothelial dysfunction [46,58]. CRP levels are elevated in otherwise healthy individuals that experience either acute total or short-term partial sleep deprivation [63]. The endothelial damage and dysfunction and pro-thrombotic state in the maternal circulation as well as in the placenta, mediated by elevated levels of CRP and other pro-inflammatory cytokines in women with OSA are probably in part responsible for maternal and perinatal complications such as pre-eclampsia, preterm birth, low birth weight and stillbirth (Fig. 1).

In humans, sleep deprivation results in over-production of adrenaline and cortisol [64]. Although the sympathetic nervous system is usually dampened during sleep with the parasympathetic system mainly responsible for maintenance of heart rate and blood pressure, sympathetic activity rebounds when there is SDB, particularly if there is persistent deprivation, or fragmentation or interruption of sleep [64]. Additionally, cognitive and attention deficits have been associated with cumulative chronic partial sleep deprivation as well as sleep fragmentation [65,66].

Some of these neuro-behavioral issues are mediated through the hypothalamic-pituitary-adrenal (HPA) axis. The HPA system is the major neuroendocrine system that coordinates the stress

response and is mediated by cortisol. Activity of the HPA axis occurs in a circadian rhythm with the release of glucocorticoids just prior to awakening [64]. Sleep deprivation and fragmentation results in elevated cortisol levels [64] as well as promoting a pro-inflammatory state as previously described. Furthermore, there is evidence suggesting that although individuals with OSA maintain the circadian variation of cortisol secretion, the early morning rise (cortisol awakening response) is muted [67].

During pregnancy, maternal cortisol normally increases with gestation, and transplacental transfer and subsequent fetal exposure is regulated by a key placental enzyme (11β-hydroxysteroid dehydrogenase type 2). The placenta also produces corticotrophin-releasing hormone, which controls both maternal and fetal cortisol levels via a feedback mechanism. It has been suggested that increased maternal cortisol levels as a result of stress can influence metabolic and neurological programming of the fetus contributing to long term insulin resistance and behavioral problems in offspring including depression, anxiety as well as attention and learning difficulties [68]. This may be related to the gestation at which the fetus is exposed to the high levels of maternal cortisol with the effects differing between early and late gestation exposure with early exposure associated with poorer outcomes [69]. Given the known impact SDB has on the immune and stress systems both within and outside of pregnancy, it is possible that changes in the ratio of pro-to anti-inflammatory cytokines as well as elevated cortisol levels may increase the risk of adverse pregnancy outcomes. The causal pathway may be separate or synergistic (Fig. 1).

Outside of pregnancy, OSA is a risk factor for diabetes mellitus [19] while in pregnancy it increases the risk of gestational diabetes regardless of maternal BMI [7,8,70]. There is now evidence suggesting that obesity is not just a risk factor for OSA due to its association with other co-morbidities but also mediated through the pro-inflammatory characteristics of adipose tissue itself [57]. TNF-α and IL-6, along with the adipostatic hormone leptin, are released from fat and their levels correlate with BMI. TNF-α is associated with heightened lipolysis, insulin resistance and leptin secretion [71]. Chronically elevated levels of leptin have been associated with increased sympathetic activation and high blood pressure, seen in OSA [71]. A similar mechanism may also play a role during pregnancy. A recent small pilot study of women with gestational diabetes mellitus showed that pro-inflammatory cytokines (IL-6, IL-8 and TNF-α) were positively correlated with the apnea hypopnea index (AHI) [72]. This relationship appeared to be independent of insulin resistance and diabetes.

Impact of SDB on placental development and homeostasis

Although placental development is largely complete by 24 wks it continues to increase in size almost linearly throughout gestation with a median placental to birthweight ratio of approximately 0.19 for boys and 0.2 for girls at 40 wks gestation [73] thus allowing the increasing metabolic demands of the fetus to be met [74]. There is evidence that nulliparous women with greater decreases in sleep duration over the course of their pregnancy have babies with lower birth weight z-scores compared to controls [75]. Ravishankar et al. [22] provide histopathological evidence of placental hypoxia in women who habitually snore as well as those who have OSA. They showed that two markers of chronic tissue hypoxia - fetal normoblastemia and carbonic anhydrase IX expression, were significantly higher in placentae from women with SDB. Another study by Tauman et al. [76] demonstrated that habitual maternal snoring was associated with elevated levels of fetal erythropoiesis and higher levels of nucleated red blood cells, erythropoietin, and IL-6 circulating in cord blood.

There is evidence that intermittent hypoxia and re-oxygenation that occurs during SDB results in elevated levels of oxidative stress and increased production of ROS, cellular necrosis and placental apoptosis [77]. Both *in-vitro* and animal models suggest that these episodic insults are associated with greater placental oxidative stress and cellular apoptosis compared to sustained hypoxia [78].

There is also evidence that levels of biomarkers indicative of placental function are altered in women with SDB. Levels of pregnancy associated plasma protein-A (PAPP-A), estriol, placental growth factor (PlGF), inhibin-A and hCG are reported to be lower in pregnant women with OSA while levels of the anti-angiogenic protein soluble fms like tyrosine kinase-1 (sFlt-1) are increased with an elevated sFlt-1/PlGF ratio [79,80]. Maternal PlGF levels increase throughout pregnancy peaking around 32 wks gestation. It is largely produced by the placenta and is reflective of placental function [81]. The gene for PlGF is located in the same chromosomal region as the gene for pituitary growth hormone and encodes a peptide hormone of 191 amino acids that differs from pituitary growth hormone by only 13 amino acids [81]. Outside of pregnancy decreased levels of pituitary growth hormone are associated with fragmented and decreased sleep [82,83]. The decreased PlGF levels seen in some women with SDB may thus possibly further aggravate maternal sleep.

In late pregnancy, estriol is a biomarker of placental function as its production is dependent on functioning fetal adrenal glands, liver and placenta. Estriol levels have been shown to be significantly reduced in women with OSA consistent with concurrent placental dysfunction [80]. (Fig. 1).

However, the data regarding placental biomarkers and OSA is conflicting with another study of biomarkers [alpha-fetoprotein (AFP), estriol, hCG, inhibin-A and PAPP-A] measured in the first and second trimesters showing no association with maternal snoring [84]. The authors postulate that snoring alone may be insufficient to impact placental function and adverse pregnancy outcomes were likely to be mediated by a different causal pathway [84]. Another possibility is that snoring is likely to increase in later gestations and therefore the timing of the insult may need to occur earlier in gestation to have an observable effect on placental biomarkers.

Collectively, both in vivo and in vitro placental biomarker studies suggest that SDB, particularly OSA, has a detrimental effect on placental development. It is likely that the relative maternal "hypoxic" state associated with OSA results in placental malperfusion and hypo-oxygenation leading to aberrations in vasculogenesis and angiogenesis with many features similar to that in other placentally mediated disorders such as pre-eclampsia [5,6,85–89]. Extraplacental consequences of altered levels of biomarkers include increased vascular permeability and extravasation of fluid into the airway interstitial space leading to constriction mediated by vascular endothelial growth factor (VEGF) in women with OSA [90].

Adverse outcomes associated with supine sleep position

Maternal sleep position was included in this review, given the association with supine sleep position and adverse maternal and perinatal outcomes including low birth weight [15] and stillbirth [15–18]. More than 80% of pregnant women spend some time sleeping in a supine position with the time in this position accounting for more than a quarter of total sleep duration [91]. Supine sleep position has significant effects on maternal hemodynamics. Compared to the left lateral position, the supine position results in a 20% reduction in maternal cardiac output [92], 45% reduction in lower limb blood flow [93] and an increase in symptomatic

hypotension [94]. These observations are largely secondary to aorto-caval compression by the enlarging gravid uterus and is most pronounced at later gestations. In contrast, sleep in the left lateral position significantly improves venous return, stroke volume and cardiac output from as early as 20 wks gestation compared to the supine position [95]. There is also evidence that maternal position can affect fetal behavioral state and heart rate [96]. Fetal activity is reduced when a woman is in a semi-recumbent supine or right lateral position with increased fetal movements and improved fetal heart rate variability seen in the left lateral position [96]. Whilst the precise mechanisms underlying the detrimental effects of supine sleep position have yet to be elucidated it is likely that they centre on the severity and chronicity of interruption of uteroplacental blood flow secondary to aorta-caval compression.

Conclusions

The available evidence from animal and human studies now suggest that the causal pathway for some adverse pregnancy outcomes in women with SDB or supine sleep position arise as a consequence of hypoxia, either acute, intermittent or chronic in nature. The cascade of events of disparate, yet interconnected, systems detailed in earlier sections culminate in placental dysfunction. However, the relationship between maternal sleep disorders and supine sleep position and adverse pregnancy outcomes is confounded by a number of maternal co-morbidities specifically obesity and pre-existing cardiorespiratory disorders. Outcomes are likely influenced by the severity and duration of SDB in pregnancy as well as the gestation at which it occurs. If significant SDB is present in early pregnancy, particularly during the window of critical placental development or at a time when the fetus is undergoing rapid growth, then complications are likely to be more severe.

It is however unlikely that a single mechanistic pathway is responsible for all possible adverse outcomes in women with SDB during pregnancy. Alterations in the angiogenic balance, endothelial dysfunction and dysregulation of the immune system with a skew towards pro-inflammatory cytokines, activation of the maternal stress system, over-production of ROS as a result of hypoxia-reperfusion events both systemically as well as within the feto-placental unit may all play a role. Some of the hypoxia mediated molecular, inflammatory and endocrine changes may also act to further aggravate maternal sleep in a feedback mechanism.

Maternal sleep position and SDB are potentially modifiable or treatable factors that if addressed appropriately have the potential for reducing poor outcomes. For increased clinical recognition of SDB/supine sleep position by obstetric practitioners as risk factors, further research and education is required, as well as the development of appropriate pregnancy specific screening and diagnostic tests for sleep disorders.

Practice points

- Sleep disordered breathing causes intermittent maternal hypoxia and re-oxygenation subsequently resulting in increased oxidative stress and the production of reactive oxygen species. The extent of this is gestation dependent.
- Pregnancy stresses the maternal respiratory system which results in an increased susceptibility to airway compromise and hypoxia.
- Hormonal and cardiovascular changes associated with pregnancy can aggravate maternal sleep in susceptible individuals.
- Maternal hypoxia results in a cascade of cytokines and anti-angiogenesis factors that heightens the pro-inflammatory state of pregnancy and aggravates placental and endothelial dysfunction.
- The predominantly pro-inflammatory state likely plays a mediating role in adverse perinatal outcomes.
- Perturbations in maternal levels of cortisol is implicated in modification of the fetal hypothalamic-pituitary axis with potential adverse consequences.
- Supine maternal sleep position is associated with adverse obstetric outcomes and is a modifiable risk factor to improve pregnancy outcomes.

Research agenda

- The impact of maternal SDB on placental function.
- The influence of gestational age and SDB on perinatal outcomes.
- Timing and diagnostic criteria for SDB in pregnancy.
- Impact of education for both clinicians and pregnant women regarding maternal sleep position.
- Impact of treatment options (e.g., continuous positive airway pressure) in pregnancy on maternal symptoms and pregnancy outcomes.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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