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Sleep-Disordered Breathing During Pregnancy: Future Implications for Cardiovascular Health

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Abstract

Importance—Cardiovascular disease (CVD) is a common condition in post-reproductive females. Key risk factors for later-life CVD include gestational hypertension (GHTN) and pre-eclampsia (PE). Although several risk factors for hypertension in pregnancy are well recognized, a novel risk factor that has emerged recently is sleep-disordered breathing (SDB), a condition characterized by repeated closure of the upper airway during sleep with disrupted ventilation and sleep fragmentation. In the non-pregnant population, SDB is now known to play a causal role in future cardiovascular disease.

Objective—To propose the hypothesis that occult SDB during pregnancy may play a role in long-term cardiovascular disease in women who had hypertensive disorders of pregnancy.

Evidence Acquisition—A review and synthesis of empirical evidence that links SDB to GHTN/PE and GHTN/PE to future cardiovascular disease.

Results—An increasing body of evidence supports the relationship between SDB and hypertensive disorders of pregnancy via mechanisms of inflammation, oxidative stress, and endothelial dysfunction. It is well established that hypertensive disorders of pregnancy are associated with long-term risk for cardiovascular disease via similar mechanisms. However, no studies have addressed the potential role for SDB in long-term outcomes of women with GHTN/PE during pregnancy.

Conclusion—Given the suggested mechanisms that explain these associations, it is plausible that SDB during pregnancy may increase long-term cardiovascular morbidity and mortality.

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Relevance—Pregnancy may offer a window of opportunity for identification and treatment of SDB which could provide substantial health benefit for many years to come.

Target Audience—Obstetricians & Gynecologists, Family Physicians

Learning Objectives—After completing this CME activity, physicians should be better able to evaluate the current evidence regarding the frequency of sleep-disordered breathing in pregnancy, its risk factors, subsequent outcomes, and treatment.

Introduction

Emerging literature suggests that habitual snoring, a key symptom for sleep-disordered breathing (SDB), is highly prevalent among pregnant women, affecting up to one third by late pregnancy.[1–5] In hypertensive pregnancies the frequency of snoring is even higher.[1] More broadly, sleep disturbance is a common complaint during pregnancy, and is most likely explained by hormonal, physiological and physical changes.[6–8] The physiological changes of pregnancy may introduce or exacerbate pre-existing sleep disorders including insomnia, restless leg syndrome, and SDB.[6, 7, 9] Of particular interest, habitual snoring has been independently associated with both gestational hypertension and pre-eclampsia (PE).[3, 5, 9–13] Notably, large epidemiologic studies from the past three decades have clearly shown that PE confers a risk for future maternal cardiovascular disease.[14, 15] Given the emerging association between SDB and hypertensive disorders during pregnancy, as well as the known relationships between gestational hypertension/PE and long-term cardiovascular disease, an intriguing question arises: Could disturbed sleep during pregnancy promote long-term cardiovascular disease in women? This hypothesis is illustrated in Figure 1.

Sleep-Disordered Breathing

A common sleep disorder, SDB represents a spectrum of respiratory disturbances that include habitual snoring, increased upper airway resistance, and obstructive sleep apnea (OSA), the latter being the most severe. Snoring and witnessed apneas are considered key symptoms of SDB. However, a diagnosis of SDB and its severity are determined by overnight polysomnography. The number of partial and complete obstructive events per hour of sleep that are associated with decreased blood oxygenation or arousals is calculated and reported as the Apnea-Hypopnea index (AHI).[16] An AHI>5 combined with reported excessive daytime sleepiness, or an AHI>15 in the absence of daytime symptoms, is required for the diagnosis of OSA.[17] The prevalence of OSA in women is estimated at 2–5%, compared with 3–7% in men.[18] However, this is likely an underestimation since the majority of women with OSA are undiagnosed.[19] Several risk factors are associated with OSA, including obesity, male gender, age, race, smoking, large neck circumference, craniofacial anatomy, asthma, and chronic rhinitis.[18, 20–22] In particular, obesity is a well-established risk factor for SDB, and increasing weight heightens the risk of SDB development or exacerbation.[23] Notably, an increase of 10% in body weight significantly increases the risk for OSA[24] and weight loss alleviates SDB symptoms;[25] this is of particular relevance to pregnant women.

In the past decade, multiple longitudinal and epidemiological studies consistently have demonstrated a clear association and a causal pathway between OSA and incident cardiovascular disease later in life, including hypertension, myocardial infarction, and stroke.[26–28] In a 12-year follow-up of more than 1,800 hypertension-free adults, the hazard ratio for incident hypertension among those with a diagnosis of OSA was 1.96 (95% CI 1.44–2.66).[27] Notably, nightly use of Continuous Positive Airway Pressure (CPAP) therapy, the first-line treatment for OSA, reduced the hazard ratio to 0.71 (95% CI 0.51–0.94).[27] A similar study from Spain compared cardiovascular mortality among patients with severe OSA; the investigators reported a hazard ratio of 3.5 (95% CI 1.23–9.98) in untreated individuals, and a hazard ratio of 0.55 in those treated with CPAP (CI 0.17–1.74).[26] In fact, occult SDB is now considered to be one of the most common underlying factors in resistant hypertension.[29]

Pregnancy as a Risk Factor for SDB

Physiological, physical, and hormonal changes that occur during pregnancy include increased weight gain, elevation of the diaphragm, fluid retention, and increased levels of circulating estrogen and progesterone. Pregnant women in comparison to non-pregnant peers have a larger neck circumference and narrower upper airways, which likely lead to increased collapsibility of the upper airway.[1, 2] Additional fat depositions in the chest and abdomen may restrict lung volumes.[22] Similarly, fluid retention, common during pregnancy, and driven by hyperemia, is an additional contributor to nasal congestion and upper airway narrowing.[6] Furthermore, upward displacement of the diaphragm to accommodate uterine expansion leads to a reduction in functional residual capacity, which decreases maternal oxygenation. Estrogen fluctuations may trigger a cascade of events, causing edema and vasomotor rhinitis that in turn contribute to upper airway narrowing or obstruction. Given the overlap between physiological changes during pregnancy and known risk factors for SDB, pregnancy appears to be a key risk factor for SDB. Indeed, increasing evidence now clearly shows that the frequency of SDB in pregnancy increases 2–4-fold compared to the pre-pregnancy state.[5, 6, 10, 30] Up to 15% of obese first trimester women have SDB when assessed by polysomnography[31] while up to 35% of third trimester women screen positive for SDB.[3] The high prevalence of SDB among pregnant women is important because it has been independently associated with adverse pregnancy outcomes, including maternal hypertensive disorders and fetal growth restriction.[3, 5, 10–1232–34] Although these findings have important clinical implications, at present few obstetric healthcare providers screen for SDB and the vast majority of affected women likely remain undiagnosed.

Sleep Disordered Breathing, Gestational Hypertension, and Preeclampsia – evidence for an association

Preeclampsia and gestational hypertension affect 3–5% and 8–10% of pregnancies respectively[35] and contribute to serious maternal and fetal complications. Of particular concern is PE, a pregnancy-specific syndrome observed after the 20th week of gestation and defined as blood pressure ≥140/90mmHg measured on two occasions at least 6 hours apart along with proteinuria.[36] From a public health perspective, it is alarming that the frequency of PE has increased by nearly one-third over the past decade.[37, 38] Pre-pregnancy

overweight and obesity have been implicated as potential culprits behind this observed change[39] but, of note, SDB has also become much more common during a similar time interval.[40]

Additional risk factors for PE include pregnancy at either extreme of reproductive age, chronic hypertension or diabetes, gestational hypertension, excessive weight-gain during pregnancy, new paternity, family-history of PE, nulliparity, and excessive placental size.[41] As an exposure, PE is in turn associated with several adverse maternal and fetal outcomes. Specifically, PE is a risk factor for stillbirth, preterm birth and intrauterine growth restriction.[35] As we discuss later, women who experience PE are also at a higher risk for future cardiovascular disease.[15]

In recent years, interest has surged in the association between SDB and pregnancy outcomes, particularly gestational hypertension and PE (see Table 1). Surveys of pregnant or recent postpartum women suggest that habitual snoring in pregnancy is associated with an approximate 2-fold increased risk for gestational hypertension and PE.[3, 5, 10, 11] Witnessed apnea has been reported to be associated with an increased risk of gestational hypertension and PE, with some studies suggesting that the risk is increased 7–8 fold.[9, 12] In the largest longitudinal study to date, that included over 1,700 pregnant women, we recently reported that new-onset snoring during pregnancy, but not chronic snoring, was independently associated with gestational hypertension, odds ratio 2.4 [95%CI 1.5–3.8] and PE, odds ratio 1.6 [95%CI 1.1–2.4] after accounting for other known risk factors, particularly BMI.[5] These findings suggest that the new-onset snoring during gestation, with little time for physiological adaptation to occur, may adversely impact maternal blood pressure.

Although large-scale objective polysomnographic data are lacking in pregnancy, several small objective studies suggest an association between a diagnosis of OSA and hypertension (Table 2).[9, 32, 33] One study of oxygen monitoring only did not find an association.[42] Conversely, a high frequency of occult OSA has been found in women with gestational hypertension and PE.[43] Indeed, from our own data, almost half of the women with gestational hypertension or PE have unrecognized OSA (O'Brien et al under review). In addition to the increased maternal morbidities, consequences of SDB also include increased risk for adverse delivery and neonatal complications such as cesarean section, preterm birth, fetal growth restriction, and admission to the neonatal intensive care unit.[31–34, 44]

Treatment of SDB

Continuous positive airway pressure (CPAP) is the first-line treatment for SDB and delivers a constant pressure to the airway, thereby acting as a splint to keep the airway open during sleep. A meta-analysis of randomized controlled trials in a non-pregnant population that allocated SDB patients to CPAP treatment and placebo groups[45, 46] reported a reduction in 24-hour ambulatory mean blood pressure among SDB patients who received CPAP. Furthermore, CPAP therapy is associated with positive long-term effects among hypertensive patients with confirmed SDB;[47] two years after initiation of CPAP therapy, blood pressure was significantly lower than baseline values for compliant CPAP users with severe hypertension. Notably, in a randomized, controlled, cross-over trial that enrolled

subjects with moderate/severe OSA and metabolic syndrome, those treated with CPAP showed an improvement in all components of the metabolic syndrome.[48]

Studies of CPAP therapy in pregnancy, however, are limited. The safety of CPAP during pregnancy has been demonstrated in a study of twelve pregnant women with confirmed SDB.[49] All women showed significant improvement over baseline in their SDB status and no adverse outcomes were observed, suggesting that CPAP treatment during pregnancy is safe and beneficial. Similarly, in small studies, CPAP use has been shown to improve blood pressure in hypertensive and pre-eclamptic women with mild forms of SDB[50–52] possibly due to improved cardiac output and reduced peripheral resistance.[53] However, the long-term cardiovascular health among women who used CPAP during pregnancy remains unknown.

Preeclampsia and cardiovascular disease - evidence for an association

Preeclampsia has been identified as a strong risk factor for future cardiovascular disease. A number of large epidemiological studies, including a meta-analysis,[54] have linked gestational hypertension and PE with long-term sequelae such as hypertension, ischemic heart disease, and stroke.[15, 55–58] A recent study assessed major cardiovascular disease risk factors in women with early onset pre-eclampsia, compared to controls, and found a high prevalence of risk factors including a 3.5-fold increase in metabolic syndrome.[59] Therefore it is plausible that maternal SDB, an emerging modifiable risk factor for hypertension and PE in pregnancy, may play a role in the future cardiovascular health of women. Data summarizing the associations between PE and cardiovascular disease are discussed below and summarized in Table 3.

Risk of Future Hypertension

A number of studies, including a meta analysis,[60] have reported robust relationships between PE and future cardiovascular and cerebrovascular diseases.[61–68] A registry-based cohort study of over 780,000 women without pre-existing cardiovascular disease who delivered in Denmark between 1978 and 2007 found that, at follow-up approximately 14.5 years later, women with severe PE in a first pregnancy had a 6-fold increased risk of hypertension later in life after adjusting for other known risk factors.[61] Significantly increased risk for future hypertension was also observed in women with mild and severe PE and women with gestational hypertension, odds ratios of 3.6, 6.0 and 5.3 respectively.[61] Similarly, among 15,065 women with a first singleton birth between 1967 and 1995, PE in a first pregnancy, as compared to normal blood pressure, was associated with higher systolic and diastolic blood pressure at follow-up 16 years later.[69] In addition, a 3-fold increased risk for use of antihypertensive medication was also found in the women with a history of PE.

In a meta-analysis of 13 cohort studies representing approximately 3.5 million pregnant women, 198,000 of whom had had PE, the latter showed a significantly increased relative risk for future hypertension (3.7 [95%CI 2.7–5.1].[66] Notably, women with two consecutive pregnancies affected by preeclampsia had particular vulnerability to hypertension in later life, with estimates suggesting a 6 to 11-fold increased risk compared with women who experienced two normotensive pregnancies.[61, 69] Even in women without PE but who had gestational hypertension during one or more pregnancies, an increased risk of subsequent

hypertension has been found.[69] A recent literature-based study demonstrated that cardiovascular risk factors did not fully explain the risk of CVD after PE and that PE conferred an independent and additive risk.[70] However, lifestyle interventions after PE were found to decrease CVD risk between 4–13%. Of note, a factor that was not acknowledged in this latter report, and which is becoming increasingly recognized as having a probable role in both PE and future CVD, is SDB. See Table 3.

Risk of Ischemic Heart Disease

In addition to increased risk of chronic hypertension later in life, women with PE as compared to normotensive pregnant peers, have double the risk for development of ischemic heart disease (IHD) and triple the risk for CVD-related death.[66, 71–73] The relative risk for future IHD is higher among women with a history of severe PE (2.9 [95%CI 2.3–3.7]) and also higher among women with mild PE (1.9 [95%CI 1.7–2.2]) as compared to women who were normotensive during pregnancy.[68] The magnitude of the risk for future maternal CVD is significantly affected by the timing of PE onset, its severity, and recurrence. In a meta-analysis of 8 studies (following 2,346,997 women for 11.7 years), the relative risk of IHD in women with PE as compared to peers with normotensive pregnancies was 2.6 [95%CI 1.9–2.5].[66]

Risk of Stroke

Pregnancy is an independent risk factor for stroke.[74] Increased risk for stroke, both ischemic and hemorrhagic, has been observed during pregnancy as well as during the puerperium and postpartum periods.[75] Stroke is estimated to occur in 34.2/100,000 deliveries in the United States,[76] and its risk is up to 3 times higher for women during pregnancy and the postpartum period compared to non-pregnant periods.[77, 78] The highest risk has been suggested to be around childbirth, from two days before to 1 day after delivery.[79] In a review of prenatal hospitalizations between 1994–1995 and 2006–2007,[80] the rate of any stroke (subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke, transient ischemic attack, cerebral venous thrombosis, or unspecified) increased by 47% (from 0.15 to 0.22 per 1000 deliveries) among hospitalized pregnant women and by 83% (from 0.12 to 0.22 per 1000 deliveries) during postpartum hospitalizations. No change in the number of delivery hospitalizations for stroke was noted. In 2006–2007, approximately 32% and 53% of prenatal and postpartum hospitalizations with stroke, respectively, involved patients with concurrent hypertensive disorders or heart disease. Changes in the prevalence of these 2 conditions from 1994–1995 to 2006–2007 explained almost all of the increase in postpartum hospitalizations with stroke during the same period. The prevalence of SDB in these women was unknown.

Hypertensive disorders during pregnancy further increase the risk for pregnancy-related stroke.[75] Compared with normotensive pregnancy, hypertensive pregnancy confers up to a 9-fold increased risk for stroke.[71, 76, 80, 81] The majority of studies that have investigated relationships between PE and stroke have focused on the perinatal period. However, in a meta-analysis of 64,000 women with an average follow-up time of 10.4 years, the relative risk for non-fatal stroke among women with previous PE, in comparison to women who had had normotensive pregnancies, ranged from 1.4 to 2.1, and the relative risk for fatal stroke

was 3.6 to 5.1.[66] Finally, stroke risk in pre-eclamptic pregnancies is significantly higher for women in third trimester, around delivery and in the puerperium periods compared to non-pregnant or earlier in their pregnancy.[79]

Does SDB play a role in future cardiovascular risk?

Given the known associations between gestational hypertension, PE, and future cardiovascular risk, together with the emerging relationships between SDB and hypertension during pregnancy, we hypothesize that maternal SDB plays a role in long term CVD in women (see Figure 2). The prevalence of gestational hypertensive disorders have risen substantially in recent years and we suggest the possibility that the population attributable fraction for future CVD (i.e., the number of cases of future CVD among women with SDB during pregnancy that can be attributed to SDB) may be reduced if undiagnosed SDB is identified and treated during pregnancy. Causal associations between SDB, PE, and long-term CVD are biologically plausible and potential mechanisms are discussed below.

Potential Mechanisms

Several mechanisms have been proposed to explain the association between SDB and cardiovascular disease including sympathetic activity, oxidative stress, inflammation and metabolic syndrome. A well-described pathway involves increased sympathetic activation engendered by frequent arousals and repetitive apneas. These surges in sympathetic activity ultimately result in elevated nocturnal and daytime blood pressures, a key factor in the pathogenesis of cardiovascular morbidity.[29, 82] In pregnant women, sympathetic over-activity is one of the hallmarks of PE.[83] Recent work suggests that *all* pregnancies have peripheral sympathetic over-activity but that this activity manifests in an extreme form in hypertensive pregnancies.[84–86] Interestingly, several small studies show that the majority of women with PE have underlying SDB.[243] This relationship is most probably bi-directional and although SDB is not likely to cause PE, it is plausible that the development or worsening of SDB during pregnancy contributes to the manifestation of PE.

Characteristic of SDB, episodes of intermittent hypoxia and re-oxygenation are involved in the generation of Reactive Oxygen Species (ROS) and reduction in the levels of circulating antioxidants. The imbalance between ROS and antioxidants leads to oxidative stress that plays a central role in endothelial damage and is associated with hypertensive disorders.[87] In addition, ROS may also induce or exacerbate inflammatory processes.[88] The inflammatory response to SDB involves activation of the pro-inflammatory cytokines TNF-alpha and IL-6 as well as adipokines and C-reactive protein.[89] A feed-back loop may also exist whereby ROS-induced inflammation may in turn exacerbate oxidative stress.[88] Such mechanisms are involved in the endothelial injury and dysfunction that result in atherosclerosis and cardiovascular disease.[87]

Normal physiological processes including embryo implantation and pregnancy are associated with induction of inflammatory pathways. Such inflammation is carefully balanced with endocrine processes that promote pregnancy success.[90] However, departure from this equilibrium could produce angiogenic imbalance and induce a cascade of pro-inflammatory cytokines.[91] Such imbalance is related to failed implantation as well as poor

pregnancy outcomes including hypertension and PE; this exacerbated inflammatory response may contribute to disrupted remodeling of blood vessels observed in PE.[92] Moreover, women with a history of PE are more likely to have myocardial damage, global diastolic dysfunction, and significant remodeling of the heart.[93] Notably, significant overlap exists between proposed mechanisms for PE and those that relate SDB to cardiovascular disease.[94, 95]

Obstructive sleep apnea also has a bi-directional association with metabolic syndrome, defined as hyperglycemia, dyslipidemia, hypertension and central obesity,[87] which in turn is a risk factor for cardiovascular disease. In addition to its link with SDB, metabolic syndrome is also associated with increased risk for diabetes. Increased sympathetic activity in the presence of elevated insulin levels, a normal phenomenon during pregnancy, may give rise to diabetes and hypertension.[94] Lower insulin sensitivity is reported among those with OSA.[96] Goodson et al proposed a synergistic effect of SDB and metabolic syndrome on cardiovascular diseases.[97] A population-based study investigated the association between OSA and metabolic syndrome among 400 women whose age range was 20–70 years.[98] Women with a confirmed diagnosis of OSA, as compared to those without, had a higher frequency of metabolic syndrome. The relationship followed a dose-response pattern, showing a higher risk for metabolic syndrome with increased AHI severity. Two recent studies compared frequencies of metabolic syndrome components between OSA-confirmed subjects and controls[99, 100] and reported a 3-fold increased risk for obesity, hypertension and diabetes among those with confirmed OSA compared to those without.[99] Non-obese subjects with OSA had a significantly higher prevalence of hypertension and dyslipidemia, in addition to two or more other metabolic abnormalities.[100] Of note, treatment of OSA has been shown to improve all components of metabolic syndrome.[44]

Conclusions

In this review we present evidence that pregnancy is a period of heightened vulnerability to SDB. The SDB in turn is likely to raise the risk for hypertensive disorders of pregnancy, which in turn may increase long-term cardiovascular morbidity and mortality. Obesity and the metabolic syndrome have important influences on all steps in this pathway, including pregnancy, SDB, gestational hypertension, and long-term CVD risk. The key insight, for the purposes of clinical practice, may be that SDB during pregnancy could translate not only into maternal and fetal complications, but also to increased risk for consequential CVD later in life. If so, pregnancy may offer a window of opportunity, for identification and treatment of SDB, which could provide substantial health benefit for many years to come. Whether SDB during pregnancy directly increases future CVD risk remains uncertain, as does the question of whether pregnancy may augment vulnerability to SDB. The possibility exists that after many years and increased weight gain, individuals whose vulnerability had been briefly revealed during pregnancy may again develop both SDB and associated CVD. Further research on SDB, gestational hypertensive disorders, and long-term cardiovascular health – each a public health priority in its own right – is likely to require significant resources, but seems likely to provide substantial return on the investment.

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Questions

1. Which of the following is true:
   - **a.** The physiological changes of pregnancy are protective against sleep-disordered breathing
   - **b.** *Pregnancy is a risk factor for sleep-disordered breathing
   - **c.** Sleep disordered breathing is benign
   - **d.** Treatment of sleep-disordered breathing is contraindicated in pregnancy
2. Which of the following is not true?
   - **a.** pregnancy is a risk factor for stroke
   - **b.** sleep-disordered breathing is a risk factor for hypertension
   - **c.** *mechanisms of pre-eclampsia are distinct from mechanisms which relate sleep-disordered breathing to cardiovascular disease
   - **d.** CPAP may improve blood pressure
3. Women with a previous history of pre-eclampsia:
   - **a.** Have a low risk for metabolic syndrome
   - **b.** Have the same long term cardiovascular risk as women without a history of pre-eclampsia
   - **c.** *Are at risk for long-term cardiovascular disease
   - **d.** Will develop sleep-disordered breathing in subsequent pregnancies
4. A pregnant woman with pre-eclampsia complains of loud snoring at night. The most likely diagnosis is:
   - **a.** pregnancy-associated rhinitis
   - **b.** *sleep-disordered breathing
   - **c.** exacerbation of pre-eclampsia
   - **d.** upper airway infection

Correct answer notated with *

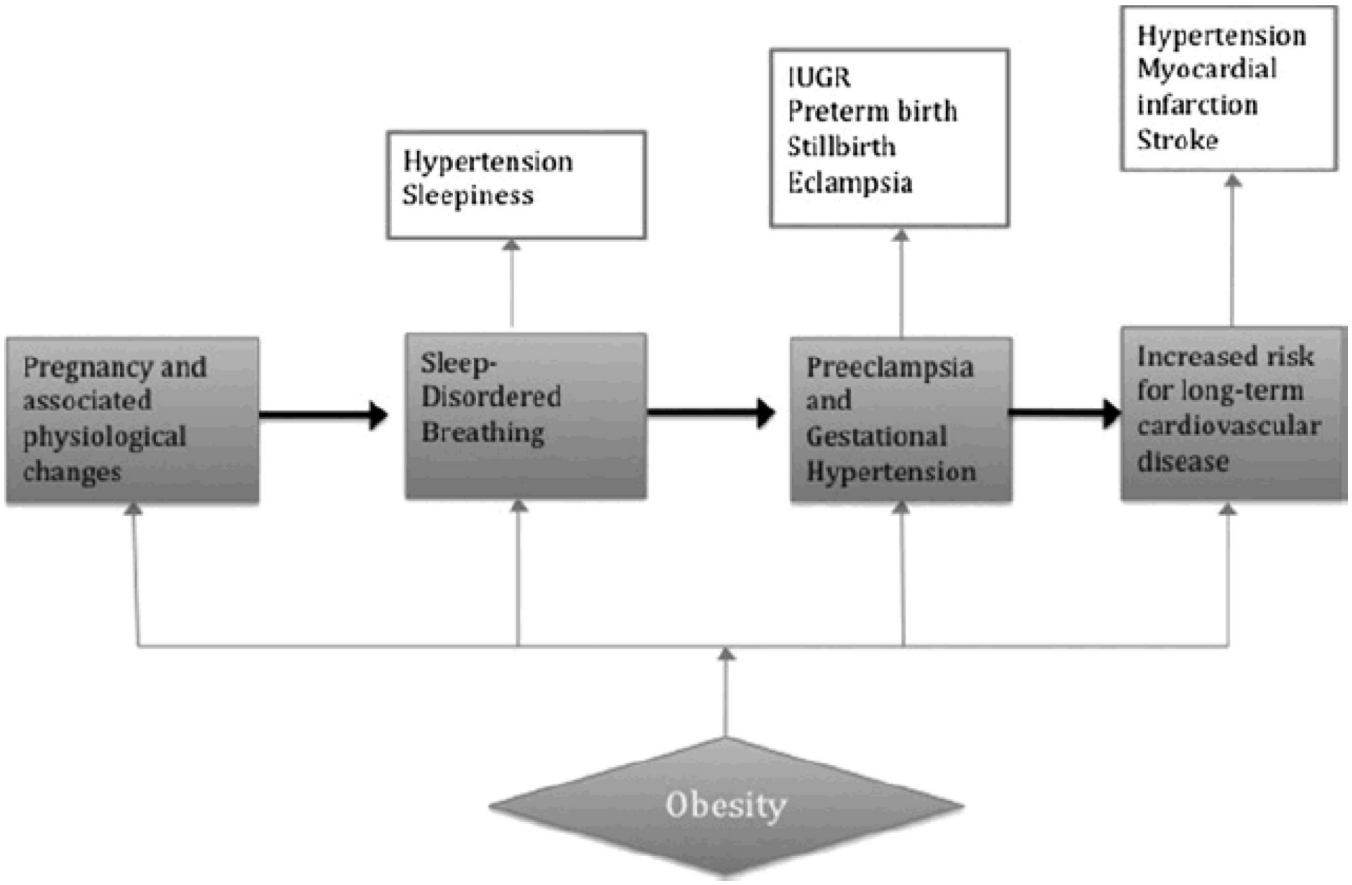

FIG. 1.
IUGR indicates intrauterine growth restriction.

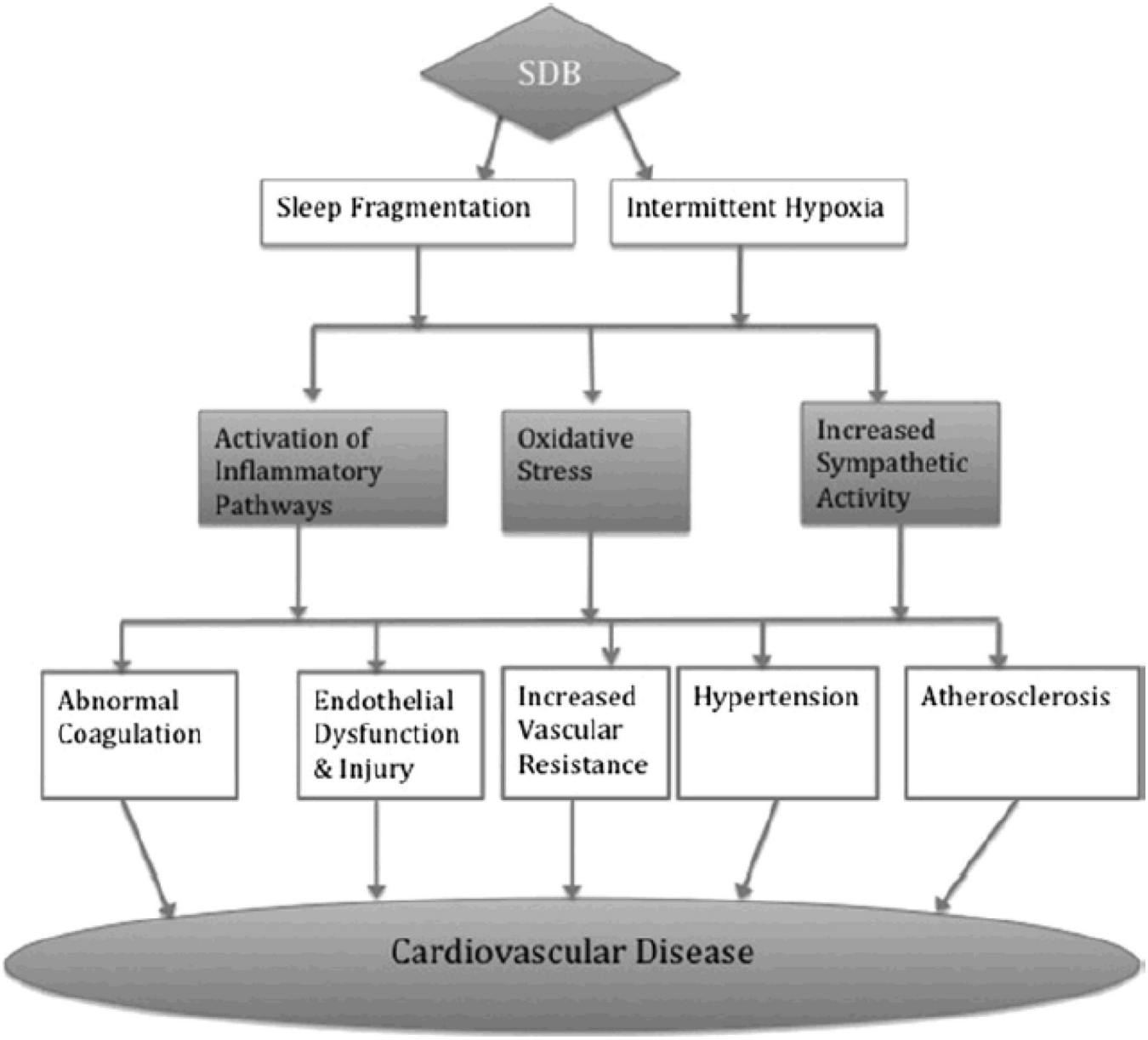

FIG. 2.

Table 1

Association of snoring with hypertensive disorders during pregnancy

Author	Year	Study Design Sample Size	OR (95% CI)	Comments
Franklin et al[10]	2000	Cross-sectional Questionnaires from n=502 pregnant women	GHTN: OR=2.03 (95%CI 1.01–4.10; p<0.05) PE: OR=2.18 (no CI provided as not quite significant; p<0.07)	Habitual snorers more likely to have GHTN compared to non-snorers, after adjusting maternal weight, maternal age, and smoking, although the relationship between snoring and PE was not significant
Izci et al[1]	2005	Cross-sectional Questionnaires from n=167 pregnant normotensive, n=82 pre-eclamptic and n=160 non-pregnant women (controls).	n/a	Snoring reported by 55% of pregnant normotensive, 85% of pre-eclamptic women, and 32% of controls, (p<0.001)
Perez-Chada et al[12]	2007	Cross-sectional Questionnaires from n=447 pregnant women.	GHTN: OR=1.82 (95%CI 1.16–2.84; p<0.01)	Occasional/habitual snorers were more likely to have GTHN than non-snorers after adjusting for pre-pregancy BMI, weight gain, neck circumference, smoking, alcohol, and age.
Ursavas et al[11]	2008	Cross-sectional Questionnaires from n=469 pregnant women, n=208 non-pregnant women- snoring vs. non-snoring	GHTN: OR=1.59 (95%CI 0.74–3.42; p=0.23) PE: OR=1.49 (95%CI 0.55–4.05; p=0.426)	Snoring was more frequent in GHTN compared to controls (19.3% vs. 10.7%, p=0.05) but there was no independent relationship after adjusting for weight before delivery, weight gain, neck circumference, age, and smoking. Snoring was not significantly more frequent in women with PE compared to controls (20% vs. 11.2%, p=0.145).
Bourjeily et al[3]	2010	Cross-sectional Questionnaires from n=1,000 pregnant women	GHTN and/or PE: OR=2.3 (95%CI 1.4–4.0)	Snoring associated with GHTN/PE including after adjusting for a prior history of diabetes mellitus, chronic hypertension, renal disease, and/or pre-eclampsia; maternal age, BMI at delivery, smoking, and multifetal pregnancy.
Ayrim et al[4]	2011	Cross-sectional Questionnaires from n=200 pregnant women and 200 controls	n/a	Habitual snoring found in 5/200 pregnant women (2.5%) and none of the controls. Occasional snoring was found in 36/200 (18%) pregnant and 7/200 controls (3.5%). There was no relationship with snoring and GHTN or PE.
O'Brien et al[5]	2012	Prospective cohort Questionnaires from n=1719 pregnant women	GHTN: OR=2.36, (95%CI 1.48–3.77; p<0.001) PE: OR=1.59 (CI 1.06–2.37; p=0.024)	Pregnancy-onset habitual snoring was independently associated with GHTN and PE after adjusting for maternal age, race, pre-pregnancy BMI, weight gain in excess of Institute of Medicine recommendations, gravidity, smoking, education level, previous or family history of gestational hypertension or pre-eclampsia; however habitual snoring before pregnancy was not.
Owusu et al[13]	2013	Cross-sectional Questionnaires from n=220 women	PE: OR=3.5 (95%CI 1.4–8.5; p=0.007)	Snoring during pregnancy was independently associated with PE after adjusting for maternal age, parity, and gestational age. Note that height and weight are not routinely obtained in Ghana and therefore BMI could not be calculated for women in this sample.

GHTN- Gestational Hypertension; PE-Pre-eclampsia; OR- Odds Ratio; CI-Confidence Interval; BMI-Body Mass Index

Table 2

Objective measures of SDB/OSA and associations with hypertensive disorders during pregnancy

Author	Year	Study/Design Methods Sample Size	OR (95% CI)	Comments
Yin et al[42]	2008	Case-control n=100 women with a hypertensive pregnancy or IUGR and n=78 women with a normal pregnancy; oxygen saturation monitoring	n/a	Number of oxygen saturation dips >4% used as a proxy measure for OSA. Frequency of "OSA" in hypertension was 0/48 (0%), in IUGR 1/33 (3%), and in normal pregnancy 1/69 (1.5%). OSA is not common in hypertensive pregnancies
Champagne et al[9]	2009	Case-control PSGs in n=50 pregnant women: n=17 with GHTN and n=33 non hypertensive; polysomnography	OR=7.5 (95%CI 3.5–16.2; p<0.001) for GHTN in those with OSA	Frequency of OSA (AHI≥15) 14/17 (82%) among hypertensive women, compared with 15/33 (45%) among the normotensive pregnant women. OSA is associated with GHTN after accounting for pre-pregnancy BMI, maternal age, gestational age, prior pregnancies, and previous live births.
Louis et al[33]	2010	Retrospective cohort n=57 women with confirmed diagnosis of OSA n=114 OSA-free obese and n=114 OSA-free non-obese women	n/a	Compared with normal weight controls, women with OSA (AHI≥5) had increased frequency of PE (19% vs. 7%; p=0.02). There were no differences in PE between OSA and non-OSA obese women, nor between non-OSA obese and normal weight women.
Reid et al[43]	2011	Case-control n=34 hypertensive and n=26 normotensive women; polysomnography	OR=8.3 (95%CI 2.1–33.4; p<0.003) for SDB in those with GHTN/PE	SDB (RDI≥5) is more prevalent among, hypertensive women than among normotensive pregnancies (53% vs. 12%; p<0.001). When adjusted for BMI there was no association between SDB and GHTN/PE.
Facco et al[32]	2012	Retrospective cohort n=143 pregnant women; polysomnography	n/a	Increasing severity of OSA (AHI≥5) associated with increased risk of composite measure of adverse pregnancy outcome (pregnancy-related hypertension/gestational diabetes/preterm birth); AHI<5,18.1%; AHI5–14.9, 23.5%; AHI≥15, 38.5% (p=0.038). Obese women with AHI≥15 had highest frequency of adverse outcome, 41.7%.

OR-Odds Ratio; IUGR-Intrauterine Growth Restriction; OSA-Obstructive Sleep Apnea; PE-Preeclampsia; SDB-Sleep Disordered Breathing; AHI-Apnea/Hypopnea Index; RDI-Respiratory Disturbance Index; BMI-Body Mass Index

Table 3

Risk for future cardiovascular events with GHTN or PE

Author	Year	Study/Design Methods Sample Size	OR (CI) / HR (CI) / RR (CI)	Comments
Irgens et al[14]	2001	Population based Cohort of registry data n=626,272 births	OR=1.2 (95%CI 1.02–1.37) for death in women with PE vs. those without OR=8.12 (95%CI 4.31–15.33) for CVD-related mortality in women with PE and preterm delivery vs. controls with term delivery	Risk of future cardiac disease or death is higher among women with PE vs. normotensive pregnant women.
Smith et al[73]	2001	Prospective Cohort n=129,920 singleton births followed for 15–19 years	HR=2.0 (95%CI 1.5–2.5) for IHD admission or death in women with PE compared to reference (women without PE, and with normal birth weight and term pregnancy). HR=7.0 (95%CI 3.3–14.5) for IHD admission or death in women with PE, preterm delivery, and lowest birth weight quintile compared to reference.	PE is associated with future hospital admission or death from IHD
Kestenbaum et al[15]	2003	Cohort n=31,239 hypertensive pregnancies; birth records linked to hospitalizations	Higher risk for cardiovascular events in pregnancies with: GHTN: HR=2.8 (95%CI 1.6–4.8) Mild PE: HR=2.2, CI (1.3–3.6) Severe PE: HR=3.3, CI (1.7–6.5)	Compared to normotensive pregnancies, hypertensive pregnancies are at higher risk for future cardiovascular events
Wikstrom et al[68]	2005	Cross-sectional population-based n=403,550 nulliparous women followed for 15 years; n=207,054 with a subsequent pregnancy	Higher risk of IHD in pregnancies with: GHTN: IRR=1.6 (95%CI 1.3–2.0) Mild PE; IRR=1.9 (95%CI 1.6–2.2). Severe PE: IRR=2.8 (95%CI 2.2–3.7) Higher risk for IHD if GHTN in first pregnancy but not second: IRR=1.9 (95%CI 1.5–2.4) Higher risk for IHD with HTN in both pregnancies: IRR=2.8 (95%CI 2.0–3.9)	Severe hypertensive disease in pregnancy has a stronger association with later IHD than mild hypertensive disease. Recurrent hypertensive disease is more strongly associated with IHD than is non-recurrent disease.
MacDonald et al[60]	2008	Meta Analysis n=116,175 PE and n=2,259,576 normotensive women; CVD >6 weeks postpartum	Increased risk for subsequent cardiac disease Mild PE: RR=2.00 (95%CI 1.83–2.19) Moderate PE: RR= 2.99, (95%CI 2.51–3.58) Severe PE: OR=5.36 (95%CI 3.96–7.27)	PE is associated with increased risk for cardiac disease.
Lykke et al[61]	2009	Registry-based cohort n=782,287 women with 1st singleton and n=536,419 women with two consecutive singleton deliveries	Increased risk for cardiovascular events: Risk for later HTN: GHTN: HR=5.31 (95%CI 4.90–5.75) Mild PE: HR=3.61 (95%CI 3.43–3.80) Severe PE: HR=6.07 (95%CI 5.45–6.77) PE 1st pregnancy only: HR=2.70 (95%CI 2.51–2.90) PE 2nd pregnancy only: HR=4.34 (95%CI 3.98–4.74) 2 PE pregnancies: HR=6.00 (95%CI 5.40–6.67) PE Risk for later thromboembolism: GHTN: HR=1.03 (95%CI 0.73–1.45) Mild PE: HR=1.53 (95%CI 1.32–1.77) Severe PE: HR=1.91 (95%CI 1.35–2.70)	Women with hypertensive pregnancies are at elevated risk for later HTN and CVD. Severity, parity, and recurrence of hypertensive pregnancy disorders increase the risk of subsequent cardiovascular events
Freibert et al[56]	2011	Registry-based cohort n=3,909 women	Complications of pregnancy (preterm delivery, PE, and/or gestational diabetes) are associated with future cardiovascular events: Risk for heart attack: One complication: OR=2.5 (95%CI 1.03–6.0) Two or more complications: OR=4.2 (95%CI 1.4–10.6)	Pregnancy complications are associated with later CVD

Author	Year	Study/Design Methods Sample Size	OR (CI) / HR (CI) / RR (CI)	Comments
			Risk for arrhythmia: One complication: OR=1.6 (95%CI 1.2–2.2) Two or more complications: OR=2.2 (95%CI 1.4–3.5)	
Fraser et al[55]	2012	Prospective cohort n=3,416 women followed for 20 years	PE associated with OR=3.1 (95%CI 1.11–1.53) for 10-year calculated CVD risk	Hypertensive disorders of pregnancy are associated with an increased CVD risk
Smith et al[57]	2012	Prospective longitudinal cohort n=99 PE and n=118 controls; 10 year, 30 year, and lifetime risk estimates of CVD	Risk of CVD in preeclampsia: 10 year risk: OR=13.08 (95%CI 3.38–85.5) 30 year risk; OR=8.43 (CI 3.48–23.23) Lifetime risk: OR=3.25 (95%CI 1.76–6.11)	History of PE is significantly associated with future CVD
Berks et al[70]	2013	Literature-based study Effects of lifestyle interventions on CVD risk	PE associated with IHD: OR=1.89 (IQR 1.76–1.98) and stroke: OR=1.55 (IQR 1.40–1.71) After PE, lifestyle interventions on exercise, dietary habits, and smoking cessation decrease CVD: OR=0.91 (IQR 0.87–0.96)	CVD risk factors do not fully explain risk of CVD after PE and may be explained by an additive risk of CVD by PE. Lifestyle interventions may decrease CVD risk.
Brown et al[54]	2013	Meta analysis and systematic review	Women with PE at increased risk of: CVD: OR=2.28 (95%CI 1.87–2.78) Cerebrovascular disease: OR=1.76 (95%CI (1.43–2.21) HTN: RR=3.13 (95%CI 2.51–3.89)	PE associated with increased CVD and cerebrovascular disease
Hermes et al[58]	2013	Longitudinal 2.5 year follow up of n=300 women with hypertensive pregnancy; n=94 women with a normotensive pregnancy at term; 10 year and 30 year risk estimates of CVD	Risk of CVD in preeclampsia: 10 year risk: IRR=5.8 (95%CI 1.9–19.0) 30 year risk; IRR=2.7 (CI 1.6–4.5).	Women with hypertensive pregnancies at term are at higher extrapolated risk of CVD
Van Rijn et al[59]	2013	Cross Sectional n=243 primiparous women with early-onset PE studied >6 months postpartum; n=374 non-pregnant controls; mean estimated 10 year CVD risk	Mean estimated 10-year CVD risk in PE: OR=1.08 (95%CI 1.04–1.12)	Risk factors for CVD (higher BMI, BP, LDL cholesterol, triglycerides, glucose, and lower HDL) are more prevalent among women with history of PE vs. controls ($p<0.01$). Estimated CVD risk is low after delivery but expected to increase rapidly with age

PE-Preeclampsia; GHTN-Gestational Hypertension; HTN-Hypertension; CVD-Cardiovascular Disease; IHD-Ischemic Heart Disease; OR-Odds Ratio; HR-Hazard Ratio; IRR-Incidence Rate Ratio; CI-Confidence Interval; IQR-Interquartile Range; BMI-Body Mass Index; BP-Blood Pressure; LDL-Low density Lipoprotein; HDL-High Density Lipoprotein