INTRODUCTION

Sleep disordered breathing (SDB) refers to episodic increases in upper airway resistance during sleep. It is generally defined as five or more episodes of apnoea (temporary cessation of breathing) or hypopnoea (decreased airflow) per hour of sleep. Obstructive sleep apnoea (OSA) is the most common form of SDB, and it is characterized by repetitive incomplete or total pharyngeal airway collapse with arousal from sleep required to re-establish airway patency (Figure 1). SDB is diagnosed using an overnight sleep test, which may record respiratory and neurological parameters (polysomnography), or respiratory parameters alone (respiratory polygraphy, Figure 2). The severity of SDB can be described using the apnoea-hypopnoea index (AHI) which describes the number of apnoea and hypopnoea events per hour of sleep. Epidemiological studies have reported that SDB is associated with adverse health outcomes including impaired glucose tolerance, type 2 diabetes, hypertension, cardiovascular events and mortality.2-6
Obesity is an important predictor of SDB and there is consistent evidence demonstrating a strong positive correlation between increasing body mass index (BMI) and prevalence of SDB.\textsuperscript{7,8} A recent study involving more than 2.8 million adults in the United Kingdom (UK) reported that, compared to adults with a normal BMI, there is a 5.8-, 12- and 22-fold increased risk of OSA in adults with BMI 30-35 kg/m\textsuperscript{2}, 35-40 kg/m\textsuperscript{2} and 40-45 kg/m\textsuperscript{2} respectively.\textsuperscript{8} Obesity contributes to the development of SDB through a variety of mechanisms including accumulation of fat in the neck leading to increased airway collapsibility, impaired chest wall compliance and reduced lung functional residual capacity (FRC).\textsuperscript{9}

The prevalence of obesity among pregnant women has increased rapidly over the last 50 years. For example, a fivefold increase from 3.1\% to 15.7\% was observed in Aberdeen, Scotland, between the 1950s and 2000s.\textsuperscript{10} Similar trends have been observed in other UK settings.\textsuperscript{11-13} In many high-income countries, it is estimated that more than 20\% of pregnant women are now obese; in the United States, the prevalence of obesity among women of reproductive age exceeds 30\%, and is greater than 50\% in non-Hispanic Black women.\textsuperscript{14-16} In addition to obesity, increasing age is an important risk factor for SDB.\textsuperscript{17} Women of advanced maternal age comprise an increasing proportion of the obstetric population.\textsuperscript{18} In this context, a growing number of women of reproductive age have an increased risk of developing SDB during pregnancy. Although the exact burden of SDB in pregnancy remains uncertain, one prospective study identified objective evidence of OSA in 40\% of obese women in...
the third trimester, compared to 14.5% of normal and over-weight women.19

Screening and diagnosis of SDB during pregnancy presents unique challenges. Symptoms typically associated with SDB, such as snoring and excessive daytime sleepiness, are commonly experienced in normal pregnancy.20 In addition, questionnaires routinely used to quantify risk of SDB in the non-pregnant population (eg the Epworth Sleepiness Scale, Berlin Questionnaire and STOP-Bang Questionnaire) are not validated in pregnant women, and studies evaluating their predictive capacity in this setting have shown conflicting results.21-23 Furthermore, emerging evidence regarding an association between snoring and adverse pregnancy outcomes has led to debate surrounding the suitability of conventional SDB definitions and diagnostic thresholds during pregnancy.24 Therefore, despite the increasing pool of pregnant women at risk of SDB, the optimal method to identify those in whom further investigation or treatment is indicated remains unknown.

2 | NORMAL RESPIRATORY PHYSIOLOGY DURING PREGNANCY

Normal pregnancy is characterized by mechanical and hormonal changes which lead to significant alterations in respiratory physiology. As the uterus enlarges, the diaphragm is gradually displaced upwards (approximately 4 cm by term), the subcostal angle widens and the chest wall circumference is increased.25 While total lung capacity is preserved by these changes, FRC and its constituent parts are reduced. In addition, the shortening of the thorax alters pleural pressure, which may potentiate earlier closure of the bronchi and airflow limitation.25,26

Ventilatory drive increases steadily across pregnancy, resulting in a 20%-50% increase in minute ventilation by term and a mild respiratory alkalosis.25,27 This is primarily a result of progesterone action at the central respiratory control centres, in addition to increased maternal metabolic rate and CO₂ production.25 Small but significant reductions in mean basal oxygen saturation are observed within the third trimester, for example 98.5% in non-pregnant control vs 95.2% in normotensive pregnant women.28,29 In addition, one study reported that 7 of 28 pregnant women in the third trimester spent more than 20% of a nocturnal pulse oximetry recording with an SpO₂ <90%.29

Significant changes in the upper airway also occur during pregnancy, driven by rising progesterone levels. Hyperaemia and oedema occur in the mucosa of the nasopharynx and oropharynx, leading to rhinitis of pregnancy.30 The Mallampati score is a clinical tool designed to predict difficult tracheal intubation based on inspection of the pharyngeal anatomy. The modified Mallampati score ranges from class 1 (lowest risk) to class 4 (highest risk).31 In a prospective study involving 242 pregnant women, the proportion of class 4 cases increased by 34% between the first and third trimesters, reflecting the reduction in pharyngeal dimensions observed in association with advancing gestation.32 These upper airway changes increase the risk of snoring, which is estimated to occur frequently in 12%-23% of pregnant women, compared to 4% of age-matched non-pregnant controls.33-35 Snoring is a sign of increased upper airway resistance and is likely to coincide with the development of SDB in a proportion of women. Women with pre-eclampsia demonstrate more marked upper airway narrowing compared to normotensive pregnant women in the seated (but not supine) position, potentially because of increased tissue oedema in the neck.36 Snoring is extremely prevalent in this population, affecting 75%-85% of women.36,37 However, no significant difference in oxygen saturation measured in the third trimester was reported in a study comparing 16 women with pre-eclampsia and 16 normal pregnant women.38

Pregnancy is associated with changes in sleep structure and architecture. Increased sleep fragmentation, reduced sleep efficiency, duration and quality occur as pregnancy progresses.28,39-42 Compared to non-pregnant women, rapid-eye movement (REM) sleep is decreased and stage 1 sleep (light sleep) is increased during pregnancy.28,39-41 The impact of pregnancy on slow-wave sleep (deep sleep) is less clear.28,39-41 Sleep may be disturbed by pregnancy-related physical discomfort, sleep disorders (eg restless legs syndrome) and nocturia, particularly in the third trimester.28

3 | RISK OF SDB IN PREGNANCY

The above physiological changes during pregnancy may contribute to either the development of new SDB in women with previously normal breathing during sleep, for example those with risk factors, or the worsening of pre-existing SDB (Figure 3). Breathing is controlled by the central and peripheral chemoreflexes, both of which are highly sensitive to fluctuations in PaCO₂.43 As a result, the respiratory alkalosis associated with pregnancy may alter the patterns of pulmonary ventilation, potentially promoting tendency to apnoea or hypopnoea events.44 Increased ventilatory drive is associated with altered inspiratory pressures at the upper airway, which may potentiate increased collapsibility of this region during sleep.44 In addition, pregnant women may be more likely to develop hypoxaemia during obstructive respiratory events as a result of reduced FRC and increased tissue oxygen consumption.29 In a small study of women with mild to severe SDB commenced on continuous positive airway pressure (CPAP) treatment prior to or during early pregnancy, an increase in CPAP pressure at 24 weeks gestation was required in 6 of 12 (50%) participants to
maintain resolution of upper airway occlusion during sleep, highlighting the dynamic changes in upper airway physiology with advancing gestation. Conversely, the reduction in REM sleep and time spent lying supine may protect against the burden of SDB in some women, as these features are typically associated with obstructive respiratory events, particularly in mild SDB which constitutes the majority of cases during pregnancy.

4.1 | Hypoxia and reoxygenation

SDB is characterized by repeated episodes of complete and partial airway collapse leading to hypoxaemia. Arousal from sleep is triggered, re-establishing airway patency and allowing reoxygenation. Intermittent hypoxia has a range of downstream effects on peripheral tissues and organ systems, many of which remain poorly understood. These effects include the activation of transcription factors, which alter gene expression and promote adaptation to hypoxic conditions, generation of reactive oxygen species (ROS) and inflammation.

Hypoxia-inducible factor-1 (HIF-1) is an oxygen-sensitive transcription factor which forms a key role in the cellular response to intermittent hypoxia. It is composed of HIF-1α and HIF-1β subunits. Under normoxic conditions, HIF-1α is rapidly degraded and inactivated. In hypoxia, HIF-1α is activated and regulates the cellular response by promoting the expression of a wide variety of genes. These include protective functions, such as promoting angiogenesis and erythropoiesis but also a potentially damaging pro-inflammatory response. HIF-1α has been established as a key regular of placental development, specifically trophoblast differentiation. Elevated placental HIF-1α levels are evident in pre-eclampsia and are hypothesized to contribute to the pathogenesis of this condition through downstream effects on angiogenic proteins, including upregulation of soluble fms-like tyrosine kinase 1 (sFlt1) and (HPA) axis and impaired glucose and insulin metabolism (Figure 4).
downregulation of placental growth factor (PlGF).\textsuperscript{50,53,54} Serum HIF-1α levels were significantly higher in males with severe OSA compared to controls and those with mild and moderate disease, returning towards normal following CPAP therapy.\textsuperscript{55} While the impact of SDB on placental HIF-1α activity is not known, the evidence of association between SDB and pre-eclampsia generates interest in the potential role of HIF-1α in the pathogenesis of SDB-related pregnancy complications.

Exposure to intermittent hypoxia in pregnant rats was associated with impaired foetal growth, low birthweight and reduced weight at 5 and 10 days of age compared to pups from mothers exposed to normoxia.\textsuperscript{56,57} Habitual snoring and SDB have been associated with increased risk of small for gestational age infants in prospective studies in human pregnancy.\textsuperscript{34,58} However, the confounding effect of maternal complications such as pre-eclampsia was not adjusted for in these analyses. Meta-analyses have reported conflicting conclusions on the association between SDB and low birthweight; a significant association has been reported when both objective and subjective measure of birthweight are included. However, this association is not present when only objective measures are considered.\textsuperscript{47-49} Additional prospective evidence is required to clarify the impact of SDB on foetal growth and development. Several mechanistic studies have assessed the impact of intermittent hypoxia on glucose metabolism outside of pregnancy in murine models (Table 1). The mechanisms associated with abnormal glucose metabolism in SDB will be considered together later in this review.

Another important consideration is the impact of intermittent hypoxia on placental function. In one study, expression of carbonic anhydrase IX, a marker of chronic tissue hypoxia (potentially signifying reduced placental perfusion), was more common in placental samples from OSA cases and habitual snorers than controls (91.3% and 81.5%, respectively, versus 57.5% in controls).\textsuperscript{59} Foetal normoblastaemia, the presence of nucleated red blood cells, an indicator of chronic hypoxic placental injury, was also significantly more prevalent in placental samples collected from women with OSA and/or snoring. An assessment of uteroplacental underperfusion was also performed, with each placenta assigned a score from 0 to 9 based on the presence/absence and extent of seven discrete histological findings. These included decidual vasculopathy, syncytial knots and villous fibrinoid necrosis. No difference in scores was reported between the groups. Another study examined similar histological variables in placentas from women with OSA (n = 10) and controls (n = 43) and reported no difference between groups.\textsuperscript{60} Significantly increased placental weight, decreased birth weight/placental weight ratio and a 1.8-fold increase in the expression of leptin RNA were reported in placentas from OSA cases, compared to controls. However, these results were not adjusted for maternal BMI. Finally, He et al compared histological findings of placentas from women with OSA and controls with no SDB, classifying results into four categories. In contrast to the aforementioned studies, they identified evidence of decidual vasculopathy, increased syncytial knots, delayed villous maturity and placental abruption in OSA placentas, findings suggestive of maternal underperfusion.\textsuperscript{61}

4.2 Oxidative stress and inflammation

In OSA, the cyclical reoxygenation which follows intermittent hypoxia promotes the production of reactive oxygen species. FIGURE 4 Potential mechanisms contributing to adverse pregnancy outcomes in pregnant women with SDB. SDB is characterized by intermittent hypoxia and reoxygenation, leading to increased production of ROS, increased inflammation and sympathetic activation. These mechanisms may contribute to the development of adverse pregnancy outcomes directly or through adverse impacts on glucose/insulin metabolism and the HPA axis. Pre-eclampsia leads to pharyngeal swelling and may reduce upper airway calibre. These changes may exacerbate pre-existing SDB, or precipitate incident SDB during pregnancy. HPA, hypothalamic-pituitary-adrenal, ROS, reactive oxygen species.
species (ROS).\textsuperscript{62} This is one of the key pathophysiological differences between intermittent and chronic hypoxia. ROS are molecules containing oxygen with an uneven number of electrons, generated during normal cellular metabolism of oxygen and eliminated by antioxidants when present in excess.\textsuperscript{51} ROS are unstable and prone to chemically react with other molecules through transfer of electrons, causing reduction-oxidation (redox) reactions.\textsuperscript{63} In the setting of intermittent hypoxia, the generation of ROS exceeds the capacity of antioxidants, leading to oxidative stress and cellular damage.\textsuperscript{63}

While tissue injury from ROS is perhaps best described in the setting of an acute interruption of blood supply and onset of ischaemia such as in myocardial infarction and stroke, increased ROS signalling has been identified in monocytes, neutrophils, plasma and urine samples in prospective cohort studies involving non-pregnant people with OSA.\textsuperscript{64-66} In all listed sample types, CPAP therapy was associated with a reduction in ROS signalling. The reported benefits were evident over a range of timescales, from 2 nights to 12 months of intervention with CPAP.\textsuperscript{64,66} Furthermore, an increase in ROS signalling in monocytes was reported after the withdrawal of CPAP for one night in people with OSA receiving long-term CPAP.\textsuperscript{65}

ROS are hypothesized to promote the production of redox-sensitive transcription factors. These include HIF-1 (although the role of ROS in HIF regulation remains uncertain) and nuclear factor κappa B (NF-κB).\textsuperscript{51,67} Activation of the pro-inflammatory factor NF-κB is essential for the production of a range of cytokines, for example, tissue necrosis factor

| Author | Subjects | Exposure | Results |
|--------|----------|----------|---------|
| Sherwani et al.\textsuperscript{108} | Tallyho/JngJ (TH) mouse model of type 2 diabetes, Age 16 wk | Over 14 days, 15 × 80-second cycles hypoxia/hour for 8 h/d | Compared to control, IH exposure associated with: • Higher glucose values with no difference in insulin levels on intraperitoneal glucose tolerance test • Increased pancreatic islet cell apoptosis • Adverse lipid profile in pancreas and plasma |
| Xu et al.\textsuperscript{109} | FVB mice | Over 4 d, 180-s cycles of alternating hypoxia and normoxia | Compared to control, IH exposure associated with: • Fourfold increase in pancreatic β-cell proliferation and death • Increased fasting plasma insulin level • Higher blood glucose values during 90-minute insulin tolerance test |
| Pae et al.\textsuperscript{110} | Sprague-Dawley rat pups, Age 1 d | Over 5 h, 7-min cycles of alternating hypoxia and normoxia, then maintained in normoxia for 3 wk | Compared to control, IH exposure associated with: • Higher fasting serum glucose levels • Lower fasting serum insulin levels • Impaired glucose tolerance response • Reduced secreted c-peptide measured in media from harvested islet cells • No difference in secreted c-peptide measured in cell lysates of harvested islet cells |
| Rafacho et al.\textsuperscript{111} | Wistar rats, Age 3 mo | Over 1 h, 10 × 45-second cycles hypoxia, interspersed with 5-min normoxia | Compared to control, IH exposure associated with: • Higher fasting and fed serum glucose levels • No difference in fasting serum insulin levels • 58% reduction in hepatic glycogen content Exposure to β-receptor agonist in IH rats prevented increase in serum glucose concentration and reduction in hepatic glycogen content. |
| Thomas et al.\textsuperscript{112} | C57BL/6J, C57BL/6J AMPKα2\textsuperscript{−/−}, muscle-specific AMPKα1α2\textsuperscript{−/−} and Swiss X Sv129 HIF-1α\textsuperscript{±} mice, Age 8-10 wk | Over 14 d, 60-s cycles of alternating hypoxia and normoxia for 8 h/d | Compared to control, IH exposure associated with: • No difference in fasting plasma glucose levels • Increased fasting plasma insulin levels • Increased HOMA-IR • Reduced whole-body insulin sensitivity • Increased whole-body glucose tolerance as a result of increased skeletal muscle glucose uptake Elevated phosphorylation of Thr172-AMPK and Ser237-TBC1D1 suggests the reported increase in skeletal muscle glucose uptake is a consequence of AMPK activation, which promotes TBC1D1-mediated glucose uptake into cells. |

Note: Control group exposed to normoxia in all studies.

Abbreviations: AMPK, AMP-activated protein kinase; HOMA-IR, homeostatic model assessment of insulin resistance; IH, intermittent hypoxia; TBC1D1, TBC1 domain family member 1.
α (TNF-α) and interleukin-1 (IL-1), and it has been shown to contribute to a range of cardiovascular disorders. In a HeLa cell culture model, exposure to cycles of intermittent hypoxia and reoxygenation was associated with NF-κB activation in a dose-dependent manner, whereas cells exposed to sustained hypoxia demonstrated moderate NF-κB activation. In the clinical setting, NF-κB activity was increased in the circulating neutrophils of adults with mild-moderate and severe OSA, and in the peripheral blood of adults with severe OSA, compared to controls in two small cohort studies.55,70 A significant positive correlation between NF-κB activity and OSA severity was evident in both the studies.55,70 Htoo et al also identified increased plasma levels of two NF-κB-controlled gene products (soluble E-selectin [sE-selectin] and soluble vascular cell adhesion molecule-1 [sVCAM-1]) in nine adults with severe OSA compared to controls.70 In five of these participants with severe OSA treated with 1 month of CPAP therapy, NF-κB activation returned to control levels, with sE-selectin and sVCAM levels showing a non-significant fall.70 Elevated levels of pro-inflammatory markers, such as TNF-α, C-reactive protein (CRP) and IL-6, have been demonstrated in OSA compared to controls, with evidence that all of these decrease or return to control levels following CPAP therapy.69,71,72 The clinical studies discussed involve either a high proportion or exclusively male participants, most of whom suffer moderate to severe OSA. Although data from women and pregnancy are much more limited, in a small prospective study involving 35 pregnant women and non-pregnant controls, sleep disruption was associated with a significant increase in serum TNF-α.73 In the second trimester, increased sleep onset latency (length of time to transition from wakefulness to sleep) was associated with reduction in serum levels of the anti-inflammatory cytokine IL-4.

4.3 Hypothalamic-pituitary-adrenal axis

The HPA axis is a key mediator of stress and inflammation. Activation of the HPA axis results in the release of cortisol from the adrenal cortex, causing multiple end-organ effects and negative feedback inhibition at the hypothalamus and pituitary gland. Pregnancy is characterized by activation of the HPA axis, and a threefold increase in total serum levels of cortisol, the major glucocorticoid in humans, occurs between the first and third trimesters.74 Notably, obese women demonstrate a blunted activation of HPA axis activation during pregnancy compared to their lean counterparts.75,76

Studies evaluating the relationship between SDB and the HPA axis have reported varying results. In a rat model, intermittent hypoxia was associated with increased serum levels of corticosterone, the major glucocorticoid in rodents.77 In human studies, OSA has been associated with increased cortisol levels in obese post-menopausal women, and obese and non-obese men.78,79 In these groups, serum cortisol measured using hourly sampling was significantly elevated across a 24-hour period and across the night-time compared to controls. There was no significant difference in daytime results. These observed elevations in cortisol reduced towards normal following the initiation of CPAP therapy in all groups. Lanfranco et al identified an exaggerated adrenocorticotropic hormone (ACTH) response to corticotrophin-releasing hormone (CRH), but no difference in cortisol response, comparing 15 obese men with OSA and 15 obese male controls.80 In contrast, lower serum basal and peak cortisol levels during 1ug ACTH and glucagon stimulation tests were observed in 26 middle-aged patients with OSA (mostly severe) compared to 15 controls.81 Sleep disruption, a central feature of SDB, was associated with increased secretion of cortisol in 10 healthy male subjects in an experimental setting.82 During each study, performed on a single night in a sleep laboratory, serum cortisol and ACTH levels were measured every 15 minutes between 11 PM and 7 AM Each subject underwent three separate sleep studies under different conditions, including undisturbed sleep and sleep disturbed repeatedly at the onset of stage 1 or 2 sleep. Arousal from sleep was associated with a peak in plasma cortisol, followed by temporary inhibition of cortisol release. Spontaneously occurring cortisol peaks of similar amplitude occurred during undisturbed sleep and were not followed by this same inhibition of cortisol release. Average nocturnal cortisol release was similar during disturbed and undisturbed sleep. Higher frequency of nightly awakenings was negatively correlated with morning awakening salivary cortisol levels in a study of 14 participants with primary insomnia and 15 healthy controls.83

Studies examining this mechanism in pregnancy are limited. In a prospective study involving 25 mostly obese women with gestational diabetes, women diagnosed with SDB (n = 4) demonstrated a flattened salivary cortisol awakening response compared to those with no SDB; however, this was not a statistically significant finding.84 There was also no significant difference in evening salivary cortisol compared to those with no SDB. During pregnancy, poor self-reported sleep quality was associated with greater evening salivary cortisol at 36 weeks gestation, but not 24 weeks, in a group of 200 women.85 Notably, this finding was significantly mediated by maternal anxiety symptoms, and the association between sleep quality and evening cortisol became non-significant when this was adjusted for. Additionally, there was no difference in salivary cortisol awakening response comparing those in the lowest and highest quartile of sleep quality. Adequate sleep during pregnancy (median gestational age: 91 days, range: 40-256), measured by self-report, was associated with a higher mean serum random cortisol level compared to women with self-perceived adequate sleep (8.5 nmol/L [95% confidence interval: 0.9-16.1]) in a Dutch cohort of more than 3000 women.86 Finally, in a study
outcomes in women with SDB.\(^\text{90}\) However, there is a lack of robust evidence examining the impact of SDB on the HPA axis during pregnancy. The small sample size and variation in methodology of available evidence limit the ability to draw meaningful conclusions. Further evidence is required to clarify the role of the HPA axis in the development of adverse pregnancy outcomes in women with SDB.

### 4.4 Sympathetic activation

Following obstructive respiratory events during SDB, chemoreceptor activation triggers increased sympathetic outflow to the adrenal medulla, heart and peripheral vasculature.\(^\text{90}\) The resultant effects, including hyperventilation, peripheral vasoconstriction and bradycardia, aim to enhance oxygen delivery to essential tissues and minimize myocardial oxygen demand. OSA is associated with increased sympathetic activity, both overnight during sleep, and also during daytime wakefulness in the absence of obstructive respiratory events.\(^\text{91}\) In a murine model of intermittent hypoxia, an associated 10-15 mmHg increase in mean blood pressure was prevented by methods to inhibit sympathetic activity, including carotid body denervation and sympathetic nerve ablation.\(^\text{90}\) Long-term exposure to sympathetic overactivity is hypothesized to precipitate chemoreflex and baroreflex dysfunction, endothelial dysfunction and alterations in the release of vasoconstricting peptides, all of which may contribute to the development of hypertension and cardiovascular disease.\(^\text{92}\)

The role of SDB and associated sympathetic overactivity in the pathogenesis of hypertensive disorders of pregnancy has generated significant research interest. Meta-analyses of observational studies suggest that SDB is associated with at least a twofold increased risk of gestational hypertension and pre-eclampsia.\(^\text{47,48}\) Increased sympathetic vasoconstrictor activity is one of the key features of pre-eclampsia pathogenesis, contributing to peripheral vasoconstriction and hypertension.\(^\text{93}\) A recent systematic review found that one or more abnormality of autonomic nervous system function was identified in 21 of 26 studies reviewed, supporting the high prevalence of sympathetic activation in women with pre-eclampsia.\(^\text{94}\) Methods of assessment in these studies include cardiovascular reflex tests, heart rate variability, cardiac baroreflex gain and biomarkers of sympathetic activity.

Case-control studies show that women with gestational hypertension and pre-eclampsia are significantly more likely to have frequent inspiratory flow limitations and SDB.\(^\text{95-98}\) In one study, pre-eclampsia was also associated with significantly worse endothelial function, assessed using the ratio of post- to pre-occlusion pulse-wave amplitude.\(^\text{98}\) Pre-eclampsia was also associated with reduced number of foetal movements, a sign of foetal well-being, measured over one night in a study involving 10 women with moderate to severe pre-eclampsia in the third trimester.\(^\text{96}\) In this study, foetal movements were reported to increase over one night with nocturnal nasal CPAP, regardless of baseline sleep study result.\(^\text{96}\) Women with OSA and pre-eclampsia have an augmented haemodynamic response to obstructive respiratory events compared to pregnant women with OSA and normal blood pressure.\(^\text{99}\) Baseline heart rate was also significantly lower in those with OSA and pre-eclampsia while no dip in heart rate occurred during non-REM sleep. This abnormal response is in keeping with abnormal sympathetic activity.\(^\text{99}\)

Treatment with nasal CPAP in women with pre-eclampsia has shown to have beneficial effects on hypertension in the short term and medium term, even among women without known SDB. A marked reduction in nocturnal blood pressure and resolution of upper airway flow limitation were observed during one night of treatment in two studies involving women with pre-eclampsia but no SDB.\(^\text{100,101}\) A prospective study involving 16 women with pre-pregnancy hypertension randomized participants to receive nocturnal CPAP in addition to antihypertensive treatment \(n = 7\) or antihypertensive therapy alone \(n = 9\).\(^\text{102}\) All participants self-reported chronic snoring but had no evidence of OSA on a baseline sleep study.\(^\text{102}\) A significant reduction in blood pressure was observed in the CPAP group compared to controls, with a gradual reduction in mean systolic and diastolic blood pressure observed from 25 weeks gestation onwards. Dose reduction of antihypertensive therapy was required in some cases. Mean blood pressure increased from a similar gestation in the control group, where escalating doses of antihypertensive therapy were required. Comparison of pregnancy outcomes revealed similar mode of delivery and birth weight between groups. A small but significant reduction in 1-minute APGAR score was observed in the offspring of the CPAP-treated group \((9.1 \pm 0.41 \text{ vs } 8.1 \pm 0.7, P = .04)\); however, 5-minute APGAR scores were similar.

In summary, there is strong evidence that sympathetic overactivity is a feature of SDB and hypertensive disorders of pregnancy. Pharyngeal swelling and upper airway narrowing are more marked in women with pre-eclampsia compared to pregnant women with normal blood pressure, potentially...
precipitating SDB. On the other hand, hypertension appears more likely to develop in women with SDB, with sympathetic dysfunction a feasible hypothesis for this relationship. Future large-scale prospective studies are required to allow greater understanding of this bidirectional relationship and to clarify the optimal role for CPAP as a treatment for pre-eclampsia, both in the presence and absence of SDB.

4.5 | Impaired glucose and insulin metabolism

SDB is independently associated with the development of glucose intolerance and type 2 diabetes in epidemiological studies of non-pregnant adults. Growing evidence supports a similar relationship between SDB during pregnancy and gestational diabetes. Gestational diabetes is characterized by the inability of pancreatic β cells to respond adequately to the increased insulin requirements of pregnancy. It is common, affecting one in seven live births worldwide, and pre-dates the onset of type 2 diabetes in approximately one-third of cases in parous women. A prospective study involving more than 3,000 pregnant women found objectively diagnosed SDB was associated with a 3.47- and 2.79-fold increased odds of developing gestational diabetes in early and mid-pregnancy, respectively, independent of confounders including BMI. Three meta-analyses of observational studies, two of which were published prior to the aforementioned study, conclude that SDB during pregnancy is associated with a 1.5- to 3-fold increased risk of gestational diabetes.

Murine models suggest that intermittent hypoxia induces impaired glucose metabolism as a result of β-cell dysfunction and insulin resistance, and also through insulin-independent mechanisms (Table 1). The increased serum glucose concentration in association with reduced hepatic glycogen content observed by Rafacho et al, which was prevented by prior administration of a β-receptor agonist, suggests a possible role for sympathetic nervous system activation leading to hyperglycaemia. Additional evidence supporting the potential contribution of insulin-independent mechanisms comes from two small studies exposing healthy human volunteers to several hours of intermittent hypoxia (25 events per hour, mimicking moderate OSA). Following 5 hours of exposure, insulin sensitivity and glucose effectiveness (the ability of glucose to mediate its own metabolism, independent of insulin) were reduced on an intravenous glucose tolerance test. Notably, there was no accompanying increase in insulin secretion. A second study reported a small but significant increase in serum glucose concentration compared to baseline after 3 hours exposure to intermittent hypoxia (5.0 ± 0.2 mmol/l vs 5.3 ± 0.2 mmol/l, P = .01). However, no difference in glucose, c-peptide or insulin response to a 75g 2-hour oral glucose tolerance test immediately after exposure was observed.

Punjabi et al performed more detailed assessment of glucose metabolism in a non-pregnant cohort comprising participants with newly diagnosed SDB (mild, n = 34; moderate, n = 22; severe, n = 23) and 39 control subjects with no SDB. Participants had no history of diabetes, and results were adjusted for BMI and % fat mass measured using dual-energy X-ray absorptiometry (DEXA) as an additional marker of adiposity. Compared with normal subjects, participants with mild, moderate and severe SDB displayed 26.7%, 36.5% and 43.7% reduction in insulin sensitivity respectively (assessed using a frequently sampled IV glucose tolerance test) (P < .0007). Pancreatic β-cell function (calculated using the disposition index) was similar in controls and mild SDB, but 28% and 44.8% lower in moderate and severe SDB respectively (P < .034). Glucose effectiveness was negatively correlated with severity of AHI (P < .039).

Overall, these findings suggest that the physiological changes observed in pregnant women with SDB may contribute to the pathogenesis of gestational diabetes. The exact mechanisms through which SDB impacts glucose and insulin metabolism remain uncertain. As previously discussed, SDB is associated with excess production of ROS. Experimental evidence from rat models suggests that the pancreatic β cells are more susceptible to damage from oxidative stress compared to muscle, kidney and liver, thought due to inadequate antioxidant systems. Upon exposure to intermittent hypoxia, transgenic mice overexpressing an antioxidant protein in pancreatic β cells demonstrated the same increase in β-cell proliferation as control mice, but were protected from the fourfold increase in β-cell death observed in control mice. It can therefore be hypothesized that increased ROS may lead to suppressed insulin secretion and impaired insulin-mediated peripheral glucose uptake.

Overall, these findings support the role of oxidative stress in the association between SDB and abnormal glucose homoeostasis. The pro-inflammatory cytokine TNF-α alters peripheral insulin sensitivity in obese individuals; therefore, the pro-inflammatory state associated with SDB may also contribute to pathological changes in peripheral insulin sensitivity. Glucocorticoids mediate the behaviour of insulin receptors and expression of peripheral glucose transporters; therefore, alterations of the HPA axis activity have the potential to alter peripheral glucose uptake and insulin sensitivity. Further mechanistic studies are required to clarify the mechanisms underpinning the association between SDB and impaired glucose metabolism.

The potential for CPAP treatment to benefit glucose metabolism in women with mild OSA and diet-controlled gestational diabetes was assessed in a small randomized trial. In all, 18 women were randomized to receive CPAP treatment and 18 women (on a CPAP waiting list) were randomized to standard care, at an average gestational age of 30.3 weeks. After 2 weeks of intervention, intention-to-treat analysis (n = 15 on CPAP, n = 17 control) found no difference in
fasting glucose, insulin sensitivity or insulin secretion between groups. However, post-hoc per-protocol analysis including only those who were adherent to intervention (n = 7 on CPAP, n = 16 control) reported that CPAP was associated with significant improvements in pancreatic β-cell function (measured using disposition index). Following the initial intervention, 14 women in the intervention group and 10 control patients chose to continue or commence CPAP. Among women who received CPAP for >2 weeks (n = 23), compared to those receiving CPAP for ≤2 weeks (including no CPAP), a significant reduction in pre-term delivery (zero vs 36.4%, P = .002), unplanned caesarean section (13% vs 58%, P = .005) and neonatal intensive care/special care admission (17.4% vs 81.8%, P < .001) were reported. However, the study was not powered to detect differences in clinical outcomes between groups. Overall, the small sample size limits the ability to draw definitive conclusions from these results. Recruitment into a larger randomized-controlled trial comparing the effect of CPAP with a nasal dilator strip on glycaemic control in gestational is ongoing.119

5 | CONCLUSION AND FUTURE WORK

Accumulating evidence suggests that an association exists between maternal SDB and an increased likelihood of adverse pregnancy outcomes, notably the development of gestational diabetes and hypertensive disorders of pregnancy. A variety of plausible mechanisms have been hypothesized to explain these relationships. However, much of the available evidence is from non-pregnancy pre-clinical models and non-pregnant human populations (often predominantly male subjects with moderate-severe OSA); therefore, the translation of these findings to pregnant women is questionable. As the main burden of disease in pregnancy is in obese women of reproductive age, with mostly mild SDB, further investigation in this population is warranted to ensure the mechanisms and consequences of SDB in this unique population are better understood.120 This should include further investigation into placental pathophysiology, which is currently lacking. A better understanding of the mechanisms linking SDB and adverse pregnancy outcomes, coupled with adequately designed clinical trials investigating the effect of CPAP in the context of pre-eclampsia and gestational diabetes, has the potential to help improve both maternal and foetal outcomes. Further study in this field of maternal medicine is of pressing importance given the rapid increase in the prevalence of maternal obesity.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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