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REVIEW ARTICLE

Effects of gestational intermittent hypoxia on the respiratory system: A tale of the placenta, fetus, and developing offspring

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Summary

Obstructive sleep apnea (OSA) is a common sleep disorder that is associated with a wide variety of health conditions, including cardiovascular, cerebrovascular, metabolic, neoplastic, and neurocognitive manifestations. OSA, as a chronic condition, is mainly characterised by repeated upper airway obstructions during sleep that cause episodes of intermittent hypoxia (IH), resulting in tissue hypoxia–reoxygenation cycles. Decreased arterial oxygen pressure (PaO_2) and haemoglobin saturation ($SatO_2$) stimulate reflex responses to overcome the obstruction. The prevalence of OSA is significant worldwide, and an underrated problem when focussing on women during pregnancy. The physiological changes associated with pregnancy, especially during its latest stages, are related to a higher prevalence of OSA events in pregnant mothers, and associated with an increased risk of hypertension, pre-eclampsia and diabetes, among other deleterious consequences. Furthermore, OSA during pregnancy can interfere with normal fetal development and is associated with growth retardation, preterm birth, or low birth weight. Carotid body overstimulation and hypoxia–reoxygenation episodes contribute to cardiovascular disease and oxidative stress, which can harm both mother and fetus and have long-lasting effects that can reach into adulthood. Because IH is the hallmark of OSA, this review examines the literature available about the impact of gestational intermittent hypoxia (GIH) on the respiratory system at maternal, fetal, and offspring levels. Offering the latest scientific data about OSA during pregnancy, we may help to tackle this condition with lifestyle changes and therapeutic approaches, that could influence the mothers, but also impact adult health problems, mostly unknown, inherited from these hypoxic episodes in the uterus.

KEYWORDS

fetus, gestational intermittent hypoxia, obstructive sleep apnea, offspring, oxidative stress, placenta, pregnancy, respiratory system

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is the most common sleep disorder worldwide (Canever et al., 2024). It is associated with cardiovascular, cerebrovascular, metabolic, neoplastic, and neurocognitive diseases (Heinzer et al., 2015; Mediano et al., 2022). OSA is characterised by repeated complete (apnea) or partial (hypopnea) obstructions of the upper airway during sleep. With each obstruction, arterial oxygen pressure (PaO_2) and haemoglobin saturation for oxygen ($SatO_2$) decrease, making OSA a chronic condition of recurrent intermittent hypoxia (IH), the severity of which is proportional to changes in $SatO_2$ (Chaudhary et al., 1998). The decrease in PaO_2 activates the carotid body (CB), stimulating motor neurons of the inspiratory and dilator muscles of the upper airways and sleep–wake control areas of the central nervous system (Gonzalez et al., 1994). Muscle action and sudden arousals overcome the obstruction, PO_2 is restored, and the cycle is repeated, resulting in IH, hypercapnia and sleep fragmentation (Song et al., 2024). CB stimulation activates respiratory reflexes, causing cardiovascular responses which minimise the deleterious effects of hypoxia. Repeated stimulation sensitises CB chemoreceptors, increasing basal sympathetic tone, leading to hypertension and cardiovascular and metabolic pathology (Prabhakar et al., 2023). The periods of reduced (hypopnea) or cessation (apnea) of breathing during OSA prevent adequate gas exchange in the lungs, accompanied by CO_2 accumulation, leading to hypercapnia. Hypercapnia in arterial blood also activates the CB, which contributes to 20%–30% of the reflex regulation of CO_2-H^+ levels in response to hypercapnic acidosis, while the central chemoreceptors are responsible for the other 70%–80%. The most widely accepted hypothesis for CB stimulus transduction is that CO_2-H sensing, like O_2 sensing, occurs in type I cells and involves K^+ channel inhibition and depolarisation coupled to Ca^{2+}-dependent secretion of one or more excitatory transmitters that increase the discharge of brainstem sensory neurons (Gonzalez et al., 1994; Iturriaga et al., 2021).

In the context of sleep-disordered breathing, a study by Jaimchariyatam et al. (Jaimchariyatam et al., 2013) using polysomnography found that 29 of 44 patients with OSA had high exhaled CO_2 levels, which were related to apnea duration and age. However, no relationship was found between hypercapnia and the apnea–hypopnea index or body mass index (BMI). Approximately 90% of obese subjects (BMI >30 kg/m^2) with hypoventilation syndrome have OSA and show daytime hypercapnia, which can be improved with continuous positive airway pressure (CPAP) treatment (Mokhlesi et al., 2008), the most effective therapies used in OSA to prevent air collapse during sleep.

Nocturnal apneas often end in brief micro-arousals, resulting in sleep fragmentation that leads to the excessive daytime sleepiness reported by OSA patients. Sleep fragmentation and intermittent hypoxaemia associated with OSA may act synergistically to generate responses that lead to systemic inflammation, sympathetic activation, and other responses that predispose to comorbidities, particularly cardiometabolic and neuropsychiatric (see McNicholas & Pevernagie, 2022).

Epidemiological data on OSA indicate the magnitude of the social, health, and economic problems it represents. Its prevalence is estimated to be 9%–24% in men and 4%–9% in women over 30 years of age, increasing with age (Young, 2009). In pregnant women, the prevalence is estimated to be around 8% in the first trimester rising to nearly 20% in the third trimester of pregnancy (Pien et al., 2014; Zhu et al., 2020).

Anatomical and physiological changes during pregnancy, or the presence of the disease prior to pregnancy, increase the prevalence of gestational OSA (Louis et al., 2018). This pathology is associated with increased morbidity and mortality and can cause hypertension, pre-eclampsia, and gestational diabetes mellitus (Eleftheriou et al., 2024). Episodes of hypoxia–reoxygenation during pregnancy can affect fetal development and postnatal development, resulting in growth retardation, preterm delivery, low birth weight, and even fetal death (Louis et al., 2014). Adult changes, such as metabolic and epigenetic alterations in male offspring, have also been described in animal models where IH exposure during pregnancy mimics the hypoxia–reoxygenation cycles of gestational OSA (Khalyfa et al., 2017). These episodes of hypoxia–reoxygenation increase the production of reactive oxygen species (ROS), causing tissue damage and an influx of inflammatory cells to the injured sites and into the fetus via the placenta (Dahlgren et al., 2006).

The repeated episodes of IH that occur during sleep, and especially during pregnancy, can have significant respiratory effects on both the mother and the developing fetus. The following sections highlight the major respiratory changes that occur during pregnancy that may contribute to the development of gestational OSA and how it can affect the pregnant woman, the fetus, and the developing offspring, into adulthood.

2 | MATERNAL RESPIRATORY CHANGES RELATED TO PREGNANCY

2.1 | Hormonal changes

Pregnancy induces hormonal alterations, which are the main cause of changes in the respiratory pattern. Plasma levels of progesterone, which act as a trigger for the primary respiratory centre, gradually increase during pregnancy, with one study showing a rise from 27.0 ± 1.5 ng/mL at week 13 to 146.0 ± 17.2 ng/mL at week 37, and then a decrease after delivery (3.5 ± 1.5 ng/mL) (Contreras et al., 1991). This remarkable increase is accompanied by a rise in the sensitivity of the respiratory centre to CO_2 (Lyons & Antonio, 1959). In addition, progesterone acts as a bronchodilator, lessening the airway smooth muscle tone, and, by acting directly on the carotid body, increasing the peripheral ventilatory response to hypoxia.

Alongside these changes, pregnancy also affects oestrogen levels, which rise in parallel with progesterone levels. This hormonal surge leads to an increase in both the number and sensitivity of progesterone receptors in the areas of the central nervous system associated with respiration, primarily the hypothalamus and medulla oblongata (Weinberger et al., 1980). Increases in prostaglandin levels during pregnancy have also been described to have a variety of effects, with

prostaglandin F2 alpha (PGF2α) causing bronchial smooth muscle constriction and prostaglandins E1 (PGE1) and E2 (PGE2) causing bronchodilation (Weinberger et al., 1980).

2.2 | Anatomical changes

Pregnancy-induced uterine enlargement increases abdominal pressure, displacing the diaphragm upwards. As a result, pleural pressure increases, leading to small airways obstruction, which reduces the functional residual capacity (FRC) (by 20%–30%), expiratory reserve volume (ERV) (15%–20%) and residual volume (RV) (by 20%–25%). The decrease in the height of the chest is accompanied by an increase in its other dimensions, which maintains the total lung capacity (TLC) (McAuliffe et al., 2002). Along with these changes in FRC and ERV, pregnancy is associated with an increase in the tidal volume (by 30%–50%) and the minute ventilation (by 20%–50%), with only a small increase in respiratory frequency.

As the diaphragm moves upwards, the thorax also undergoes significant changes during pregnancy. There is an increase in the subcostal angle of the rib cage (from 68 to 103 degrees) due to relaxation of the lower rib cage ligaments, and an increase in the circumference of the lower chest wall (5 to 7 cm). These anatomical changes peak at week 37, and largely return to normal by week 24 after delivery (although the subcostal angle remains 20% wider than at baseline) (Contreras et al., 1991). This increase in chest wall size also helps to compensate for the upward displacement of the diaphragm mentioned above.

In addition, pregnant women have significant upper airway narrowing during the third trimester of pregnancy (Izci et al., 2006). This upper airway narrowing may be related to the increased incidence of snoring and sleep-disordered breathing in pregnancy. Alongside this observation, women with pre-eclampsia have also been described to have narrower upper airways when in the supine position compared with pregnant and non-pregnant women without this condition (Izci et al., 2003). Besides this narrowing, they have larger neck circumferences, which may be due to differences in fat deposition around the neck or tissue oedema, which is present in most women with pre-eclampsia. All these factors would certainly promote or increase the severity of OSA.

Besides these effects, the mucosa of the upper airways is also affected during pregnancy, with an increase in the mucopolysaccharide content and phagocytic activity, resulting in nasal congestion. This common nasal congestion is known as pregnancy rhinitis, and affects up to 65% of pregnant women, lasting 3 or more weeks (Bende & Gredmark, 1999) and resolving spontaneously 2 weeks after delivery. Although the aetiology is unclear, some contributing factors may be smoking, nasal allergy or infections, with the potential of further complications. Nasal obstruction would exacerbate snoring and therefore sleep-disordered breathing.

The respiratory muscles play a key role in pushing during labour. It has been described in animal models that a long period of stretching causes muscle fibres to add sarcomeres in the longitudinal direction, thereby increasing tension (Williams & Goldspink, 1978). This may well be what happens to the diaphragm and abdominal muscles during the long stretching period of pregnancy, to improve their efficiency in developing expulsive force during labour.

3 | EFFECT OF INTERMITTENT HYPOXIA IN THE PREGNANT WOMEN

3.1 | Respiratory pattern

Physiological changes in pregnancy can lead to new-onset OSA or worsen a previous condition. Altered inspiratory pressures increase the collapsibility of the upper airways, while respiratory alkalosis during pregnancy shifts the ventilatory pattern increasing the frequency of apneic/hypopneic events (Johns et al., 2020).

Among the aforementioned physiological changes associated with pregnancy, the decrease in FRC, alongside the increased oxygen consumption, makes pregnant women more susceptible to hypoxaemia during obstructive respiratory events (Bourne et al., 1995). In a study following 12 pregnant women with preexisting mild to severe sleep-disordered breathing (either OSA or upper airway resistance syndrome) who had been treated with CPAP since early pregnancy, half had to increase the pressure of their CPAP device to prevent the upper airway occlusion (Guilleminault et al., 2004). This readjustment clearly highlights the dynamic changes in upper airway physiology and the exacerbation of preexisting conditions in pregnant women.

3.2 | ROS production and inflammation

Repeated episodes of IH during pregnancy activate transcription factors such as hypoxia-inducible factor-1 (HIF-1), and more specifically its HIF-1α subunit, while increasing ROS production and causing inflammation, among others. HIF-1α is activated by hypoxia and drives protective gene expression (angiogenesis or erythropoiesis), but also harmful inflammatory responses (see Garvey et al., 2009). Elevated serum levels of HIF-1α were reported in pre-eclamptic women (Rath et al., 2016), but also in men with severe OSA (Lu et al., 2017), with levels returning to normal after CPAP therapy. ROS production exceeding antioxidant capacities also increases the production of other redox-sensitive transcription factors, such as the pro-inflammatory factor NF-κB (see Lavie, 2012), involved in the production of cytokines such as TNF-α and IL-1 and linked to a range of cardiovascular diseases. Several systemic and cellular responses in OSA patients and experimental models due to increased ROS signalling (see Prabhakar et al., 2007). are improved following CPAP therapy (Schulz et al., 2000). With data scarce in pregnant women one study found an association between sleep disruption and serum TNF-α levels (Okun & Coussons-Read, 2007), with lower serum levels of the anti-inflammatory cytokine IL-4 related to longer sleep onset latency times. More recently, Alonso-Fernandez et al. (Alonso-Fernández et al., 2021) quantified the plasma cytokine levels (TNF-α, IL-1β, IL-6,

IL-8, and IL-10) during the third trimester of pregnancy in women with and without (less than 5 events/h) OSA, in a population homogeneous in age and BMI. They reported a direct correlation between the obstructive apnea index and TNF-α levels, and between the AHI and IL-1β levels. These results led them to conclude that IH episodes in the pregnant population, especially during REM sleep, are associated with higher systemic inflammation than in healthy pregnant women without OSA. In addition, they found an inverse correlation with newborn weight and age. Another study by the same group (Serednytskyy et al., 2022) found a higher sympathetic tone, as assessed by plasma normetanephrine levels, in women with gestational diabetes and OSA than in women with gestational diabetes alone. Additionally, they also found an association between lower nocturnal oxygenation and higher levels of IL-1β.

3.3 | Vascular function

The cycles of hypoxia/reoxygenation also affect the vascular bed through morphological and functional modifications, leading ultimately to endothelium impairment (see Schulz, 2005). For example, Yinon et al. (Yinon et al., 2006) evaluated endothelial function using the reactive hyperaemia test. Briefly, they measured the ratio of pulse-wave amplitude between post- and pre-occlusion of one arm as an endothelial function index (EFI). They found that pregnant women with pre-eclamptic toxaemia, a pregnancy-specific disorder characterised by hypertension, proteinuria, and oedema, had a higher respiratory disturbance index (RDI) and a lower EFI than controls. They speculated that the respiratory disturbances damaged the endothelium of blood vessels in women with pre-eclamptic toxaemia.

One of the functions of the vascular endothelium is to release relaxing factors, such as NO, to induce vasodilation and to prevent organ ischaemia. The loss of this ability due to endothelial dysfunction leads to peripheral vasoconstriction and, potentially, hypertension (see Dharmashankar & Widlansky, 2010), among other deleterious effects. Injury to the endothelial wall, and therefore endothelial dysfunction, is considered to be a major contributor to the pathogenic mechanisms of cardiovascular diseases (Hadi et al., 2005). Endothelin-1, a biologically active substance released by the endothelium, acts through the endothelin type A receptor (ETAR) and the endothelin type B receptor (ETBR). A recent study from Song et al. (Song et al., 2024) in a rat model of GIH showed that the resulting hypertension and endothelial dysfunction induced by IH were linked to the suppression of ETBR mediated signalling in pregnant experimental rats.

3.4 | Maternal-fetal complications

A retrospective analysis of 4326 pregnant women diagnosed with OSA in the United States found a direct association between sleep apnea and an increased likelihood of maternal–fetal complications (Lui et al., 2021). Along with higher rates of pre-eclampsia and caesarean delivery, there was also a higher prevalence of pulmonary oedema, although there was no significant association with an increased risk of mortality. Another study with pregnant women in Turkey (Sağ et al., 2021) examined the relationship between OSA syndrome and pregnancy complications. They found a higher rate of maternal complications (pre-eclampsia, gestational diabetes, preterm labor, premature rupture of the membranes, and caesarean section) in patients at high risk of OSA syndrome, identified using the Stop Bang questionnaire, than in women at lower risk. Following this trend, a longitudinal study in Taiwan with 8346 pregnant women who reported adverse birth outcomes (premature delivery, abortion, and stillbirth) (Sun et al., 2022) found an association between the risk of these outcomes and OSA. Interestingly, they also found a dose–response effect, with women who experienced OSA for a longer period being more likely to experience these adverse outcomes.

4 | EFFECTS OF INTERMITTENT HYPOXIA IN THE PLACENTA

The placenta is an organ essential for feeding, breathing, protection and hormone production during fetal development (Maltepe & Fisher, 2015). During pregnancy, the placenta is exposed to a variety of environmental cues that can have an impact on the placental development, fetal growth, and the postnatal phenotype of the offspring. These factors include low oxygen levels, which can be caused by maternal anaemia, umbilical cord occlusion, or poor placental vascularisation, as well as high-altitude pregnancies or maternal OSA (Hutter et al., 2010; Zamudio, 2003). Studies that experimentally mimicked such conditions in animals, including mice, rats, and guinea-pigs, have shown that placental and fetal weights are altered (see Sferruzzi-Perri & Camm, 2016). In general, these studies show that the specific effects on the placenta appear to depend on the type and the severity of the challenge, as well as its duration and timing relative to placentation. In addition, sexual dimorphism has been reported in the formation, function, and adaptation of the placenta (Kalisch-Smith et al., 2017), which, like the fetus, is genetically XX or XY.

4.1 | Gas exchange in the placenta

Similarly to the postnatal role of the lung, the placenta is a "respiratory organ" where fetal blood gases are exchanged indirectly with the environment by a concentration gradient-dependent passive extraction of oxygen from maternal blood, like the process of diffusion and transfer of oxygen from alveolar gas. The human placenta consists of an extensively branched fetal villous tree that is bathed by maternal blood circulating in the intervillous space. The interface between fetal placental tissue and maternal blood is the syncytiotrophoblast, which acts as the endothelium for the intervillous space (Caruso et al., 2012). Oxygen transfer across the placental barrier is achieved as fetal blood circulates from the umbilical arteries to the capillaries within the placental villi and back to the umbilical vein, whereas

maternal blood is filtered through a high-volume intervillous compartment, making the exchange process slower and less efficient than at the alveolar–capillary interface (Goplerud & Delivoria-Papadopoulos, 1985). In addition, the placenta is a high consumer of oxygen, resulting in a PO_2 in fetal blood leaving the placenta through the umbilical vein which is significantly lower than the PO_2 in the maternal artery (Goplerud & Delivoria-Papadopoulos, 1985). This is not a limitation under normal conditions of oxygenation but may compromise gas exchange during sustained hypoxia or with the IH episodes that occur in OSA. Notably, there is evidence of hypoxia in the human placenta in OSA (Ravishankar et al., 2015). Fluctuations in oxygen delivery from the maternal circulation into the intervillous space following IH during the process of gas exchange in the placenta result in hypoxia–reoxygenation events that can overwhelm local antioxidant defences and lead to oxidative stress and pathological placental changes (Al-Gubory et al., 2010; Hung et al., 2001). The effects of hypoxia–reoxygenation are well documented in other organs such as the heart, brain, and intestine, where its detrimental effects are mainly due to its ability to generate high levels of ROS, oxidative stress, and increased inflammation (Lavie, 2003). It is therefore biologically plausible that OSA, via one of these pathways, may adversely affect placental tissue perfusion and oxygenation, potentially predisposing to the development of placental-mediated adverse outcomes.

4.2 | Hypoxia-induced changes in placental structure and function

It has been described that the severity of maternal sustained oxygen deprivation in animal models affects the structure and function of the placenta in a sex dependent manner. Maternally induced sustained hypoxia of 12%–13% during the last third of gestation in mice resulted in a selective expansion of the labyrinth vascular branching in placentas from female foetuses. In addition, mRNA expression of *Glut1*, *Igf2*, and *Igf1r*, genes important for placental growth, nutrient transport, and glucocorticoid signalling, was reduced only in placentas from female fetuses (Cuffe et al., 2014; Higgins et al., 2016). Conversely, when maternal inspired oxygen is reduced to levels of 10% oxygen, the labyrinth zone is reduced with a concomitant increase in the volume density of the junctional zone and activation of the invasive endovascular trophoblast cell lineage (Rosario et al., 2008). The sustained hypoxia-induced changes in gross placental morphology have been associated with altered expression of genes and proteins involved in proliferation, apoptosis, oxidative stress, and cell lineage differentiation in which the participation of hypoxia-inducible factors (HIF) appear to be essential (Adelman et al., 2000; Higgins et al., 2016; Sferruzzi-Perri & Camm, 2016).

Placental structure and function are also affected by GIH. It has been reported that GIH impairs uterine artery function and causes placental oxidative stress and hypoxia in the rat (Badran et al., 2019). A morphological study (Valverde-Pérez et al., 2023) showed an increase in fetal capillary branching, expansion of maternal blood spaces, and an increased number of cells of the external trophectoderm in the placentas from GIH-exposed mothers. These changes precede the growth of the fetus and could lead to lower fetal weights.

4.3 | Placental development in hypoxia

Placental development during normal pregnancy occurs in a low-oxygen environment (~2%–8% O_2) and this "physiological hypoxia" appears to be critical for early placental development and angiogenesis (Genbacev et al., 1997; Jauniaux et al., 2006). Vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF2) are two potent angiogenic factors that have been implicated in placental angiogenesis (Ferrara et al., 2003; Zygmunt et al., 2003). Sustained hypoxia increased the expression of VEGF and its receptors VEGFR-1 and VEGFR-2 in endothelial cells (Ramakrishnan et al., 2014). In a different study hypoxia also increased the expression of FGF receptors and altered the distribution of FGF2 in different cellular compartments (Dailey et al., 2005). It has been reported that hypoxia may differentially modulate angiogenic factor-stimulated placental angiogenesis depending on the severity and duration of hypoxia exposure. Wang et al. (Wang et al., 2009) showed that in vitro exposure to sustained hypoxia (3% O_2) in human placental artery endothelial (HPAE) cells enhanced FGF2 and VEGF-stimulated HPAE cell proliferation but did so independently of the canonical MEK1/ERK1/2 and PI3K/AKT1 pathways, suggesting that hypoxia may induce a very complex signalling network in the placenta. Although limited research has explored whether IH produces similar complex changes in the placental signalling pattern, Weng et al. (Weng et al., 2022) and Badran et al. (Badran et al., 2019) found that in mice GIH also induced impairments in placental angiogenesis with an imbalance in production of pro-angiogenic (VEGF and PlGF) and anti-angiogenic factors (sFlt-1 and sENG), and in vascular remodelling.

Along the same lines, human trophoblasts proliferate in vitro under low O_2 conditions, but differentiate at higher O_2 levels, mimicking the developmental transition they undergo when invading the placental bed to establish the maternal–fetal circulation in vivo. Using both a human trophoblast cell line (HTR8/SVneo) and a primary culture of extravillous trophoblast cells (EVTs), Song et al. (Song et al., 2020) reported that, in contrast to sustained hypoxia, IH blocks trophoblast proliferation and induces excessive trophoblast apoptosis by activating the ER stress signalling pathway. They found that IH can also significantly impair the invasive and migratory ability of trophoblasts which they attributed in part to the reduced secretion of matrix metalloproteinase-2. These changes in trophoblast function may have deleterious implications for proper pregnancy development (Giannubilo et al., 2024).

However, there is contrary evidence supporting the hypothesis that the influence of OSA on the development of adverse pregnancy outcomes may be mediated at sites other than the placenta. Findings in rats shows that HIF-1α mRNA and its target genes are not altered in placentas at E19 during GIH exposure, despite a decrease in the arterial oxygen saturation in the mother to ~80%–85% with each hypoxic episode (Vanderplow et al., 2022). Also, gene expression profiling studies of placenta from women with obesity and OSA showed that there were no statistically significant differences in the placental transcriptome between women with OSA and women with no OSA (Johns et al., 2022).

4.4 | Maternal–fetal hypoxia attenuation

In this context, how intermittent hypoxaemia is transmitted from the mother to the fetus in OSA deserves some comment. By simultaneously measuring PO_2 in the maternal artery and umbilical vein, Almendros et al. (Almendros et al., 2019) showed in a sheep pregnancy model that the PO_2 fluctuations resulting from experimental maternal obstructive apnea are significantly smaller in fetal blood than those registered in maternal blood, due to the damping effect of oxygen transfer across the placenta. This work raises an important question about the potential effects of IH on the fetus during pregnancy, as the placenta may attenuate the severity of hypoxaemic changes in the fetus. In addition to potential differences in the structure and physiology of the placenta in sheep and humans and, therefore, in the attenuation of the swings in PO_2 which penetrate through the placenta in both species, the study by Almendros et al. (Almendros et al., 2019) raises several considerations when translating the findings to pregnant women. Since the severity of hypoxaemic swings is attenuated in the fetus, it could be anticipated that hypoxia–reoxygenation, and thus the oxidative stress induced in the various fetal organs and tissues would be lower than that experienced by adult tissues (Almendros et al., 2011). It is also possible that the sensitivity and tolerance of fetal tissues to very short episodes of IH hypoxia, which have so far not been studied, are different from those in adults. Moreover, the impact of intermittent hypoxaemia, even of low amplitude, could be different in the fetus and the adult, since fetal mechanisms to regulate the distribution of blood flow among organs are markedly different from those in adults (Cahill et al., 2014; Carter, 2015; Giussani, 2016). These potential differences could influence the epigenetic changes observed in the offspring after GIH (Cortese et al., 2015; Cortese et al., 2017; Iqbal & Ciriello, 2013).

5 | FETAL RESPIRATORY DISTRESS IN GESTATIONAL INTERMITTENT HYPOXIA

As a result of maternal GIH, there is a reduction in oxygen saturation in the maternal blood which could compromise oxygen delivery from the placenta to the fetus, leading to fetal hypoxaemia (see Burton et al., 2021). However, the extent to which the placenta protects the fetus, and therefore the amount of oxygen that reaches the fetus is still unknown as mentioned above.

5.1 | Fetal breathing movements (FBM)

Although there is not a functional, fully developed gas exchange system in the lungs of the fetus, it does not mean that they remain inactive. There are rhythmic contractions of the diaphragm and other respiratory muscles, known as fetal breathing movements (FBM), which play a key role in lung maturation. They are a distinctive adaptation to the intrauterine environment.

With completely unique characteristics that differ from neonatal and adult breathing, they also differ from maternal respiratory movements. In humans, FBM begin at around week 10 of gestation and increase in frequency with gestational age, occurring up to 35% of the time around week 30 of pregnancy (Koos, 2008; Koos & Rajaee, 2014). They occur at a frequency of approximately 30–70 contractions/breaths per minute in each bout, followed by apneic periods that can last up to 2 h near term (Patrick et al., 1980a). Between 28 and 36 weeks, FBM are closely correlated with maternal REM states, with less frequent FBM occurring in non-REM states (Arduini et al., 1986). The frequency of FBM episodes is also correlated with other factors, such as glucose levels, with a higher incidence described in humans after maternal meals (Patrick et al., 1980b). In terms of respiratory gases, high levels of $PaCO_2$ (hypercapnia) increase the incidence of FBM, while low levels of PaO_2 (hypoxia) inhibit FBM in studies in ewes (Koos et al., 1990) and humans (Platt et al., 1978).

5.2 | Alveolar and arterial O_2 and CO_2 levels

Based on umbilical cord blood analysis, one study found that maternal snoring during pregnancy was associated with enhanced fetal erythropoiesis (Tauman et al., 2011), suggesting that the fetus becomes hypoxic in utero, at least to some extent, during repeated bouts of IH. These episodes of fetal hypoxaemia, if prolonged or severe, could impair fetal development and increase the risk of adverse perinatal outcomes.

Due to the increased metabolic demands of the fetus during pregnancy, increases in O_2 consumption (20%) and CO_2 production (35%) have been described in pregnant individuals when compared with their respective controls. These changes do not correlate exactly with the changes in minute ventilation described in the previous section, which were around 20% and 50%. This greater increase in minute ventilation translates into an increase in the alveolar (PAO_2) and arterial partial pressures of O_2 (PaO_2) and a decrease in the corresponding partial pressures of CO_2 ($PACO_2$ and $PaCO_2$). These increases in oxygen tension are important to facilitate oxygen transfer across the placenta. Thus, measurements of PaO_2 during pregnancy found control values of PaO_2 around 93 mmHg rising to 105–106 mmHg during the first trimester, and 101–106 mmHg near term (Templeton & Kelman, 1976). Despite this increase in oxygen tension, the oxygen reserves of pregnant women are lower, making them, and consequently the developing fetus, more susceptible to hypoxic episodes during periods of apnea.

As for the $PaCO_2$ levels, they have been shown to go from 37 mmHg in the non-pregnant state to 28–29 mmHg in the first trimester and 26–30 mmHg near term (Templeton & Kelman, 1976). These low $PaCO_2$ values lead to chronic respiratory alkalosis, with compensatory renal mechanisms acting to excrete bicarbonate. This causes stimulation of 2,3-diphosphoglycerate (2,3-DPG) synthesis. The resulting increase in 2,3-DPG levels reduces the affinity of maternal haemoglobin for O_2, allowing more O_2 to be delivered to the fetus, whose major haemoglobin, called fetal haemoglobin or HBf, has a higher affinity for O_2 than the adult haemoglobin or HbA.

5.3 | Other effects

The transition from fetal to postnatal breathing includes, among other events, the absorption of lung fluid, gaseous expansion of the lungs, activation of the Hering-Breuer reflexes and the appearance of continuous respiration. Birth itself is a delicate process which has hindered more detailed research. Thus, many of the factors involved in the birth process are not yet fully understood. Asphyxia, umbilical cord occlusion or the rise in PaO_2 with the first postnatal breath may be involved in the process (Dawes, 1968; Longo, 2013), although neither the afferent input from the carotid sinus nerve (Herrington et al., 1971) nor the interruption of umbilical circulation (Chou et al., 1974) seem to play a role in this process.

6 | OFFSPRING RESPIRATORY DISORDERS FOLLOWING GESTATIONAL INTERMITTENT HYPOXIA

Although key components of the respiratory system such as phrenic motoneurons and diaphragm muscle begin to develop in utero, there is also an important postnatal maturation process. After birth there is a transition from fetal breathing movements to functional gas exchange. With a less efficient respiratory system, infants develop several counteractive mechanisms to compensate for the increased vulnerability of their respiratory system.

6.1 | Ventilatory parameters

Looking at the evolution of some respiratory values in humans it is known that respiratory rates fall progressively with age, going from 40 breaths/min in neonates to around 12–18 breaths/min in adults, with tidal volume values (adjusted by weight) remaining virtually identical throughout life.

Besides the rapid breathing rate of the fetus, its minute ventilation is higher at any level of CO_2 in neonates and infants compared with adults (Cohen & Katz-Salamon, 2005), even though chemoreceptor pCO_2 sensitivity is almost mature at term. However, preterm infants showed an attenuated sensitivity (and slower response) to CO_2 (Rigatto et al., 1975).

As for the peripheral pO_2 receptors, they need a few weeks of readjustment (Kumar & Hanson, 1989) to gain sensitivity to the higher levels of oxygen of the environment compared with the uterus. This adaptation results in a depression of ventilatory responses to hypoxia that can last up to 6 months after birth in humans (Richardson et al., 2007). Immediately after birth, rats showed a weak ventilatory response to a hypoxic challenge (Liu et al., 2009), even though their ventilatory rate was relatively high, probably to compensate for their immature gas exchange machinery.

6.2 | Airways and chest wall properties

Regarding the airways, they are a component of the respiratory system that also shows differences between neonates and adults. Thus, the paediatric upper and lower airways are characterised by a higher resistance to flow, mainly due to a smaller diameter, higher collapsibility, and lower pharyngeal muscle tone (Trachsel et al., 2022). Focussing on the upper airways, they have an elliptical shape in neonates. From the subglottic to the cricoid ring, the airways are narrower in the transverse dimension than in the anteroposterior dimension (Wani et al., 2017), whereas observations of airways in children over 1 year of age showed a circular shape. Smaller and softer, they are more prone to inspiratory collapse. The closure of newborn upper airways is behind central apneas. This closure may be due to either passive pharyngeal collapse or active laryngeal closure (Praud & Reix, 2005). Nevertheless, the cartilaginous structure lengthens and stiffens with maturation during childhood.

Respiratory immaturity is associated with breathing instability, while immature breathing control manifests as central apneas. Both events have been linked, although controversially, to the sudden infant death syndrome (Ramanathan et al., 2001). There is an improvement with progressive maturation, with the frequency and duration of central apneas decreasing during the first 12 months of life, with values of 15 apneas longer than 3 s per hour reported at 12 months (Daftary et al., 2019).

Newborns also have unique chest wall properties which disappear with time. Thus, newborns have up to 3 times higher compliance levels than adults to allow for greater expansion during breathing. The ribs also contribute to this end, as they are more flexible in the newborn, while they are positioned more horizontally than in the adults, moving only upwards, and not upwards and outwards, as in the adult rib cage. This difference is the main limitation to increase tidal volumes and the reason why infants under 12 months of age rely mainly on diaphragmatic breathing (Hershenson et al., 1990).

The values of the functional reserve capacity (FRC) are also subjected to significant changes, with values that increase rapidly after birth (Rosen, 2008). FRC is directly related to the number of alveoli; fewer alveoli in immature lungs provide less support and can lead to peripheral airways collapse. As the lungs grow, they undergo a process of alveolarisation which also helps to increase the surface area available for gas exchange.

6.3 | Respiratory control

Exposure to adverse conditions in utero, such as those caused by GIH, may lead to epigenetic changes that affect the postnatal development of the respiratory control. Animal studies have shown that prenatal exposure to IH can alter respiratory control mechanisms and increase the susceptibility to respiratory diseases later in life (Johnson et al., 2018). However, the effects of IH protocols during pregnancy on the developing respiratory system are not yet fully characterised.

The first study of the effects of GIH on respiratory responses in neonatal rats found that normoxic ventilation was increased in GIH offspring compared with their respective controls (1- and 4-months of age), although hypoxic responses were similar (Gozal et al., 2003). It was postulated that this maladaptive response to postnatal hypoxia could contribute to events such as the sudden death syndrome. Nevertheless, this study had several limitations, one of which was that it did not distinguish between male and female pups.

6.4 | Inflammatory status and oxidative stress

A study of inflammatory status in neonatal GIH-treated rats recorded respiratory motor bursts in brainstem–spinal cord preparations (Johnson et al., 2018). In newborn rats (0–3 days old) burst frequency was unchanged in GIH animals, although the rhythm was more regular and the rise time tended to be faster, with no effects of gender on these variables in any of the groups. When testing the respiratory motor output elicited by an inflammatory challenge, males showed a significantly reduced burst frequency compared with normal conditions, with no differences between control and GIH animals. However, in preparations from female animals, only the control preparations showed a decrease in burst frequency with the inflammatory challenge, while the GIH group showed no change. Although GIH did not alter the expression of pro-inflammatory factors tested in the brainstem or spinal cord (IL-1β, TNFα, and COX-2), it did affect the offspring response to a later postnatal inflammatory challenge, in a sex-dependent manner. The authors hypothesised that GIH reprogrammes the neuroinflammatory response pathways in the female animals so that there is less cytokine production during inflammatory challenges. Cytokines are linked to the sensitivity of the brainstem respiratory centres, which modulate the respiratory frequency in a complex way, ranging from hyperventilation and even respiratory stress syndrome (as in the worst cases of Covid-19, associated with cytokine storm) (Soy et al., 2020), to respiratory depression. If this were the case, female GIH offspring would have an impaired ability to trigger an immune response against infection, from birth, and perhaps even into adulthood, especially at the level of respiratory system pathologies.

At birth, the newborn comes into an oxygen-rich environment, and oxygenation through the lungs instead of the placenta raises tissue oxygenation within minutes. ROS are normally neutralised by antioxidant defence systems. In preterm infants, these defences are immature, making them more prone to oxidative tissue injury. In addition, preterm infants with inflammation also have an increased incidence of apnea and are at a greater risk for adverse neurodevelopmental outcomes and mortality rates (see Di Fiore et al., 2013).

The frequent episodes of IH associated with preterm birth have been linked to adverse respiratory outcomes, with a recent article (Raffay et al., 2023) linking them to high levels of oxidative stress. Thus, more than 65% of preterm infants suffer at least one infection during their hospitalisation (Stoll et al., 2004). By noninvasively measuring lipids, proteins, and DNA oxidative stress biomarkers in urine samples from 1 week and 1 month old premature babies (<31 weeks of gestation), the authors found a direct association between IH and the various oxidative products quantified. In this sense, it could be possible that most of the effects of GIH on the offspring are indirectly caused by the maternal stress. Thus, OSA events in pregnant women were associated with higher levels of systemic inflammation, which was related to the number of obstructive events, especially during the REM phases of sleep (Alonso-Fernández et al., 2021).

It is known that gestational stress can induce permanent epigenetic changes in the offspring, as shown by an increase in the levels of some chemokines and altered expression of their receptors in a rat model (Ślusarczyk et al., 2015). In this context, sex-specific effects of stress during gestation and development of respiratory control have been described (Fournier et al., 2013), with a higher rate of pathological apneas in newborn male rats, which was associated with a deficit of medulla-derived serotonin (5-HT). A recent study (Song, Mishra, Dangudubiyyam, Antony, et al., 2022) has found that GIH impairs endothelial NO synthesis in rat offspring vessels, highlighting the fact that some detrimental effects of gestational hypoxia may persist well into adulthood.

Underscoring the importance of inflammation in the neonatal respiratory system, even low levels of inflammation in neonatal rats have been proved to impair respiratory control networks (Morrison et al., 2020). Using brainstem spinal cord preparations, these authors found differential sensitivities of the respiratory control areas to inflammation. Lower levels of inflammation were more disruptive, affecting amplitude and frequency, while more severe inflammation affected frequency only.

Despite OSA being more prevalent in men, the occurrence in late pregnancy women rises to levels comparable to men. In males, the key contributors to chronic IH-induced cardiovascular dysfunction elicited by inflammation and oxidative stress include TLR4/MyD88/NF-κB/MAPK, miRNA/NLRP3, and COX signalling (see Song et al., 2024), although this information is mostly missing in pregnant females and their offspring. Future research should evaluate inflammatory targets in females subjected to GIH and their offspring.

Neonatal inflammation also affected CB chemosensitivity, induced spontaneous apneas in vivo and caused significant O_2 desaturation (Master et al., 2016). Levels of dopamine, an inhibitor of CB activity, were increased in the CB due to neonatal inflammation. Inflammatory responses in neonates and adults may involve similar mechanisms although it could be that neonatal signalling pathways are different (see Beyeler et al., 2020). Nevertheless, the paucity of scientific studies on GIH exposure and respiratory control makes it difficult to draw firm conclusions. Not many studies are available either on the role of the respiratory muscles, the final effectors in the respiratory control system. A study of the diaphragm function in rats exposed to GIH found it had no effect on the force-generating capacity of the diaphragm (McDonald et al., 2016a), in either male or female animals. Similar results were observed in the same study when the animals were subjected to IH shortly after birth (postnatal days 22 and 42), suggesting a relative resilience of the diaphragm muscle to hypoxic stress during the perinatal period. However, when examining the sternohyoid, one of several pharyngeal dilator muscles, the same

authors found evidence of weakness in the postnatally exposed animals (McDonald et al., 2016b). This effect persisted into adulthood (16 weeks of age). They suggested that this mismatch between the diaphragm and sternohyoid muscles could contribute to a higher risk of airway collapse.

6.5 | Other effects of GIH in the offspring

In addition to the respiratory effects of GIH, there are other long-term effects that we would like to briefly mention in this section.

Prenatal exposure to GIH has been shown by Song et al. (Song, Mishra, Dangudubiyyam, Antony, et al., 2022) to cause fetal growth restriction in both male and female animals, with postnatal catch-up, and the development of hypertension in males only. This hypertensive sexual dimorphism affecting only male offspring was accompanied by impaired endothelium-dependent vasodilation, a decrease in eNOS activity and an increase in sex steroid hormone levels, particularly testosterone and oestradiol.

Data from the same group (Song, Mishra, Dangudubiyyam, Baker, et al., 2022) showed hypertension in female offspring at prepubertal age in a GIH rat model, which became normotensive after 10 weeks of age, coinciding with the pubertal period in these animals. This regulation of hypertension coincides with the increase in the oestradiol levels associated with puberty. In contrast, after this time point and into adulthood, male offspring are more susceptible to hypertension, pointing to a protective role of oestradiol.

Going back to the growth of the fetus, there are conflicting data in the scientific literature. A recent systematic review with meta-analysis (see Sanapo et al., 2024) found that the association of snoring and OSA was associated with high birth weight, while only OSA was related with an increased risk of low birth weight, thus pointing to the disparity in outcomes depending on the disorder and the diagnostic method used. Also using a rat model of GIH a recent article (Suzuki et al., 2024) found alterations in postnatal maxillofacial bone growth and cartilage metabolism in male offspring at 5 and 10 weeks of age.

On the long term effects of maternal OSA a recent paper by Wang et al. (Wang et al., 2024) found evidence of metabolic dysfunction linked to increased susceptibility to fatty liver disease in male offspring using 6-month old rats.

Interestingly, the effects of late GIH do not stop at physiological changes, as pointed out in a recent paper by Mabry et al. (2023). Using a rat model of late GIH, they examined the behaviour and brain activity of the offspring during puberty and young adulthood. They found interesting differences between male and female animals, with female offspring displaying social impairment and male offspring showing cognitive dysfunction.

7 | CONCLUSIONS

Overall, GIH can have remarkable effects on both maternal and fetal health, with a concomitant risk of adverse pregnancy outcomes and also an increased risk of respiratory dysfunction in the offspring which may persist into adulthood (Figure 1).

Multidisciplinary care involving obstetricians, sleep specialists, and respiratory therapists should be the approach adopted by national health services for the comprehensive management of sleep apnea

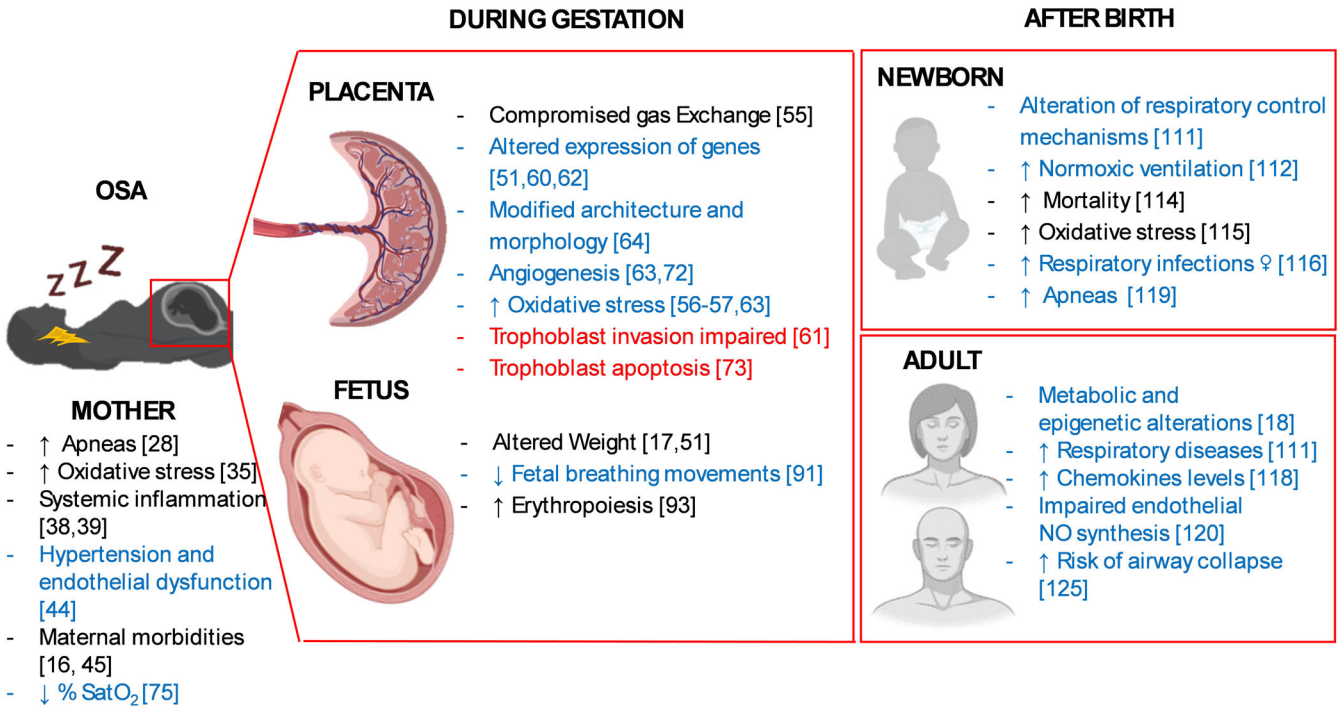

FIGURE 1 Effects of gestational intermittent hypoxia on maternal, fetal and offspring respiratory system. In black, effects in humans; in red, in vitro effects; in blue, effects in animal models.

during pregnancy. Early detection of OSA during pregnancy should be an essential tool for timely intervention. Questionnaires and polysomnography should be first line tools to help clinicians identify women at higher risk for OSA and respiratory disturbances.

Once identified, CPAP therapy is usually the treatment of choice. It helps to improve upper airway patency and maternal oxygenation. Other interventions include lifestyle changes, such as weight management, positional therapy, and avoidance of sedatives and alcohol.

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Esther Valverde-Pérez: Writing – review and editing. **Elena Olea:** Writing – review and editing. **Asunción Rocher:** Conceptualization; writing – original draft. **Philip I. Aaronson:** Writing – review and editing. **Jesús Prieto-Lloret:** Conceptualization; writing – original draft.

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The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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