OCCASIONAL REVIEW

Sleep disordered breathing and pregnancy

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Many changes in the respiratory system occur during pregnancy, particularly during the third trimester, which can alter respiratory function during sleep, increasing the incidence and severity of sleep disordered breathing. These changes include increased ventilatory drive and metabolic rate, reduced functional residual capacity and residual volume, increased alveolar-arterial oxygen gradients, and changes in upper airway patency. The clinical importance of these changes is indicated by the increased incidence of snoring during pregnancy, which is likely also to reflect an increased incidence of obstructive sleep apnoea/hypopnoea syndrome. For the respiratory physician asked to review a pregnant patient, the possibility of sleep disordered breathing should always be considered. This review first examines the normal physiological changes of pregnancy and their relationship to sleep disordered breathing, and then summarises the current knowledge of sleep disordered breathing in pregnancy.

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PHYSIOLOGICAL CHANGES IN RESPIRATORY FUNCTION DURING PREGNANCY

Pulmonary mechanics (measured during the day) are markedly altered during pregnancy, with a 20% reduction in functional residual capacity (FRC)[1–3] arising from elevation of the diaphragm to accommodate the enlarging uterus. This becomes particularly important during sleep because it compounds the fall in FRC associated with sleep itself. With reduced FRC, maternal oxygenation is decreased, compounding the increased aterial/oxygen gradient found in pregnancy.[4] Increased airway closure may occur during tidal ventilation resulting in increased ventilation/perfusion mismatch.[5] This effect is exacerbated in the supine position. However, there is some compensation for these changes as a result of a right shift of the oxyhaemoglobin desaturation curve in normal pregnancy, such that delivery of oxygen to the placenta and maternal tissue is enhanced.[6]

Hormonal changes associated with altered respiratory function during pregnancy

Circulating oestrogen and progesterone levels increase markedly during pregnancy, both primarily being responsible for maintaining the pregnancy. However, there are many other physiological changes produced by these hormones which are unrelated to maintenance of the pregnancy. Progesterone markedly upregulates ventilatory drive at the level of the central chemoreceptors (located on the ventrolateral surface of the medulla).[7 8] As a result, there is a reduced arterial carbon dioxide pressure ($Paco_2$) and an associated respiratory alkalosis with a mean arterial pH of 7.44 (compared with 7.40 in the non-pregnant state). This resting respiratory alkalosis can lead to instability in the respiratory control pathways which may become unbalanced during sleep. While it is well known that hypocapnia and respiratory alkalosis can lead to central apnoeas during non-rapid eye movement (NREM) sleep in non-pregnant subjects, particularly during the transitional period from wakefulness to sleep,[9] this has not been investigated during pregnancy.

In keeping with the upregulation of central respiratory drive, there is increased diaphragmatic effort leading to greater negative inspiratory pressures at the level of the upper airway. This may be related to an increased tendency for the upper airway to collapse during sleep.

Upper airway changes in pregnancy

Patency of the upper airway is well known to be an important predictor of the presence and severity of sleep disordered breathing, with reduced dimensions of the pharynx being strongly associated with obstructive sleep apnoea.[10] Reduced pharyngeal dimensions during pregnancy have been demonstrated using the Mallampati score.[11] Nasal patency is also reduced during pregnancy, with 42% of women at 36 weeks gestation reporting nasal congestion and rhinitis.[12] These symptoms may be related to a combination of the increasing progesterone and oestrogen levels as pregnancy progresses. Increments in circulating oestrogen concentrations have been linked with nasal rhinitis, both during the luteal phase of the menstrual cycle[13] and during pregnancy.[14] In addition, the increase in circulating blood volume associated with pregnancy may also contribute to nasal congestion.

There are therefore a number of physiological changes that occur during pregnancy which may predispose women to exacerbation of pre-existing sleep disordered breathing or to the development of new disease.

Other physiological changes during pregnancy

Pregnancy is characterised by significant increases in heart rate, stroke volume, and cardiac output, with marked reductions in peripheral vascular resistance. Overall, the net outcome in normal pregnancy is a marginal reduction in systemic arterial blood pressure. Furthermore, it is

well known that normal pregnancy is associated with a normal circadian blood pressure rhythm, with a nocturnal dip in both blood pressure and heart rate.[15]

Changes in sleep architecture during pregnancy

The hormonal and physical changes that occur during pregnancy are associated with altered sleep architecture as pregnancy progresses. While total sleep time increases marginally in the first trimester compared with the non-pregnant state,[16] thereafter it progressively decreases and is significantly reduced during the third trimester.[16 17] Sleep stages 3 and 4 and NREM sleep (deep sleep) are reduced after the first trimester of pregnancy,[16 18] as is REM sleep.[16 17 19 20]

PATHOLOGICAL CHANGES IN PREGNANCY

Snoring

The incidence of snoring in a US population of healthy pregnant women was found to be 14%, significantly greater than the 4% incidence found in a matched non-pregnant population.[21] However, there may have been a selection bias in this study, limiting the incidence of snoring, as questionnaires were only administered to women attending the "non-risk" antenatal clinics. In contrast, a recent study in Sweden of 502 pregnancies found that 23% of the population reported regular snoring[22] while only 4% of the same sample reported regular snoring before pregnancy. However, both of these figures may be an underestimate of the true incidence of snoring in pregnant women as it has been found that women in general tend to under-report snoring on questionnaires.[23]

Hypoxia during sleep

Several studies have investigated maternal oxygenation during sleep in late pregnancy with conflicting results. Brownell *et al*[24] found no compromise in maternal oxygenation during sleep in six healthy subjects at 36 weeks gestation, but Hertz and colleagues[19] showed a small but significant reduction in nocturnal Sao_2 during pregnancy in 12 women during the third trimester of pregnancy compared with postpartum studies in the same subjects. Furthermore, marked nocturnal hypoxaemia was recently demonstrated in a study of 13 normotensive and 15 hypertensive pregnant subjects at more than 35 weeks gestation.[25] In the normotensive group five of 13 had a mean overnight Sao_2 of <95%, three of whom spent at least 20% of the night with an Sao_2 of <90%; in the hypertensive group six of 15 had a mean overnight Sao_2 of <95%, four of whom spent at least 20% of the night with an Sao_2 of <90%.[25]

Obstructive sleep apnoea in pregnancy

While the exact prevalence of sleep disordered breathing in pregnancy is not known, the increased incidence of snoring would suggest that the prevalence of obstructive sleep apnoea (OSA) may well be increased. In a population with no clinical evidence and no predisposing factors for sleep disordered breathing, Brownell *et al*[24] found that the respiratory disturbance index (RDI) is marginally reduced during pregnancy compared with the postpartum period. However, this study was performed in healthy subjects with no evidence of sleep disordered breathing before the pregnancy in whom the change in RDI was of little clinical significance (increasing from 1.1 events per hour antenatally to 2.7 events per hour in the postnatal period). More recent data have confirmed that normal pregnancy is not associated with precipitation of sleep apnoea in non-obese women.[26] However, this same study investigated obese subjects during early and late pregnancy and found a marginal increase in RDI. Although the changes in RDI are not of clinical significance, it is interesting that there is a marginal deterioration in those women predisposed to the development of obstructive sleep apnoea.

There have been no large prospective studies measuring the effect of pregnancy on breathing during sleep. To date, studies of OSA during pregnancy have predominantly been case reports,[27–33] with few longitudinal studies and no population based epidemiological studies. Thus, while it is known that the prevalence of OSA in women of reproductive age is approximately 5%,[34] the true prevalence of OSA in pregnancy is unclear. The largest reported study was performed by Schoenfeld and colleagues who investigated a cohort of eight patients and followed up the outcome of their pregnancies.[35] Only one report has suggested that OSA may have been precipitated or aggravated during pregnancy.[31] We have recently investigated a cohort of women with severe OSA during pregnancy, and followed them through delivery and up to 6 months postnatally. This cohort demonstrated a marked improvement in the severity of sleep disordered breathing following delivery (unpublished data). These studies suggest that OSA may develop during pregnancy in patients with a pre-existing tendency towards sleep disordered breathing, and may increase the severity of the disease in those women who already suffer from OSA.

Maternal complications associated with sleep disordered breathing in pregnancy

Snoring during pregnancy may be an important finding as it has been associated with maternal hypertension and pre-eclampsia.[22] One of the important clinical findings in pre-eclampsia is the reversed diurnal blood pressure rhythm[15] similar to that described in OSA,[36] which suggests that there may be a common link occurring during sleep in these two groups. We have recently investigated 12 women with pre-eclampsia diagnosed on standard international criteria.[37] Using full overnight polysomnography, we found that all had partial airflow limitation during sleep, with a mean reduction in tidal volume of 10% for approximately 70% of the time spent asleep.[37] These women did not have classic obstructive sleep apnoea/hypopnoea syndrome characterised by repetitive episodes of partial or complete cessation of airflow associated with cyclic hypoxaemia. The RDI in these subjects was less than 10 events per hour, fitting more closely the criteria for the upper airways resistance syndrome.[38] However, the long periods of partial upper airway obstruction were associated with increased systemic arterial blood pressure, which was found to be reduced with the application of nocturnal nasal continuous positive airway pressure (CPAP).

While it now appears clear that there is an association between the existence of sleep disordered breathing and hypertension during pregnancy, the primary causal abnormality has not been proved. Increased oedema in the upper airway resulting from the generalised vascular changes found in pre-eclampsia may precipitate sleep disordered breathing. However, with the strong link between sleep disordered breathing and hypertension in the general population,[39] there is the possibility that pre-existing sleep disordered breathing may actually induce hypertension and/or pre-eclampsia during pregnancy.

Many case reports describe OSA, diagnosed during the third trimester, in women with pregnancy related complications including pulmonary hypertension,[29] pre-eclampsia,[27 31 33 40] and gestational diabetes mellitus.[29 40 41] While this may simply reflect the fact that women with these disorders are clinically investigated for other problems such as sleep disordered breathing, the recent case report describing treatment of OSA with CPAP with a marked clinical improvement and spontaneous diuresis of more than 45 litres implies that OSA may have been responsible for at least some of the right ventricular failure.[29]

Fetal complications associated with sleep disordered breathing in pregnancy

Repetitive episodes of obstructive respiratory events during sleep give rise to cyclic episodes of maternal hypoxaemia. Furthermore, hypertension and peripheral vasoconstriction are commonly associated with OSA, with both complications being associated with reduced placental delivery to the fetus. The

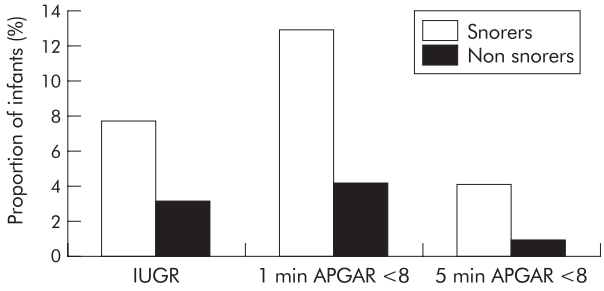

Figure 1 Incidence of complications in infants of women who reported snoring during pregnancy. Compiled from data in Franklin *et al*.[22]

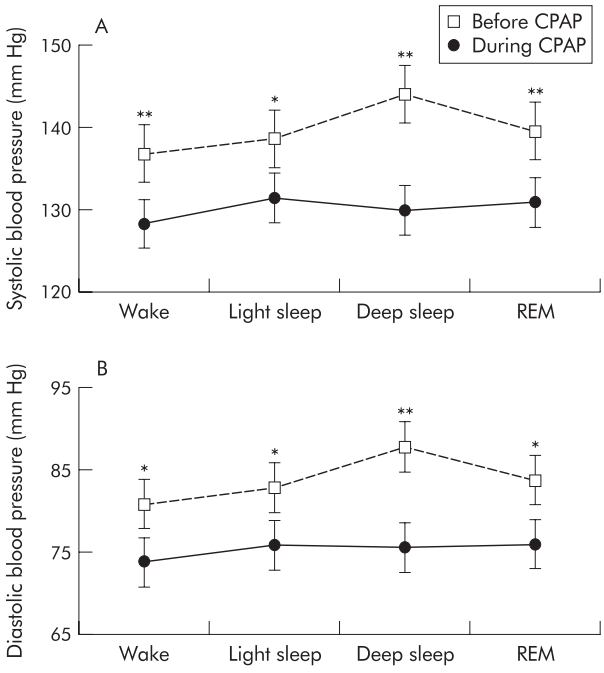

Figure 2 Blood pressure according to sleep stage before treatment and during treatment with nasal continuous positive airway pressure (CPAP) in women with pre-eclampsia; *p<0.05; **p<0.02. Compiled from data in Edwards *et al*.[37]

clinical outcome of OSA during pregnancy has not been extensively studied, but early reports suggest that it may represent a new risk factor to the fetus. In a large study of snoring in pregnancy, fetal compromise was clearly demonstrated with adverse outcomes including intrauterine growth restriction[21 22] and lower APGAR scores at birth (fig 1).[22] Furthermore, of the reports available on fetal outcome in women with OSA diagnosed during pregnancy, either on the basis of clinical examination or using polysomnography, approximately half the infants were diagnosed with intrauterine growth restriction.[27 35 42] Those pregnant patients with OSA who had infants of normal birth weight tended to have been diagnosed before the third trimester and started on treatment (either with tracheostomy or nasal CPAP).[28–30] However, at the individual level, the immediate fetal effects are unclear. A case report of severe OSA during pregnancy revealed normal fetal heart rate reactivity on cardiotocographic (CTG) recording, even during maternal apnoeic episodes with associated severe oxyhaemoglobin desaturations.[41]

TREATMENT OF RESPIRATORY SLEEP DISORDERS IN PREGNANCY

The standard treatment for OSA is nasal CPAP, although previously treatments such as tracheostomy were occasionally required. Nasal CPAP has been used in a number of pregnant patients with a good outcome.[29 31 33 37 43] We found nasal CPAP to be particularly useful in reducing nocturnal blood pressure increments in women with pre-eclampsia when used to treat sleep related nasal flow limitation (fig 2).[37]

CONCLUSIONS

A number of physiological changes occur during normal pregnancy which may potentially compromise the respiratory system. Many of these changes are compounded during sleep due to a combination of both postural and sleep related phenomena. Related to these factors, the incidence of snoring is increased during pregnancy. While the true incidence of OSA during pregnancy is not yet known, recent studies by our group and others have shown that the severity of OSA is increased during pregnancy. Preliminary data suggest that recognition and treatment of OSA during pregnancy may lead to improved outcomes.

When a respiratory physician is asked to review a pregnant patient, the possibility of sleep disordered breathing should always be considered. CPAP has been proved to be a safe and effective treatment of OSA in a wide variety of patients. With better recognition of the deleterious outcomes of untreated OSA during pregnancy, it is anticipated that earlier intervention with CPAP may improve the outcome for pregnant women with OSA.

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