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Sleep and Pregnancy: Sleep Deprivation, Sleep Disturbed Breathing and Sleep Disorders in Pregnancy

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1. Introduction

There are many factors that can influence an individual's sleep pattern and quantity and quality of sleep. These factors can be cultural, social, psychological, behavioural, pathophysiological and environmental. Sleep patterns can also be influenced by society and by changes within society. In recent times we have seen the introduction of longer working hours, more shift-work and 24-7 availability of commodities. At the same time secular trends of curtailed duration of sleep to fewer hours per day across westernized populations (Akerstedt & Nilsson 2003) has led to increased reporting of fatigue, tiredness and excessive daytime sleepiness (Bliwise, 1996). It is of interest that whilst some studies indicate that women may have better sleep than men in general (Lindberg et al, 1997; Goel et al, 2005), they also report a larger difference in the estimated time of sleep that they believe they require and the actual sleep time they achieve than men. This might indicate that their sleep debt (amount of sleep deprivation) is higher in women than in men (Lindberg et al, 1997). There is now a wealth of evidence to support the epidemiological link between quantity of sleep (short and long duration) and quality of sleep (like difficulties in falling asleep or of maintaining sleep) and cardiovascular risk factors. These include hypertension (Cappuccio et al, 2007; Stranges et al, 2010), type-2 diabetes (Cappuccio et al, 2010a) and obesity (Cappuccio et al, 2008; Stranges et al, 2008; Cappuccio et al 2011a) as well as cardiovascular outcomes (Cappuccio et al, 2011b) and all-cause mortality (Ferrie et al, 2007; Cappuccio et al, 2010b). Additionally, there may be important gender differences in sleep and associated health outcomes (Miller, 2009 et al; Cappuccio et al, 2007). The deleterious effects of sleep deprivation can be seen on a variety of systems within the body, with detectable changes in metabolic (Knutson, et al. 2007; Spiegel, et al. 2009), endocrine (Spiegel, et al. 1999; Taheri, et al. 2004) and immune pathways (Miller & Cappuccio 2007; Miller et al, 2009).

The physiological and hormonal changes that occur in pregnancy increase the risk of developing Sleep Disordered Breathing (SDB). It has been estimated that 10-27% of pregnant women may suffer from habitual snoring (Pien & Schwab, 2004) and there is growing evidence to suggest that snoring and sleep apnoea during pregnancy are associated with an increased risk of gestational hypertension and pre-eclampsia. SDB and short sleep duration in pregnant women may also be associated with the risk of gestational diabetes.

This chapter will examine the evidence that suggests that short sleep duration and poor quality are associated with adverse maternal and foetal outcomes. Furthermore, it will examine the potential mechanisms which may underlie these associations including activation of the sympathetic nervous system, oxidation and inflammation and mechanisms leading to the development of insulin resistance (Izci-Balserak & Pien, 2010). It will also consider the prevalence of sleep disorders in pregnancy. The diagnosis, management and treatment of sleep disorders in pregnancy will be discussed along with implications for public health policy, etc.

2. Sleep and pregnancy

Pregnancy is associated with many maternal physiological and psychological changes both of which may have an effect on sleep. In the first trimester, hormonal changes may disrupt sleep and in the third trimester the large baby and the anxiety regarding delivery may have associated effects on sleep. Likewise post-partum, a newborn may disrupt sleep patterns. The review by Lee in 1998 demonstrated that there was a paucity of studies, which addressed the alterations of sleep in pregnant women, moreover many of these studies lacked sufficient power to allow consistent interpretation and replication of the results (Lee, 1998). Since then a number of studies have now been conducted but more research is still required to establish whether for example, a woman's pre-pregnancy sleep pattern can affect outcome and to determine whether there is any effect of parity on sleep related maternal and foetal outcomes. The changes in circadian rhythm of various hormones and the associated changes to sleep architecture that occur throughout pregnancy are discussed by Wolfson and Lee (2005) in 'The Principles and Practice of Sleep Medicine' (Kryger, Roth and Dement (Eds)).

2.1 Sleep deprivation: Adverse sleep changes in pregnancy quantity and quality

Due to the lack of good longitudinal studies there is still little information on what constitutes normal sleep quality and quantity both during pregnancy and in the period following delivery. In a recent study however Signal et al quantified the change and variability in sleep duration and quality across pregnancy and post-partum in 8 healthy nulliparous and 11 healthy multiparous women (Signal et al, 2007). The women wore an actigraph and completed a sleep diary for seven nights during the second trimester, one week prior to delivery, and at one and six weeks post-partum. They observed that compared to multiparous women, nulliparous women generally had less efficient sleep, spent more time in bed and had greater wake after sleep onset in the second trimester, and spent less time in bed and had fewer sleep episodes a day at one week post-partum. The largest change in sleep however occurred during the first week after delivery with the women obtaining 1.5h less sleep than during pregnancy. In a more recent and larger study sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) in 260 women during the second and third trimester of pregnancy (Naud et al, 2010). Of the 260 women, 192 (73.6%) had a term delivery without any adverse outcome. The investigators reported that there were no differences in sleep parameters between pregnancies with adverse outcome and without adverse outcome. The PSQI scores however indicted that sleep quality deteriorated from the second (5.26 ± 3.16) to the third trimester (6.73 ± 4.02 ; $P < 0.01$). This deterioration was displayed in five of seven sleep components ($P < 0.01$). Scores in the "poor sleeper" range were recorded by 36% of women in the second trimester and 56%, of women in the third ($P < 0.01$). "Poor sleep" in both trimesters was associated with low or high

weight gain, low annual family income, and single motherhood ($P < 0.01$). A weak but not significant effect of season on sleep scores was recorded: The mean PSQI scores were 6.06 (± 3.96) in winter, 5.21 (± 3.21) in spring) 5.33 (± 3.04) in summer and 5.53 (± 2.41) in autumn; ($P=0.076$). In a similar study of 189 nulliparous women Facco et al demonstrated that compared with the baseline assessment (mean gestational age (13.8 (± 3.8)) the mean sleep duration was significantly shorter at 30.0 (± 2.2) weeks gestation ($p < 0.01$). They also observed that in the third trimester the proportion of patients who reported frequent snoring (at least three nights per week) was significantly increased, and that there was an increase in those who met the diagnostic criteria for the recognised sleep disorder 'restless leg syndrome'. Furthermore, poor sleep quality, as defined by a Pittsburgh Sleep Quality Index score greater than 5, became significantly more common as pregnancy progressed (Facco et al, 2010).

In a separate study Wilson et al also found that sleep efficiency was decreased in late pregnancy and was associated with an increase in cortical arousals when compared to women in early pregnancy and non-pregnant women. Compared to a control group, they found that women in the third trimester of pregnancy had more awakenings and had poorer sleep efficiency. They had less stage 4 sleep and more stage 1 sleep and spent less time in rapid eye movement (REM) sleep (Wilson et al, 2010).

Sleep quality also decreases as a woman approaches labour (Evans et al, 1995) but whilst little is known of the effect of sleep disturbance on labour or delivery outcome it has been common practice to administer morphine sulphate to women in either early or non-progressing latent phase labour to induce sleep. It has been observed that on awakening the contractions are more regular and active.

2.2 Sleep disorders in pregnancy

Sleep-Disordered breathing (SDB) is the term used to describe a group of disorders which are characterized by abnormalities of respiratory pattern (pauses in breathing) or the quantity of ventilation during sleep. A recent study evaluated the frequency of sleep disordered breathing in women with gestational hypertension compared to healthy women with uncomplicated pregnancies. They observed that women with gestational hypertension may have a significantly higher frequency of sleep disordered breathing than do healthy women with uncomplicated pregnancies of similar gestational age. The frequencies of sleep disordered breathing in the more obese gestational hypertension group and the healthy group were 53% and 12% ($p < 0.001$) (Reid et al, 2011).

Obstructive sleep apnoea (OSA) is the most common of these sleep disorders and is characterized by the complete or partial collapse of the pharyngeal airway during sleep. To resume ventilation, feedback mechanisms arouse the individual, which leads to sleep disruption. OSA is associated with an increased CVD risk. Although, men are twice as likely to develop OSA as women, the risk is increased in women if they are overweight. Moreover, data from recent studies indicates that snoring and OSA increase during pregnancy. The prevalence of OSA is very low in normotensive women low-risk pregnancies but is increased among normotensive pregnant women with high risk pregnancies and, in those with gestational hypertension (pregnancy-induced hypertension (PIH)/pre-eclampsia) during pregnancy, the prevalence is even higher.

PIH is characterised by high blood pressure with a flat circadian rhythm and in particular does not have the normal nocturnal dip associated with sleep. Risk factors for PIH include first time pregnancy, long periods (>10 years) between pregnancies, multiple pregnancies,

women younger than 20 or older than 35 or women who are overweight, have a history of hypertension or kidney disease or diabetes. Recent studies indicate that OSA per se is an independent risk factor for gestational hypertension/pre-eclampsia and may contribute to other poor obstetrical outcomes. Good blood pressure control in pregnancy is important. Continuous Positive Airway Pressure (CPAP), which is used to treat OSA, may also have beneficial effects on blood pressure (Champagne et al, 2010). It may therefore be very useful in patients with PIH as this condition is associated with both increased blood pressure and a significantly narrowed upper airways and limited airflow during sleep (Izci et al, 2003). Continuation of treatment for OSA following the pregnancy may also be required.

Insomnia is a sleep disorder which is characterised by a difficulty in initiating or maintaining sleep in combination with adverse daytime consequences. The daytime effects may include excessive fatigue, impairment of performance or emotional changes. Data from self-reported questionnaires suggests that sleep complaints are more frequent in pregnancy and that sleep disturbances increase as the pregnancy progresses. In a recent study of 300 women (100 women in each trimester of pregnancy) it was observed that there was a significant increase in insomnia in the 2nd trimester, excessive daytime sleepiness (EDS) was also increased in pregnancy and the rate for specific awakenings increased by 63% in the first trimester, by 80% in the second trimester and by 84% in the third trimester ($p < 0.001$) (Lopes et al, 2004).

Restless leg syndrome is a neurosensory sleep disorder which begins in the evening. The associated symptomatic leg movements can prevent a person from falling asleep and contribute to poor sleep quality. Pregnant women have at least two or three times higher risk of experiencing restless legs syndrome (RLS) than the general population and women affected by pre-existing RLS often complain of worsening symptoms during pregnancy. It is associated with iron deficiency anaemia. The women who are most at risk are those with low folate, ferritin or haemoglobin prior to conception. Data from the existing epidemiological studies suggests that the rates may be as high as 27% in the third trimester (Lee et al, 2001; Manconi et al, 2004). Whilst RLS is a reversible syndrome in pregnancy and is typically limited to the third trimester it has been associated with adverse pregnancy outcomes and therefore needs to be taken seriously. The standard medications for RLS that contain dopaminergics or opioids should be avoided but preventative measures to increase the amount of folate should be encouraged at the first prenatal visit.

Complaints of heartburn increase during pregnancy and if these progress to severe nocturnal oesophageal reflux may also contribute to sleep disruption.

2.3 Sleep disturbances and adverse maternal and foetal outcomes

In Western societies adverse pregnancy outcomes have been on the increase and in the United States over 1 million pregnancies are associated with adverse outcomes including increased maternal and infant morbidity. The current known risk factors however are insufficient for early detection of at risk individuals and attention has focused on sleep as an emerging new risk factor (Okun et al, 2009). A recent prospective cohort study of low-risk pregnant women suggested that there may be no differences in sleep parameters between pregnancies with adverse outcome and without adverse outcome (Naud et al, 2010). Other studies however have indicated that sleep deprivation in pregnancy may be associated with adverse maternal outcomes including gestational hypertension, pre-eclampsia and diabetes and difficulties with labour and delivery, depression and adverse effects on the foetus. Data suggests that women who snore or suffer from obstructive sleep apnea during pregnancy are more likely to suffer from gestational hypertension and pre-eclampsia. Data is also

accumulating to suggest that both short sleep duration and sleep-disordered breathing may be associated with an increased risk of gestational diabetes (Izci-Balserak & Pien, 2010). A study of Taiwanese women compared sleep quality using the PSQI between 150 second-trimester and 150 third-trimester pregnant women and 300 non-pregnant women. (Ko et al, 2010). The study demonstrated that the prevalence of poor sleepers was increased in pregnant as compared to non-pregnant women and that sleep quality of pregnant women was related to stress and depression.

There is evidence to suggest that sleep deprivation during pregnancy increases the risk of preterm delivery and postpartum depression, and that systematic inflammation may be an important underlying mechanism in the association (Okun et al, 2009; Okun, et al 2011a, Chang et al, Okun et al, 2011b). Approximately 14.5% of women will experience an episode of post partum major depression (PPMD) and 25% will experience a recurrent episode (Wisner et al, 2006). Women with PPMD are also more likely to experience impaired relationships with their infant (Gavin et al, 2005). In a recent study 56 pregnant women with past history of PPMD but with no evidence of depression in their current pregnancy, had blood samples collected at 8 times during the first 17 weeks postpartum. The PSQI was also administered. Recurrence of depression was measured by two consecutive 21-item scores of ≥ 15 on the Hamilton Rating Scale for Depression (HRSD) and by clinical interview. The blood was analysed for estradiol, prolactin, cortisol and IL-6. The results indicated that in this study, self-reported poor sleep quality but not hormone or cytokine levels were associated with PPMD recurrence (Okun et al, 2011a).

Fatigue and sleep disturbance in late pregnancy are important determinants of both labour duration and delivery type. A prospective observational study of 131 women in their ninth month of pregnancy demonstrated that those women who slept less than 6 hours per night, as determined by 48-hour wrist actigraphy, sleep logs and questionnaires, had had longer labours and were 4.5 times more likely to have caesarean deliveries. Labours were also longer and were 5.2 times more likely end in caesarians in those women who had poor quality sleep (Lee & Gay, 2004).

Amongst pregnant women snoring is common and it may have adverse effects on the foetus. In particular, foetal hypoxia may occur leading to an increase in systemic inflammation and an elevation in the number of circulating nucleated red blood cells (nRBCs) with an associated decrease in foetal wellbeing (Tauman et al, 2011). A recent population-based case-control study investigated whether snoring, sleep position and other sleep practices in pregnant women were associated with risk of late still birth, i.e. ≥ 28 weeks' gestation)(Stacey et al, 2011). No relation was found between snoring or daytime sleepiness and risk of late stillbirth. However, women who slept on their back (O.R. 2.54, 95% C.I. 1.04 to 6.18) or on their right side (1.74, 0.98 to 3.01) on the night preceding the stillbirth or interview were more likely to experience a late stillbirth compared with women who slept on their left side. In addition women who got up to go to the toilet once or less on the last night (2.28, 1.40 to 3.71) and those who regularly slept during the day in the previous month (2.04, 1.26 to 3.27) were also more likely to experience a late stillbirth than the respective control counterpart. Possible mechanisms for the effect of sleeping position are: inhibition of venous return by compression and ensuing reduction in uterine blood flow (Milson & Forssman, 1984; Jeffreys et al., 2006), reduction in foetal oxygen saturation (Carbonne et al., 1996), reduced pulsatility index of the foetal middle cerebral artery (a surrogate for foetal hypoxia)(Khatib et al., 2011). An alternative explanation of these

findings, however, could be of reverse causality, due to reduced foetal movement, one of the most common symptoms seen before stillbirth (Chappell & Smith, 2011).

The altered circadian patterns that accompany shift work are known to disrupt reproductive function in women. Female shift workers have more menstrual cycle irregularities than non-shift workers (Labyak et al, 2002) and some report more sleep disturbances. A link between adverse pregnancy outcomes and shift work has also been suggested (Kutson, 2003) although in a recent study no relationship was found between rotating shift work and adverse pregnancy outcomes but an increase in late abortions/still births was reported in women who were working fixed night shifts (Schlünssen et al, 2007).

The intense physical and psychological changes which women undergo during pregnancy may be associated with increased stress and reduced quantity and quality of sleep. These effects may in turn affect the mother-infant relationship either through pregnancy-related hormonal changes, changes in inflammatory markers, maternal fatigue or postpartum depression (Pires et al, 2010; Okun et al, 2011a).

2.4 Mechanisms

Sleep disturbances may affect maternal and foetal morbidity and mortality through a number of potential mechanisms. For example, increased nocturia (due to decreased bladder capacity and increased overnight sodium excretion) disrupts sleep. Gastro-oesophageal reflux also leads to awakening and disruption of sleep; first due to a relaxed lower oesophageal sphincter (progesterone working as a muscle relaxant); and then due to pressure on the stomach and reduced gastric emptying (Bourjeily & Rosene-Montella, 2009). Restless legs, leg cramps and increasing frequency of contractions all also contribute to disturbed sleep (Bourjeily & Rosene-Montella, 2009). Furthermore, sleep disordered breathing can be magnified or occur in pregnancy as a result of poor sleep and decreased functional reserve capacity, increased weight from gestation and pregnancy related nasopharyngeal oedema (Izci-Balserak, 2008; Pien & Schwab, 2004).

Sleep is not a passive state but is an active process in which memory consolidation, tissue restoration, metabolic and haemostatic processes occur (Adam, 1980; Alvarez & Ayas, 2004; Ancoli-Israel, 2006; Benca & Quinlan, 1997 as cited in Okun, 2011). Sleep disturbances are known to have effects on oxidation, glucose metabolism and the sympathetic nervous system and there is strong evidence to support an association with cardiovascular outcomes (Cappuccio et al, 2011b). Furthermore, the association between sleep deprivation and hypertension has been shown to be stronger in women than in men (Cappuccio et al, 2007). Cardiovascular disease is relevant to many adverse pregnancy outcomes including pre-eclampsia and intrauterine growth restriction (IUGR) both of which are also associated with a greater risk of developing cardiovascular disease in later life (Okun et al, 2009). Inflammatory processes have been shown to be important in the development of cardiovascular disease and emerging evidence has demonstrated an association between increased inflammation and medical morbidity, including various pregnancy complications. Some of the mechanisms by which sleep deprivation may lead to adverse maternal and foetal outcomes are discussed in more detail below.

2.4.1 Oxidation and inflammation

Increased oxidative stress, endothelial dysfunction and inflammation are important in the development of cardiovascular disease. In OSA, the associated sleep disordered breathing

leads to episodes of hypoxia and then normoxia. This in turn leads to oxidative stress and a subsequent increase in inflammation. There is strong evidence that during pregnancy inflammation and oxidative stress is increased (Okun et al, 2009). There is also evidence that inflammatory markers and reactive species are present in a higher proportion of pregnant women who report sleep disturbances than those who do not.

Okun et al recently put forward a model for the possible role of sleep and inflammation in the pathogenesis of adverse pregnancy outcomes (Okun et al, 2009). They proposed that disturbed sleep has its major effects in the first 20 weeks of pregnancy. It is at this time that major physiological events occur, including the re-modelling of maternal blood vessels to the placenta so as to increase blood flow. This process is abnormal in pre-eclampsia and IUGR; *in vitro* studies indicate that this in part is due to excessive inflammation which inhibits trophoblastic invasion. It is postulated that in non pregnant individuals disturbed sleep in pregnancy may contribute to this increased inflammatory state. Increased circulating cytokines through a positive feed forward process may in turn contribute to sleep disruption. In addition poor health behaviours including smoking, alcohol and obesity can also contribute to the increase in inflammation; thus having a profound effect on vascular re-modelling and hence leading to adverse pregnancy outcomes.

Interleukin 6 (IL-6) is a significant pro-inflammatory and anti-inflammatory agent. It is also released in several disease states, from muscles during exercise, from adipose tissue and blood vessel walls. In sleep, there is an increase in the availability of soluble IL-6-receptors during the late nocturnal period which enhances IL-6 signalling and was thought to have a positive effect on memory consolidation. The administration of intranasal IL-6 in a study in 2009 was shown to increase slow wave activity and the consolidation of only emotional memories during sleep in test subjects compared to a placebo (Benedict et al, 2009).

IL-6 is also increased in pregnancy as early as mid-gestation in women who report poor sleep duration and efficiency, poor sleep duration and sleep disordered breathing (SDB) (Okun et al, 2007a). In complicated pregnancies involving foetal hypoxia, there is evidence of foetal erythropoiesis shown by increased levels of circulating nucleated red blood cells (nRBCs). Levels of IL-6 and erythropoietin (EPO) mediate the production of nRBCs and, interestingly, a study on pregnant women who reported snoring (assessed using a sleep questionnaire) found high circulating levels of IL-6 and EPO in the umbilical cord blood shortly after birth (Tauman et al, 2011). In women suffering from pre-eclampsia compared with pregnant controls, levels of IL-6 are also markedly raised (Bernardi et al, 2008, Sharma et al, 2007). In addition they are shown to be more fatigued and suffer more from snoring and nasal airflow limitation (Bachour et al, 2008). This suggests that IL-6 could be a marker for foetal well-being raised in response to poor/disturbed sleep. It is also important because IL-6 is involved in the pathogenesis of insulin resistance and type 2 diabetes and gestational diabetes mellitus (Mohamed-Ali et al, 1997; Wolf et al, 2004).

Disordered sleep in the pregnant state has correlation with increased levels of IL-10 across all trimesters (Okun et al, 2007b). CRP is raised in both non-pregnant and pregnant states that report poor sleep. Studies on women with pre-eclampsia compared to normal control pregnancies offer differing results. One by Bernardi et al shows no change in IL-10 levels and others show decreased IL10 in pre-eclamptic women (Zusterzeel et al, 2001). This would suggest a non typical pattern of inflammation in these women as they do not have raised IL-10 or IL-1 β (Bernardi et al, 2008). However, a major drawback of these studies is the measurement of IL-10 only once after diagnosis. Recent studies have suggested time

dependent lipid peroxidation in pre-eclamptic patient which allows the use of plasma 8-isoPGF (2- α) as a marker for oxidative stress between 24-32 weeks but not 34-37 weeks of gestation. In a separate study whilst short sleep duration and poor sleep efficiency in both mid and late pregnancy were associated with higher stimulated levels of IL-6 there were no relationships were observed for TNF- α (Okun et al, 2007a).

Adiponectin has insulin sensitising and anti-inflammatory properties (Makino et al, 2006). Oxidative stress, TNF- α and IL-6 have been shown to reduce adiponectin, a hormone released by adipose tissue in people with SDB/OSA (Makino et al, 2006; Lain & Catalano, 2007). Insulin resistance increases in normal pregnancy, but is also associated with short sleep duration and SDB (Punjabi et al, 2004). Some studies have shown an increased risk of GDM in pregnant women who have lower levels of adiponectin and high levels of CRP (Willaims et al, 2004; Wolf et al, 2003; Qiu et al, 2004). Other studies have shown that pregnant women with GDM have lower levels of adiponectin TNF- α , IL-6 and IL-10 compared with controls (Ategbo et al, 2006).

One study has found that pregnant women with SDB have higher levels of malondialdehyde (MDA) than their non snoring controls. However this study found no comparable difference between any negative foetal outcomes after birth (Koken et al, 2007). Other studies conclude that SDB and the resulting hypoxia/re-oxygenation increase reactive oxygen species which can cause cellular damage (Jerath et al, 2009; Roberts & Hubel, 2004). This is hypothesised to contribute to pre-eclampsia and gestational diabetes in pregnant women (Roberts & Hubel, 2004).

2.4.1.1 Inflammation and maternal and foetal outcomes

Increased inflammation (higher levels of IL-6, TNF- α and CRP) is also associated with adverse pregnancy outcomes such as pre-eclampsia, Intra-Uterine Growth Retardation (IUGR) and preterm birth (Bartha et al, 2003, Romero et al, 2006 and Freeman et al, 2004). It is unclear if the increase in cytokines occurs as a result of increased stress or if sleep deprivation is a contributing factor. In a high proportion of these outcomes, studies have found a failure of remodelling of spiral arteries, a process necessary for adequate placental perfusion following trophoblast invasion (Arias et al 1993). TNF- α was shown to interfere with trophoblast invasion in experimental studies (Fluhr et al, 2007 and Salamonsen, et al 2007).

Some studies have also linked the increase in inflammatory markers and maternal depression to pre term labour and babies with low birth weight. Groer & Morgan found that of the 200 women who were 4 – 6 weeks postpartum, those who were depressed, had significantly smaller babies and more negative life events. These women also had low levels of cortisol, suggesting an ineffective restrain on inflammation (Groer & Morgan, 2007). A study in Goa, India of 270 women also had similar results, and in addition positively correlated the severity of depression to the risk of low birth weight (Odds Ratio 2.5) (Patel & Prince, 2006).

Studies in the field of psychoneuroimmunology have shown that mothers suffering from postnatal depression have much higher levels of inflammatory markers than their non depressed controls. These markers include CRP, IL-6, interleukin-1 β (IL-1 β), TNF- α and IFN- γ (Miller et al, 2005). In the last trimester of pregnancy, raised markers are adaptive and prevent infection. However at abnormally large levels they increase the risk of depression (Maes et al, 2000). It was also shown that these women had lower levels of cortisol; however in response to an acute stressor, they produced much higher levels of IL-6 and TNF- α

compared to the non-depressed controls. The authors from this study of 72 women concluded that they had "cortisol blunting" (Miller et al, 2005).

| Author | Study Population | Maternal Effects | Foetal Effects | Inflammatory marker | Summary |
|-----------------------|--|---|--------------------------|--|--|
| Tauman et al (2011) | 122 pregnant women recruited, of which 39% had SDB | Sleep Disordered Breathing | Increased Erythropoiesis | IL-6, EPO, nRBCs | In pregnant women who were habitual snorers, there was evidence of increased foetal erythropoiesis shown by increased umbilical cord levels of nRBCs, EPO and IL-6 |
| Bachour et al 2008 | 15 pre-eclamptic women and 14 pregnant controls | Increased time with nasal flow limitations, generalised oedema, increased fatigue and poorer pregnancy outcomes | | IL-6 , TNF- α , and CRP | Pre-eclamptic women presented with more snoring and had increased levels of IL-6 and TNF- α compared with controls. Overall their pregnancy outcomes were worse than controls. |
| Bernardi et al (2008) | 35 pre-eclamptic women and 35 normotensive women | Pre-eclampsia | | IL-6, IL-10, IL-1 β TNF- α , protein carbonyls and plasma thiobarbituric acid | IL-6, TNF- α , protein carbonyls and plasma thiobarbituric acid were higher in pre-eclamptic patients. IL-6 and carbonyls had significant correlation with blood pressure as well as each other. No increase in IL-1 β and IL-10 in pre-eclamptic patients. Effect of sleep disorders or complaints not investigated. |

| Author | Study Population | Maternal Effects | Foetal Effects | Inflammatory marker | Summary |
|------------------------------|---|--|----------------|--|--|
| Okun et al (2007a) | 19 Women in mid – late pregnancy | Sleep complaints associated with increased inflammation. | | IL-6 | Short sleep and poor sleep efficiency in mid to late pregnancy is associated with higher stimulated and circulating levels of IL-6. Women having sleep problems as early as mid gestation could also have increased inflammation. |
| Okun & Coussons-Read (2007b) | 35 pregnant women seen once a trimester. 43 non-pregnant women seen once. | Sleep complaints associated with increased inflammation. | | IL-10, CRP and TNF-α | IL-10 and CRP were higher in pregnant women throughout the three trimesters. In women reporting sleep problems, TNF-α was significantly higher in pregnant women (across all trimesters) and CRP in non pregnant women. |
| Koken et al (2007) | 40 snoring pregnant women and 43 non snoring pregnant women | Snoring | | Glutathione peroxidase (GSH-Px), Malondialdehyde (MDA) and Myeloperoxidase (MPO) | Levels of GSH-Px were lower in the group that snored, and levels of MDA were much higher. Levels of MPO were comparable between the groups. There were no adverse outcomes associated with infants born to the mothers who snored. |

Table 1. Sleep disturbances, pregnancy and inflammation

The table summarises the studies to date on the effect of sleep disruption on markers of inflammation and the possible association with maternal and foetal outcomes.

There is evidence to support the increase in inflammatory cytokines measured in amniotic fluids leads to preterm birth. A prospective cohort study of 681 women showed that depressed women were more than twice as likely to have preterm birth than their non depressed counterparts (9.7% vs. 4%; OR: 3.3). Prostaglandins in particular have a major role in uterine contractions and may be released early in response to increased pro-inflammatory cytokines in disturbed sleep. (Dayan et al, 2006). IL-6 and TNF- α have a role in ripening the cervix before birth; and in women who have preterm birth, these markers are raised in a study of 30 pregnant women. This suggests a link between inflammation and preterm birth, although in these women, stress was being assessed instead of sleep disturbances as a cause of raised cytokines. In a more recent study of 166 pregnant women, sleep was assessed by means of the PSQI. It was observed that for every one point increase in the PSQI score the odds of a preterm birth increased by 25% in early pregnancy and by 18% in late pregnancy (Okun et al, 2011b). Women who have SDB during pregnancy are also more likely to need an emergency caesarean (Leung et al, 2005).

2.4.2 Activation of neuroendocrine pathways

Activation of the sympathetic Nervous System (SNS) leads to the release of adrenal hormones (catecholamines), which can have an effect on sleep (Guggisberg, 2007). Furthermore, the production of catecholamines may stimulate the production of inflammatory cytokines. Inflammatory processes are modulated by numerous feedback and feed forward mechanisms. The Hypothalamic-pituitary-adrenal axis also regulates inflammatory processes via cortisol secretion, which is secreted in a diurnal manner following the sleep-wake cycle. Cortisol can suppress the production of pro-inflammatory cytokines and, as part of the negative feedback mechanism designed to prevent uncontrolled inflammation, pro-inflammatory cytokines stimulate the HPA axis to produce cortisol. However, as in the case of SDB and the resulting hypoxia, plasma cortisol is chronically raised (Meerlo et al, 2000). Prolonged cortisol secretion leads the glucocorticoid receptors becoming desensitised and results in a decrease in the protective effects of cortisol against inflammation (Sapolsky et al, 2000). Disrupted sleep can lead to mild stimulation of the HPA axis and increased inflammation, thus providing another mechanism whereby disrupted sleep in pregnancy may lead to dysregulation of normal homeostatic processes and potentially lead to adverse pregnancy outcomes (Okun et al, 2009).

2.4.3 Insulin resistance

Accumulating evidence suggests that both poor sleep quantity and quality are associated with impaired glucose tolerance and diabetes (Cappuccio et al, 2010a). Until recently little has been known about the effect of poor sleep during pregnancy on glucose tolerance and gestational diabetes. Qui et al interviewed a large cohort of 1,290 women during early pregnancy. They collected information regarding sleep duration and snoring during pregnancy. They obtained information on gestational diabetes mellitus (GDM) from the screening and test results in their medical records. They found that those women who slept 4 hours or less had a greater risk of GDM than those sleeping 9 hours per night. Furthermore they observed that whilst the increased relative risk was 3.23 (95% CI 0.34-

30.41) for lean women ($<25 \text{ kg/m}^2$) this was increased to 9.83 (95% CI 1.12-86.32) for overweight women ($\geq 25 \text{ kg/m}^2$). Snoring was also associated with a 1.86-fold increased risk of GDM and the risk of GDM was 6.9 xs higher in overweight than lean women (Qiu et al, 2010). These findings are consistent with data in non-pregnant women and warrant further investigation to determine the effect on pregnancy outcome.

2.4.4 Passive smoking

In Japan, two surveys were conducted to determine if passive smoking might have any effect on the sleep disturbances observed in pregnant women. 16,396 pregnant women were surveyed in 2002 and 19,386 in 2006. This is particularly important as 80% of passive environmental smoking comes from the spouse and in Japan there is a very high smoking rate amongst men (53%). The results indicated that passive smoking is independently associated with increased sleep disturbances during pregnancy. They observed that pregnant woman who were exposed to passive smoking were likely to suffer from difficulty in initiating sleep, short sleep, and snoring; those women who smoked suffered from the same disturbances and also reported early morning awakenings and excessive daytime sleepiness (Ohida et al, 2007). The authors suggest that some of the negative health outcomes observed in pregnant women may be mediated by the effect of active and passive smoking on sleep.

2.5 Diagnosis and management of sleep disorders in pregnancy

There are many different ways in which sleep data can be collected, the gold standard, however, is to measure sleep using polysomnography (PSG) as this provides an objective assessment of the sleep-wake cycle over the entire sleep period (Baker et al, 1999). Much of the data regarding sleep in pregnancy is limited to self-administered questionnaires and to diaries: very few recent studies have used PSG. However, it is recognised that undertaking multiple sleep studies at different time points during pregnancy is difficult. Despite this there is evidence to suggest that sleep disorders in pregnancy can in certain individuals have adverse outcomes for the mother or baby and therefore it would be useful to develop a screening tool that could be administered quickly by health professionals during routine pregnancy consultations. A simple and cost-effective alternative to PSG is to use actigraphy and sleep diaries. There are now many wrist-watch style actigraphs available. They are activated by movement and can differentiate when a person is awake or asleep, many also now have light monitors incorporated in them as well. They are useful in identifying night time awakenings and for determining their subsequent duration. When used in conjunction with self-recorded sleep diaries, actigraphs can help to establish a very detailed sleep pattern. Questionnaires administered to a bed partner can also help to establish a diagnosis of sleep disordered breathing. OSA is a common but often unrecognised condition in women of childbearing age. The likelihood is increased however in women with a past or current history of polycystic ovary syndrome, depression, hypertension, diabetes, hypothyroidism, metabolic syndrome, obesity (Champagne et al, 2010). The diagnostic test of choice would be a PSG, and referral to a sleep specialist to confirm and treat primary sleep disorders may be required. Further research is also required to establish if the management thresholds for treatment of OSA in non-pregnant women are applicable to pregnant women.

Pharmacological treatment of sleep disorders in pregnancy needs to be viewed with caution, given the potential for harm to the foetus. Similar caution needs to extend to women who are breastfeeding.

2.6 Implications for public health

In the general population sleep duration has been declining. Women now occupy an increasingly prominent position in the workplace but often they do so without any reduction in their home responsibilities. Consequently sleep needs are often of low priority. Preterm birth is a major public health priority and is a common adverse outcome in pregnancy. Sleep quantity and quality are not only important determinants of maternal and foetal health but are also important for general health and need to be particularly addressed in the post-partum period where sleep disruption is likely to be very common. There is also some evidence to suggest that the effects of sleep deprivation may be greater in women than in men. Despite this, the majority of studies undertaken are in men and there is now a clear need for more, large, multicentre, prospective studies to be performed in women.

There is also a paucity of studies evaluating sleep disturbances in the post-partum period and research is required to look at the effects of sleep deprivation on both maternal and paternal functioning and the effect on maternal-infant interaction. Factors such as the type of delivery, the type of infant feeding, return-to-work time and infant temperament may be important, along with the degree of support from the father or other family members. A recent randomised trial set out to investigate if modification to the bedroom environment could improve the sleep of new parents (Lee & Gay, 2011). They evaluated a modified sleep hygiene intervention for new parents (infant proximity, noise masking, and dim lighting) in anticipation of night-time infant care in two samples of new mothers of different socioeconomic status. They were randomized to the experimental intervention or attention control, and sleep was assessed in late pregnancy and first 3 months postpartum using actigraphy and the General Sleep Disturbance Scale. The investigators observed that whilst the sleep hygiene strategies evaluated did not benefit the more socioeconomically advantaged women or their partners they did improve postpartum sleep among the less advantaged women suggesting that simple inexpensive changes to the bedroom environment can improve sleep for new mothers.

Further studies are required fully to investigate the effects of smoking on sleep and associated adverse pregnancy outcomes but meanwhile educational programmes could be used to educate women on the possible harmful effects. Research to determine if other health behaviours could have beneficial effects on sleep in pregnant women is also required. For example, physical activity is recommended to pregnant women for health benefits but as yet there are insufficient studies to determine if this has any effect on improving sleep duration or quality.

3. Conclusion

A lack of sleep is known to affect both our physical and mental health. The few studies that have investigated sleep in pregnancy have found both an increase in total sleep time and an increase in daytime sleepiness in the first trimester whereas the third trimester appears to be associated with a decrease in sleep time and an increase in the number of awakenings. Sleep has an important impact on maternal and foetal health. It has been associated with an increased duration and pain perception in labour, with a higher rate of caesarean delivery and with preterm labour. Some pregnant women develop sleep disorders such as RLS or OSA or insomnia and others develop postpartum depression. Longitudinal studies are required to fully evaluate the effect of sleep deprivation on maternal and foetal outcome.

Better methods to measure sleep disturbances in pregnancy are required along with evaluation of the underlying cause so that appropriate and effect treatment can be administered. Particular attention needs to be given to women who develop leg complaints, who are overweight or become obese during pregnancy or develop conditions such as diabetes or PIH.

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For progress to be maintained in a clinical field like sleep medicine, unimpeded, unrestricted access to data and the advances in clinical practice should be available. The reason why this book is exciting is that it breaks down the barriers to dissemination of information, providing scientists, physicians, researchers and interested individuals with a valuable insight into the latest diverse developments within the study of sleep disorders. This book is a collection of chapters, which can be viewed as independent units dealing with different aspects and issues connected to sleep disorders, having in common that they reflect leading edge ideas, reflections and observations. The authors take into account the medical and social aspects of sleep-related disorders, concentrating on different focus groups, from adults to pregnant women, adolescents, children and professional workers.

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