HHS Public Access

Author manuscript

Soc Personal Psychol Compass. Author manuscript; available in PMC 2020 May 01.

Published in final edited form as:

Soc Personal Psychol Compass. 2019 May ; 13(5): . doi:10.1111/spc3.12451.

Sleep Disturbances and Modulations in Inflammation: Implications for Pregnancy Health

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Abstract

When a woman becomes pregnant, there is a vast series of physiological, vascular, and psychological changes. Among the most commonly reported changes are those involving sleep. Pregnant women report that their ability to maintain sleep and acquire continuous refreshing sleep is impaired during the perinatal period as compared to the non-pregnant period. A growing literature supports the hypothesis that disturbed sleep (which comes in many forms) during the perinatal period is associated with an increased risk of adverse maternal, delivery, and infant outcomes. Among the suggested biological pathways linking sleep and adverse outcomes are disturbances in the immune and hormonal systems. The following paper will discuss (1) the various sleep processes that are commonly disturbed during the perinatal period and the methods used to collect sleep data; (2) the evidence linking sleep to adverse outcomes; and (3) how one specific biological pathway, the immune system, likely mediates these associations. The goal of this paper is to clarify the role that sleep disturbance has during pregnancy.

Keywords

Sleep; Pregnancy; inflammation; Outcomes; Stress; Cytokines; Postpartum

Introduction

The state of pregnancy is accompanied by numerous physical and emotional changes. Among these are immunological and alterations in sleep patterns. These changes, either solo or in concert with one another, can impact the outcome of the pregnancy either positively or negatively.

A normal pregnancy is one in which the health of the mother and baby are secure; there are no complications associated with gestation, labor, or delivery. An aberrant pregnancy is one in which the health of the mother or child is compromised. This can take many forms but the most noteworthy and commonly experienced are preeclampsia, preterm labor/delivery, small-for-gestational-age babies, or maternal gestational diabetes. During pregnancy, it is critical that the maternal immune system does not reject the child. The literature suggests that for a normal pregnancy to occur, there must be a maternal shift to a Th2 or an anti-

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Conflict of Interest: The author has no conflicts to report

inflammatory cytokine (immune) profile which appears protective for the allograft fetus. Anomalous pregnancies may be characterized by either a failure of this shift to occur or by an over-secretion of Th1 or pro-inflammatory cytokines. Subsequently, it can have consequences for the mother and/or child if not attended to in the earliest of stages.

Numerous factors that influence a pregnancy and its subsequent outcome have been identified, including illness (Hartert et al., 2003; Lapinsky, 2010; Ellington et al., 2011; O'Brien et al., 2014; Guntupalli, Hall, Karnad, Bandi, & Belfort, 2015; Atta et al., 2016; Mouyis, Thornton, Williams, & Giles, 2017), stress(Sandman, Wadhwa, Chicz-Demet, Dunkel-Schetter, & Porto, 1997; Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999; Carmichael & Shaw, 2000; Livingston, Otado, & Warren, 2003; Coussons-Read, Okun, & Nettles, 2007; Davis, Glynn, Waffarn, & Sandman, 2011; Christian, 2014), emotional states such as depression and anxiety (Orr, James, & Blackmore, 2002; Diego et al., 2004; Abedian, Soltani, Mokhber, & Esmaily, 2015; Lewis, Austin, Knapp, Vaiano, & Galbally, 2015), and disturbed sleep (Lee, 2006; Okun, Hall, & Coussons-Read, 2007; Okun, Hanusa, Hall, & Wisner, 2009; Okun, Schetter, & Glynn, 2011; Tomfohr, Buliga, Letourneau, Campbell, & Giesbrecht, 2015). While there is an extensive literature about the immunological consequences of illness, stress, and psychopathology during gestation, (Christian, Franco, Iams, Sheridan, & Glaser, 2010; Christian, 2014; Corwin & Pajer, 2008; Coussons-Read et al., 2007; Madan et al., 2009; Maes et al., 2000; Spradley, Palei, & Granger, 2015), little is known regarding the effects of chronic or persistent sleep loss/ disruption during pregnancy and its impact on immune dysregulation that may impact maternal and fetal health and pregnancy outcomes.

The goals of the current review are to provide the reader with a general understanding of the importance of sleep, how pregnancy affects sleep, the role that sleep plays in increased risk for adverse pregnancy outcomes, and the biological pathways that link sleep with outcomes. At the conclusion of the paper, the reader should have a basic understanding of the importance of sleep, the various methods used to ascertain sleep data, a broad overview of the how sleep is disrupted during various points in pregnancy, common sleep disorders, and how immune parameters are impacted by disrupted sleep.

1. Importance of Sleep

Overview of Sleep—Sleep is gaining recognition as an important factor to consider when studying or treating pregnant women. For example, many epidemiological reports have linked poor sleep or insomnia to poor health outcomes, including depression(Okun et al., 2011; Okun, Kiewra, Luther, Wisniewski, & Wisner, 2011; Volkovich, Tikotzky, & Manber, 2016; Wolynczyk-Gmaj et al., 2017; Yang et al., 2017; Hux, Roberts, & Okun, 2017), preterm birth (Okun et al., 2011; Okun et al., 2011; Blair, Porter, Leblebicioglu, & Christian, 2015; Li et al., 2016), and longer labor times (Evans, Dick, & Clark, 1995; Lee & Gay, 2004). The undisputed association between stress and sleep is particulary poignant in pregnancy, as stress is independently associated with poor pregnancy outcomes (Okun et al., 2013; Palagini et al., 2014; Hux et al., 2017).

Restorative Function of Sleep—Although sleep is essential for survival, it is only in the past three decades that the role of sleep in restoring and repairing the human body, including protein synthesis and mitotic division has been identified (Adam & Oswald, 1977; Adam & Oswald, 1984; Adam, Tomeny, & Oswald, 1986; Akerstedt & Nilsson, 2003; Born, Muth, & Fehm, 1988; Born, Lange, Hansen, Molle, & Fehm, 1997; Born & Fehm, 2000). The need for sleep is a basic physiological need and has similar homeostatic properties to hunger or thirst in that sleep reverses sleepiness (Saper, Cano, & Scammell, 2005). There is an intrinsic 24-hour sleep-wake cycle that parallels the circadian rhythm of the endocrine and immune systems. This circadian cycle governs many of an individual's behaviors (Saper et al., 2005). Hence, the impact of sleep loss reaches beyond the immediate realm of just making an individual sleepy. It impacts the entire biological entity either directly or indirectly, due to the multiple brain regions, endocrine factors, and various neurotransmitters involved in sleep regulation (Benca & Quintas, 1997). We know that certain hormones, neuropeptides, and cytokines are secreted in particular slepe stages. For instance, bodily restitution is thought to occur during slow wave sleep (SWS) as Growth Hormone (GH) is secreted primarily during these Stages and cortisol secretion is suppressed during sleep (Akerstedt & Nilsson, 2003). GH stimulates growth, cell regeneration and cell reproduction. Hence, SWS is an important and necessary sleep stage. Additionally, during SWS memory is consolidated, the body tends to conserve energy, there is a cooling of the body and brain, and certain aspects of immune function are promoted (Bryant, Trinder, & Curtis, 2004).

To Provide a Stress Free Period—Born and Fehm (2000) discuss and describe how sleep, especially sleep occurring earlier in the night, can be regarded from a psychoneuroendocrinological perspective as a stress-free period. The release of adrenocorticotropic hormone (ACTH) and cortisol by pituitary-adrenal activity follows a circadian rhythm and is synchronized to the sleep-wake cycle. In typical situations, ACTH/cortisol concentrations are at a minimum in the early hours of sleep coinciding with SWS and are at their maximum during the second half of the night coinciding with REM sleep. The authors point out that this pattern of endocrine activity is unique to the state of sleep and can be modified by various forms of stress (Born & Fehm, 2000).

They acknowledge that various physical and psychological stressors can negatively influence the sensitivity of neuroendocrine regulation during sleep, thus shifting how much and when the nadirs of ACTH/cortisol occur. It has long been known that cortisol secretion is inhibited during sleep (Weitzman, Zimmerman, Czeisler, & Ronda, 1983). Furthermore, sleep restriction and poor sleep can alter secretion of cortisol (Born et al., 1986; Garde AH, Karlson B, Hansen AM, Persson R, & Akerstedt, 2012; Hori et al., 2011). Could pregnancy and the sleep disruption experienced during pregnancy be viewed as a chronic (albeit time constrained) stressor that can alter neuroendocrine activity? Or is altered endocrine activity during pregnancy a causal influence on the sleep disruption reported? There is vast support for the notion that sleep disruption is a stressor (McEwen, 2006; McEwen & Karatsoreos, 2015; Riemann et al., 2010). Events that simulate an immune challenge by stimulating the release of pro-inflammatory cytokines (including IL-1 and TNF-α) are considered stressors. Since total sleep deprivation showed increased pro-inflammatory cytokine levels, it can be argued that sleep deprivation is a stressor. However, the distinction between total sleep

deprivation and partial sleep disruption and what that leads to immunological or endocrinological dysregulation during pregnancy has yet to be determined.

Restorative Function of Sleep during Pregnancy—Data suggest that sleep during pregnancy supports restoration and facilitation of the developing fetus similar to what was previously discussed (Adam & Oswald, 1977; Adam, 1980). Recognition of the myriad alterations in metabolism and arousal that occur as a result of pregnancy is important to better understand how sleep may biologically influence outcomes. Pregnancy is a high metabolic effort situation and much of the maternal energy is directed toward the fetal-placental component in a time-dependent manner (Richardson, 1996). There is a shift in the favoring of anabolic activity. This physiological shift is timed to facilitate the appropriate growth and maturation of the fetus, as well as to be protective (Richardson, 1996). This occurrence may explain why expectant mothers describe their activity levels as more passive. Their bodies may be in a mode of energy conservation during high metabolic expenditure. An interesting phenonmonon that supports the energy conservation hypothesis is that the sleep architecture (percent time spent in SWS or REM) of the non-pregnant state is maintained during pregnancy. While some some studies show some alterations in SWS and in Stage 1 at various points of gestation (Driver & Shapiro, 1992; Hertz et al., 1992; Schorr et al., 1998; Wilson et al., 2011), the patterns are quite similar to non-pregnant women. This is observed even in the incidence of an increase of arousals and number of minutes spent awake at night. This suggests that there may be an evolutionary and/or adaptive process to the increased time spent awake at night observed during pregnancy. The mother learns, prior to having the child, to be more adept at acquiring consolidated sleep in shorter time periods. This may be conducive to allow the mother to attend to the newborn's requirements during the postpartum. This hypothesis remains speculative as there are no data to support or deny the possibility that there is an evolutionary benefit associated with disrupted sleep.

2. Pregnancy and Alterations in Sleep

From conception through delivery, sleep is distinctly altered in the pregnant woman. Sleep disturbances are typically classified as: disturbed sleep quality, poor sleep continuity, insomnia, short/long sleep duration, restless legs syndrome, and sleep disordered breathing. A methodological concern with many studies is the definition used to define poor sleep. For example, sleep quality can be defined by a single question or a series of validated questions. Likewise, sleep apnea is defined as having > 5 breathing events per hour determined by in-lab or in-home PSG. The broader term, sleep disordered breathing refers to a group of disorders characterized by abnormal respiratory patterns or insufficient ventilation during sleep. These can include sleep apnea, snoring, or hypoxia. The terms are often used interchangeably. Equally, insomnia can be determined with a single question or clinically which rely on the report of significant sleep complaints accompanied by significant daytime impairment.

Sparse data are available that inform women what to expect with regards to the timing, degree, frequency, and/or severity of a specific pregnancy-related sleep disturbance. Although up to 75% of pregnant women experience some form of sleep disruption during

pregnancy, the number of women who report significant sleep complaints, of any kind, in the first trimester is about 25% (Okun & Coussons-Read, 2007; Okun, 2013). It is clear that sleep quality and quantity fluctuations vary by trimester. The changes in sleep have been previously described (Lee, Zaffke, & McEnany, 2000; Lee, 2006; Okun, 2013). So the focus here will be on the various methods used to ascertain or record sleep, their pros and cons, and any significant findings.

Reports that utilize validated measures indicate that sleep disorders are quite common during pregnancy. Insomnia, affects ~12% in early pregnancy with rates as high as 75% in late pregnancy (Okun et al., 2013; Okun, Buysse, & Hall, 2015), whereas SDB affects about 4% in early pregnancy and 8.3% in mid pregnancy (Louis et al., 2018). Moreover, according to the National Sleep Foundation, up to 26% report restless legs syndrome and 30–50% have gastroesophageal reflux disease (GERD). Taken together, it is clear that sleep problems and complaints are significantly greater in the pregnant state compared to the non-pregnant state.

Measurement of Sleep

Polysomnography (PSG): Polysomnography (PSG) is the current gold standard for measuring sleep. It is a technique that collects multiple physiologic parameters of sleep via surface electrodes, including brain dynamics of electroencephalography (EEG), eye movements, muscle activity, heart physiology, and respiratory function (Marino et al., 2013). Sleep is composed of two distinct states, REM sleep and NREM sleep. REM sleep is a unique phase of sleep in that it has physiological similarities to wake, characterized by rapid, high-frequency, low amplitutde EEG waves. The distinguishing feature of REM sleep is the random/rapid movement of the eyes, low/diminished muscle tone, and the propensity to experience vivid, hallucinogenic-like dreams. Its function is postulated to involve immune function stability, memory preservation (e.g., procedural, spatial and emotional memory), and brain development during infancy (Hall, Okun, Atwood, Buysse, & Strollo, 2008; Patel & Araujo, 2018). Within NREM sleep three distinct stages can be identified by characteristic EEG waveforms. Lighter stages of sleep N1 and N2 are characterized by low-amplitude, fast frequency EEG activity, whereas the deepest stage of sleep, N3, is characterized by high amplitude, slow frequency EEG(Hall et al., 2008) Figure 1. N1 is referred to as transition sleep and lasts only 5–10 minutes. This is where physiological changes occur, including heart and breathing rate slowing, muscles relax, and body temperature decreases. N2 is typified by additional physiological markers such as sleep spindles and K-complexes which are thought to play a role in transitioning to a deeper sleep (Patel & Araujo, 2018). N3 is where deep sleep occurs. It is thought that this sleep is necessary for an individual to feel refreshed and restored the next day. REM and NREM alternate within one sleep cycle (~80–110 minutes).

Actigraphy—Actigraphy is a method commonly used in perinatal sleep assessment. Actigraphy is a non-invasive method of monitoring human rest/activity cylces. The actigraph is a wrist-watch like device that measures gross motor activity constantly. The unit has a piezoelectric accelerometer that uses a low-pass filter to remove everything except the 2–3 Hz band (Ancoli-Israel et al., 2015; Marino et al., 2013; Martin & Hakim, 2011). By measuring wrist movements with an accelerometer in a wrist worn device, the presence or

absence of sleep or wake can be determined (Marino et al., 2013). This approach supports evaluation of larger sample sizes and longitudinal assessments as it is inexpensive, unobtrusive, and enables measurement across a wide range of circumstances and locations. The majority of studies that use actigraphy also use sleep diaries (see below) as they help corroborate the data.

Subjective Reports—Subjective data can be acquired via many methods. The most common is self-report questionnaires, such as the Pittsburgh Sleep Quality Index(Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), the Insomnia Symptom Questionnaire (Okun et al., 2009), or the Epworth Sleepiness Scale (Johns, 1991). These are retrospective accounts of one's habitual sleep. They can provide information on sleep quality, insomnia, or daytime sleepiness. Visual analogue scales are also a simple tool to determine the previous night's sleep quality, quantity or other dimension. The reliance on questionnaire-derived sleep duration (or other variable) may lead to spurious associations among studies that evaluate sleep and health outcomes in pregnancy(Herring et al., 2013). Although not considered methodologically ideal, purely restrospective and subjective studies often provide a beginning point to further inquiry. It is often a cost-effective means to ascertain pilot data for future study. A frequently used method that provides prospective, daily sleep data, is the sleep diary. It is used in conjunction with actigraphy to corroborate validity. The sleep diary allows for prospective daily accounting of specific aspects of sleep including sleep onset latency, number of awakenings, wake after sleep onset and sleep duration. This method is extememely useful for ascertaining long term sleep and variablity in sleep patterns.

What is the best choice to study sleep in pregnant women?—The appropriate method relies heavily on the hypotheses, resources, sample size and parameters of interest of the investigators. If a health psychologist wants to address sleep as a covariate, then the easiest method would be questionanires. If temporal questions regarding a health condition are put forth, for instance, then actigraphy and sleep diaires should suffice. The focus in the last decade has been on collecting sleep data from as many women as possible or for long periods of time. This has resulted in actigraphy, questionnaires, and sleep diaries to be the predominant methods used. These methods are ideal for gathering sleep duration, sleep quality, sleep continuity, and insomnia data. For investigations of SDB, in-home sleep testing devices have become so small and portable, there is little need to bring pregnant women to the laboratory for an over-night sleep study.

Findings on sleep disturbance during pregnancy

Polysomnography: Older data collected via PSG in perinatal women suggested an increase in REM sleep (paradoxical sleep) during late pregnancy(Branchey & Petre-Quadens, 1968). Others show an increase in awake times, differences in total sleep time (compared to non-pregnant and across pregnancy), an increase in slow wave sleep (SWS), and a decrease in REM sleep across pregnancy(Brunner et al., 1994; Driver & Shapiro, 1992; Hertz et al., 1992; Schorr et al., 1998). Recent data from Wilson and colleagues who conducted PSG in first and third trimester women and compared them to non-pregnant controls, found that their results confer with the older studies. Sleep duration is longer in the first trimester compared to the third, and pregnant women have shorter sleep duration than non-pregnant

women(Wilson, Fung, Walker, & Barnes, 2013; Wilson et al., 2011). Taken together the sparse data and restricted sample sizes suggest that sleep architecture is not significantly modified during pregnancy. The modest change is sleep duration and awakenings, for instance, are likely a reflection of the changing habitus and hormone fluctuations, rather than an adaptive and important mechanism. The primary utility of using PSG to study pregnant women presently appears to be to identify pathological conditions such as sleep apnea or periodic leg movements. This segment of the literature is riddled by a small number of studies and vast methodological differences among the studies described. It has been argued that 1–2 nights of PSG-collected sleep data will not facilitate a complete understanding of sleep patterns and how they impact health outcomes in perinatal women. Other methodologies appear to be better suited to address this question.

Actigraphy—As mentioned, actigraphy is a method that determines sleep based on the absence or presence of movement, It is less intrusive and able to collect longitudinal sleep data. A consistent finding, similar to PSG, is that sleep is quite disturbed in the 1st trimester, modestly improves in the 2nd trimester, and progressively worsens by the end of gestation (Lee & Gay, 2004; Bei, Milgrom, Ericksen, & Trinder, 2010; Elek, Hudson, & Fleck, 1997; Okun et al., 2013; Volkovich et al., 2016; Tsai, Lee, Lin, & Lee, 2016; Reid et al., 2017; Shinkoda, Matsumoto, & Park, 1999). The nocturnal sleep period is peppered by an increase in awakenings, often to urinate or result of physical discomfort. It is further characterized by restless sleep and a decline in total sleep time that increases daytime fatigue and sleepiness (Bourjeily, Raker, Chalhoub, & Miller, 2013; Herring et al., 2013). Unfortunately, since actigraphy defines sleep by *lack* of movement, many movements are identified as wake. Likewise, non-movement while awake is identified as sleep. Hence, there is often a large discrepancy between questionnaire-derived data and actigraphy-meausred sleep time(Herring et al., 2013). Thus, a major caveat of actigraphy is that it often overestimates awakenings and underestimates sleep duration (Herring et al., 2013). Nonetheless, it is an excellent method to use in order to collect longitudinal sleep in pregnant women.

Subjective Reports: There are dozens of studies utilizing various subjective reports. Two early studies assessed the primary reasons for sleep disturbance during pregnancy. The need to urinate was the main complaint found in a secondary analysis by Baratte-Beebe & Lee (Baratte-Beebe & Lee, 1999) of women in childbearing years before and during pregnancy. This increase is primarily a result of bladder compression by the uterus, during the 1st trimester, and the descending fetus pressing on the bladder during the 3rd trimester (Baratte-Beebe & Lee, 1999). The second most common complaint was nighttime awakenings. Mindell & Jacobson (Mindell & Jacobson, 2000) questioned 127 women at one of four points during pregnancy about their sleep habits and sleep disturbances. Consistent with other studies, nighttime awakening was the most common sleep disturbance. In support of an insomnia-like sleep disturbance, a significant number of women in this sample reported difficulty staying and/or falling asleep as well as waking too early. Also, over 40% reported “thoughts” as the cause for these problems, another indication of an insomnia-like disorder. It is known that pregnancy-related anxiety is indeed associated with adverse pregnancy outcomes (Abedian et al., 2015; Lewis et al., 2015; Misri & Swift, 2015; Dolatian et al., 2016; Tham et al., 2016). While it is unclear as to whether there is an adaptive advantage to

the increase in nocturnal awakenings and disrupted sleep (i.e., preparation for caring for infant), the evidence supports the hypothesis that abnormal sleep patterns, (e.g., insomnia, short sleep duration or poor sleep continuity) are associated with an increase risk in medical conditions, such as preterm birth or growth restricted babies(Micheli et al., 2011).

3. Sleep and Adverse Pregnancy Outcomes

A rapidly growing literature supports an independent and substantive role for antenatal sleep disturbance to negatively affect maternal and infant outcomes. Sleep disorders such as sleep disordered breathing and insomnia, as well as poor sleep quality, circadian misalignment, and short sleep duration are implicated in increased risk for adverse outcomes. Poor sleep quality, short sleep duration, and insomnia, for instance, are associated with new and recurrent depressive episodes (Bei et al., 2010; Dorheim, Bjorvatn, & Eberhard-Gran, 2012; Goyal, Gay, & Lee, 2007; Kamysheva, Skouteris, Wertheim, Paxton, & Milgrom, 2009; Okun et al., 2009; Okun et al., 2011; Okun et al., 2013; Skouteris, Wertheim, Germano, Paxton, & Milgrom, 2009), preterm birth(Guendelman et al., 2013; Micheli et al., 2011; Okun et al., 2011; Strange, Parker, Moore, Strickland, & Bliwise, 2009), gestational diabetes(Balserak BI, Jackson N, Ratcliffe SA, Pack AI, & Pien GW, 2013; Bourjeily, Raker, Chalhoub, & Miller, 2010; Facco, Grobman, Kramer, Ho, & Zee, 2010; O'Brien et al., 2012; O'Keeffe & St-Onge, 2012; Qiu, Enquobahrie, Frederick, Abetew, & Williams, 2010; Reutrakul et al., 2011), gestational hypertension/preeclampsia(Ayrim et al., 2011; Bourjeily et al., 2010; Champagne et al., 2009; O'Brien et al., 2012; Williams et al., 2010), labor and delivery outcomes (Beebe & Lee, 2007; Evans et al., 1995; Lee & Gay, 2004), immune/endocrine dysregulation(Okun & Coussons-Read, 2007; Okun et al., 2007; Okun et al., 2011; Okun, Luther, Wisniewski, & Wisner, 2013), and a few examining infant outcomes(Ayrim et al., 2011; Bourjeily et al., 2010; Franklin et al., 2000; Goyal, Gay, & Lee, 2009; Nishihara & Horiuchi, 1998). Sleep disordered breathing, which involves hypoxia and sleep disruption, is similary associated with the adverse outcomes, and predominantly associated with preeclampsia, gestational diabetes, gestational hypertension, intrauterine growth restriction, and low birth weight (Carnelio, Morton, & McIntyre, 2017). Despite the increased interest, our knowledge remains limited by predominantly retrospective studies or small sample sizes. With regards to infant outcomes, our knowledge is even more limited. Historically, the emphasis has been on sleep disordered breathing (SDB) or sleep apnea and infant outcomes(Bourjeily et al., 2010; Chen et al., 2012; Franklin et al., 2000; Koken et al., 2007; Tauman et al., 2011), however recent data has emphasized sleep quality and insomnia and how they impact the neonate(Dorheim et al., 2012; Okun et al., 2011; Okun et al., 2015; Rognmo, Sivertsen, & Eberhard-Gran, 2016; Sivertsen, Hysing, Dorheim, & Eberhard-Gran, 2015; Wolynczyk-Gmaj et al., 2017).

It is not entirely clear as to how sleep increases risk for adverse outcomes, however there are various mechanistic pathways proposed to mediate the association between sleep and adverse pregnancy outcomes. Sleep is not merely the absence of waking. On the contrary, it is a state during which specialized physiological activities occur in the brain and throughout the body. It is an active process in which metabolism, tissue restoration, memory consolidation, and general homeostatic balance is maintained (Fuller, Gooley, & Saper, 2006; Markov & Goldman, 2006). Homeostatic and circadian influences dictate that we

spend approximately one-third of our lives asleep(Saper et al., 2005). Yet, to date, the primary focus in the pathogenesis of disease has been on the role of waking factors with little attention to sleep. Okun et al (Okun, Roberts, Marsland, & Hall, 2009) proposed a conceptual model as to how sleep may increase risk of hypertensive disorders of pregnancy. They indicate that disturbed sleep affects several biological pathways associated with cardiovascular morbidity, including neuroendocrine, metabolic, and inflammatory systems. One way that disturbed sleep may increase cardiovascular disease is by exacerbating well recognized cardiovascular risk factors, such as obesity and insulin resistance. Importantly, many of these are also risk factors for adverse pregnancy outcomes. While increased oxidative stress, endothelial dysfunction and inflammation are implicated in the pathogenesis of cardiovascular disease and adverse pregnancy outcomes, this paper will focus on dysregulation of the immune system.

4. Pregnancy and Alterations in Immune Function

The clinical data showing an association between poor pregnancy outcomes and high pro-inflammatory cytokine levels strongly suggest that an appropriate shift to a response favoring anti-inflammatory cytokine secretion appears to be crucial in maintaining normal gestation and delivery. Th1 cytokines relevant to pregnancy include interleukin 1 β (IL-1β), interleukin 8 (IL-8), tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6). Elevated levels of IL-6, IL-8, and TNF-α are associated with premature labor and delivery (Arck et al., 2001; Coulam, 2000). Failure to effectively switch off aspects of the inflammatory response during pregnancy also has been associated with the development of preeclampsia (Hennessy, Pilmore, Simmons, & Painter, 1999; Schiessl, 2007; Dekker & Sibai, 1999). Significantly more TNF-α, IL-6, and IL-1β are produced by lymphocytes from preeclamptic women than those produced by lymphocytes from women with normal pregnancies (Hayashi, Ueda, Ohkura, & Inaba, 2005; Saito et al., 1999; Munno et al., 1999). These data show that the balance of the maternal immune system in pregnancy is critical for successful pregnancy, and that increased levels of Th1-type or pro-inflammatory cytokines may be related to the development of serious complications.

Pregnancy is characterized by a plethora of immunologic change and these changes are often referred to as the “immunological paradox of pregnancy” because even with the paternal antigens present, the fetus is immunologically tolerated by the mother and often brought to term (Clark et al., 1996; Coussons-Read et al., 2002; Hegde, Ranpura, D’Souza, & Raghavan, 2001; Piccinni, Scaletti, Maggi, & Romagnani, 2000; Saito et al., 1999; Wadhwa, 2005). Some researchers purport that in order to maintain the viability of the fetus, a chronic immunosuppressive state must take place (Hegde et al., 2001; Piccinni et al., 2000). Some have even stated the maternal-fetal relationship is unique and represents a more step-by-step, programmed interactive symbiosis, rather than a simple host/tumor or host/allograft relationship (Chaouat et al., 2002). Data indicate that immediately following insemination, the female reproductive tract undergoes inflammatory changes in response to semen (Hegde et al., 2001). These inflammatory changes are due to the high levels of immunoregulatory molecules called prostaglandins, which are a potent immunosuppressor contained in seminal fluid (Hegde et al., 2001). Similarly, the uterus is exposed to antigens from the fetus once conception has occurred and the maternal-fetal compartment is able to distinguish between

self and non-self. Because of this remarkable ability, other scientists contend that the preponderance of the changes occur at the maternal-fetal interface, not throughout the entire body (Luppi, Haluszczak, Trucco, & DeLoia, 2002; Piccinni et al., 2000). Regardless of the degree of immunosuppression, including a shift from a pro-inflammatory to an anti-inflammatory cytokine profile along with secretion of appropriate anti-abortive chemicals such as TGF-β and IL-10, it is accepted that various immune modifications must take place in order to achieve a successful pregnancy.

5. Consequences of the Inflammatory Response During Pregnancy

Despite advances in medical technology adverse pregnancy outcomes continue to plague pregnant women all over the world. For instance, preterm birth complicates almost 12% of all pregnancies (CDC, 2014; Peltier, 2003). Preterm labor and delivery appear to be a consequence of an early or premature inflammatory response. Normal parturition involves three physiologically interdependent processes: (1) restructuring of the cervix to allow it to stretch; (2) weakening and rupture of membranes; and (3) initiation of rhythmic contractions that will force the fetus and placenta out (Peltier, 2003). It appears that certain pro-inflammatory cytokines play a significant role in initiating this normal process. With a decrease of progesterone, IL-8, IL-1β, IL-6, and TNF-α production is increased, which commences the cascade of labor events (Peltier, 2003). It is infection or an inflammatory response that results in a premature rise in pro-inflammatory cytokine levels that ultimately begins an early labor process (Peltier, 2003). If infection accounts for 30% of all preterm labor and delivery (Peltier, 2003), other factors, such as stress and **sleep loss**, may account for a significant portion of the remaining variance. These associations are actively being evaluated.

Similar to preterm birth, preeclampsia affects the newborn and its health. However, preeclampsia is especially dangerous to the health of the mother and contributes to mortality in childbirth (Tjoa, Oudejans, van Vugt, Blankenstein, & van Wijk, 2004). Recent studies have attempted to identify markers that may indicate susceptibility to preterm birth or preeclampsia prior to the development of the disease (Bertran et al., 2005; Fialova et al., 2004; Freeman et al., 2004; Tjoa et al., 2004). One example is C-reactive protein (CRP) as a potential marker. CRP is a sensitive indication of tissue damage and inflammation. It has been shown that women with preeclampsia (Fialova et al., 2004; Tjoa et al., 2004) and gestational diabetes mellitus (Qiu, Sorensen, Luthy, & Williams, 2004) have elevated levels of CRP. By measuring CRP levels early in pregnancy, data suggest that an early warning of compromised placental development may be indicated (Bertran et al., 2005; Tjoa et al., 2004). To date, no single biomarker has proven to be reliably indicative of an adverse pregnancy outcome.

A growing concern is the development of gestational diabetes mellitus (GDM) and its subsequent impact on the health and lifestyle of the mother and infant. Gestational diabetes mellitus afflicts approximately 4% of all pregnancies annually and may be as high as 14% annually (Qiu et al., 2004). In order to maintain a proper provision of maternal nutrients to the feto-placental unit, some insulin resistance is required (Radaelli, Varastehpour, Catalano, & Hauguel-De, 2003). When women develop GDM, insulin resistance is more severe with

accelerated fetal development as one result. GDM increases the risk of fetal macrosomia and other neonatal morbidities including hypoglycemia, hypocalcemia, polycythemia, and jaundice. GDM is associated with an increased frequency of maternal hypertensive disorders and the need for cesarean delivery (Qiu et al., 2004). Comparable to the use of CRP in early detection of preeclampsia, increased leukocyte counts are used as a marker of inflammation that is associated with development of type 2 diabetes. There is growing evidence that insufficient sleep may contribute to GDM.

Women who have several recurrent spontaneous abortions (RSA) have higher levels of Th1-type cytokines (IL-2, IFNγ and TNFα) than women who had normal pregnancies(Arck et al., 2001; Liu et al., 2011; Nepomnaschy et al., 2006; Raghupathy, 1997). The same studies also showed that normal pregnancies were associated with higher levels of IL-4, IL-5, IL-6 and IL-10 than those women with RSA (Raghupathy, 2001). Some investigators purport that the absence of a type 2 bias may be associated with, and possibly a predictor of, pathologic events(Marzi et al., 1996). Thus, from an immunological point of view, successful pregnancy is characterized by altered ratios of Th1-type and Th2-type cytokines in a fashion that is consistent with at least partial immunosuppression and downregulation of a cell-mediated immune response. The data clarify the need to understand and better interpret how inflammation can influence the progression and success of pregnancy, and how the behavior of sleep influences these processes.

Disordered Sleep and Immune Function in Pregnancy—Pregnancy is typically associated with changes in immune function, changes that may be associated with beneficial or harmful outcomes (i.e., uncomplicated birth or preeclampsia). Changes in immune function during pregnancy may also exert negative effects on sleep. For example, the shift toward a pronounced Th2 or anti-inflammatory cytokine profile seen in pregnancy would intimate that Th1 or pro-inflammatory cytokines, such as interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-α), would be reduced. IL-1 and TNF-α not only defend against antigens, but they also are important mediators of the sleep process (Krueger et al., 1998). Hence, one would anticipate a reduction in sleep during normal pregnancy as a consequence of this decrease in IL-1 and TNF-α. When considering the complex interactions among sleep, the physiological state of pregnancy, and the altered immune functions occurring during pregnancy, it is possible that exacerbated sleep disruption may occur in pregnancy. This could ultimately skew the pro-inflammatory cytokine profile leading to an inflammatory state rather than the desired anti-inflammatory state. For this reason, excessive sleep disruption and/or deprivation may be a potential contributor to poor maternal health during pregnancy as well as negative pregnancy outcomes.

The concept that sleep disruption alters cytokine profiles and immune function in nonpregnant populations has previously been addressed (Krueger & Fang, 1999; Opp & Krueger, 2015). What is of interest here is how disturbed sleep experienced during pregnancy can dysregulate inflammation during pregnancy which thereby increases risk for adverse outcomes. To date, only a handful of studies have assessed disrupted sleep and immune function in pregnant women, and even fewer have considered sleep disorders and their impact on immune function in pregnany.

Summarizing the literature affords a plausible pathway in which sleep disturbance throughout pregnancy may negatively affect immune functioning and impact outcomes. It is known that secretions of IL-1β and TNF-α occur primarily during SWS, while increases in secretion of IL-6 are linked to REM sleep (Krueger et al., 1998; Redwine, Hauger, Gillin, & Irwin, 2000; Opp & Krueger, 2015). Abberations in these cytokines have been implicated in the development of pregnancy complications(Piccinni et al., 2000; Saito et al., 1999). Some evidence suggests that dramatically reduced REM sleep is commonly seen in preeclampsia (Edwards, Blyton, Kesby, Wilcox, & Sullivan, 2000) which could affect the nocturnal secretion of IL-6. However, data suggest that high levels of IL-6 are in fact associated with preeclampsia. Others suggest that a dramatic increase in Stage 2 sleep may be the cause of elevated IL-6(Brunner et al., 1994). Reductions in SWS are correlated with increases in IL-1β and TNF-α (Krueger et al., 1998). Importantly, TNF-α has been shown to inhibit trophoblast growth and subsequent recurrent miscarriages and preeclampsia (Dekker & Sibai, 1999). The paucity of research, even to this day, indicates significant gaps in the knowledge regarding disturbed sleep and immunity during pregnancy.

To date, only a few studies have considered assaying immune parameters associated with both sleep and pregnancy simultaneously. Okun and colleagues have published the majority of the available literature. They found that poor sleep quality was associated with higher circulating and stimulated levels of IL-6(Okun & Coussons-Read, 2007; Okun et al., 2007; Okun, Coussons-Read, & Hall, 2009), and that symptoms of insomnia and poor sleep quality dysregulate several cytokines(Okun, Roberts JM, Begley, Catov, & Patrick, 2013; Okun et al., 2013). One other study corroborated these findings(Blair et al., 2015). All of the aforementioned cytokines play a role in both sleep and pregnancy. How the interleukins, the interferons and other immune substances interact with one another during these two physiological events is currently under investigation, but the evidence strongly suggests a synergistic relationship.

Conclusion

Clearly pregnant women experience more sleep disturbance than their non-pregnant counterparts. The degree to which this occurs appears to be quite variable, not only by trimester but within an individual as well. Disturbed sleep is emerging as a prominent factor contributing to risk for adverse pregnancy outcomes. Inflammation is a key biological pathway linking myriad behaviors with health outcomes. The evaluation of sleep and inflammation as a contributing factor to adverse pregnancy outcomes is still in its nascency. Hopefully this will change. In a previous publication, Okun and colleagues proposed a model linking sleep disturbances in early gestation to adverse pregnancy outcomes via increased inflammation(Okun et al., 2009). Specifically, they proposed a feed forward loop between sleep disruption and inflammation during a critical period of early pregnancy when inflammation can act, for instance, to inhibit the trophoblast invasion and associated remodeling of maternal blood vessels that perfuse the placenta. This author purports that in order to truly understand the implications of disturbed sleep on health, both the immediate and long-term effects of disturbed sleep on immunocompetence need to be ascertained through longitudinal study designs. Assessing sleep disturbances as a risk factor for adverse

outcomes could provide a target for intervention especially since sleep problems are amenable to treatment.

Acknowledgements:

Funding sources NIH NR010813 for financial support

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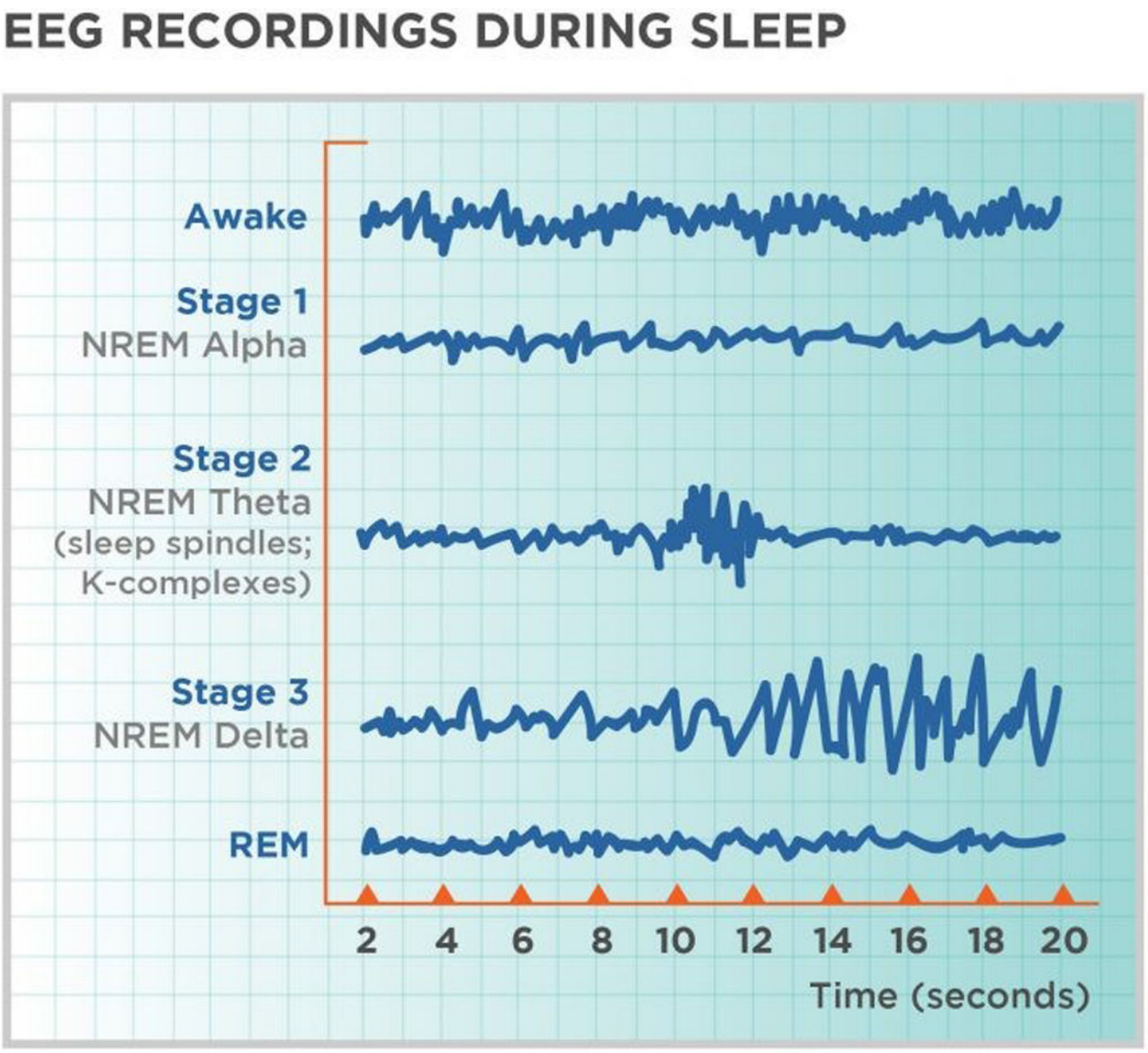

Figure 1.
Visual depiction of the sleep stages assessed by PSG.