Chapter

Sleep Disorders in Pregnancy

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Abstract

Sleep disturbances and changes in circadian rhythms are commonly observed in pregnant women. These disorders can result from anatomical, physiological, psychological, and hormonal alterations that can influence sleeping during this phase. Sleep disorders during pregnancy can be responsible for detrimental effects on both mother and foetus. In this chapter we will focus on the epidemiology of sleep disorders, physiological sleep mechanisms and their alterations during pregnancy, as well as on risk factors for sleep disorders in pregnancy. We will then focus of the most frequent sleep disorders during pregnancy, also considering eventual adverse implications for both mother and child, prognosis, and possible pharmacological and non-pharmacological treatments.

Keywords: Circadian Rhythms, Insomnia, Hypersomnia, Sleep disorders

1. Introduction: sleep disorders and changes of circadian rhythms during pregnancy

Sleep architecture and sleep regulation mechanisms are different depending on gender. Indeed, women are used to perceive worse subjective sleep quality when compared to men, as demonstrated by shorter circadian period in this population. Moreover, female tend go to bed earlier and fall asleep later and present a larger melatonin production pattern [1–6]. The prevalence of sleep disorders is also different in males and females. Hence, some disturbances, such as hypersomnia, insomnia, parasomnia, and restless legs syndrome are more frequent in women, while narcolepsy, arousal disorders, Klein-Levine syndrome, and sleep behaviour disorder with rapid eye movement are more frequent in men [7–9].

Pregnancy and perinatal period (one year after childbirth) represent particularly vulnerable periods for women, due to anatomical, hormonal, and psychological changes that infuence women's global health [10]. Poor sleep is a common condition during this period especially during the third trimester [11]. Indeed, 52-61% of women during the last eight weeks of pregnancy show reduced and poor sleep quality, with even higher prevalence among women with a diagnosis of current or previous depressive disorder or history of smoking [7].

Moreover, pre-existing sleep disorders may become more serious during pregnancy and these disturbances increase as the gestational period progresses. Sleep changes in pregnancy are detected by polysomnogram measurements, which during the third trimester usually show an increase in wakefulness after sleep onset and a decrease in Rapid Eye Movement (REM) sleep compared to non-pregnant women [12].

During pregnancy, sleep disorders may contribute to the occurrence of irritability, diurnal hypersomnia with reduction in efficiency, abuse of hypnotic/anxiolytic drugs, impulse control disturbances, also leading to the development of mood

disorders and to increased suicidal ideation with a risk of suicidal behaviours [12, 13]. Moreover, low birth weight and morphological abnormalities may occur in the foetus and his/her circadian rhythms may also be disrupted, since these are regulated by maternal factors. To note, the foetus does not produce melatonin, a hormone with an essential role in sleep–wake rhythm regulation. Further circadian rhythms that may be altered as consequence of sleep–wake disorders are: body temperature, physical activities, eating patterns, and hormone secretion, particularly melatonin and glucocorticoids These alterations can also explain why pregnant shift-workers display a higher risk of low birth weight, spontaneous abortion, and premature birth, and have sons affected by insomnia or low-birth weight, but also a higher risk of infertility, miscarriage, and pre-eclampsia [7, 13–17].

Previous studies reported different data about the incidence of sleep disorders during pregnancy, but consensus was reached about pregnant women having more disturbed sleep than during other times in their lives. Particularly, about 25% of pregnant women report significant sleep disturbances during the first trimester, with rates rising up to almost 75% during the third trimester [18]. Some authors also argue that up to 97% women report disturbed sleep during pregnancy [19].

2. Factors affecting sleep during pregnancy and action of sexual hormones

Poor sleep quality and insufficient sleep duration are common in the general population and can result from environmental and psychosocial factors, as well as from medical and psychiatric disorders. During pregnancy, possible causes of sleep complaints, such as hormone release alterations, increase their incidence. A relevant role is also played by anatomical and physiological changes.

Sleep disturbances seem to be caused by different factors during the three trimesters of gestation. During the first trimester, the main causes of disturbed sleep are vomiting, nausea, and history of infertility. Gastrointestinal disorders appear to be sleep-disturbing factors also in the second trimester [11], whilst in the last trimester women with muscular-skeletal pain, overweight, restless legs, reflux, uncomfortable positions, and snoring present more sleep disturbances [20].

The main precipitating factors are listed below:

- Anatomical and physiological factors, such as ligament stretching, uterine contractions, or foetal movement;
- Breathing difficulties due to increased uterine volume raising the diaphragm;
- Nocturnal incontinence due to increased sodium excretion during the night;
- Impairment in body movements;
- Hormonal changes, especially ovarian ones;
- Widespread pain and cramps;
- Increased sympathetic nervous system activities;
- Gastrointestinal disorders, such as gastro-oesophageal reflux, constipation, delayed gastric emptyng;
- Anxiety, stress, and tension [10, 21–24] (see **Table 1**).

Pathogenetic factors
- **Socio-demographic**
- age > 30 years old;
- educational level
- single marital status
- history of infertility
- **Psychiatric disorders/symptoms**
- anxiety
- depression
- increased stress level
- predisposing personality traits (internalisation, perfectionism, obsessive, neurotic, and dependent on gratification)
- **hormonal, metabolic and anatomical changes**
- sex hormone fluctuations (increased oestrogen and progesteron, studies about activity of two hormones are still conflicting)
- amplified hypothalamic–pituitary–adrenal axis
- reduced melatonin
- inhibition of the dopaminergic system
- increased prolactin
- nutritional deficiency
- joint pain
- chronic diseases
- cramps
- nausea
- enlarged abdomen and weight gain
- respiratory disorders
- posture restrictions
- nocturia
Pathophysiological consequences of poor sleep quality in pregnant women
- elevate glucocorticoids levels
- oxidative stress
- decreased glucose tolerance
- increased inflammatory cytokines
- dysfunction of serotoninergic system and hyperactivity of noradrenergic system
- deficits in neuroplasticity
- hypertension
Main pathological conditions detected
- psychiatric disorders (anxiety, depression, psychosis and substance or alcohol abuse, suicidal ideation)
- gestational diabetes
- hypertension, pre-eclampsia and eclampsia
- low birth weight and preterm birth
- morphological alterations and foetal disorders
- spontaneous abortion
- increased risk of caesarean section

Table 1.
Overview of the development of new pathological conditions in pregnancy from sleep-altering physio-pathological conditions.

3. Consequences of sleep disorders during pregnancy on women

Sleep is a fine mechanism regulated by different factors and its alteration presents consequences for both the mother and the child. Furthermore, discomfort and frustration experienced by women may also influence their partners, who may in turn present sleep disorders. The most frequent consequences of sleep disorders during pregnancy are discussed in this section.

3.1 Affective disorders and suicidal ideation

Sleep plays a fundamental role in learning, by influencing the development new neuronal circuits. Subsequently, sleep restriction can lead to a disruption of neuroplasticity, thus triggering some among the pathophysiological mechanisms responsible for the development of depression. The pathophysiological mechanisms underlying both sleep disorders and depression are regulated by common neurobiological systems, i.e., hyperactivity of the hypothalamic–pituitary–adrenal axis, dysfunction of serotoninergic system, and hyperactivity of noradrenergic system [25]. Indeed, these specific systems play a role in the regulation of basic emotional responses, such as fear and reward. Therefore, insomnia may compromise adequate emotional processing and may underpin a greater susceptibility to develop psychopathology, particularly anxiety and depressive symptoms and, to a lesser extent, psychosis and substance or alcohol abuse [26].

This may explain why disturbed sleep is reported in up to 90% subjects with depression and REM sleep disturbances may precede the clinical expression of depression itself, aiding the identification of individuals at high risk for developing the disease [27].

However, there are conflicting studies on the correlation between sleep disorders and depression during pregnancy. In previous reports, insomnia did not predict post-partum depression in women with no prior history of depression, as evidenced in a longitudinal study carried out in women at the 17th and 32nd week of gestation and eight weeks after childbirth. This study underlined women suffering from depression before pregnancy also reported more severe residual insomnia symptoms compared to those who scored low for depression at both times [28]. On the contrary, another study showed that poor sleep may represent a potential risk factor for depression during both the prenatal and post-partum period [29]. An Italian study reports that pregnant women with high stress-related sleep reactivity, compared to those with low reactivity, reported more symptoms of insomnia, higher rates of depression, anxiety, and suicidality [13].

Post-partum depression (PPD) is a condition that affects 10-15% of women during pregnancy. It presents with depressive symptoms, such as low mood, hopelessness, sleep disturbances, emotional lability, feelings of guilt, changes in appetite, suicidal ideation, memory loss, fatigue, difficulty in concentrating, and irritability, usually compromising the mother-baby relationship [30]. Physiological, hormonal and metabolic changes occurring during pregnancy often interrupt mother's sleep–wake cycle, and the loss of the sedative effects of endogenous progesterone can lead to post-partum insomnia. In addition, women may wake up several times during the night to take care of their baby and all these factors can contribute to the development of depressive symptoms. Women with a previous history of mood disorders and obsessive–compulsive disorder, as well as women who already presented circadian rhythm disruptions, were also more susceptible to developing this condition. The correlation between sleep disorders and post-partum depression can also be demonstrated by the evidence that treatments for sleep disturbances in pregnant women, i.e. trazodone or

diphenhydramine, may contribute to a consequent reduction in symptoms of post-partum depression [12, 30].

Suicidal behaviour is the leading cause of injury and death during pregnancy and suicidal ideation is often considered a key predictor of subsequent suicide attempts [25]. During pregnancy, the prevalence of suicidal ideation can reach between 5 and 14%, which appears to be twice as high as in women without sleep disorders [25, 31]. The presence of comorbid depression leads to a further increase of suicidal risk. Main predisposing factors that lead a pregnant woman to plan suicide are: history of abuse, accidental pregnancy, marital status, family dynamics, low level of education, partner violence, mood disorders, and sleep disorders [25]. The correlation between sleep and suicidal ideation or behaviour can be explained since poor sleep quality may contribute to changes in cognitive, emotional and behavioural processes, and the resulting irritability and emotional lability may encourage suicidal attitude [25, 31].

3.2 Gestational diabetes

Sleep disruptions can exacerbate glucose intolerance. This mechanism can explain why mothers with gestational sleep deprivation during early pregnancy may be up to 4.5 times more likely to develop gestational diabetes than other mothers [32]. Furthermore, mothers with sleep deprivation during pregnancy more frequently give birth to children with a 40% increased risk of overweight and obesity [21].

3.3 Hypertension, pre-eclampsia and eclampsia

Hypertension and pre-eclampsia present an incidence of 5–10% during pregnancy and they can be identified as the main causes of maternal and perinatal morbidity and mortality [33, 34]. Sleep disturbances during pregnancy have been associated with increased gestational weight gain, which can lead to hypertension, pre-eclampsia, and eclampsia [9, 6, 17, 32]. This risk can be even higher during the last trimester, when the increase in oestrogen levels leads to an increase the development of these complications [7].

3.4 Low birth weight and preterm birth

The World Health Organisation (WHO) defines low birth weight (LBW) as a birth weight under 2,500 g, very low birth weight (VLBW) as less than 1,500 g and extremely low birth weight (ELBW) as <1,000. Pre-term delivery is the main cause of perinatal morbidity and mortality. It is also the cause of 75% deaths during childbirth and represents half of long-term neonatal morbidity causes [35]. Reduced maternal sleep duration tends to be associated with lower birth weight [36]. Indeed, LBW incidence appears to be lower among sons/daughters born from women who sleep 9-9.9 hours every night, than among those women sleeping 6-7.9 hours [37]. Sleep deprivation during pregnancy is associated with longer labour during childbirth, lower pain threshold and discomfort, higher caesarean section rates, and preterm delivery [36]. These factors can result from the increase of proinflammatory cytokines, such as interleukin-6, promoting the release of prostaglandins that trigger the onset of labour, thus leading to an increased risk of preterm delivery [36]. This is particularly evident among specific populations, i.e., Afro-American women, that show a risk of pre-term birth increased by 10 times in the presence of sleep disorders when compared to those who have good sleep quality [38]. At the same time, babies who were born prematurely cause concern in new mothers,

who will sleep worse and will be more susceptible to postpartum depression [38, 39]. However, further studies on the relationship between sleep and inflammatory markers are needed to better understand their actual correlations [18].

3.5 Morphological alterations and foetal disorders

An association among maternal breathing disorders during sleep and foetal pathologies is already known, but during recent years specific foetal problems also appeared to be associated with other sleep disorders. Indeed. sleep disorders can lead to altered hormone levels, which can activate pathophysiological mechanisms that cause dysfunctions in offspring [40]. Short sleep duration is associated with an exaggerated inflammatory response, i.e., increased circulating and stimulated levels of inflammatory cytokines and sleep disturbances, particularly during the first 20 weeks of pregnancy, may contribute to the activation of inflammatory processes, also by causing stress, which represents a well-known activator of inflammation [16–18]. This hypothesis is based on *in vitro* data, suggesting that an increase in cytokine levels inhibits trophoblast invasion, that would result in subsequent disruption of maternal vascular bed and placental remodelling, an abnormality present in pre-eclampsia, premature birth, and pregnancies with intrauterine growth retardation [18]. Sleep deprivation during the last week of pregnancy caused reductions in the number of nephrons and increased blood pressure in the offspring [41]. Furthermore, gestational sleep deprivation may be associated with an increased risk of overweight and higher blood pressure in offspring up to the age of 11 years, with more pronounced effects in girls than boys [32].

4. Insights into the most common sleep disorders during pregnancy

The following is a description of the most common psychiatric disorders that can be found in pregnant women. Undoubtedly, the most common disorder is insomnia [42], but other disorders such as restless legs syndrome and narcolepsy are should also be considered in order to preserve the health of both mothers and children. Respiratory disorders, such as sleep apnoea syndrome and snoring, may also be encountered during pregnancy [9]; these disorders are not of direct psychiatric interest, but can be differentially diagnosed from other sleep disorders and can sometimes be the cause for these (as in the case of insomnia) and therefore require specialist monitoring [10].

4.1 Insomnia

4.1.1 Definition, predisposing factors and epidemiology

Recent classifications listed in the Diagnostic and Statistical Manual-5th Edition (DSM-5) [43] and in the International Classification of Sleep Disorder- Third Edition (ICSD-3) [44] deleted the distinction between primary and secondary insomnia (that is, dependent on other medical and mental disorders) in favour of a single diagnostic category. Insomnia is defined whether as an independent diagnostic entity or as a comorbidity of other mental, medical, and sleep disorders without the need to establish causal relationships. Spielmann et al. in 1987 proposed the diathesis-stress model of insomnia, which relies on the conceptualisation of the 3P model: predisposing, precipitating and perpetuating factors contribute to the development and maintenance of insomnia [27, 45]. Predisposing factors are already present before the onset of insomnia. Female sex, pre-menstrual syndrome, pregnancy,

post-partum, and menopause may influence the risk of developing insomnia. Moreover, reduced melatonin levels, which may be inversely related to gonadotropin secretion, play a relevant role. Anyway, the main of these is represented by sleep vulnerability in response to stress, namely sleeping difficulty due to stressful precipitating stimuli [46]. Furthermore, internalisation, perfectionism, obsessive, neurotic, and dependent personality traits are other factors that may contribute to these effects [47–49]. All this explains particular sleep vulnerability in pregnancy, both because pregnancy itself is a predisposing factor, but also since stress and sex hormones interfere with sleep [16, 17, 50]. Among precipitating factors, there are mechanisms that promote higher likelihood of developing sleep disorders, thus determining the transition from pre-morbid insomnia to acute insomnia. If these disturbing factors are not eliminated, early insomnia may evolve into a chronic form. The main among these precipitating factors are: stress, health problems, pain, anxiety, mood lowering [45].

Insomnia in pregnancy has a prevalence from 5–38% of women in early pregnancy, and it is reported as high as 60% in the eight weeks before the childbirth [7, 9]. Pregnancy is a period characterised by worries, fears and doubts about the health of the baby and this can be a precipitating factor of insomnia as well. As for perpetuating factors, these are mainly represented by behavioural, cognitive and physiological factors that persist in subjects already presenting with insomnia and may lead to chronic insomnia in 80% cases, such as drinking caffeinated beverages in the evening or engaging in stressful activities while lying in bed [45, 51]. Pregnant women with predisposing factors for insomnia and some neuroendocrine alterations can develop precipitating factors, increasing both inflammation modulating factors and amplifying hypothalamic–pituitary–adrenal axis with activation of allostatic load that can cause adverse pregnancy outcomes [16, 17]. Sleep also plays a fundamental role in learning through new neuronal circuits development, and sleep restriction can thus lead to a disruption of neuroplasticity and to the development of the pathological mechanism of depression, given the correlation between the two systems. Therefore, insomnia may compromise adequate emotional processing and may predispose to greater susceptibility to the development of psychiatric symptoms, such as anxiety, depression and, to a lesser extent, psychosis and substance or alcohol abuse [26].

Insomnia in pregnancy can be differentially diagnosed with various disorders that may in turn be comorbidities, causes or consequences of insomnia. The adequate identification of insomnia, as well as other comorbidities, is crucial in order to. The conditions that may underpin differential diagnosis issues with insomnia are the following: Major Depressive Disorder (MDD); Bipolar Disorder (BD); Generalised Anxiety Disorder (GAD); Post-Traumatic Stress Disorder (PTSD); Panic Disorder (PD); Obsessive Compulsive Disorder (OCD); Obstructive Sleep Apnea-Hypopnea (OSAH); Restless Leg Syndrome (RLS) [42].

4.1.2 Pathophysiological mechanisms underlying the development of insomnia during pregnancy

Hormonal changes are the most important factors influencing duration, quality, and physiology of sleep. The action of sex hormones in sleep could be observed in preclinical studies conducted on ovariectomised rats [52]. Steroid hormones, namely oestrogen and progesterone, increase during pregnancy with different and often complementary effects on sleep and respiratory physiology. The early increase in progesterone during the first trimester improves slow-wave sleep and activity through induction of GABA receptors. Indeed, allopregnanolone, a metabolite of progesterone, is a strong modulator of the GABA-A receptor and produces sedative

and anxiolytic effects. Progesterone acts as a stimulant of the respiratory drive, as in obese women, increasing the activity of the genioglossus muscle, thereby dilating the diameter of the upper airways. Counterpart to this protective effect against obstructive sleep apnoea (OSA) may be an increased risk of central apnoea, due to hormone-induced re-setting of chemoreceptors that favours hyperventilation/hypocapnia coupling, as well as an increased pressor response to hypercapnia and apnoea [10, 23, 53, 54]. Literature shows that high levels of oestrogens promote sleep [55]. At the same time, some studies report that during the luteal phase of the menstrual cycle (the phase where progesterone levels evidently increase) some women may experience worse sleep [56, 57]. Low levels of oestradiol (E2) due, for example, to lower ovarian production, are associated with worst sleep quality and higher prevalence of insomnia [58]. Studies in rats that were administered oestradiol after sleep deprivation have shown variable results, as sleep worsened according to some authors, while according to others sleep recovery could be facilitated [59]. In postmenopausal women that were given hormone replacement therapy with oestrogen, a subjective improvement in sleep was detected, whether oestrogen was administered orally or transdermal, or when combined with progestin [60, 61]. Different results from several reports may be consequence of a different individual sleep responses to sex hormones activities [55].

4.1.3 Treatment for insomnia

For ethical reasons, investigational drugs are never tested on pregnant women and literature focused on treatments for this population is scant. However, some reports seem to provide preliminary answers. Approximately 1% of women use melatonin during pregnancy. Melatonin is not monitored by the Food and Drug Administration and therefore doses and timing of administration are not well-known or regulated yet [62, 63]. Maternal melatonin is required to synchronise foetal circadian rhythms, but an alteration in endogenous production, including external administration, could alter the amount of melatonin receptors in the foetus. In fact, clinical studies on its use during pregnancy are inconclusive and conflicting [64] Some studies show that melatonin does not cause adverse effects in the offspring and it and may have a protective activity due to its antioxidant properties. Particularly, a study conducted in 2016 showed that prenatal treatment with melatonin significantly reduced neonatal biometry and birth weight [65]. In addition, melatonin treatment increased the duration of gestation by 7.5% and shifted childbirth time, also reducing glucose tolerance and altering hormone levels [19]. Subsequently, the use of melatonin in pregnancy is currently discouraged until more reliable data are available [63]. Although there are concerns about the administration of exogenous melatonin in pregnancy and its impact on the development of circadian rhythms and reproductive function in offspring, exogenous melatonin may also have some potential protective effects on the foetus [9].

Among the drugs most safely used in pregnancy antihistamines are listed, which are used by 10-15% of pregnant women for nausea and vomiting, and which also present sedative effects, so these properties seem to be useful for insomnia treatment [10, 63]. Trazodone can also be proposed as a sedative drug during pregnancy [10, 30] since some studies exclude an association with congenital malformations, although literature is limited [42]. Sedative-hypnotics such as zolpidem have limited data on reproductive safety and therefore their use in pregnancy is limited [33]. However, benzodiazepines can be considered for treatment during pregnancy, taking into account the risk/benefit ratio [9, 42].

Insomnia can be treated both with medication and non-pharmacological treatments. Short-duration and self-limited conditions may not need to be treated,

whilst if the disorders are debilitating, it is necessary to assess maternal or foetal adverse effects and impact on quality of life [9].

Pregnant women are reluctant to the assumption of drugs, due to the fear of adverse events on the foetus. For these reasons, women are willing to accept non-pharmacological treatments such as cognitive behavioural therapy (CBT), for which promising results are demonstrated [66, 67]. Further non-pharmacological interventions, such as sleep restriction, stimulus control, relaxation techniques, sleep hygiene and sleep education led to a subjective improvement in sleep quality as well as subclinical anxiety and depressive symptoms [9].

4.2 Disorders of circadian sleep–wake rhythms in pregnancy

4.2.1 Definition and prevalence

According to DSM-5, the diagnostic criteria for circadian sleep–wake rhythm disorders are: persistent or recurrent pattern of sleep disruption due mainly to an alteration of the circadian system or a mismatch between endogenous circadian rhythm and the sleep–wake rhythm required by an individual's physical condition or imposed by social or work commitments; sleep disruption leads to excessive sleepiness, insomnia or both and sleep disruption causes clinically significant distress or impaired functioning in cognitive, social, occupational or other important areas. The prevalence of circadian rhythms disorders is about 3-10% [68].

4.2.2 Pathophysiological mechanisms of circadian sleep–wake rhythm disorders in pregnancy.

Circadian rhythms that may be altered as consequence of sleep–wake disorders are: body temperature, physical activities, eating patterns, melatonin and glucocorticoids secretion [14]. The activation of this system occurs through the action of light, which activates photoreceptive cells in the retina that produce melanopsin and through the retino-hypothalamic tract projected to the suprachiasmatic nucleus of the hypothalamus, regulating various pathways. Alterations in circadian rhythms are known to occur in depressed patients. Indeed, this population of subjects can present abnormalities in the secretion of cortisol, TSH and melatonin, as well as increased internal body temperature at night. Furthermore, there is a clear worsening of depressive symptoms with darkness, which may be clearly evident in seasonal affective disorder, as light therapy is effective in circadian rhythms disorder and SAD [14, 69, 70]. Of particular importance is the interaction between maternal melatonin and glucocorticoid secretion and effects in the foetus [71], as melatonin has a pleiotropic biological action with consequent antioxidant, antidepressant, antihypertensive, epigenetic, and trophic effects on the foetus [72, 73]. At the same time, increased cortisol leads to elevated levels of glucocorticoids and if these are excessive could interfere with foetal tissue [74].

4.2.3 Main clinical manifestations in pregnancy.

Pregnant women may also be affected by circadian rhythms disorders and in this case, in addition to the mood disorders mentioned above, they may present with other pathological conditions and the effects of these alterations are clearly evident in shift workers, who have a higher risk of low birth weight, spontaneous abortion and premature birth, but also a higher risk of infertility, miscarriage, pre-eclampsia [7, 14, 15]. In pregnant rats subjected to altered sleep–wake rhythms an increase of adiposity may occur, together with impaired glucose tolerance, and insulin resistance manifesting in offspring 12 months later [75].

4.2.4 Treatment

In this care, treatment is purely non-pharmacological, based on a correct sleep/wake pattern and bright light therapy [7], but there are still doubts about the actual beneficial effects of this therapy in adult offspring; effectiveness of alternative therapies such as: phytotherapy, acupuncture, acupressure, aromatherapy, reflexology, music therapy and yoga are unknown [71].

4.3 Restless legs syndrome

4.3.1 Definition and epidemiology

Restless legs syndrome (RLS) or Willis-Ekbom disease is a motor-sensory disorder of the lower limbs associated with increased likelihood of sleep–wake disorders, such as poor sleep, poor daytime function and excessive daytime sleepiness in pregnancy. This condition is almost twice as common in women as in men, but reasons for this imbalance in prevalence are not precisely understood [76]. Indeed, the first known epidemiological study of RLS during pregnancy reported a prevalence of 11.3%, but in the third trimester prevalence appeared to rise up to 30%. Pregnancy is a cause of a transitory form of the syndrome, but after several pregnancies it can also become persistent [10].

4.3.2 Pathophysiological Mechanisms.

The main mechanism involved in the pathogenesis of restless legs syndrome is a dysregulation of the dopaminergic system, so a reduction in the absorption of this neurotransmitter favours the development of the disease. In general, pathogenetic factors facilitating the appearance of RLS during pregnancy appear to be:

- Elevate levels of oestrogen, (especially oestradiol, particularly in the third trimester of pregnancy)
- Increased prolactin (decreased action of dopamine)
- Iron-deficiency- related anaemia (common disorder in pregnancy)
- Hypertension (bidirectional relationship) [7, 77, 78].

4.3.3 Treatment

In pregnancy, a correct treatment for RLS can be iron supplementation when needed. Other pharmacological agents, such as clonazepam, clonidine, and opioids may be needed in severe conditions, despite there is a high risk of neonatal withdrawal with these drugs [9, 18]. Non-pharmacological treatments that can be used in pregnant women with RLS are physical exercise and behavioural strategies, such as reduced caffeine intake [76].

4.4 Narcolepsy

4.4.1 Definition epidemiology, pathogenesis

Narcolepsy is a sleep disorder characterised by excessive sleepiness, associated with cataplexy, sleep paralysis, and hypnagogic hallucinations [79]. The prevalence

Disorder	Prevalence	Risk factors	Clinical features	Drug treatments	Non-pharmacological treatments
Insomnia	5–38% of women in early pregnancy, 60% in the eight weeks before childbirth	• Pre-existing predisposing factors • Hormone changes • Physical pathologies • Psychiatric pathologies	• Hypersomnia during the day • Irritability • Mood deflection • Anxiety disorders • Dysregulation of hypothalamic–pituitary–adrenal axis • Excessive inflammatory activation	• Benzodiazepines (selected cases) • Trazodone (assessing risks and benefits) • Difenidramine (assessing risks and benefits) • Melatonin (uncertain)	• Cognitive behavioural therapy for insomnia (CBT-I) • Good sleep hygiene
Restless legs syndrome	11.3% (up to 30% in third trimester)	• Iron deficiency • High levels of oestrogen	• Motor sensory-disorder	• Iron supplements	• Exercise • Reducing caffeine intake
Disorders of circadian rhythms in pregnancy	3-10%	• Alterations in sleep phases • Shift work • Impaired secretion of melatonin and glucocorticoids	• Hypersomnia during the day • Low birth weight • Spontaneous abortion • Premature birth • Sons affected by insomnia • Miscarriage • Pre-eclampsia • Impaired glucose tolerance	• Not recommended	• Correct sleep/wake • Light therapy pattern and bright
Narcolepsy	14/10000 (such as general population)	• Pre-existing disorder • Deficit reticular activating system (RAS)	• Excessive sleepiness • Cataplex • Sleep paralysis • Hypnagogic hallucinations	• Fluoxetine (uncertain)	• Regular naps

Table 2.
Summary of major sleep disorders during pregnancy.

of narcolepsy in the general population is 14/1,000 inhabitants and in pregnant women a similar prevalence can be described. Under a pathogenetic point of view, narcolepsy is the result of an alteration of the nuclei of the reticular system (SRA) that promote wakefulness [7, 80].

Narcolepsy in pregnancy causes adverse effects such as excessive maternal weight gain and gestational diabetes, whilst cataplexy contributes to a higher risk of emergency caesarean section [9].

4.4.2 Treatment

Narcolepsy is less common in pregnancy than other sleep disorders, but is more difficult to manage during pregnancy and in the perinatal period, also due to possible adverse effects of the drugs that may be used. In fact, amphetamines can cause low birth weight and increased risk of miscarriage is reported in women using sodium oxybate [7, 9, 81]. Data on the safety of selective serotonin reuptake inhibitors are conflicting, since there are not significant association with birth defects with use of fluoxetine, but it may contribute to transient neonatal complications during the third-trimester and to risk of social-behavioural abnormalities in childhood [82]. Subsequently, non-pharmacological treatment options are recommended, such as avoiding drugs can cause daytime sleepiness, intermittent napping and practising good sleep hygiene [9] (See **Table 2**).

5. Conclusions

According to Immanuel Kant, 'Heaven has given man three things to compensate for the difficulties of life: hope, sleep and a smile'. Indeed, hope and a smile can also be a consequence of satisfactory sleep, especially during pregnancy, but physical changes and conflicting emotions during this period can at the same time alter sleep patterns. Paying attention to sleep disorders during pregnancy could prevent the development of serious health consequences both for the health of mother and child. Identifying sleep disorders also encourages their adequate and early treatment, thus preventing the development of general symptoms such as asthenia, irritability, and emotional lability, or more serious psychiatric disorders, such as depression, mania and psychosis. At the same time, a multidisciplinary approach to sleep disorders in pregnancy is required. Indeed, the cooperation of psychiatrists, neurologists, gynaecologists, and psychologists may allow a improved sleep quality and increase overall well-being of women, children, and their family.

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References

[1] Adan A, Natale V. *Gender differences in morningness-eveningness preference*. Chronobiol Int. 2002 Jul;19(4):709-720. doi: 10.1081/cbi-120005390. PMID: 12182498.

[2] Bailey M, Silver R. *Sex differences in circadian timing systems: implications for disease*. Front Neuroendocrinol. 2014 Jan;35(1):111-39. doi: 10.1016/j.yfrne.2013.11.003. Epub 2013 Nov 25. PMID: 24287074; PMCID: PMC4041593.

[3] Cain SW, Dennison CF, Zeitzer JM, Guzik AM, Khalsa SB, Santhi N, Schoen MW, Czeisler CA, Duffy JF. Sex *differences in phase angle of entrainment and melatonin amplitude in humans. J* Biol Rhythms. 2010 Aug;25(4):288-96. doi: 10.1177/0748730410374943. PMID: 20679498; PMCID: PMC3792014.

[4] Duffy JF, Cain SW, Chang AM, Phillips AJ, Münch MY, Gronfier C, Wyatt JK, Dijk DJ, Wright KP Jr., Czeisler CA. *Sex difference in the near-24-hour intrinsic period of the human circadian timing system*. Proc Natl Acad Sci U S A. 2011 Sep 13;108 Suppl 3(Suppl 3):15602-8. doi: 10.1073/pnas.1010666108. Epub 2011 May 2. PMID: 21536890; PMCID: PMC3176605.

[5] Tonetti L, Fabbri M, Natale V. *Sex difference in sleep-time preference and sleep need: a cross-sectional survey among Italian pre-adolescents, adolescents, and adults*. Chronobiol Int. 2008; Sep25(5):745-759. doi: 10.1080/07420520802394191. PMID: 18780201.

[6] Roenneberg T, Kuehnle T, Juda M, Kantermann T, Allebrandt K, Gordijn M, Merrow M. Epidemiology of the human circadian clock. Sleep Med Rev. 2007 Dec;11(6):429-38. doi: 10.1016/j.smrv.2007.07.005. Epub 2007 Nov 1. PMID: 17936039

[7] Abbott M, Attarian H, Phyllis C. Zee, *Sleep disorders in perinatal women*. Best Practice & Research Clinical Obstetrics & Gynaecology. 2014;**28**(1):159-168 ISSN 1521-6934

[8] Krishnan V, Collop N. *A Gender differences in sleep disorders, Current Opinion in Pulmonary Medicine*: November 2006 - Volume 12 - Issue 6 - p 383-389 doi: 10.1097/01.mcp.0000245705.69440.6a

[9] Miller MA, Mehta N, Clark-Bilodeau C, Bourjeily G. Sleep Pharmacotherapy for Common Sleep Disorders in Pregnancy and Lactation. Chest. 2020 Jan;157(1):184-197. doi: 10.1016/j.chest.2019.09.026. Epub 2019 Oct 14. PMID: 31622589; PMCID: PMC6965691.

[10] Silvestri R, Aricò I. Sleep disorders in pregnancy. Sleep Sci. 2019 Jul-Sep;12(3):232-239. doi: 10.5935/1984-0063.20190098. PMID: 31890101; PMCID: PMC6932848.

[11] Zhang H. Li P, Fan D, Zhen Wu S., Rao J, Lin D., Huang O., Liu Z. *Prevalence of and Risk Factors for Poor Sleep During Different Trimesters of Pregnancy Among Women in China: A Cross-Sectional Study* Nat Sci Sleep. 2021; 13: 811-820. Published online 2021 Jun 17. doi: 10.2147/NSS.S303763

[12] Obeysekare JL, Cohen ZL, Coles ME, et al. *Delayed sleep timing and circadian rhythms in pregnancy and transdiagnostic symptoms associated with postpartum depression*. Transl Psychiatry. 2020;**10**:14 https://doi.org/10.1038/s41398-020-0683-

[13] Palagini L, Cipollone G, Masci I, Novi M, Caruso D, Kalmbach DA, et al. *Stress-related sleep reactivity is associated with insomnia, psychopathology and suicidality in pregnant women: preliminary results*. Sleep Med. 2019; Apr;**56**:145-150. DOI: 10.1016/j.sleep.

2019.01.009 Epub 2019 Jan 21. PMID: 30803833

[14] Logan RW, McClung CA. *Rhythms of life: circadian disruption and brain disorders across the lifespan*. Nat Rev. Neurosci. 2019 Jan;20(1):49-65. doi: 10.1038/s41583-018-0088-y. PMID: 30459365; PMCID: PMC6338075.

[15] Lyu J, Ye X, Chen Y, Xia Y, Zhu J, Tong S, Yin Y, Qu J, Li S. Children's Sleep May Depend on Maternal *Sleep Duration During Pregnancy: A Retrospective Study.* Nat Sci Sleep. 2020 Mar;10;12:197-207. doi: 10.2147/NSS.S239001. PMID: 32210651; PMCID: PMC7071877.

[16] Palagini L, Biber K, Riemann D. *The genetics of insomnia--evidence for epigenetic mechanisms?* Sleep Med Rev. 2014a; Jun;**18**(3):225-235. DOI: 10.1016/j.smrv.2013.05.002 Epub 2013 Aug 7. PMID: 23932332

[17] Palagini L, Gemignani A, Banti S, Manconi M, Mauri M, Riemann D. Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. Sleep Med. 2014b;**15**(8):853-859. DOI: 10.1016/j.sleep.2014.02.013 Epub 2014 May 27. PMID: 24994566

[18] Okun ML, Schetter CD, Glynn LM. *Poor sleep quality is associated with preterm birth*. Sleep. 2011 Nov 1;34(11): 1493-8. doi: 10.5665/sleep.1384. PMID: 22043120; PMCID: PMC3198204.

[19] Nodine, Matthews *Common sleep disorders: management strategies and pregnancy outcomes J* Midwifery Womens Health, 58 (4) (2013), pp. 368-377.

[20] Sedov ID, Cameron EE, Madigan S, Tomfohr-Madsen LM. *Sleep quality during pregnancy: A meta-analysis*. Sleep Med Rev. 2018 Apr;**38**:168-176. DOI: 10.1016/j.smrv.2017.06.005 Epub 2017 Jun 15. PMID: 28866020

[21] Ferraro ZM, Chaput JP, Gruslin A, Adamo KB. *The potential value of sleep hygiene for a healthy pregnancy: a brief review.* ISRN Family Med. 2014 Feb 17;2014: 928293. doi: 10.1155/2014/928293. PMID: 24967333; PMCID: PMC4041265.

[22] National Sleep Foundation. Sleeping By the trimesters: 1st trimester https://www.sleepfoundation.org/articles/sleeping-trimesters-1st-trimester

[23] Pengo MF, Won CH, Bourjeily G. *Sleep in Women Across the Life Span.* Chest. 2018 Jul;154(1):196-206. doi: 10.1016/j.chest.2018.04.005. Epub 2018 Apr 19. PMID: 29679598; PMCID: PMC6045782.

[24] Wang J, Zhou Y, Qian W, Zhou Y, Han R, Liu Z. *Maternal insomnia during the COVID-19 pandemic: associations with depression and anxiety* Soc Psychiatry Psychiatr Epidemiol. 2021 Apr 23: 1-9. doi: 10.1007/s00127-021-02072-2

[25] Bao C, Xu L, Tang W, Sun S, Zhang W, He J, Zhao K, Xu D, Ye X. *Poor Sleep and Decision-Making Disturbance Are Associated With Suicidal Ideation in Pre-natal Depression.* Front Psychiatry. 2021 May 28; 12:680890. doi: 10.3389/fpsyt.2021.680890. PMID: 34122192; PMCID: PMC8193041.

[26] Hertenstein E, Feige B, Gmeiner T, Kienzler C, Spiegelhalder K, Johann A, et al. *Insomnia as a predictor of mental disorders:* A systematic review and meta-analysis. Sleep Med Rev. 2019;**43**: 96-105. DOI: 10.1016/j.smrv.2018.10.006 Epub 2018 Nov 16. PMID: 30537570

[27] Palagini L, Baglioni C, Ciapparelli A, Gemignani A, Riemann D. *REM sleep dysregulation in depression: state of the art*. Sleep Med Rev. 2013; Oct;**17**(5):377-390. DOI: 10.1016/j.smrv.2012.11.001 Epub 2013 Feb 5. PMID: 23391633

[28] Dørheim SK, Bjorvatn B, Eberhard-Gran M. *Can insomnia in pregnancy predict postpartum depression? A longitudinal, population-based study*.

PLoS One. 2014 Apr 14;9(4):e94674.doi: 10.1371/journal.pone.0094674. PMID: 24732691; PMCID: PMC3986207.

[29] Mellor R, Chua SC, Boyce P. *Antenatal depression: an artefact of sleep disturbance?* Arch Womens Ment Health. 2014;**17**:291-302 https://doi.org/10.1007/s00737-014-0427-6

[30] Khazaie H, Ghadami MR, Knight DC, Emamian F, Tahmasian M. *Insomnia treatment in the third trimester of pregnancy reduces postpartum depression symptoms: a randomised clinical trial*. Psychiatry Res. 2013;**210**(3):901-905. DOI: 10.1016/j.psychres.2013.08.017 Epub 2013 Aug 30. PMID: 23993464

[31] Gelaye, Addae, Neway, Larrabure-Torrealva, Qiu, Stone, Luque Fernandez MA, Sanchez, Williams MA. *Poor sleep quality, antepartum depression and suicidal ideation among pregnant women*. J Affect Disord. 2017 Feb;209:195-200. doi: 10.1016/j.jad.2016.11.020. Epub 2016 Nov 18. PMID: 27930912; PMCID: PMC5360461.

[32] Harskamp-van Ginkel, Ierodiakonou, Margetaki, Vafeiadi, Karachaliou, Kogevinas, Vrijkotte, Chatzi, *Gestational sleep deprivation is associated with higher offspring body mass index and blood pressure, Sleep*, Volume 43, Issue 12, December 2020, zsaa110, https://doi.org/10.1093/sleep/zsaa110

[33] Bhattacharya S, Campbell DM. The incidence of severe complications of preeclampsia. Hypertension Pregnancy. 2005;24(2):181-90. doi: 10.1081/PRG-200059873. PMID: 16036402.

[34] von Dadelszen P, Menzies JM, Payne B, Magee LA; *PIERS (Pre-eclampsia Integrated Estimate of RiSk) Study Group. Predicting adverse outcomes in women with severe pre-eclampsia*. Semin Perinatol. 2009 Jun;33(3):152-157. doi: 10.1053/j.semperi.2009.02.009. PMID: 19464505.

[35] Goldenberg RL, Culhane JF, Iams JD, Romero R. *Epidemiology and causes of preterm birth*. Lancet. 2008 Jan 5;371(9606):75-84. doi: 10.1016/S0140-6736(08)60074-4. PMID: 18177778; PMCID: PMC7134569.

[36] Warland D. Morrison, O'Brien, *Maternal sleep during pregnancy and poor fetal outcomes: A scoping review of the literature with meta-analysis*. Sleep Medicine Reviews. 2018;**41**:197-219, ISSN 1087-0792 https://doi.org/10.1016/j.smrv.2018.03.004

[37] Murata K. Fukuda, et al. *Maternal sleep duration and neonatal birth weight: the Japan Environment and Children's Study*. BMC Pregnancy Childbirth. 2021;**21**(295) https://doi.org/10.1186/s12884-021-03670-3

[38] Blair P. Leblebicioglu. Christian *Poor sleep quality and associated inflammation predict preterm birth: heightened risk among African Americans Sleep*. *2015;38:1259-1267*

[39] Chang JJ, Pien GW, Duntley SP, Macones GA. *Sleep deprivation during pregnancy and maternal and fetal outcomes: is there a relationship*? Sleep Med Rev. 2010 Apr;14(2):107-14. doi: 10.1016/j.smrv.2009.05.001. Epub 2009 Jul 21. PMID: 19625199; PMCID: PMC2824023.

[40] Raimundo JR, Bergamaschi CT, Campos RR, Palma BD, Tufik S, Gomes GN. *Autonomic and Renal Alterations in the Offspring of Sleep-Restricted Mothers During Late Pregnancy*. Clinics (Sao Paulo). 2016 Sep;71(9):521-7. doi: 10.6061/clinics/2016(09)07. PMID: 27652834; PMCID: PMC5004573.

[41] Thomal JT, Palma BD, Ponzio BF, Franco MoC, Zaladek-Gil F, Fortes ZB, et al. *Sleep restriction during pregnancy: hypertension and renal abnormalities in young offspring rats. Sleep.* 2010;33((10)):1357-6.

[42] Hashmi AM, Bhatia SK, Bhatia SK, Khawaja IS. *Insomnia during pregnancy: Diagnosis and Rational Interventions.* Pak J Med Sci. 2016 Jul-Aug;32(4):1030-7. doi: 10.12669/pjms.324.10421. PMID: 27648062; PMCID: PMC5017073.

[43] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorder, DSM-5*. American Psychiatric Publishin, Washington, DC 2012.

[44] American Academy of Sleep Medicine. *ICSD-3-International Classification of Sleep Disorder*. American Academy of Sleep Medicine, Chicago 2014.

[45] Spielman AJ, Caruso LS, Glovinsky PB *A behavioural perspective on insomnia treatment.* Psychiatr Clin North Am. 1987; Dec10(4):541-553. PMID: 3332317.

[46] Kalmbach DA, Cuamatzi-Castelan AS, Tonnu CV, Tran KM, Anderson JR, Roth T, Drake CL. *Hyperarousal and sleep reactivity in insomnia: current insights. Nat* Sci Sleep. 2018 Jul;17;10:193-201. doi: 10.2147/NSS.S138823. PMID: 30046255; PMCID: PMC6054324.

[47] Akram U, Ellis JG, Barclay NL. *Anxiety Mediates the Relationship between Perfectionism and Insomnia Symptoms:* A Longitudinal Study. PLoS One. 2015 Oct 14;10(10): e0138865. doi: 10.1371/journal.pone.0138865. PMID: 26465774; PMCID: PMC4605553.

[48] Brand S, Kirov R, Kalak N, Gerber M, Pühse U, Lemola S, Correll CU, Cortese S, Meyer T, Holsboer-Trachsler E. *Perfectionism related to self-reported insomnia severity, but not when controlled for stress and emotion regulation*. Neuropsychiatr Dis Treat. 2015 Feb;311:263-71. doi: 10.2147/NDT.S74905. PMID: 25678791; PMCID: PMC4322891.

[49] van de Laar M, Verbeek I, Pevernagie D, Aldenkamp A, Overeem S. The role of personality traits in insomnia. Sleep Med Rev. 2010 Feb;**14**(1):61-68. DOI: 10.1016/j.smrv.2009.07.007 Epub 2009 Nov 7. PMID: 19897388

[50] Olcese JM. *Melatonin and Female Reproduction: An Expanding Universe*. Front Endocrinol (Lausanne). 2020 Mar; 6;11:85. doi: 10.3389/fendo.2020.00085. PMID: 32210911; PMCID: PMC7067698.

[51] Riemann D, Nissen C, Palagini L, Otte A, Perlis ML, Spiegelhalder K. *The neurobiology, investigation, and treatment of chronic insomnia*. Lancet Neurol. 2015; May;**14**(5):547-558. DOI: 10.1016/ S1474-4422(15)00021-6 Epub 2015 Apr 12. PMID: 25895933

[52] Deurveilher S, Rusak B, Semba K. *Estradiol and progesterone modulate spontaneous sleep patterns and recovery from sleep deprivation in ovariectomized rats*. *Sleep.* 2009;**32**(7):865-877

[53] Baker, Sassoon, Kahan, Palaniappan, Nicholas, Trinder, Colrain *Perceived poor sleep quality in the absence of polysomnographic sleep disturbance in women with severe premenstrual syndrome* J. Sleep Res., 21 (2012), pp. 535-545, 10.1111/j.1365-2869.2012.01007.x

[54] van Broekhoven, T. Bäckström, R.J. Verkes. *Oral progesterone decreases saccadic eye velocity and increases sedation in women* Psychoneuroendocrinology. 2006;**31**(10):1190-1199 ISSN 0306-4530 https://doi.org/10.1016/j.psyneuen.2006.08.007

[55] Morssinkhof MWL, van Wylick DW, Priester-Vink S, van der Werf YD, den Heijer M, van den Heuvel OA, Broekman BFP. *Associations between sex hormones, sleep problems and depression: A systematic review,* Neuroscience & Biobehavioral Reviews, Volume 118,2020, Pages 669-680, ISSN 0149-7634, https://doi.org/10.1016/j.neubiorev.2020.08.006.

[56] Kravitz HM, Janssen I, Santoro N, Bromberger JT, Schocken M, Everson-Rose SA, Karavolos K, Powell LH. *Relationship of day-to-day reproductive hormone levels to sleep in midlife women*. Arch Intern Med. 2005Nov 14 ;165(20):2370-2376. doi: 10.1001/archinte.165.20.2370. PMID: 16287766.

[57] Shechter, P. Lespérance, Ng Ying, N.M.K. Kin, D.B. Boivin *Nocturnal polysomnographic sleep across the menstrual cycle in premenstrual dysphoric disorder* Sleep Med., 13 (2012), pp. 1071-1078, 10.1016/j.sleep.2012.05.012

[58] Kische, Ewert, Fietze, Gross, Wallaschofski, Völzke, Dörr, Nauck, Obst, Beate Stubbe, Penzel, Haring, Sex *Hormones and Sleep in Men and Women From the General Population: A Cross-Sectional Observational Study*, The Journal of Clinical Endocrinology & Metabolism, Volume 101, Issue 11, 1 November 2016, Pages 3968-3977, https://doi.org/10.1210/jc.2016-1832

[59] de Zambotti M, Colrain IM, Baker FC. *Interaction between reproductive hormones and physiological sleep in women*. J Clin Endocrinol Metab. 2015 Apr;100(4):1426-33. doi: 10.1210/jc.2014-3892. Epub 2015 Feb 2. PMID: 25642589; PMCID: PMC4399298.

[60] Donati Sarti, Chiantera, Graziottin, MD; Ognisanti, Ferdinando MD; Sidoli, Cristina MD; Mincigrucci, Parazzini, Gruppo di Studio IperAOGOI *Hormone therapy and sleep quality in women around menopause,* Menopause: September 2005 - Volume 12 - Issue 5 - p 545-551 doi: 10.1097/01.gme.0000172270.70690.5e

[61] Sarti CD, Chiantera A, Graziottin A, Ognisanti F, Sidoli C, Mincigrucci M, Parazzini F; Gruppo di Studio IperAOGOI. *Hormone therapy and sleep quality in women around menopause.* Menopause. 2005 Sep-Oct;12(5):545-51. doi: 10.1097/01.gme.0000172270.70690.5e. Epub 2005 Sep 1. PMID: 16145308.-Sedov ID, Cameron EE, Madigan S, Tomfohr-Madsen LM. *Sleep quality during pregnancy: a meta-analysis. Sleep Med Rev*. 2018; 38:168-176. doi: 10.1016/j.smrv.2017.06.005

[62] Freeman MP, Sosinsky AZ, Moustafa D, Viguera AC, Cohen LS. *Supplement use by women during pregnancy: data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics* Arch Womens Ment Health, 19 (3) (2016), pp. 437-44.

[63] Simriti K. Chaudhry, Leah C. Susser, *Considerations in Treating Insomnia During Pregnancy: A Literature Review,* Psychosomatics, Volume 59, Issue 4, 2018, Pages 341-348, ISSN 0033-3182, https://doi.org/10.1016/j.psym.2018.03.009.

[64] Tamura H, Nakamura Y, Terron MP, Flores LJ, Manchester LC, Tan DX, et al. Melatonin and pregnancy in the human. Reprod Toxicol. 2008 Apr;**25**(3):291-303. DOI: 10.1016/j.reprotox.2008.03.005 Epub 2008 Apr 1. PMID: 18485664

[65] González-Candia A, Veliz M, Araya C, Quezada S, Ebensperger G, Serón-Ferré M, Reyes RV, Llanos AJ, Herrera EA. *Potential adverse effects of antenatal melatonin as a treatment for intrauterine growth restriction: findings in pregnant sheep.* Am J Obstet Gynecol. 2016 Aug;215(2):245.e1-7. doi: 10.1016/j.ajog.2016.02.040. Epub 2016 Feb 20. PMID: 26902986.

[66] Felder JN, Epel ES, Neuhaus J, Krystal AD, Prather AA. *Efficacy of Digital Cognitive Behavioural Therapy for the Treatment of Insomnia Symptoms Among Pregnant Women: A Randomised Clinical Trial.* JAMA Psychiatry. 2020 May 1;77(5):484-492. doi: 10.1001/jamapsychiatry.2019.4491. Erratum in: JAMA Psychiatry. 2020 Jul 1;77(7):768. PMID: 31968068; PMCID: PMC6990703.

[67] Manber R, Bei B, Simpson N. *Cognitive behavioural therapy for prenatal*

insomnia: a randomised controlled trial. *Obstet Gynecol.* 2019;**133**(5):911-919

[68] Kim JH, Duffy JF. Circadian Rhythm Sleep–Wake Disorders in Older Adults. Sleep Med Clin. 2018 Mar;**13**(1):39-50. DOI: 10.1016/j.jsmc.2017.09.004 Epub 2017 Nov 27. PMID: 29412982

[69] Menculini G, Verdolini N, Murru A, Pacchiarotti I, Volpe U, Cervino A, et al. *Depressive mood and circadian rhythms disturbances as outcomes of seasonal affective disorder treatment: A systematic review*. J Affect Disord. 2018;**241**:608-626. DOI: 10.1016/j.jad.2018.08.071 Epub 2018 Aug 15. PMID: 30172213

[70] Monteleone P, Martiadis V, Maj M. *Circadian rhythms and treatment implications in depression*. Prog Neuropsychopharmacol Biol Psychiatry. 2011; Aug 15;**35**(7):1569-1574. DOI: 10.1016/j.pnpbp.2010.07.028 Epub 2010 Aug 5. PMID: 20691746

[71] Hsu CN, Tain YL. *Light and Circadian Signalling Pathway in Pregnancy: Programming of Adult Health and Disease*. Int J Mol Sci. 2020 Mar 23;21(6):2232. doi: 10.3390/ijms21062232. PMID: 32210175; PMCID: PMC7139376.

[72] Naitoh W. Matsumura, *et* al. *Alteration by maternal pinealectomy of fetal and neonatal melatonin and dopamine D1 receptor binding in the suprachiasmatic nuclei*. Biochem Biophys Res Commun. 1998;**253**(3):850-854

[73] Tain YL, Huang LT, Hsu CN. *Developmental Programming of Adult Disease: Reprogramming by Melatonin?* Int J Mol Sci. 2017 Feb 16;18(2):426. doi: 10.3390/ijms18020426. PMID: 28212315; PMCID: PMC5343960.

[74] Wharfe MD, Mark PJ, Waddell BJ. *Circadian variation in placental and hepatic clock genes in rat pregnancy*. Endocrinology. 2011; Sep;**152**(9):3552-3560. DOI: 10.1210/en.2011-0081 Epub 2011 Jul 19. PMID: 21771885

[75] Varcoe T.J., N. Wight, A. Voultsios, *et al. Chronic phase shifts of the photoperiod throughout pregnancy programs glucose intolerance and insulin resistance in the rat* PLoS One, 6 (2011), p. e18504.

[76] Seeman MV. *Why Are Women Prone to Restless Legs Syndrome?* Int J Environ Res Public Health. 2020 Jan 6;17(1):368. doi: 10.3390/ijerph17010368. PMID: 31935805; PMCID: PMC6981604.

[77] Almeneessie AS, Alyousefi N, Alzahrani M, Alsafi A, Alotaibi R, Olaish AH, Sabr Y, Bahammam AS. *Prevalence of restless legs syndrome among pregnant women*: A case–control study. Ann Thorac Med. 2020 Jan-Mar;15(1): 9-14. doi:10.4103/atm.ATM_206_19. Epub 2020 Jan 2. PMID: 32002041; PMCID: PMC6967142.

[78] Dzaja A, Wehrle R, Lancel M, Pollmächer T. *Elevated estradiol plasma levels in women with restless legs during pregnancy.* Sleep. 2009 Feb;32(2):169-74. doi: 10.1093/sleep/32.2.169. PMID: 19238803; PMCID: PMC2635580.

[79] American Academy of Sleep Medicine. *The international classification of sleep disorders*: diagnostic and coding manual, vol. xviii, American Academy of Sleep Medicine, Westchester, Ill. (2005), p. 297.

[80] Slowik JM, Collen JF, Yow AG. Narcolepsy. 2021 Jul 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 29083681.

[81] Thorpy M, Zhao CG, Dauvilliers Y. *Management of narcolepsy during pregnancy*. Sleep Med. 2013; Apr;**14**(4):367-376. DOI: 10.1016/j.sleep.2012.11.021 Epub 2013 Feb 21. PMID: 23433999

[82] Clinical Pharmacology Database Fluoxetine. https://www.elsevier.com/solutions/clinical-pharmacology Elsevier, 2019. Accessed May 10, 2019.