Sleep and chronotype during pregnancy, and the bright light treatment of perinatal depression

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Corrado Garbazza

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Approved by the Faculty of Medicine

On application of

Prof. Dr. sc. nat. Christian Cajochen

Prof. Dr. med. Stefan Borgwardt

Prof. Dr. rer. soc. Dipl.-Psych. Dieter Riemann

Basel, 21. März 2022

Prof. Dr. Primo Leo Schär

Dean

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List of abbreviations

AD	antidepressant drugs
AND	antenatal depression
BD	bipolar disorder
BLT	bright light therapy
DRL	dim red light
EPDS	Edinburgh Postnatal Depression Scale
HDRS	Hamilton Depression Rating Scale
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	major depressive disorder
MEQ	Morningness-Eveningness Questionnaire
MCTQ	Munich Chronotype Questionnaire
NREM	non-rapid eye movement sleep
PDL	placebo dim light
REM	rapid eye movement sleep
RCT	randomized controlled trial
PND	perinatal depression
PPD	postpartum depression
PSG	polysomnography
RLS	restless legs syndrome
SAFTEE	Systematic Assessment of Treatment Emergent Effects
SCN	suprachiasmatic nuclei
SE	sleep efficiency
SSRIs	Selective Serotonin Reuptake Inhibitors
SWS	slow-wave sleep
TST	total sleep time

Summary

Background

Perinatal depression (PND) is a severe mental disorder with disruptive consequences on the health and well-being of mothers, children, and their families. Due to the induced socioeconomic burden, it also represents a major public health problem for society as a whole, and is therefore considered a priority target of health prevention strategies at a global level. There is, in fact, general consensus among experts that PND is still prevalent, underrecognized and undertreated.

While research on the pathophysiological mechanisms of PND is contributing to an increased knowledge of the multifactorial causes of this condition, and is likely to provide new biomarkers for medical use in the near future, none of these is currently available for the everyday clinical practice. Conversely, there is an urgent need of easy and universal screening instruments, as well as safe and affordable treatments that all women can have access to.

Sleep and circadian rhythm disruption are commonly experienced by women during the perinatal period, but there is limited evidence on the objective changes in sleep parameters occurring during pregnancy and how these relate to health outcomes. Moreover, the role of sleep and circadian factors in the etiology of PND and as potential targets for treatment is still underestimated and underinvestigated. As an example, the influence of different circadian preferences for sleep-wake times (chronotypes) on the development of depressive symptoms across the perinatal period has never been investigated. Likewise, the efficacy and safety of bright light therapy (BLT) for the treatment of PND with onset before and/or after delivery have never been tested.

Objectives

Manuscript 1: to perform the first systematic review and meta-analysis of polysomnographic studies during pregnancy, in order to identify possible objective markers of sleep disruption in pregnant women.

Manuscript 2: to investigate whether chronotype is a risk factor for PND and to explore the association between chronotype, maternal sociodemographic characteristics, and lifestyle habits, in relation to PND.

Manuscript 3: to conduct the first randomized controlled trial (RCT) aimed at testing the efficacy and safety of BLT for PND occurring over a 12-month observation period.

Methods

Manuscript 1: by carefully following the PRISMA guidelines, we conducted the first systematic review of polysomnographic studies during pregnancy available in the literature. In addition, we performed a meta-analysis of the data collected on two sleep variables (TST and SE). This was instead not possible for other sleep parameters, due to the large heterogeneity of the reviewed studies.

Manuscript 2: as a part of the "Life-ON" project, a multicenter, prospective, cohort study on sleep and mood changes during the perinatal period, 299 women were followed-up from the first trimester of pregnancy until 6 months postpartum. Chronotype was assessed at baseline using the MEQ, while mood was repeatedly evaluated at several timepoints with depression rating scales (i.e., EPDS, HDRS, and MADRS). The influence of time and chronotype on the different scales was estimated by constructing multilevel linear mixed regression models. A Cox proportional-hazard regression model was built to evaluate the association between chronotype and incidence of depression.

Manuscript 3: in the frame of the "Life-ON" project, a RCT was conducted in a subsample of women with an EPDS score >12 at any time point from the second trimester of pregnancy up to 6 months postpartum. Participants received either BLT (10'000 lux) or DRL (19 lux) for 6 weeks, 30 minutes in the morning, within 20 minutes after wake up, and at a distance of 30 cm from the light box. Multilevel linear models were constructed to test for the influence of time and treatment group on EPDS values and log-linear models to test for socioeconomic factors influencing PND remission.

Results

According to our systematic review, the main changes in objective sleep parameters during pregnancy consists in a reduction of sleep duration and a fragmentation of sleep continuity, with an increased number of awakenings and superficial sleep stages (N1, N2), and a simultaneous decrease of SWS, REM sleep, and SE. The meta-analysis revealed a significant reduction of TST by 26.8 min between the first and third trimester of pregnancy, as well as a decrease of SE by 4% within the same time frame.

Pregnant evening chronotypes, as compared to the other chronotypes, are more vulnerable to PND symptoms, especially in the immediate postpartum period. Although the survival analysis did not show a statistically significant influence of chronotype on the overall risk of PND, a trend towards an increased risk for PND in evening chronotypes and a reduced risk in intermediate types, as compared to morning types, was observed. Furthermore, in line with the literature, pregnant women with evening chronotype in the Life-ON study were more likely subject to health problems and negative pregnancy outcomes than the other chronotypes, and presented adverse sociodemographic characteristics and lifestyle attitudes, that are commonly associated with a higher risk for PND.

Finally, in a RCT testing 6-week morning BLT (10'000 lux) vs. DRL (19 lux) for treating PND, the active light intervention (BLT) showed a remarkable efficacy in inducing a rapid remission from PND compared to DRL. The multilevel linear model revealed a significant influence of time on EPDS score and a group-time interaction, with a greater and sustained reduction in the BLT-group across the whole follow-up period.

Conclusion

We found evidence that the subjective experience of sleep deterioration, that many women report during pregnancy, is related to objective alterations in sleep architecture, particularly during late gestation. These can only be appropriately recorded by PSG, which should be therefore considered a valuable and sometimes necessary instrument to correctly diagnose sleep disorders, also during pregnancy, by overcoming under- or overestimation bias due to subjective reports of sleep problems. Interestingly, despite several physiological factors may be involved in the subjective worsening of sleep quality across gestation, is not pregnancy per se, that causes major PSG-assessed sleep disorders in healthy, normal-weight women. Rather, it is likely the combination of predisposing factors, such as obesity, higher maternal age or

hypertension, and physiological changes occurring during pregnancy, that may contribute in particular to the development of obstructive sleep apnea (OSA) in at-risk pregnant women.

Evening chronotype is associated with a time-dependent, greater severity of PND. Thus, assessing chronotype during pregnancy via the administration of an easy screening questionnaire, may help identify women who are likely to experience more severe perinatal depressive symptoms, especially in the early postpartum, and provide them with psychiatric/psychological support and treatment.

BLT can not only induce a rapid and significant remission from PND compared to DRL, but the resulting improvement in mood can be maintained over time after treatment completion. These new findings support the integration of BLT as effective and safe chronotherapeutic tool, based on solid scientific evidence, to the equipment available to clinicians for the treatment of PND, thus responding to the need for affordable, easy-to-use, and accessible therapies for patients.

INTRODUCTION

1. Perinatal Depression

Definition and epidemiology

Maternal mental health represents a priority objective for the main international public health agencies. As such, it has been consistently included since 2000 in the United Nations Millennium Development Goals for the year 2015 (Goal 5 - Improving Maternal Health)[1] and the following Sustainable Development Goals (Goal 3 - Good Health and Well-being)[2] that are intended to be achieved by the year 2030.

In this regard and according to the established concept that there is "no health without mental health"[3], the World Health Organization states that "the links between mental health problems and maternal health are a major cause for concern, as they directly or indirectly increase maternal morbidity and mortality" and therefore calls for "attention to mental health problems of pregnant women and mothers and integration of mental health care in the existing maternal health programs and activities"[4].

The large majority of research studies on maternal mental health examine non-psychotic common perinatal mental disorders (CPMDs), and most of them focus specifically on depression during the perinatal period[5]. This important phase in a woman's life, which represents the transition to motherhood, is in fact a particularly vulnerable time for the development of mental health disorders, including perinatal depression (PND)[6].

The Diagnostic and Statistical Manual of Mental Disorders-5th edition (DSM-5) defines PND as the occurrence of a major depressive episode during pregnancy or within 4 weeks after delivery[7]. This new "peripartum" specifier for depression thus combines the traditionally used terms of antenatal depression (AND) and postpartum depression (PPD), and replaces the previous DSM-IV "postpartum onset" specifier[8]. Although the requirement that depression begins within 4 weeks after delivery remains the same as in the DSM-IV, most experts consider any depressive episode occurring in the first year postpartum as PND, regardless of the time of onset. In fact, while biological factors mainly affect mood right after delivery, numerous psychosocial stressors with a significant impact on women also emerge in the first 12 months postpartum and can contribute to the onset or recurrence of depression[9].

Prevalence estimates from high-income countries (HICs) revealed that one in every 7-10 women experience depression during pregnancy and 1 in every 5-8 after delivery[10]. However, PND is even more common in low- and middle-income countries (LMICs). According to a recent systematic review and meta-regression[11], the pooled prevalence of depression is significantly higher in LMICs as compared to HICs in both the antepartum (19.2%, 95% CI 18.0–20.5 vs. 9.2%, 95% CI 8.4–10.0, respectively) and the postpartum (18.7%, 95% CI 17.8–19.7 vs. 9.5%, 95% CI 8.9–10.1, respectively) period. The same authors calculated an overall adjusted pooled prevalence of PND of 11.9% (95% CI 11.4–12.5), with a significantly higher prevalence in women from LMICs (13.1%, 95% CI 12.2–14.1) than in women from HICs (11.4%, 95% CI 10.8–12.1)[11].

In general, prevalence rates vary widely and are likely underestimated. In the United States (US), for example, it has been estimated that 50%–70% of women with AND or PPD remain undiagnosed, and nearly 85% untreated[12]. Underreporting and undertreatment may be due to several factors, including:

- an inadequate screening and referral system[13]
- a challenging clinical assessment, due to the overlap between somatic symptoms that are commonly considered normal during the peripartum period, such as fatigue or changes in appetite, and depressive symptoms[14,15]
- a broad range of patient-, provider-, and system-related barriers that prevent to properly identify and treat women suffering from PND, such as stigma towards mental illness, fear of psychiatric medications, limited access to mental health care, insufficient resources and mental health training among perinatal care providers, and poor coordination between them and mental health professionals[16]

For these reasons, the American College of Obstetricians and Gynecologists recommends a routine depression screening of women in the perinatal period, as well as prompt psychiatric care and referral for behavioral therapy, when indicated, accompanied by an adequate follow-up[17,18].

Few screening instruments have been validated and are available for detecting PND[17]. Although no consensus has been achieved on a standard screening tool for PND, the Edinburgh Postnatal Depression Scale (EPDS) is the most frequently used in clinical and research settings[19]. The main advantages of adopting the EPDS are related to its brevity (only 10 items), and, unlike other tools, to the detection of symptoms of the anxiety spectrum, which are typical of perinatal

affective disorders, while less specific somatic symptoms that commonly occur during the peripartum period are excluded[17].

Finally, there is recent evidence that maternal mental health has considerably deteriorated worldwide, particularly in poor countries, as a result of the pandemic caused by the novel coronavirus (SARS-CoV-2)[20,21]. Data from China show increased rates of depressive symptoms in perinatal women[22,23]. Similar, elevated rates of depressive (34.1%) and anxiety (34.6%) symptoms have been found in a US sample of mothers with children aged 0–18 months[24]. Therefore, PND prevalence rates should likely be reassessed in light of the immediate and long-term effects of the current pandemic situation.

Clinical presentation

Perinatal depression must be distinguished from the so called ‘‘postpartum blues or baby blues,’’ a colloquial name for a temporary psychological state experienced by up to 80% of new mothers after giving birth, which is characterized by fluctuating mood, tearfulness, fatigue, and labile emotions, such as irritability or anxiety[25]. “Baby blues” are thought to be mainly due to regulatory hormonal changes that occur as early as the first few days after delivery and are short-lived, generally resolving within the first 10–14 postpartum days[6].

Patients with perinatal depression may present with some or many of the following symptoms
Sadness
Depressed mood and energy
Weepiness
Impaired appetite or overeating
Either excessive sleep or insomnia
Feelings of unworthiness
Anxiety
Panic attacks
Worrying constantly about the well-being of the baby, engaging in obsessive or ritualistic activities
Being afraid to leave the house
Feeling numb, wooden, and void of feelings
Indifferent mood, with neither joy nor sadness
No attachment or interest in the baby
Inertia
Hopelessness or thoughts of harming self or baby
Somatic complaints
Presentation of vague and continuous body symptoms that persist for weeks, including headaches, body pains, feeling of racing heart, constant fatigue
Active anger and resentment of the baby
Constant irritability and negative mood

Table 1: Common symptoms of perinatal depression. From: Van Niel MS and Payne JL (2020)[10]

By contrast, PND lasts longer that 2 weeks, has a more severe impact on women's quality of life and presents with the same main symptoms of major depression, including depressed mood, lack of energy and/or interest in daily activities, sleep problems or appetite/weight changes, poor concentration, feelings of worthlessness, guilt and/or hopelessness, and suicidal thoughts[10]. These are often accompanied by a range of additional symptoms particularly focused on the experience of motherhood or on the baby, that can aid in the diagnosis.
Table 1 lists the most common symptoms of PND.

Etiology and risk factors

According to the current pathophysiological models, several factors are involved in the etiology of PND. This is likely based on a complex interaction between genetic, neuroendocrine, psychological, environmental variables and socioeconomic context, which would explain, for example, why PND affects women of all races, cultural backgrounds, and economic statuses[26,27]. In fact, while some of them are likely to be more sensitive to fluctuations in reproductive hormone levels during the perinatal period, others may have a prior underlying mood disorder that is not recognized[28]. The main risk factors for PND are listed in Table 2.

Category	Risk factors
History of psychiatric disorders	• Family history of depressive disorders or perinatal disorders • Personal history of depressive, bipolar, anxiety or substance abuse disorder
Personality traits	• Neurotic personality, low self-esteem
Pregnancy-related factors	• Unwanted or teenage pregnancy • Multiple birth • Difficult or traumatic pregnancy or birth, obstetrical stressors
Baby-related factors	• Ongoing health problems with the baby • Infant with difficult temperament
Socioeconomic status	• Lack of social support • Single marital status • Poor relationship quality • Financial difficulties, lower income • Lower education
Traumatic experiences	• History of physical or sexual abuse • Adverse childhood experiences • Intimate partner violence/domestic abuse • Stressful life events
Ethnicity	• American Indian/Alaska and Hawaii Native heritage: 30% higher PND incidence
Health factors	• Smoking • Lower frequency of exercise • Obesity and overweight.18
Hormonal factors	• Sudden drop in estradiol levels in the first few postpartum days
Genetic factors	• Genetic variations (chromosome 1q21.3–q32.1)

Table 2: Risk factors for perinatal depression. From: Dagher RK et al. (2021)[25]

Finally, a recent meta-analysis and meta-regression of 291 studies from 56 countries showed that 73% of the variation in the global prevalence of postpartum depression across countries is attributable to higher rates of income inequality, maternal and infant mortality, or longer working schedules (40 hours a week) in women[29].

Health consequences for mothers and children

There is broad scientific evidence that untreated PND is associated with severe consequences for mothers, their children, and families[10].

AND has been linked to a higher incidence of gestational complications, such as preeclampsia, placental abnormalities, delayed fetal development, preterm delivery, and spontaneous abortion[30,31]. Moreover, the effects on the baby at birth go from low weight and lower Apgar score, to behavior disturbances, and infant sleep problems[20].

PPD also has significant negative repercussions for both the mothers and their newborns leading, for example, to failure or shortened duration of breastfeeding and to a lack of interest in the child, which result in poor maternal bonding and interaction with the infant[10,20]. This has been associated with impaired cognitive, behavioral, and emotional development[32], delayed social and communication skills, lower levels of attentiveness, as well as physiological changes characterized by elevated cortisol levels and decreased levels of dopamine and serotonin[33] in children born to mothers with untreated postpartum mood disorders[34–37].

Ultimately, PND also affects maternal quality of life, intimate relationships[38] and the father's mental health[39].

The most dramatic consequences of a severe and untreated PND are represented by the ideation of self-harm or of harming the infant, and at its worst, by suicide of the mother or infanticide. Suicides of women in the first year postpartum are the second-leading cause of death in this period[40,41], accounting for 20% of deceases and for up to 20% of overall maternal mortality[27]. Thoughts of harming the baby have been reported by 41% of depressed mothers vs. 7% of controls[42].

Treatment challenges

Treatment of PND is challenging for both patients and clinicians. The widespread social convention that motherhood should be a time of happiness still greatly influences women's expectations towards this experience. As a consequence, those who develop depressive symptoms during the perinatal period may refuse to recognize them, feel guilty or fearful for not being able to enjoy their pregnancy, not seek help and thus remain untreated.

Psychotherapy and/or antidepressant drugs are the most commonly used approaches in the treatment of PND.

Among psychological therapies, the largest evidence from research studies is available for interpersonal psychotherapy (IPT) and cognitive behavioral therapy (CBT)[20]. Recent meta-analyses showed that both IPT and CBT are effective in reducing PND symptoms as compared to control conditions in both prevention and treatment studies[43,44]. However, due to logistical issues, such as childcare arrangements and expenses, the limited availability of trained professionals and the need for an individual predisposition to talking therapy, women with PND may be less open to psychotherapy than patients suffering from other forms of depression.

As regards pharmacological interventions for PND, a recent Cochrane review concluded that, while there is some evidence that antidepressants may be more effective than placebo in reducing the severity of postpartum depression, studies comparing antidepressants to other treatments for PND are insufficient to draw conclusions[45]. The major concerns about the use of antidepressants in women during pregnancy and breastfeeding are related to the risks of teratogenicity, pregnancy complications, poor neonatal adaptation, or neurodevelopmental disorders. However, the literature on this subject is not consistent.

On the one side a 2018 review on the pharmacotherapy of PND argued that selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and bupropion have an acceptable safety profile, although double-blind placebo-controlled studies are lacking[46]. Another extensive systematic review and meta-analysis also suggested a generally small teratogenic effect of SSRIs[47] and data from a multisite case-control study in the US showed that maternal psychiatric disorders, but not SSRIs treatment during preconception and pregnancy per se, predispose to an increased risk of neurodevelopmental disorders in offspring[48].

On the other hand, however, antidepressant use during pregnancy has been associated with several negative health consequences for the newborns , including pulmonary hypertension, cardiac malformations, and neonatal withdrawal and toxicity[49–51], as well as to alterations in fetal brain development, particularly in regions critical for emotional processing[52].

A further issue is represented by the passage of the active ingredients of the drugs into the mother's milk and therefore to the infant during breastfeeding. Also in this regard, while a meta-analysis of 67 studies found that out of 15 different antidepressants, all could be traced in breast milk at varying levels[53], other studies showed that the drugs metabolites are not always detectable in the child's serum, even if they are present in breast milk[53,54]. For example, serum sertraline levels were found to be low to negligible in children of breastfeeding mothers taking therapeutic doses of this commonly prescribed SSRI[55,56]. However, the effects of a chronic exposure to even low levels of antidepressants on newborns are still unknown.

Finally, despite the risks of a pharmacological approach in women with PND, most experts agree that treatment decisions should weigh both the potential consequences of drug exposure to the fetus or newborn, as well as those of a severe, untreated psychiatric illness of the mother on the health of the child and the whole family.

Role of sleep and circadian rhythm disruption in the perinatal period

Pregnancy is associated with a wide range of dynamic physiological changes, not only affecting hormonal balances but also metabolic function and anatomical structures[57–60]. A large variety of those changes can potentially affect different aspects of sleep, including its duration and continuity, as well as nocturnal breathing and moving pattern. For example, nocturnal micturition due to increased nightly sodium excretion[61], uterus contractions caused by a nocturnal peak in oxytocin levels[62], and stress on the musculoskeletal system related to the increasing size of the uterus[57,63], can all potentially lead to sleep disruption. Steroidal sex hormones (estrogen and progesterone), which are exponentially excreted during pregnancy, are known to profoundly influence sleep physiology, architecture, and both the circadian and homeostatic components of sleep regulation[64]. Pregnancy is also associated with changes in iron and folate metabolism, which has been proposed as a mechanism behind the increased prevalence of restless legs syndrome (RLS) among pregnant women[65–67]. Moreover, as the peripartum period can be perceived as a very stressful time for women and linked to

heightened levels of mental rumination and cortical arousal, this could further perpetuate or worsen insomnia symptoms, like difficulties falling or staying asleep[68].

Sleep problems are very prevalent during pregnancy, with up to 78% of women describing disturbed sleep, especially in the third trimester[69–71]. However, poor sleep quality, disrupted sleep and insomnia, occur during all stages of pregnancy, and may persist or even worsen in the postpartum period[70,72,73]. An increasing number of studies point to an association of disturbed sleep during pregnancy with adverse pregnancy outcomes and common pregnancy-related complications, such as gestational diabetes[74], emergency cesarean section[75], premature birth and low birth weight[76].

A recent meta-analysis by Emamian et al. found poor sleep quality during the perinatal period to be a prospective risk factor for PND, with a moderate and significant link between insomnia and depressive symptoms[77]. However, the authors reported a high heterogeneity of the included studies, possibly reducing the reliability of their results. Another longitudinal study evaluating 530 women in the first trimester of pregnancy and at 8 weeks postpartum, found an association between the occurrence of insomnia during pregnancy and postpartum symptoms of anxiety and obsessive-compulsive disorder (OCD)[78].

Goyal et al. followed 124 women longitudinally from the last month of pregnancy until 3 months postpartum and observed a link between self-reported sleep disturbances and depressed mood at both timepoints. In particular, women with higher depressive symptom severity also showed a higher frequency of sleep disruption, sleep onset and sleep maintenance insomnia, and daytime sleepiness[79]. Another study from Lee at al. analyzing objective sleep measures in women with positive affect compared to those with negative affect at 1 month postpartum, found an 80 min reduction in total sleep time (TST) among women in the negative affect group[80]. Moreover, Wolfson et al. studied the relationship between sleep pattern and self-reported depressive symptoms in 38 pregnant women and showed that women developing depressive symptoms at 2-4 weeks postpartum, as compared to those who reported fewer depressive symptoms at the same timepoint, had significantly different sleep schedules in late pregnancy, with later rise times, longer naps, and more TST[81]. Sleep duration also decreased from the end of pregnancy to the early postpartum weeks in depressed mothers, while non-depressed mothers showed an increase in TST during the same period. The authors concluded that a possible explanation of the longer sleep duration found in depressed mothers during the prenatal period might be due to the inclusion of already depressed women at baseline or,

alternatively, that women with greater sleep needs may be more vulnerable to PPD if their needs in late pregnancy are not met[81].

Time awake after sleep onset, as a measure of sleep disruption in pregnant women, and its relationship to mood disturbances were also investigated. An association between increased time awake during the night, together with poor subjective sleep quality in the immediate postpartum period, and lower mood, was described[82]. Comparing new primiparous mothers with non-postpartum women, Swain at al. found a significant increase in depressed mood in the first 3 postpartum weeks in new mothers. Interestingly, this effect disappeared after adjusting for the ''amount of time up or time awake during the previous night'', suggesting that shorter sleep duration was primarily associated with the observed depressed mood[82].

Regarding the underlying pathophysiological mechanisms linking sleep disturbances and increased risk of PPD, a dysregulation in the neurochemical transmission and modulation of the hypothalamic–pituitary–adrenal (HPA) axis, caused by inflammation and involved pro-inflammatory cytokines, has been discussed as a possible etiological factor[83–85].
In cancer patients, increased depressive symptoms were observed together with higher levels of pro-inflammatory cytokine concentrations after administration of cytokine therapy, such as interleukin 2 (IL-2)[86]. The possible connection between development of depressive symptoms and administration of immunotherapy might be a facilitation of central nervous system and immune system interactions, with the key mediators being IL-1, IL-6 and tumor necrosis factor (TNF), which are responsible for reactions such as fever and alteration of sleep patterns[87]. In particular IL-1 and TNF are implicated in the regulation of non-rapid eye movement (NREM) sleep and the injection of these cytokines leads to increased NREM sleep, while IL-6 causes increased daytime sleepiness[87,88]. A number of studies have examined blood levels of pro-inflammatory cytokines in women suffering from major depressive disorder or postpartum depression. Sluzewska et al. measured plasma concentrations of IL-6, soluble IL-6 receptor (sIL-6R), soluble interleukin-2 receptor (sIL-2R), transferrin receptor (TfR), C-reactive protein (CRP), and alpha 1-acid glycoprotein (AGP) in 49 patients with major depression and compared them with levels in 15 normal control individuals, reporting significantly higher serum levels of the aforementioned cytokines in patients with major depression[89]. In a study by Corwin et al., higher serum levels of interleukin 1 beta (IL-1b) were associated with increased fatigue in the immediate postpartum period, which led the authors to speculate an indirect link to depression through fatigue[90]. Furthermore, higher serum levels of IL-6 and IL-1 receptor

antagonist were documented in women with postpartum depression compared to non-depressed controls[91].

It is noteworthy that the same mechanisms discussed above, entailing sleep disruption as a stress factor activating the HPA axis, are also hypothesized to be involved in the association between sleep deprivation and development of gestational diabetes[92] and gestational hypertension[93], as well as in the pathogenesis of adverse pregnancy outcomes such as preterm birth[93,94], and intrauterine fetal growth[93].

In conclusion, while prior literature suggests a possible association between sleep and depressive symptoms during pregnancy, drawing definitive conclusions based on those findings remain difficult for various reasons, such as heterogenous assessment of sleep quality and quantity and controlling for possible confounding factors, including preexistent mood disorders. Since longitudinal studies assessing the connection between sleep and mood are still lacking, the question of a possible cause-effect relationship remains unanswered. Further research using objective sleep assessment methods and controlling for AND or preexisting mood disorders, are warranted, as they may clarify the role of sleep restriction/poor sleep quality during pregnancy as a risk factor for PPD. However, based on the current evidence, a thorough assessment and management of sleep disturbances during the perinatal period should be recommended and implemented in the clinical practice.

Circadian rhythm disruption has been associated with mood disturbances in the general population[95,96]. To explore whether this association also applies to perinatal mood disorders, researchers started describing circadian rhythms in normal pregnancy, by assessing subjective and objective circadian parameters in healthy pregnant women without gestational complications or comorbid mood disorders.

Actigraphy provides a range of rest-activity variables, that can be essentially divided into two different categories: those based on cosinor analysis, using a cosine curve to fit linear regression for a period of 24 hours, and those derived from nonparametric analysis, which yields data about stability and variability of the rest-activity rhythm across time[97].
The mesor (i.e., the midline y-intercept of the cosine curve) indicates the mean adjusted activity in 24 hours, while the amplitude is calculated as the difference between peak activity values and the mesor. The ratio of these two parameters is called circadian quotient and can be

considered an index of rhythms' strength. The acrophase, corresponding to the clock time of the peak activity levels, provides information on chronotype (morningness or eveningness).
Among the values derived from nonparametric analysis, the two most commonly reported are the interdaily stability (IS), a measure of circadian entrainment to external *Zeitgebers* (higher values indicate greater stability), and the intradaily variability (IV), a measure of rhythm fragmentation based on the frequency of transitions between rest and activity (higher values indicate greater variability).

According to some actigraphic studies, the acrophase of the circadian rest-activity rhythm in the postpartum period varies between 15:12 h and 17:01 h, without significant influence of the different postpartum weeks on these values[98–103]. In a longitudinal analysis, Thomas et al.[102] found an increased rhythm amplitude, stability, and strength from 4 to 12 weeks postpartum, indicating a gradual stabilization of the circadian rhythm after delivery.
Matsumoto et. al[104] used actigraphy from late gestation (34 weeks) to 16 weeks postpartum and also observed an increase in amplitude during the postpartum period, after a decrease from late gestation, without reaching the same levels as during pregnancy. New mothers also had more unstable and irregular rhythms, characterized by longer daytime naps in the immediate postpartum, which in turn decreased throughout the postpartum period.

Krawczak et. al[100,105] examined self-reported circadian rhythm disruption measured by the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), a questionnaire designed to assess biological rhythms in the clinical setting[106], in 45 healthy women from the third trimester of pregnancy to 6-12 weeks postpartum, with a subset of participants also being assessed by actigraphy. Subjective circadian disruption (increase in BRIAN score) from pregnancy to postpartum was mirrored by a decrease in mesor and acrophase, and an increase in amplitude, circadian quotient, and IV, while IS did not change. These findings of decreased and less regular self-reported sleep-wake rhythms from pregnancy to postpartum, were also reported in another large-scale study in 101 Japanese new mothers[107].
Finally, a single study[108] found different urinary 6-sulfatoxymelatonin (a metabolite of melatonin) secretion patterns in postpartum women compared to non-pregnant women, with lower mean and maximum values of metabolite secretion in the postpartum period.

Besides describing circadian rhythm parameters in normal pregnancy, some of the above-mentioned studies also investigated rhythm changes in pregnancy-related mood disorders.

Krawczak et. al[100,105] analyzed sleep and circadian rhythms in relation to EPDS scores in women with mood disorders from late pregnancy to 6-12 weeks postpartum. Changes in subjective circadian rhythm disruption (BRIAN scores) during the observation period predicted worsening of depressive symptoms in women with and without mood disorders. Participants with mood disorders also showed greater increase in circadian rhythm amplitude and more sleep disturbances across the perinatal period, as assessed by actigraphy.

A recent study by Slyepchenko et. al[109] examined longitudinal changes in subjective and objective sleep and circadian rhythm parameters in 100 women during the third trimester of pregnancy, as well as at 1–3 weeks and 6–12 weeks postpartum (n=73). Among the assessed circadian rhythm variables, the most strongly associated with higher depressive and anxiety symptoms across the peripartum period were circadian quotient, activity during rest at night, and probability of transitioning from rest to activity at night. The authors did not find changes in dim light melatonin onset (DLMO) (i.e., the time of the evening increase of endogenous melatonin) from pregnancy to the postpartum period in patients at risk for PPD.

In contrast, Sharkey et. al[110] previously reported an association of phase shift in DLMO from the third trimester of pregnancy to 6 weeks postpartum in women with depressed mood, as measured by HDRS. It is noteworthy, that changes in peripartum melatonin secretion have not only been linked to depressive symptoms[111], but also to obsessive-compulsive and manic symptoms during the pre- and postpartum period[112].

In conclusion, circadian rhythm disruption seems to be implicated in perinatal mood disorders, but evidence to date is overall scarce and more studies, using sound chronobiological methods, are needed to further explore and understand this relationship.

2. Chronotype

Definition, epidemiology, and assessment

Most physiological processes in the human body oscillate throughout the day with a period close to 24-hours, but usually a little longer in humans[113,114]. These are referred to as circadian rhythms (from the Latin "circa diem" = about a day) and include cerebral activity (sleep-wake cycles), metabolism and energy homeostasis, core body temperature, heart rate, blood pressure, and the secretion of hormones such as melatonin and cortisol. Circadian rhythms are controlled by an endogenous timing system, which ensures the integration of hierarchically organized multi-oscillators. At the top of the hierarchy is a "master clock" located in the suprachiasmatic nuclei (SCN) in the ventral hypothalamus, which regulates neuronal activity and peptide release[115]. The SCN coordinate all circadian rhythms by communicating with the peripheral clocks, that are present in practically every organ and cell of the body, via neuronal and humoral signals[116] in a process called "internal synchronization".

In addition, circadian rhythms are also synchronized by external periodic signals from the environment, also known as *Zeitgebers* (from the German "time givers"), which result from the 24-hour light-dark cycle of the earth's rotation. This daily adjustment of the phase and period of the circadian oscillator to the external time is called "circadian entrainment"[117]. Light is the strongest time cue for synchronizing the circadian system and as such it has relevant effects on mood, wellbeing, alertness, and cognitive performance. Besides light, however, other weaker, non-photic *Zeitgebers*, such as social stimuli, meals, and physical activity, also promote the alignment between the exact 24-hour day and the endogenous circadian rhythms[113,114].

There are inter-individual variations in the specific temporal relationship to the *Zeitgebers*, which correspond to a different "phase of entrainment" between internal and external time and define different chronotypes. Chronotypes therefore reflect a distinct phase relationship between daily biological and environmental events, which not only depends on the strength of the *Zeitgebers*, the most robust of which is light, but also on age, gender, genetic variants, as well as on how individuals cope with social time and duties (e.g. work schedules etc.)[118]. Moreover, there is evidence that chronotypes also differ in light sensitivity[119] and not only in the circadian regulation of the sleep-wake rhythm, but also in the dynamics of sleep homeostasis[120,121].

Chronotypes in the general population are normally distributed, ranging from morning types (early falling asleep in the evening and early wake up in the morning) to evening types (late falling asleep in the evening/night and late wake up in the morning), with intermediate types falling between these two extremes[122] (see Figure 1).

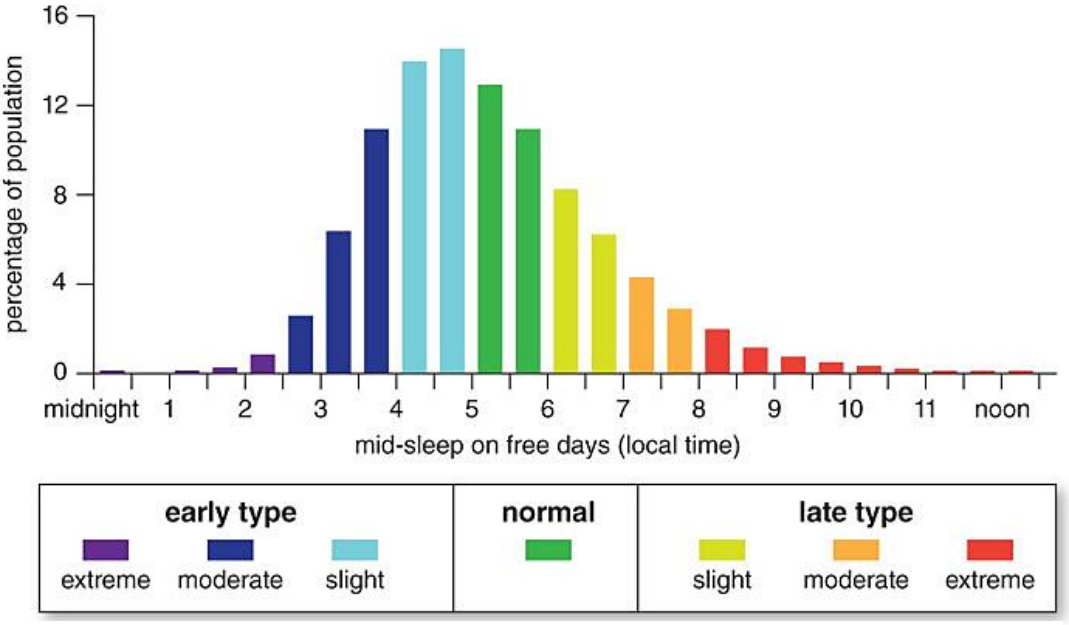

Figure 1: Distribution of chronotypes based on mid-sleep of free days. Adapted from: Roenneberg, T and Merrow, M (2007)[239]

Individual chronotypes can interfere with demands related to school times, working hours, or leisure activities, which define a socially acceptable time for sleep and wakefulness. Thus, in order to adapt to daily activities, late chronotypes may be forced to get up before their biologically driven wake-up time, whereas early chronotypes may have to stay up longer into their biological night. This generally leads evening and, to lesser extent, morning types to accumulate sleep debt on workdays and compensate for it by sleeping longer or midday napping on work-free days[123].

The degree of misalignment between biological and social time is normally referred to as social jetlag and can be quantified as the absolute difference between the timing of midsleep on workdays and on work-free days[124]. Later chronotype and greater social jetlag are strongly correlated[124], and both conditions are associated with adverse health consequences and unhealthy habits[125]. Evening chronotypes report a higher incidence of poor sleep quality and increased daytime sleepiness[126,127] and have a higher risk for depression and suicides than the other chronotypes[128–132]. They also show less healthy dietary habits[133–136], consume more alcohol, nicotine, and caffeine[137–139], are less often engaged in physical activity[140] and tend to have increased body mass index (BMI) and obesity[125,141]. Consequently, evening chronotypes

are also more prone to suffer from chronic diseases, such as arterial hypertension, type 2 diabetes[142], and bronchial asthma, as compared to other chronotypes [143]. Health-related hazards among evening chronotypes are summarized in Table 3.

Physiology	Condition	Disease
Brain	Alcohol misuse	Alcohol abuse
	Smoking	Nicotine dependence
	Irregular or unhealthy diet	
	Low physical activity	
	Irregular or deprived sleep	
	Sleeping difficulties	Insomnia
	Overweight	
	Sleep disturbances	Sleep apnea
	Depressive symptoms	Depressive disorder
	Depression, hypomania, or mania	Bipolar disorder
	Anxiety	Anxiety disorder
		Personality disorder
Heart and blood vessels		Arterial hypertension
Lungs and respiratory tract	Wheezy breathing	Bronchial asthma
	Allergic respiratory symptoms	Hay fever
Endocrine organs	Reduced insulin sensitivity, reduced glucose tolerance, poorer glycemic control	Type 2 diabetes
	Difficulties in getting pregnant	Infertility

Table 3: Health-related hazards among evening chronotypes. From: Partonen, T (2015)[228]. With permission of the publisher (license number: 5236990238071).

There are various methods for assessing chronotype. One option is to use self-administered tools, such as the Morningness-Eveningness Questionnaire (MEQ)[144] and the Munich Chronotype Questionnaire (MCTQ)[123]. Although the MEQ and MCTQ are highly correlated, the MEQ inquiries about individual time preferences to engage in certain activities, such as sleep, while the MCTQ estimates the current midpoint of bedtimes on workdays and work-free days from questions about sleep-wake behavior as an approximation of the entrainment phase. That is, the difference between a given phase of a circadian rhythm (e.g., the nadir of core body temperature or the midpoint of sleep) and the phase of the time cue (e.g., twilight or darkness) is calculated[145].

On the other hand, it is possible to measure the so-called “dim light melatonin onset” (DLMO), i.e., the time of the evening increase of endogenous melatonin based on five saliva samples collected under dim light conditions and possibly coupled with a recording of the rest-activity cycle over 1-2 weeks (actigraphy). In addition to the chronotype, this makes it possible to determine the degree of social jet lag and the phase difference between the time when the melatonin rises in the evening and the onset of sleep[146].

Gender differences in chronotype and influence on pregnancy

According to a recent systematic review and meta-analysis of studies assessing chronotype by using the MEQ, there are gender differences in the distribution of chronotypes, with women being more likely morning types and men, conversely, being more evening oriented[147]. However, research findings are generally not consistent. For example, in a large, population-based study in Finland, evening types have been estimated to represent 11–13% of the adult individuals, with eveningness being slightly more prevalent among females than males[148]. By contrast, an analysis of wearable devices data in the Chinese population (n=49,573) did not show any gender differences in chronotype[149]. Other researchers examined diary data to estimate the distribution of individual chronotypes in the US population and found that women are on average earlier chronotypes than men until the age of 40, but later types thereafter[150]. The authors hypothesized hormonal changes in women to act as modulators for an aging circadian system, causing a shift to eveningness between 35 and 50 years.

Fluctuations in reproductive hormones, particularly in estrogen and/or progesterone levels, also seem to influence changes in chronotype and activity levels during pregnancy in both women and female mice, as measured by wrist actigraphy and running wheel activity, respectively. While the time of sleep onset during the first and second trimesters was earlier in both groups than before pregnancy, this reverted to the pre-gestational state during the third trimester[151]. However, not only chronotype may be affected by hormonal factors, but conversely, it also appear to modulate reproductive functions in women, such as the length of menstruation and the likelihood for pregnancy[152]. Furthermore, evidence suggests that, similarly to what seen in the general population, but especially in women, a later chronotype might represent an unfavorable factor in the onset of physical or mental disorders[153] and be associated with adverse childhood experiences[154].

As regards the perinatal period, pregnant evening chronotypes reported greater seasonal variations in mood and behaviour than morning types[155], had a higher prevalence of insomnia and depression before and during pregnancy[156], and more symptoms of mania and obsessive-compulsive disorder in the postpartum[157]. Also, findings from a large cohort of 1,646 pregnant women, showed that evening-types were more often smokers and had more illnesses or disabilities as compared to the other women[155]. Other investigations pointed that pregnant women with evening chronotype tend to have a poor diet quality[158], food craving traits, and to gain weight in the early gestational period[159] than other chronotypes. Finally, a recent study

conducted in 53 pregnant women with gestational diabetes mellitus (GDM) found that evening chronotypes have a more unstable marital status, a higher prevalence of insomnia and depression before and during pregnancy, and are more likely to develop adverse pregnancy outcomes, such as pre-eclampsia and neonatal ICU admission[156].

3. Light Therapy

Bright light therapy for affective disorders

The intrinsic property of light to enhance mood states has been known since ancient times[160]. However, it is primarily the research advances in chronobiology that have occurred since the second half of the last century, which have led to the scientific validation of bright light therapy (BLT) as a chronotherapeutic tool and have promoted its implementation in clinical practice, starting with the treatment of mood disorders.

For almost four decades now, after the description of the first case series in 1984, BLT has been established as the first-line treatment for seasonal affective disorder (SAD)[161]. In more recent years, a growing scientific literature and several meta-analyses of randomized trials have shown that BLT is superior to placebo and well-tolerated, not only in seasonal depression, but also in moderate to severe non-seasonal unipolar depression, with effect sizes equivalent to those observed in trials using SSRIs[162–164]. Moreover, as compared to antidepressant drugs (AD) that mainly target mood, BLT has the advantage of improving both sleep and circadian rhythms, which are commonly altered in depression[165].

In addition, BLT implementation has also been tested as augmentation therapy to AD in non-seasonal depression, particularly for major depressive disorder (MDD) and bipolar disorder (BD)[160]. In up to 50-60% of patients who did not respond to AD alone[166], BLT used as add-on treatment increased the number of responders[167], thus raising the question whether the combination of AD and BLT should be recommended as a first-line approach, rather than as possible, secondary augmentation strategy, in order to maximize patients' response rates and achieve a shorter duration of untreated depression[168,169].

In this regard, a recent meta-analysis showed no differences between BLT and AD efficacy when these interventions were introduced as a first line treatment in MDD with and without seasonal pattern. However, BLT induced faster antidepressant benefits than AD and also improved circadian rhythm alterations. Finally, the synergistic combination of the effects of AD and BLT

showed a clear superiority over AD alone, as well as a good tolerance and safety profile, even regarding retinal health[169].

Rationale for using bright light therapy in perinatal depression

BLT may be a suitable treatment for women suffering from PND, because it is low-cost, home-based, and its efficacy for other types of depression has been well established.
Most importantly, however, the greatest advantage of BLT over pharmacotherapy for perinatal women is that BLT has a much more favorable safety profile than AD[162]. In fact, most pregnant women have legitimate concerns about the adverse effects of AD on the developing fetus or newborn, leading many of them to refuse pharmacotherapy. This also applies to the postpartum period, due to the possible risks associated with the passage of drugs metabolites into breast milk, and to the desire of many mothers not to give up breastfeeding, which is an important and beneficial step for bonding with the child.
On the other hand, psychotherapy is also an effective treatment for PND[170,171], not involving the intake of medications. However, various logistical and economic barriers can make it unattractive for women with PND *(see page 6, treatment challenges).*

Besides practical advantages, several factors related to the pathophysiology of depression and the effects of light on mood and brain circuits support the use of BLT for treating PND:

- PND might be associated with reduced daylight exposure, which can be counteracted by implementing artificial light in the domestic environment. During the perinatal period, women tend to reduce their level of physical activity and time spent outdoors, particularly due to mobility problems in late gestation and care of the newborn in the home setting after delivery[172]. Although a small study by Wang et al. in the San Diego area did not show any differences in light exposure of postpartum women vs. matched control women, nor a correlation between postpartum mood with illumination levels in the postpartum sample[173], some more recent findings confirmed a seasonal trend in PND symptoms. In particular, a delivery during fall and early winter months, when daylight is of significantly shorter duration, has been associated with an increased risk of PPD[174,175]. Also, higher scores (35%) of depressive symptoms in late third trimester and at each postpartum assessment have been found when days were shortening (from August to first 4 days of November) as compared to other day length categories[176].

- women with PND may present circadian misalignment (i.e., a mismatch between the endogenous circadian timing system and the 24-hour environmental cycles) and the antidepressant effects of BLT may be related to the resynchronization of circadian rhythms[177]. Light, as the most robust *Zeitgeber*, keeps most biological and behavioral rhythms internally synchronized, which is crucial for physical and mental health. The SCN receive photic signals from the environment via direct retinal projection from a population of intrinsically photosensitive retinal ganglion cells (ipRGCs). These express the photopigment melanopsin[178,179], which is particularly sensitive to short-wave light in the blue range of the light spectrum (between 460 and 480 nm)[180]. Interestingly, it has recently been reported that the ipRGCs also communicate with other brain areas besides the SCN, such as a thalamic area known as peri-habenula, which is responsible for mediating the effect of light on affective behavior[181] (Figure 2). Thus, circadian sleep-wake disruption and chronic circadian misalignment, which are commonly observed in psychiatric and neurodegenerative diseases, can be treated using BLT, with beneficial effects not only on sleep quality, but also on mood, alertness, and cognitive performance.

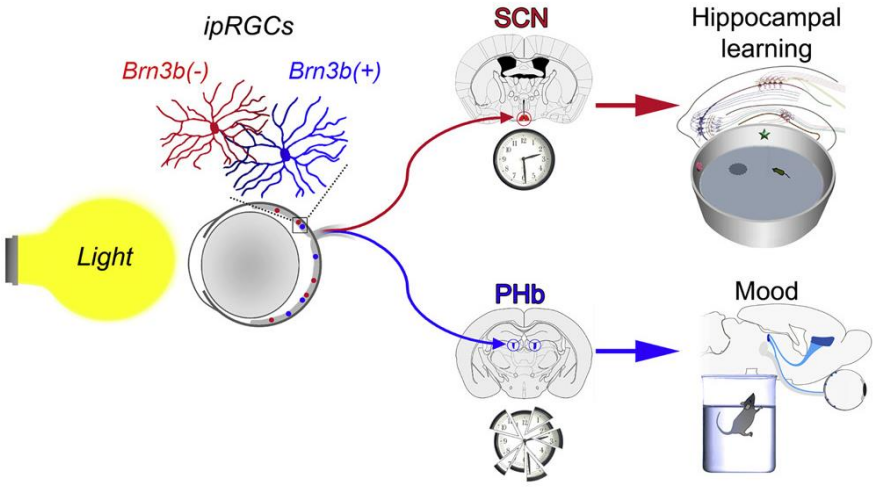

Figure 2: Light affects mood and learning through distinct retina-brain pathways. From: Fernandez, DC et al. (2018). With permission of the publisher (license number 5243140161196)

- PND may be associated with dysregulation of brain serotonin levels, which can be counterbalanced by bright light exposure[182]. In women with PPD, platelet serotonin levels are reduced by 50% in respect to normal levels[183]. Moreover, a significant association between postpartum depressive symptoms and genetic polymorphisms of

the serotonin-transporter-linked promoter region (5-HTTLPR) has been found[184], with 5-HTTLPR short allele carriers having an increased vulnerability to depression during the perinatal period[185,186]. Also, the serotonin 1A receptor (5-HT1A) binding potential in the brain is reduced by 20–28% in women with PPD as compared to healthy postpartum women, with the anterior cingulate and mesiotemporal cortices being the most significantly affected brain areas[187].

Serotonin dysregulation during the perinatal period has also been attributed to alterations in tryptophan (a precursor of serotonin synthesis), estrogen, and hypothalamic-pituitary-adrenal (HPA) axis activity[188–190].

On the therapeutic side, SSRIs are considered the pharmacological treatment of choice for PND[191], and have been shown to be effective in improving maternal role functioning in women with PPD[192,193]. Light is also likely to exert its mood-enhancing effects through serotonergic mechanisms. It has been demonstrated that the antidepressant effects of BLT can be reversed following tryptophan depletion[194], which leads to a reduced availability of serotonin in the brain, which in turn can trigger depressive symptoms[195]. Conversely, the mood lowering effect of tryptophan depletion in healthy women can be hindered by exposure to bright light (3,000 lux) but not dim light (10 lux)[196]. BLT might therefore improve the regulation of the serotonergic system in women with PND.

- PND may be influenced by alterations in estrogen, which could be corrected with bright light exposure. The estrogen and serotonin systems are closely related, which may explain why some women are more vulnerable to mood disorders due to hormonal fluctuations, including PPD, and why in these cases estrogen has been shown to be an effective therapeutic option[197,198]. The alternation of a high rise in estrogen and progesterone levels during pregnancy, followed by a rapid decline of these hormones after childbirth, has been implicated in the etiopathogenesis of PND[199]. There is limited evidence that BLT may stimulate the release of luteinizing hormone (LH), a gonadotropin hormone involved in the production of estrogen and progesterone[200], and therefore exert its therapeutic effects through the LH-dependent modulation of estrogen levels.

- BLT can help improve fatigue and sleep disturbances during the perinatal period, which are supposed to be risk factors for PND *(see pages 7-12, role of sleep and circadian rhythm disruption in the perinatal period).* An association has been shown between short sleep duration and adverse maternal and fetal outcomes[201–203], as well as between sleep

problems and maternal depression[204]. In fact, fatigue and sleep disturbances are evaluated in the diagnosis of PND and are among the most commonly experienced symptoms in women with PPD[205]. Studies indicate that women with PND report substantially poorer sleep than healthy antepartum and postpartum matched women[79]. The well-known non-visual effects of light include decreased daytime fatigue, improved sleep, and alertness[206–208], thus representing a rationale for the use of BLT in women with PND.

Evidence on bright light therapy for antenatal and postpartum depression

Given that it is estimated that only about 15% of women with PPD are treated, there is an evident need to increase access to treatment by adopting intervention that are affordable, easy-to-use, and as effective as traditional pharmacologic approaches[209]. Although BLT has confirmed to have these qualities, the current literature on its use for perinatal mood disorders is scarce. Only six studies so far investigated the effects of BLT on depression occurring during pregnancy or the postpartum. Four were randomized controlled trials and two were open trials[210].

In an open trial, Oren et al. administered daily BLT (10'000 lux for 60 minutes in the morning, within 10 minutes of awakening) to 16 pregnant women with AND[211]. After 3 weeks, they found a decrease by 49% from baseline mean scores on the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version (SIGH-SAD). For 7 patients who continued the treatment up to 5 weeks, an even greater reduction, by 59% from baseline mean SIGH-SAD ratings, was observed.

Based on these findings, a first randomized, controlled trial (RCT) in women with AND was conducted by Epperson et al.[212], in which 10 participants received either BLT (7'000 lux, n=5) or placebo dim light (PDL) (500 lux, n=5) for 5 weeks, 60 minutes per day, within 10 minutes of awakening. Results did not show any differences between the two study groups at 5 weeks, with SIGH-SAD scores being similarly reduced by bright light and dim light. However, when the treatment was extended to 10 weeks, a greater reduction in depressive symptoms emerged in women receiving active treatment vs. placebo.

In a larger RCT, using a similar protocol for BLT (7'000 lux, for 60 minutes daily for 5 weeks) but a lower illuminance level in the control group (70 lux), Wirz-Justice and colleagues[213] randomly assigned women with AND to receive either bright light (n=16) or PDL (n=11).

Participants in the BLT group showed significantly greater scores improvement in the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS) and the 17-item Hamilton Depression Rating Scale (HDRS) than those in the PDL group. Moreover, the response rate (HDRS ≥ 50% improvement) at week 5 was significantly greater for BLT (81.3%) as compared to PDL (45.5%) and clinical remission (HDRS ≤ 8) was attained by 68.6% in the BLT group vs. 36.4% in the PDL group ($p < 0.05$).

A recent RCT examined the effectiveness of BLT vs. PDL in a large sample of pregnant women of 12-32 weeks gestational age. Bais et al.[214] randomly allocated 67 participants to either daily BLT (9,000 lux, 5000 K) or dim red light (DRL, 100 lux, 2700 K) for 6 weeks, 30 min in the morning after awakening. Follow-up assessments at the end of the trial, 3 and 10 weeks after treatment, as well as 2 months postpartum, showed no statistically significant differences in depression rates between the BLT and the RDL group on the SIGH-SAD, HDRS, and EPDS. The authors therefore concluded that median depression scores were improved in both treatment arms and raised the question whether these results were due to a real treatment response, a placebo effects or a combination hereof. In this regard, however, similarly as in the study from Epperson et al.[212], the antidepressant effects of even low-intensity placebo lights remain unclear, considering that illuminance levels as low as 100 lux has been demonstrated to phase-shift human circadian rhythms[215].

As regards the use of BLT for PPD only two studies are reported. In a case series by Corral et al.[216] n=2 participants received 4-week BLT at 10'000 lux for 30 min between 7:00 am and 9:00 and showed substantial clinical improvement (75% reduction in HDRS scores). The same first author, however, later performed a RCT[217] which showed no differences between BLT (10'000 lux, n = 10) and placebo (600 lux DRL, n = 5), administered for 6 weeks for 30 min/day between 7:00 am and 9:00 am. Both treatments elicited a 49% reduction in SIGH-SAD scores. Also, similar increases in SIGH-SAD scores were found following withdrawal of the treatments.

RESEARCH OBJECTIVES AND METHODS

Research Questions, Hypotheses and Aims

Research on PND offers many possibilities for development, given the numerous gaps in our knowledge of many aspects of this disorder, from risk factors to pathophysiological mechanisms, to the best approaches to diagnosis and treatment. Thus, not surprisingly, within the already existing field of women's mental health care, a subdiscipline known as reproductive psychiatry is expanding[218], with the aim of focusing efforts on the investigation and clinical management of mental disorders specific to the reproductive age of women.

With this in mind, for the purpose of this thesis it was necessary to formulate few precise research questions to be answered through the original manuscripts that will be presented in the following chapters. This also in order to concentrate the data analysis on a part of the large number of variables collected in the "Life-ON" study, on which this thesis is based, and which is described under "methods". The research questions, hypotheses and aims of the manuscripts composing this thesis are summarized in Table 4.

Manuscript Title	**Questions**	**Hypotheses**	**Aims**
Polysomnographic features of pregnancy: a systematic review	What is the current evidence on the objective sleep features of pregnancy? Have the studies available so far ever been summarized in a systematic review?	Subjective sleep disturbances during pregnancy correspond to objective alterations in sleep architecture, that can only be detected by PSG recording. Studies using PSG in pregnant women have never been systematically reviewed before.	To perform the first systematic review and meta-analysis of PSG studies during pregnancy, in order to identify possible markers of sleep disruption in pregnant women with and without comorbidities.
Influence of chronotype on the incidence and severity of perinatal depression in the "Life-ON" study	Is the chronotype of pregnant women a possible risk factor for the onset/severity of PND?	Evening chronotype is predictive of PND occurrence and symptom severity. Pregnant evening chronotypes present unfavorable social conditions and lifestyle attitudes predisposing them to PND.	To investigate whether chronotype is a risk factor for PND and to explore the association between chronotype, maternal socio-demographic characteristics and lifestyle habits, in relation to PND.
Sustained remission from perinatal depression after bright light therapy: a randomized, placebo-controlled trial	Is BLT safe and effective for the treatment of PND?	BLT is effective for treating PND irrespective of the time of onset (pre- and/or postpartum).	To conduct the first RCT aimed at testing the efficacy and safety of BLT for PND occurring over a 12-month observation period.

Table 4: Summary of the research questions, hypotheses and aims of the manuscripts composing the thesis. RCT: randomized controlled trial. PSG: polysomnography.

Methods

The following section and the figures and tables reproduced therein are derived and adapted from the protocol of the "Life-ON" project, published by the candidate as co-author at the beginning of the study[219]. Reference to the manuscript is here reported:

Baiardi, S., Cirignotta, F., Cicolin, A., **Garbazza, C.**, D'Agostino, A., Gambini, O., Giordano, A., Canevini, M., Zambrelli, E., Marconi, A. M., Mondini, S., Borgwardt, S., Cajochen, C., Rizzo, N., & Manconi, M. (2016). Chronobiology, sleep-related risk factors and light therapy in perinatal depression: the "Life-ON" project. *BMC psychiatry*, *16*(1), 374. https://doi.org/10.1186/s12888-016-1086-0

The "Life-ON" project: rationale and design of a multicenter, cohort study on sleep and light therapy in perinatal depression

Working hypotheses

The "Life-ON" project was designed starting from the fundamental hypothesis that sleep structure and its possible alterations during pregnancy might contain essential information for the early identification of women at risk for developing PND. Furthermore, considering its well-established efficacy and safety profile as a treatment for seasonal and non-seasonal depression, as well as the encouraging findings from the few available studies on AND or PPD, it has been hypothesized that BLT might be a valid tool for both preventing PND onset and treating PND in women already affected. Null hypotheses were that neither polysomnographic sleep features during pregnancy or subjectively and objectively assessed sleep disorders occurring during the perinatal period are related to PND. Also, that BLT is not effective in preventing or treating PND.

Specific aims

Primary aim

To systematically explore and identify potential predictive factors for PND, by prospectively assessing sleep parameters, biochemical and hormonal blood markers, and mood changes during the perinatal period (Life-ON main study).

Secondary aims

1) To investigate the possible association between specific genetic polymorphisms and the development of PND (substudy Life-ON 1)

2) To test the efficacy, safety, and tolerability of BLT for treating PND (substudy Life-ON 2)

3) To test the feasibility of using BLT in non-depressed pregnant women, in order to prevent the onset of PND during late gestation and the postpartum period (substudy Life-ON 3)

Design of the Life-ON main study

The Life-ON project is a prospective, both observational and interventional, multicenter, cohort study, which has been conducted from 2016 to 2020 in three sleep centers located in northern Italy (Bologna, Milan, Turin) and one in southern Switzerland (Lugano). A total of 439 women attending the gynecological outpatient clinics of the involved centers and who gave a written informed consent, were recruited during the first trimester of pregnancy (10^{th}-15^{th} gestational week) and followed-up until 12 months after delivery. Inclusion and exclusion criteria of the study are listed in Table 5. The use of any drug prescribed by other physicians and necessary for women in their normal clinical care pathway in parallel with the study was allowed. Participants underwent scheduled visits conducted by a multidisciplinary team consisting of a gynecologist or obstetrician, a psychologist or psychiatrist, and a neurologist expert in sleep medicine. During the periodic follow-up assessments, a broad range of variables were collected, including demographic and medical/gynecological data, subjective and objective sleep measurements, and psychological evaluations of mood changes, stressful life events and personality traits using semi-structured interviews and validated rating scales. In particular, depressive symptoms were assessed every three months during an observation period of 18 months, from study inclusion up to 1 year postpartum, with a higher sampling rate (every two weeks) during the first two months after delivery. PND was diagnosed using the EPDS, accompanied by other tools administered by staff mental health professionals (Table 6).

As regards the sleep evaluation, this consisted of an entry interview with a sleep expert, to record lifetime and current sleep disturbances, supplemented with questionnaires assessing sleep quality, insomnia, daytime sleepiness, chronotype, sleep-related movement disorders and parasomnias (Table 6). A home-based polysomnography (PSG) was performed in all women during the second trimester of pregnancy (20^{th}-25^{th} gestational week). This included electroencephalogram (F3, C3, O1 referenced to the contralateral mastoid M2), bilateral electro-oculogram, surface electromyogram of submentalis muscles and bilateral tibialis anterior muscles, electrocardiogram and sleep respiratory parameters (nasal air flow, thoracic and abdominal respiratory effort, oxygen saturation). Sleep was scored by a sleep specialist according to the international guidelines[220]. Rest-activity cycles during pregnancy and postpartum were assessed by 7-days actigraphic recordings repeated for 3 times: between the

20th-25th gestational week, around the 3rd trimester (90-105 days) and between the 11th-12th month after delivery.

Pregnant women who accepted to participate in the observational Life-ON main study, were also asked to take part additionally and voluntarily in the Life-ON 1 substudy (genetic investigation). The substudy Life-ON 2 was proposed to women who develop PND during pregnancy or within 9 months after delivery. Finally, a group of non-depressed pregnant women was asked to participate in the Life-ON 3 substudy, consisting of a preventive trial with BLT for PND. A dedicated written informed consent was signed by every woman for each substudy. Participants had the possibility to withdraw their consent at any time (Figure 4).

Inclusion criteria	Exclusion criteria
• Age 18-50 years • Medically healthy • Normal ocular function • Gestational age between 10-15 weeks at time of screening • Written informed consent	• Diagnosis of bipolar I or II disorder (DSM-5) • Recent history (previous 6 months) of or current major depression or EPDS > 12 at time of inclusion • Any psychotic episode, substance abuse, recent history of suicide attempt (previous 12 months) • Use of antidepressants or other pharmacologic treatments for depression in the previous 6 months • Fetal malformations and intrauterine fetal death

Table 5: Inclusion and exclusion criteria of the Life-ON main study[219]. EPDS: Edinburgh Postnatal Depression

Figure 3: Experimental light conditions in the Life-ON 2 substudy.
Left: bright light (10'000 Lux). Right: red dim light (19 lux).

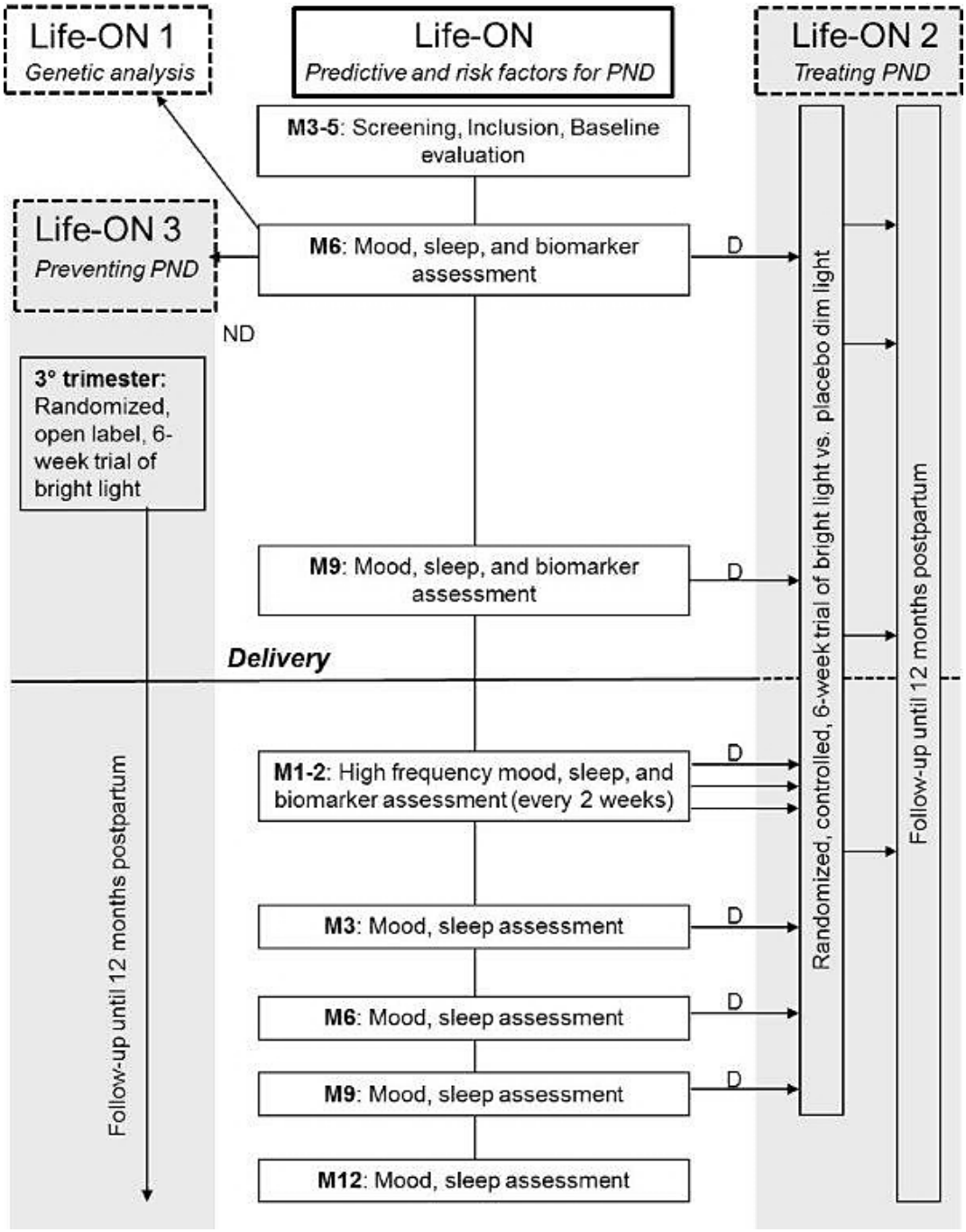

Figure 4: Flowchart of the study protocol[219]. D: depression. M: month. ND: no depression. PND: perinatal depression. PPD: postpartum depression

Life-ON											
	PREPARTUM			***POSTPARTUM***							
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
	10-15W	23-25W	34-36W	1W (5-12gg)	3W (19-26gg)	5W (33-40 gg)	7W (47-54gg)	3M (90-105gg)	6M (180-195gg)	9M (270-285gg)	11-12M
Demographic assessment	x										
Gynecologic evaluation	x			x		x		x	x		x
Psychiatric evaluation											
• MINI Plus	x										
• MINI			x			x			x		x
• EPDS + VAS	x	x	x	x	x	x	x	x	x	x	x
• HDRS-21	x		x			x			x		x
• MADRS	x		x			x			x		x
• TCI	x										
• SLE	x										
Sleep evaluation											
• PSQI	x	x	x		x			x	x		x
• ISI	x	x	x		x		x	x	x	x	x
• ESS	x	x	x		x			x	x	x	x
• RLS criteria + severity scale	x	x	x	x		x		x	x	x	x
• Parasomnia scale	x	x	x					x			x
• MEQ	x										
• Actigraphy		x						x			x
• PSG		x									
Blood tests (haemochrome, progesterone, estrogens, prolactin, cortisol, CRH, ACTH, TSH, oxytocin, ferritin, vitamin B12, folic acid, creatinine, transaminase)	x	x	x			x					

Table 6: Schedule of assessments. MINI: MINI International Neuropsychiatric Interview; MINI Plus: MINI International Neuropsychiatric Interview Plus; EPDS: Edinburgh Postnatal Depression Scale; VAS: Visual Analog Scale; HDRS-21: Hamilton Depression Rating Scale – 21 items (during trial also on days 0 – 21 – 42 of treatment); MADRS: Montgomery-Asberg Depression Rating Scale (during trial also on days 0 – 21 – 42 of treatment); TCI: Temperament and Character Inventory; IRLE: Interview for Recent Life Events; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; ESS: Epworth Sleepiness Scale; RLS: Restless Legs Syndrome; MEQ: Morningness-Eveningness Questionnaire; PSG: Polysomnography; SAFTEE: Systematic Assessment of Treatment Emergent Effects (during trial after 3 and 7 weeks of treatment).

Experimental substudies

Substudy Life-ON 1

The Life-ON 1 substudy consisted of a genetic analysis based on a single blood sample taken during the 20th-25th gestational week, with the aim to identify possible specific genetic polymorphisms, that may be associated with PND. Part of the biological samples collected were processed and stored in a biobank for future research.

Substudy Life-ON 2

The Life-ON 2 substudy was designed as an interventional trial investigating the effectiveness of BLT in treating PND. Women who were likely affected by PND based on a EPDS score > 12 at any time point from the study inclusion to 9 months postpartum, were invited to enter a single-blind RCT. They were divided into blocks of 10 and then randomly assigned to either 6 weeks of morning BLT or dim red light (DRL). Participants were asked to maintain their habitual bedtime and wake-up schedules, and to begin the light treatment within 20 min of habitual wake-up time. They were instructed to sit in front of the light box (Philips EnergyUp HF 3419) at a specified distance (around 30 cm) and to be exposed to an active light source (10'000 lux) or DRL (19 lux) for ½ hour (Figure 3). Safety was monitored using the self-report version of the Systematic Assessment of Treatment Emergent Effects (SAFTEE). Similar to the Life-ON main study, all participants were followed up for up to 12 months after delivery.

Substudy Life-ON 3

The Life-ON 3 substudy was an open-label interventional trial, in non-depressed pregnant women, aimed at testing the efficacy of BLT for preventing PND. A subsample of ca. 80 women with an EPDS score ≤ 12 at the second trimester of pregnancy was consecutively recruited to receive 6-week BLT with an identical protocol to the Life-ON 2 substudy. However, no placebo control group was created. Safety was monitored using the SAFTEE questionnaire. All participants were followed-up until 12 months postpartum. The main outcomes in this substudy were the incidence of PPD in women receiving BLT during pregnancy, compared to women with no treatment.

Adverse events assessment

Adverse Reactions (ADRs) and Serious Adverse Event (SAE) were monitored and recorded only for the substudies involving treatment with BLT.

Manuscript 1

Polysomnographic features of pregnancy: a systematic review

Corrado Garbazza [a, b, c, *], Sandra Hackethal [a], Silvia Riccardi [a], Christian Cajochen [b, c], Alessandro Cicolin [d], Armando D'Agostino [e], Fabio Cirignotta [f], Mauro Manconi [a]

[a] Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital of Lugano (EOC), Via Tesserete 46, Lugano, CH-6903, Switzerland

[b] Centre for Chronobiology, University of Basel, Basel, Switzerland

[c] Transfaculty Research Platform Molecular and Cognitive Neurosciences, University of Basel, Basel, Switzerland

[d] Sleep Medicine Center, Neuroscience Department, AOU Citta della Salute e della Scienza - Molinette, Università di Torino, Torino, Italy

[e] Department of Health Sciences, Università degli Studi di Milano, Milan, Italy

[f] DIBINEM, University of Bologna, Bologna, Italy

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Summary

Symptoms of sleep disturbances are common among pregnant women and generally worsen across gestation. Pregnancy-related sleep disorders are not only associated with a poor quality of life of the affected mothers, but also with adverse perinatal outcomes, including perinatal depression, gestational diabetes, preeclampsia, and preterm birth. The current knowledge about the impact of sleep disorders during pregnancy largely derives from the results of sleep surveys conducted in various populations. However, the number of studies examining changes in objective sleep variables during pregnancy via polysomnography has progressively increased in recent years.

Here we systematically reviewed the polysomnographic studies available in the literature with the aim to describe the sleep pattern and to identify possible markers of sleep disruption in pregnant women.

Based on our analysis, subjective worsening of sleep quality across gestation is related to objective changes in sleep macrostructure, which become particularly evident in the third trimester. Pregnancy per se does not represent an independent risk factor for developing major polysomnography-assessed sleep disorders in otherwise healthy women. However, in women presenting predisposing factors, such as obesity or hypertension, physiological changes occurring during pregnancy may contribute to the onset of pathological conditions, especially sleep-disordered breathing, which must be carefully considered.

Introduction

Pregnancy is a physiological condition of relatively short duration in a woman's life, but characterized by profound biological changes, which have a significant influence on sleep [1]. The typically increased secretion of several hormones across pregnancy considerably impacts on both the circadian and homeostatic components of sleep regulation, leading to modifications of sleep architecture [2]. In human studies, non-rapid eye movement sleep (NREM) has been shown to be enhanced by progesterone and prolactin [3,4], while rapid eye movement sleep (REM) is decreased by progesterone and increased by estrogens [5,6]. Oxytocin peaks during the night, promoting uterine contractions leading to sleep fragmentation [2]. Cortisol and growth hormone levels are also elevated, affecting sleep quality and inducing daytime sleepiness [2].

Besides hormones, other factors contribute to sleep disruption during pregnancy: gastroesophageal reflux, affecting up to 75% of pregnant women [7]; nocturnal micturition, due to an increase in overnight

sodium excretion [8]; anatomical changes related to the growing uterus and increased body weight [9]. Moreover, iron and folate deficiency may play a role in the occurrence of sleep-related movement disorders in pregnant women [10,11].

Subjectively reported sleep disturbances are very common during pregnancy, with increasing rates from the first (13%), to the second (19%), and third (66%) trimester of gestation [12,13]. A recent meta-analysis showed that 46% of women experience poor sleep quality during pregnancy, with an average score of the Pittsburgh Sleep Quality Index (PSQI) of 6.4 (95% CI, 5.3 - 6.85) and with a worsening trend from the 2nd to the 3rd trimester by an average of 1.68 points (95% CI, 0.42 - 2.94) [14]. While at early gestational age women mainly attribute sleep problems to nausea/vomiting, urinary frequency, and backpain [15], in late gestation up to 69.9% of women report difficulty in maintaining sleep, 34.8% early morning awakenings, and 23.7% difficulty falling asleep [16], mainly due to fetal movements, heartburn, cramps or tingling in the legs, and shortness of breath [13,17 - 19]. By the end of pregnancy almost all women suffer from recurrent and long wake episodes during the night [17,20].

Self-reported sleep duration also declines across pregnancy [21]. Moreover, objectively assessed sleep duration and quality are related to age and ethnicity, with non-Hispanic black and Asian women having the shortest sleep duration, and younger pregnant women having the highest amount of wake after sleep onset (WASO), the lowest sleep efficiency (SE), and the latest sleep midpoint [22].

To date, the available literature on sleep during pregnancy is mostly based on subjective information from screening questionnaires or interviews [14,19]. However, in recent years, an increasing number of studies investigated sleep in pregnant women objectively, by using polysomnography (PSG) or actigraphy. Sleep parameters derived from actigraphy may significantly differ from those obtained by PSG recordings and should therefore be interpreted with caution [23]. Thus, PSG remains the gold standard for sleep depiction, being the only reliable tool to precisely describe sleep macro- and microstructure, correctly estimate respiratory and motor events, and permit an accurate identification of pregnancy-related sleep disorders.

We here present the first systematic review of polysomnographic studies conducted in pregnant women, with the aim to provide a detailed overview about the intrinsic, objective features of sleep in normal, healthy pregnancy, as well as in some typical pregnancy-related complications.

Methods

We performed a systematic review of the literature by searching for studies reporting objective sleep parameters obtained by PSG in pregnant women until February 1, 2019. The review process followed the PRISMA statement guidelines [24].

Search strategy

The terms 'pregnancy' OR 'gestation' AND 'polysomnography' OR 'PSG' were searched in the databases Medline, Scopus and Embase. The search terms had to be included in the Title, Abstract or Keyword section of the articles. The first author reviewed the automatically generated list of items and classified every manuscript, based on its abstract, as "eligible", "not eligible" and "maybe eligible", according to the selection criteria described below. Articles considered "not eligible" were excluded from a further analysis. Afterward, the first and second authors independently examined the "eligible" and "maybe eligible" full-text articles in a blinded fashion, to determine whether they met the criteria to be included in the review. The inter-rater agreement calculated as Cohen's kappa coefficient (k) was 0.92. In case of disagreement, they consulted the senior author (MM) for a final decision.

Selection criteria

The following criteria were applied:

1) Sleep assessment: only studies reporting PSG data recorded during pregnancy and using a minimal montage of at least one EEG channel either in mono- or bipolar, electrooculogram (EOG), chin electromyogram (EMG) were included. Studies based on other objective sleep assessment methods than PSG (e.g., actigraphy or polygraphy) or using subjective tools (e.g., questionnaires) were excluded;
2) Number of nights recorded: at least one full night PSG recording
3) Sample size: only studies with a sample size of ≥10 women
4) Language: English;
5) Type of study: original studies on human subjects; no single case reports, reviews, commentaries/letters, editorial, conference abstracts;
6) Control group: studies including either a control group (healthy pregnant or non-pregnant women) or without a control group were included.

Additionally, the authors went through the reference lists of the selected articles to identify further studies. Unpublished manuscripts were not included.

Quality assessment

The quality assessment of the studies included in the systematic review was performed using the Newcastle-Ottawa scale (NOS) adapted for cross-sectional studies (according to Herzog et al. [25]), cohort studies, and case-control studies (available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The NOS consists of several items included in three domains (selection of the study groups, comparability of the groups, and outcome/exposure assessment). Each item is evaluated based on a 'star system'. Trials included in our review were

evaluated using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [26] and the Cochrane Collaboration's risk of bias in non-randomized studies (ROBINS-I) [27].

Statistical analysis

Mean and standard deviation of longitudinal studies reporting total sleep time (TST) and SE were pooled in order to evaluate changes in these sleep variables from the first to the third trimester of gestation. Weighted mean difference (WMD) with 95% confidence interval (95% CI) was used to estimate absolute differences of continuous outcomes. I^2-statistics was adopted to measure the percentage of variance attributable to study heterogeneity (I^2>50%). The Egger's weighted regression test was used to detect publication bias. Statistical analysis was performed using StatsDirect software version 3.0 (Cambridge, UK).

Results

Literature search

A detailed flowchart of the results of the literature search process is presented in Fig. 1. Finally, 40 studies were considered for the qualitative analysis (systematic review). Twenty-four of them were cross-sectional studies (n = 24), ten prospective cohort studies (n = 10), five clinical trials (n = 5), and one case-control study (n = 1). Out of 40 studies, n = 27 included a control group, while n = 13 were not controlled. Regarding the country of origin, most studies were performed in the USA (n = 20), followed by Australia (n = 9) and Canada (n = 4). Sample sizes examined ranged between 10 and 234 women. Main findings of the reviewed studies are highlighted in Table 1.

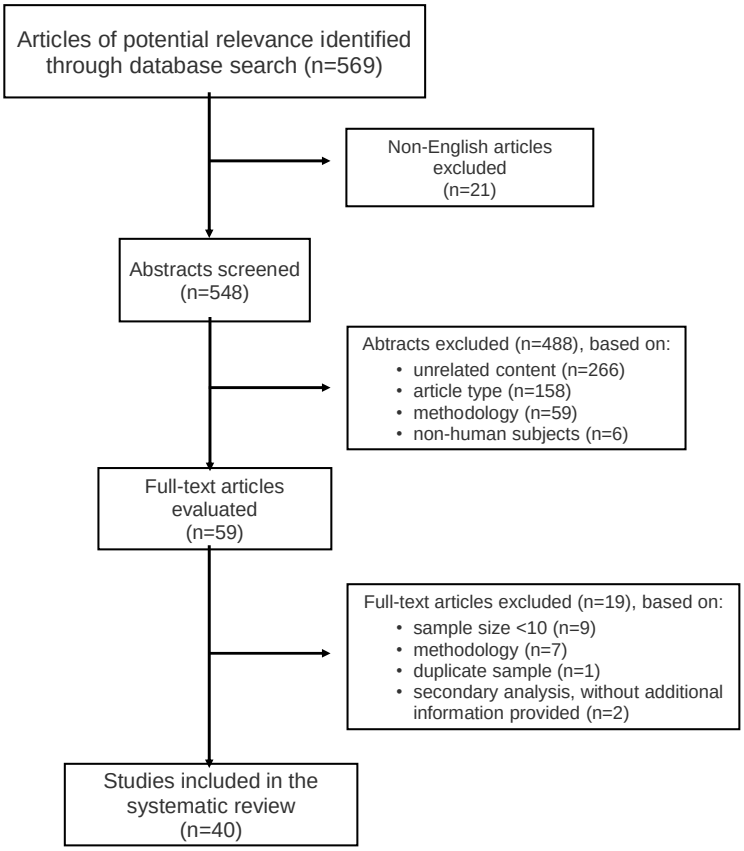

Fig.1: Flowchart of study selection according to systematic review process

Authors	Year	Type of patients evaluated	GA (in weeks)	Change in sleep variables in cases in respect to controls/control conditions									
				TST	SE	AI	SL	REM	SWS	RDI	AHI	ODI	OSA%
Healthy pregnancy													
Izci-Balserak et al. [34]	*2018*	Healthy pregnant women in the first (controls) compared to the third trimester (cases).	12.05 ± 1.80 (controls) 33.61 ± 2.56 (cases)	↓	↓	↔	↔	↓	↓		↑		↑
El-Helbawy et al. [39]	*2017*	Healthy pregnant women (cases) and healthy non-pregnant women (controls).	23.03 ± 8.88 (cases)								↑	↑	
Rimpilä et al. [29]	*2017*	Healthy pregnant women (cases) and healthy non-pregnant women (controls).	33 ± 1	↓	↓		↔	↓	↓		↔	↔	
Wilson et al. [30]	*2011*	Pregnant women in the first and third trimester of pregnancy (cases) and healthy non-pregnant controls (controls).	Controls and first trimester (9–14) vs. third trimester (30–38)		↔	↑	↔	↔	↔				↑
			Controls vs. third trimester (30–38)		↓		↔	↓	↓				↑
Trakada et al. [43]	*2003*	Healthy pregnant women pre- (cases) and postpartum (controls).	36 (cases) 4–6 mo PP (controls)	↔	↔	↔		↔	↔				
Lee et al. [32]	*2000*	Healthy women pre-, during and after pregnancy.	Pre-pregnancy (controls) 11-12 (cases)	↑	↓		↔	↔	↓				
			35-36 (cases) 3–4 wk PP (controls)	↑	↑		↔	↔	↓				
Hertz et al. [28]	*1992*	Healthy pregnant women (cases) and non-pregnant healthy women (controls).	30–38	↔	↓		↔	↓	↔				
Hypertensive disorders of pregnancy													
Suri et al. [59]	*2018*	Pregnant women with PE and/or GH (cases) and healthy pregnant women (controls).	34.9 ± 1.7 (cases) 35.7 ± 2.0 (controls)			↑					↑		↑
Wilson et al. [56]	*2018*	Pregnant women with GH/PE (cases) and healthy pregnant women (BMI and GA match, controls).	33.5 ± 3.4 (cases) 33.1 ± 2.4 (controls)	↔	↔	↔	↔	↓	↔	↔	↔	↔	↑
Reid et al. [55]	*2016*	Pregnant women with GH (cases) and healthy pregnant women (controls).	34.2 ± 3.3 (cases) 34.5 ± 3.2 (controls)	↓	↔	↔		↓		↑	↔		
O'Brien et al. [52]	*2014*	Pregnant women with CHTN, GHT and PE (cases) and healthy pregnant women (controls).	24.6 ± 8.1 (cases, cHT) 33.0 ± 2.9 (cases, GHT) 30.1 ± 4.2 (cases, PE) 33.8 ± 3.8 (controls)	↔							↔		↑
Blyton et al. [69]	*2013*	Pregnant women with PE (cases) and healthy pregnant women (controls).	33.3 ± 3.5 (cases) 33.9 ± 2.0 (controls)	↔		↔		↔	↑		↑	↔	
Reid et al. [53]	*2011*	Pregnant women with GH (cases) and healthy pregnant women (age and GA match, controls).	34.7 ± 3.2 (cases) 34.7 ± 2.6 (controls)	↓	↓	↔		↓	↔	↑	↑	↔	↑
Blyton et al. [68]	*2004*	Pregnant women with PE (cases), 50% with CPAP, and healthy pregnant women (controls).	33 ± 4 (cases) 34 ± 2 (controls)	↔				↓		↔			
Edwards et al. [54]	*2001*	Pregnant women with OSAS and PE (cases) and normotensive pregnant women with OSA (controls).	34 ± 1 (cases) 32 ± 2 (controls)	↔		↔		↔		↔			
Edwards et al. [57]	*2000*	Pregnant women with PE (cases) and normotensive healthy pregnant women (controls).	33 ± 1 (cases) 34 ± 1 (controls)	↔	↔	↔	↔	↓	↑	↔			
Gestational diabetes mellitus													
Bisson et al. [61]	*2014*	Pregnant women with newly diagnosed GDM and BMI ≤ 35 (cases) and healthy pregnant women matched for GA, BMI and age (controls).	31.6 ± 1.4 (cases) 32.3 ± 1.0 (controls)	↔	↔	↔	↔	↔	↔		↔	↔	↔
Izci Balserak et al. [62]	*2013*	Healthy pregnant women stratified for the presence (cases) and absence (controls) of GDM, PSG in first trimester and third trimester.	12 ± 2.1 3rd trimester	↔ ↔		↔ ↔					↔ ↔		
Reutrakul et al. [60]	*2013*	Pregnant women with GDM (cases), healthy pregnant women (controls).	33.3 ± 3.5 (cases) 33.9 ± 2.0 (controls)	↓		↔		↔	↔		↔	↔	
		Healthy pregnant women (cases) and healthy non-pregnant women (controls).	33.9 ± 2.0 (cases)	↔		↑		↓	↔		↑	↔	
Clinically suspected OSAS or risk factors for OSAS													
Bourjeily et al. [40]	*2014*	Pregnant women with suspected OSAS (cases) and healthy non-pregnant women matched for age, BMI and AHI (controls).	26.6 ± 7.6 (cases)	↓	↔	↔	↔	↔	↓	↔	↔		
Edwards et al. [44]	*2005*	Pregnant women with suspected OSAS (cases) and postpartum (controls).	33 ± 2 (cases) 4 ± 2 mo PP (controls)	↔	↑		↑	↓	↑		↑		
Maasilta et al. [42]	*2001*	Obese pregnant women (cases) and normal-weight healthy pregnant women (controls).	≥12 ≥30	↔ ↔	↔ ↔	↑ ↑	↔ ↔	↔ ↔	↔ ↔	↑ ↑	↑ ↑	↑ ↑	
Guilleminault et al. [38]	*2000*	Pregnant women with chronic snoring and/or SaO2 drop ≥ 5% in a screening examination (cases), and healthy pregnant women matched for age and BMI (controls).	24	↔					↑		↔		
Restless legs syndrome													
Dzaja et al. [45]	*2009*	Pregnant women with RLS (cases) and healthy pregnant women (controls).	35.9 ± 1.9 (cases and controls)	↔			↔	↔	↔				

AHI — apnea/hypopnea index, AI — arousal index, BMI — body mass index, CHTN — chronic hypertension, CPAP — continuous positive airway pressure, GA — gestational age, GHTN — gestational hypertension, GDM — gestational diabetes mellitus, ODI — oxygen desaturation index, OSA — obstructive sleep apnea, PE — pre-eclampsia, RDI — respiratory disturbance index, REM — rapid-eye-movement sleep, RLS — restless legs syndrome, TST — total sleep time, SE — sleep efficiency, SL — sleep latency, SWS — slow-wave sleep, PP-post partum, mo- months, wk- weeks.

Table 1: Changes in sleep variables in pregnancy and pregnancy-related complications

Polysomnographic findings

Sleep structure

Subjective perception of poor sleep quality reported by women across gestation is related to objective changes in sleep structure. We found three cross-sectional studies investigating the differences in sleep parameters of pregnant women vs. non-pregnant controls.

Hertz et al. reported a significantly decrease in SE, due to a substantial increase in WASO and number of awakenings in 12 women during late pregnancy compared to 10 age-matched non- pregnant controls [28]. NREM sleep stage S1 was also increased in the pregnant group with, in turn, a decrease of both

REM sleep and SWS. Rimpilä et al. obtained similar results studying 18 healthy pregnant in the third trimester, compared to 12 non-pregnant controls [29].

In a larger PSG investigation (27 women in the first trimester of gestation, 21 in the third trimester, and in 24 healthy non-pregnant controls), Wilson et al. [30] confirmed women during the third trimester having poorer SE, more awakenings, less stage 4 sleep, more stage 1 sleep and fewer minutes spent in REM sleep compared to control group. Interestingly, higher progesterone levels within third-trimester women were associated with an increase in WASO and arousals. Three studies assessed changes in sleep parameters in the same individuals across the perinatal period in a longitudinal setting. Coble et al. [31] performed PSG at three time points during pregnancy and two during the postpartum, comparing pregnant women with (n = 13, in remission) vs. without (n = 20) a history of affective disorders. They found that women with a previous depression have a longer TIB and TST in early pregnancy, an earlier onset and more pronounced sleep disruption, as well as a reduced REM-latency in late pregnancy, compared to control women.

Lee et al. [32] examined women during the follicular phase (n = 33), the first (n = 33) and third trimester of pregnancy (n = 29), as well as postpartum (n = 29). Changes were already evident in the first trimester, with an increase of TST, decrease of SE and a marked reduction of SWS during pregnancy, compared to pre-pregnancy baseline. No variation in REM sleep was noted. These changes remained relatively stable in the course of pregnancy and improved after delivery.

In a secondary analysis of their 2013 dataset [33], Izci-Balserak et al. [34] evaluated changes in sleep architecture and spectral EEG bands during pregnancy in 123 women who underwent PSG in early pregnancy and in 97 of them also in late pregnancy. They found a shorter sleep duration, poorer SE, more awakenings, more stage N2 sleep, less SWS and REM sleep in late compared to early pregnancy, thus partially replicating the results from one of the first longitudinal studies on PSG-assessed sleep across pregnancy [35].

In summary, changes in sleep structure during pregnancy seem to mainly affect the third trimester of gestation, which is generally characterized by a shorter sleep duration and a more disrupted sleep, with an increased number of awakenings and superficial sleep stages, as well as a reduction of SWS and REM sleep. These findings are more evident when comparing pregnant women with non-pregnant controls, but they have also been recently confirmed in the same individuals recorded at early and late GA [34].

Breathing pattern

Sleep-disordered breathing (SDB) is estimated to affect 10 - 32% of pregnant women, depending on its definition [36]. Obstructive sleep apnea (OSA), in particular, is estimated to be a frequent condition during pregnancy, with a pooled worldwide prevalence of 15% (95% CI 12 - 18%), and it has been

associated with gestational hypertension, gestational diabetes, pre-eclampsia, C-section, postoperative wound complication, and pulmonary edema [37]. Moreover, OSA is related to an increased risk for preterm birth (aOR = 1.62) and neonatal intensive care unit admission (aOR = 1.28) [37]. Based on these findings, the analysis of respiratory parameters in pregnant women has become the main target of sleep research studies.

Guilleminaut et al. [38] screened 267 healthy pregnant women with a normal BMI (23.7 ± 0.8 kg/m2 at study entry) regarding the presence of daytime sleepiness and snoring. A selected subgroup based on stratified questionnaire results (n = 26) underwent overnight PSG. None of the subjects showed an apnea-hypopnea index (AHI) > 5/h but chronic snorers presented breathing abnormalities such as esophageal pressure crescendos in S1 and S2 and abnormal sustained effort during SWS, which were associated with higher systolic and diastolic blood pressure increases, as well as a non-dipper profile in the 24-hour blood pressure (24 h-BP) recordings (six out of 13 snorers).

Small cross-sectional studies in pregnant women compared to non-pregnant controls also reported slightly decreased mean and minimum oxygen saturation (SaO2) values but no differences in AHI and/or oxigen desaturation index (ODI) or transcutaneous carbon dioxide (TcCO2) levels [28,29].

However, El-Helbawy et al. [39], examining 30 primiparous pregnant women vs. 30 age-matched non-pregnant controls found a higher mean AHI (4.38/h ± 4.45 vs. 1.77/h ± 1.2), ODI (3.72/h ± 4.03 vs. 2.27/h ± 1.11), and snoring index (8.19/h ± 6.87 vs. 1.08/h ± 1.75) in the pregnant group. Among pregnant women, 36.7% had a mild OSA and 53.3% were snorers. Patients with OSA had a significantly higher GA, BMI, a larger neck circumference, a higher ODI, flow limitation index, snoring index, and Epworth sleepiness scale (ESS) score compared to healthy subjects. GA and BMI, in particular, emerged as independent risk factors for OSA during pregnancy, with odds ratio of 2.23 and 4.99 respectively.

Izci-Balserak et al. [34], by applying a longitudinal design, found a statistically significant increase in AHI (2.09/h ± 3.17 vs. 3.41/h ± 4.60, $p < 0.002$) and OSA cases [AHI>5 events/h; n = 14 (11.38%) vs. n = 26 (26.80%), $p < 0.004$] during late compared to early pregnancy.

An elevated BMI has been often associated with a higher risk for developing SDB during gestation. To assess pregnancy as an independent risk factor for SDB, Bourjeily et al. performed a third trimester PSG in obese pregnant women (BMI 44.1 ± 6.9) compared to BMI- and age-matched non-pregnant controls [40,41]. AHI and oxygen desaturation showed no differences between groups, with 8/25 within the case group qualifying as OSA (AHI > 5/h). However, pregnant women had significantly more flow limitations during TST and in each sleep stage compared to controls.

Maasilta et al. [42], compared obese with normal weight women, during early and late pregnancy. They found no difference in sleep structure, but an increase in AHI (1.7/h vs. 0.2/h; $p < 0.05$), RDI (7.4/h vs.

0.8/h; $p < 0.001$), ODI (5.3/h vs. 0.3/h $p < 0.005$) and snoring time (32% vs. 1%, $p < 0.001$), as well as a worsening in sleep- related breathing parameters in the obese group.

Pien et al. [33] studied 105 women (mean BMI 33.4 ± 6.4) during the first and third trimester of pregnancy. The mean AHI increased across gestation from 2.07 events/h to 3.74 events/h. BMI and maternal age at the beginning of pregnancy positively correlated with the occurrence of OSA in late pregnancy. Moreover, in a secondary analysis of the same cohort [34], including 123 women recorded in early and 97 also in late pregnancy, the authors reported a higher AHI (3.41/h ± 4.6 vs. 2.09/h ± 3.17) and a higher periodic leg movements during sleep index (PLMSI) index (5.62/ h ± 12.65 vs. 2.47/h ± 6.23) in late compared to early pregnancy. Also in this cohort, the increase in AHI was conceivably related to the increase in BMI, with values of 30.56 ± 7.22 kg/m2 in early vs. 33.3 ± 6.25 kg/m2 in late pregnancy ($p < 0.001$).

Trakada et al. [43] studied 11 healthy pregnant women at 36 wk of gestation and again at 4 - 6 mo postpartum with measurement of Partial pressure of oxygen (PaO2) every two hours. The AHI was significantly lower during late pregnancy compared to postpartum (5.81/h ± 2.1 vs. 12.1/h ± 2.7, $p < 0.05$) with a longer mean duration of apneas/hypopneas in the postpartum period. The overall mean SaO2 (%) did not differ between the two time-points, but the mean PaO2 (%) in supine position was significantly lower in the antenatal period compared to the one in postnatal period (90.1 ± 0.6 vs. 99.2 ± 0.4, $p < 0.001$). Edwards et al. [43] investigated 10 pregnant women (BMI 30 ± 3 kg/m2) with OSA diagnosed in the third trimester with a second PSG 4 mo after delivery (BMI 27 ± 3 kg/m2). Women were treated with CPAP until delivery. The postnatal recordings showed consistent improvement of both AHI (63/h ± 15 vs.18/h ± 4, $p = 0.03$) and minimum SaO2 (86% ± 2% vs. 91% ± 1%, $p = 0.01$) with reduced severity of blood pressure responses to apneas (170 - 180 mmHg vs. 130e140 mmHg), contrasting results of previous studies [43]. No significant relationship between changes in either weight or BMI from the antenatal to the postnatal sleep studies and changes in AHI were found.

Periodic limb movements during sleep (PLMS)

Few studies reported data on PLMS [28-30,34]. Most of them found no [28-30] or only a clinically non-significant increase [34] of the PLMS-Index measured across normal gestation or compared to non-pregnant controls.

Dzaja et al. [45] studied 10 pregnant women with RLS and 9 without RLS around the 36th wk of gestation and 12 wk post-partum. Women with RLS showed more PLMS before ($F_{1,13} = 6.11$, $p < 0.05$) and after delivery ($F_{1,13} = 3.21$, $p < 0.1$) than controls. In particular, during pregnancy, PLMS were significantly more frequent in the RLS group in wake ($F_{1,13} = 7.19$, $p < 0.05$), S1 ($F_{1,13} = 11.72$, $p = 0.005$), and S2 ($F_{1,13} = 4.87$, $p < 0.05$) sleep stage. Interestingly, subjects affected by RLS also had higher blood estradiol levels

during pregnancy compared to controls. However, there was no correlation between PLMS index and RLS severity within the RLS group. Overall, PLM activity showed a negative correlation with estradiol levels in RLS patients ($r = -0.66$, $p < 0.05$), but not in the control group ($r = 0.03$, ns).

Subjective and other objective sleep assessment vs. polysomnography

Zhu et al. [23] analyzed the agreement between actigraphy and PSG in estimating basic key sleep parameters (TST, SE, WASO and sleep onset latency (SOL)) of 38 healthy pregnant women during the third trimester. The best correspondence to PSG-derived parameters was obtained by using the 10 immobile/mobile minutes for sleep onset/end with an activity threshold of 10 (10-by-10), while the default scoring setting (10-by-40) provided significantly different results from the PSG ($p < 0.01$).

By examining possible discrepancies between subjectively reported and objective PSG parameters in 33 women in the third trimester of gestation, 16 in the first trimester, and 15 non-pregnant women, Wilson et al. [46] found that the first group slightly over- estimated TST, whereas the second and third groups tended to underestimate TST. Sleep latency was overestimated by all groups and corresponded closest to the first epoch of 10 min uninterrupted sleep or first epoch of SWS.

The same group later screened 380 pregnant women during the second trimester by means of the Berlin Questionnaire (BQ) and the Multivariable Apnea Risk Index (MAP-Index) [47]. Forty-three participants repeated the questionnaires and additionally underwent PSG at 37 wk of gestation, which in 15 cases (35%) showed an RDI>5/h. Overall, both the BQ and the MAP-index had low to moderate predictive value and were judged inadequate as screening instruments for SDB in pregnancy.

In a recent secondary analysis of their previous longitudinal study [33], Balserak et al. [48] tested the predictive value for OSA of the Sleep Apnea Symptom Score (SASS) vs. a combined model incorporating questionnaire data with clinical measures, in 94 women not meeting the diagnostic criteria for OSA according to PSG in the first trimester of gestation. In the third trimester, 17 women (15.98%) had incident OSA (AHI>5 events/h). The mean SASS administered in the first trimester showed acceptable validity and reliability to predict OSA. However, when adding maternal age, BMI, and bedpartner-reported information, the combined model performed better than the SASS alone in predicting OSA.

Finally, Sharkey et al. [49] and O'Brien et al. [50] tested the validity of two portable devices, compared to PSG, for the assessment of SDB during pregnancy. Both the Apnea Risk Evaluation System (ARES) [49] and the Watch-PAT-200 wrist-worn screening device [50] showed good sensitivity and specificity in the identifi- cation of SDB among pregnant women.

Polysomnographic findings in pregnancy-related complications

It is estimated that about 5% of all pregnancies are affected by the occurrence of gestational complications, ranging from minor diseases to potentially life-threatening conditions for both mother and fetus [51].

Sleep disorders during pregnancy may play a role in inducing or exacerbating gestational complications, but these, in turn, may also deteriorate sleep. Few PSG studies addressed the topic of sleep in women affected by typical pregnancy-related complications, such as gestational hypertension (GHTN), preeclampsia (PE), and gestational diabetes (GDM), with the aim to shed more light on the bidirectional relationship between sleep and health problems occurring during pregnancy.

Hypertensive disease of pregnancy (HDP)

Three studies examined sleep in HDP. O'Brien et al. [52] studied 51 pregnant hypertensive women, of which 59% with chronic hypertension (CHTN), 23% GHTN and 18% PE, compared to 16 pregnant healthy women. Subjects belonging to the hypertensive group had a mean BMI>30 kg/m^2 vs. 28.1 ± 4.7 of the control subjects. Snoring was significantly more reported by hypertensive women (n = 31; 61%) compared to controls (n = 3; 19%). Snoring hypertensive women had a significantly higher AHI (19.9/h ± 34.1 vs. 3.4/h ± 3.1, p = 0.013), a significantly lower SpO2% nadir (86.4% ± 6.6 vs. 90.2% ± 3.5, p = 0.021) and were significantly more likely to have undiagnosed OSA (AHI>5; 53% vs. 24%, p = 0.03), than non-snoring hypertensive women. Thus, the authors pointed out that pregnant women presenting with a combination of hypertension and snoring are at risk of developing OSA with clinically significant oxyhemoglobin desaturation.

Reid et al. [53] investigated 34 obese pregnant women with GHTN, compared to 26 healthy pregnant women. Sleep-disordered breathing (SDB) was significantly more frequent in the cases compared to the controls (53% and 12% respectively, p < 0.001). Nocturnal blood-pressure monitoring showed no group specific differences in hemodynamic response to respiratory events including flow limitations, contrasting the results from another recent study by Edwards et al. [54]. However, in both groups, upper airway obstructive events of any severity were associated with a substantial transient blood pressure response, as shown by a later secondary analysis of the dataset [55].

Wilson et al. [56] compared obese women with HDP with normotensive pregnant controls matched for BMI, age and gestational age. SDB was found to be more common (52.5% vs. 37.5%) and more severe (35% vs. 15% of subjects with RDI>10/h, p = 0.039) in the HDP vs. control group, although RDI did not differ (p = 0.20) between groups.

Pre-eclampsia (PE)

Four studies examined the sleep pattern of women with PE. Edwards et al. [57] performed third trimester PSG in 25 women suffering from PE and 17 healthy pregnant control subjects. Pre- eclamptic patients showed an increase in SWS (43 ± 3% vs. 21 ± 2%, $p < 0.001$), a longer REM sleep latency (205 ± 23 vs. 92 ± 11 min, $p < 0.001$) and a reduced REM-sleep percentage (10 ± 2% vs. 18 ± 1%, $p < 0.001$). REM-related sleep changes were possibly due to clonidine medication in the patient group.

In a later study, the same authors performed PSG in pregnant women in the third trimester suffering from OSA (n = 10) or both OSA and PE (n = 10) [54]. Blood-pressure responses to obstructive respiratory events during sleep were significantly increased in patients affected by both conditions, compared to normotensive OSA patients. No significant difference between groups in heart rate response was found, but, as compared to control OSA patients, heart rate did not show any modification during sleep and wakefulness in PE patients, suggesting a possible alteration in the normal pattern of reduced sympathetic tone during NREM sleep in this group.

Guilleminaut et al. [58] performed PSG in 12 women with risk factors for PE (hypertension, obesity and prior PE). None of them had oxygen desaturations >3% but all participants showed significant SDB (mean RDI 8.5/h ± 2.6). All women received nasal CPAP treatment for the remainder of pregnancy, which was effective in alleviating SDB symptoms and ameliorating blood pressure control in patients with pre-existing hypertension, but did not prevent negative pregnancy outcomes associated with obesity and PE.

Suri et al. [59] conducted a prospective PSG study in 40 patients with PE or GHTN aged 25.3 ± 3.9y (mean GA 34.9 ± 1.7 wk) and 60 healthy pregnant controls aged 25 ± 3.5 y (mean GA 35.7 ± 2.0 wk). Pre-pregnancy and present BMI, as well as AHI, snoring, systolic (SBP), diastolic (DBP), and mean (MBP) blood pressures were significantly higher in cases than in controls. SDB was more frequent ($p = 0.018$; OR 13.1) and more severe ($p = 0.001$; OR 1.8) in hypertensive pregnant women vs. healthy pregnant women, even after controlling for pre-pregnancy BMI. AHI was significantly associated with blood pressure, even after adjustment for BMI. Therefore, the authors concluded that not only obesity may play a role in the causation of hypertension and SDB, but also SDB may be implicated in the development of hypertension ($r = 0.612$; $p = 0.01$).

Hyperglycemia and gestational diabetes mellitus (GDM)

Three studies examined sleep in women with GDM. Reutrakul et al. [60] analyzed PSG features of healthy pregnant women, pregnant women with GDM and non-pregnant healthy controls (n = 15 individuals for each group). When comparing pregnant women with and without GDM, the first group showed a lower TST (median 397 vs. 464 min, $p < 0.02$), a higher AHI (median 8.2 vs. 2.0, $p < 0.05$) and a higher

prevalence of OSA (73% vs. 27%, $p < 0.01$). In multivariate analysis, after adjusting for pre-pregnancy BMI, the diagnosis of OSA was associated with GDM (OR 6.60). In pregnant women, a higher AI was significantly associated with higher HbA1c and fasting glucose levels, which, in turn, were positively associated with ODI.

By contrast, Bisson et al. [61], evaluating sleep characteristics of pregnant women with and without GDM, found no statistically significant differences between groups regarding sleep structure, breathing variables, and movement parameters.

In their large prospective PSG study, Izci Balserak et al. [62] examined the correlation between SDB and glucose tolerance (measured with Oral glucose tolerance test (OGTT) at enrollment) in a cohort of 104 pregnant women, recorded in the first and third trimester (83 women). No differences in sleep structure and breathing parameters were found between the hyperglycemia (Glucose challenge test (GCT)>135, n = 11) and normoglycemia (GCT<135, n = 93) groups. Although RDI and flow-limitations were not reported, symptoms of SDB (snoring 9.3% vs. 45.5%, $p < 0.01$; daytime nap duration 1.49 ± 1.3 h vs. 2.27 ± 1.4, $p = 0.07$; MAP- index 0.52 ± 0.8 vs. 1.53 ± 1.1, $p < 0.01$) rather than objective breathing parameters were associated with maternal impaired glucose tolerance.

Adverse fetal outcomes

Sahin et al. [63] performed third trimester PSG in 35 healthy pregnant women who reported frequent snoring. Among the four women, who were found to suffer from OSA (mean BMI 37.5 ± 8.4, mean AHI 13.5 ± 5.5), two also had GDM and one cardiovascular disease. Three of them showed fetal heart deceleration accompanying maternal desaturation and their neonates had lower APGAR scores, as well as birth weights compared to those from women without OSA.

More recently, Pamidi et al. [64] explored the relationship between PSG-diagnosed SDB in the third trimester of pregnancy and delivery of small for GA infants (SGA, defined as growth <10th percentile for the corresponding GA) in a prospective cohort study of 234 women. Twenty-seven (12%) women delivered a SGA infant. SDB symptoms in the third trimester were found to be not predictive of delivering an SGA infant and their overall sensitivity and specificity for predicting a PSG-based diagnosis of SDB was also poor. By contrast, a PSG-based diagnosis of SDB in the third gestational trimester was associated with a significantly increased odds of delivering an SGA baby (using a AHI cut-off of 10 events/h, OR 2.65).

In their prospective study, Fung et al. [65] investigated the effects of maternal OSA on fetal growth. Of 371 screened women, 41 patients (n = 26 high-risk and n = 15 low-risk) underwent PSG during the second trimester and subsequent fetal growth assessment in the third trimester. Fourteen women received a PSG- confirmed diagnosis of OSA (RDI>5/h). The remaining 27 subjects represented the

control group. Impaired fetal growth was observed in 43% of cases, vs. 11% of non-OSA controls (RR 2.67; 1.25 - 5.7; p = 0.04). Logistic regression analysis identified OSA (OR 6; 1.2 - 29.7, p = 0.03) and BMI (OR 2.52; 1.09 - 5.80, p = 0.03) as significant predictor of fetal growth restriction. However, when adjusting for BMI in multivariate analysis, the association did not reach statistical significance (OR 5.3; 0.93 - 30.34, p = 0.06).

Finally, Kneitel et al. [66] compared women without OSA or treated with PAP-therapy in a retrospective caseecontrol setting. There was no difference between the percentage of infants with growth restriction (SGA, <10th percentile) from women with or without OSA, although in logistic models the presence of OSA was predictive of slowing fetal growth in the third trimester.

Interventional approaches in pregnancy

CPAP during pregnancy

As for non-pregnant women, CPAP is generally considered the first-line therapy for pregnant women affected by OSA. Three studies objectively assessed the effects of CPAP on sleep during pregnancy.

Guilleminaut et al. [67] treated 12 women with OSA with nasal CPAP (mean AHI 21 events/h, mean RDI 33 events/h). Full PSG was performed at study entry, during CPAP titration, and repeated at 6 mo of GA. An additional home monitoring of cardio-respiratory

variables was conducted at 8 mo GA. From the first to the second PSG recording, a moderate worsening of PLM score and snoring was noted in three women, and CPAP pressure had to be increased in six cases. Subjective measures of sleepiness, fatigue and snoring improved significantly compared to study entry and CPAP showed overall a good compliance and safety.

Blyton et al. [68] studied the effect of CPAP treatment on blood pressure, heart rate and cardiac stroke volume in 24 women with severe PE, who were randomly assigned to either receive nasal CPAP (n = 12) or no treatment (n = 12). PSG was performed on two consecutive nights (baseline and treatment). Objective sleep features were compared between groups and to a healthy pregnant control group (n = 15). The amount of REM sleep (%) was reduced in PE women regardless of treatment status compared to control subjects (23 ± 3, 12 ± 6, and 12 ± 7% of TST in control, no-CPAP, and CPAP subjects, respectively, p < 0.001). The RDI was slightly increased in both PE groups compared to control subjects (9 ± 4 events/h, 19 ± 10 events/h, and 22 ± 23 events/h in control, non- CPAP, and CPAP subjects, respectively, p = 0.10) and all cases showed upper-airway flow limitations. Pre-eclamptic women had increased daytime BP, a reversed nocturnal BP decrement and a significantly lower heart rate in NREM, as well as a significant decrease of cardiac stroke volume during sleep compared to control cases.

Furthermore, total peripheral vascular resistance was heightened, and cardiac output reduced. All the above-mentioned variables improved or normalized with CPAP treatment.

The same authors [69] also performed third trimester PSG in 20 women with PE and 20 healthy pregnant women (BMI 31.9 ± 3.2 vs. 30.6 ± 2.5 kg/m2, p = 0.15). Preeclamptic patients showed significantly more flow limitations, higher AHI and increased number of oxygen desaturation especially during REM sleep, compared to controls. Fetal wellbeing, measured by movement pattern and hiccups, was also significantly reduced in PE patients and responded to CPAP.

Positional therapy

In the third trimester, the majority of pregnant women spend up to 25% of TST in supine position [70 - 72], which is considered to be a risk factor for still births (SB), with an attributable risk between 3.7% and 37% [73,74]. Avoiding supine position during sleep in pregnant women could therefore significantly reduce the occurrence of late SB.

Kember et al. [75] performed a two-night, in-lab, PSG study with a cross-over design in 20 pregnant women in the third trimester, in order to evaluate the effect of a positional therapy device (PrenaBelt), compared to a sham device, in discouraging healthy pregnant women to sleep in supine position. Considering all available recordings (n = 40 nights), the median percentage of sleep time spent in supine position was reduced from comparable low baseline values of 16.4% on the sham night to 3.5% on the PrenaBelt night (p = 0.03), with overall good compliance and tolerability. Sleep macrostructure and sleep-related breathing and movement parameters did not significantly differ between groups and remained within the normal range, as expected in this low-risk population.

Quantitative analysis (meta-analysis)

Five studies reporting TST and six reporting SE were selected for inclusion in the meta-analysis. Results are presented as forest plots in Figs. 2 and 3. TST was overall significantly reduced from the first to the third trimester of pregnancy by 26.8 min (pooled WMD, 95% CI = 12.14 - 41.56).

Similarly, SE was reduced between first and third trimester by 4% (pooled WMD, 95% CI = 1.50 - 6.65). A significant statistical heterogeneity between studies was found for both sleep parameters evaluated (I^2>50%). Egger's test detected no significant publication bias for studies reporting TST (p > 0.1), but a possible publication bias for studies reporting SE (p = 0.072).

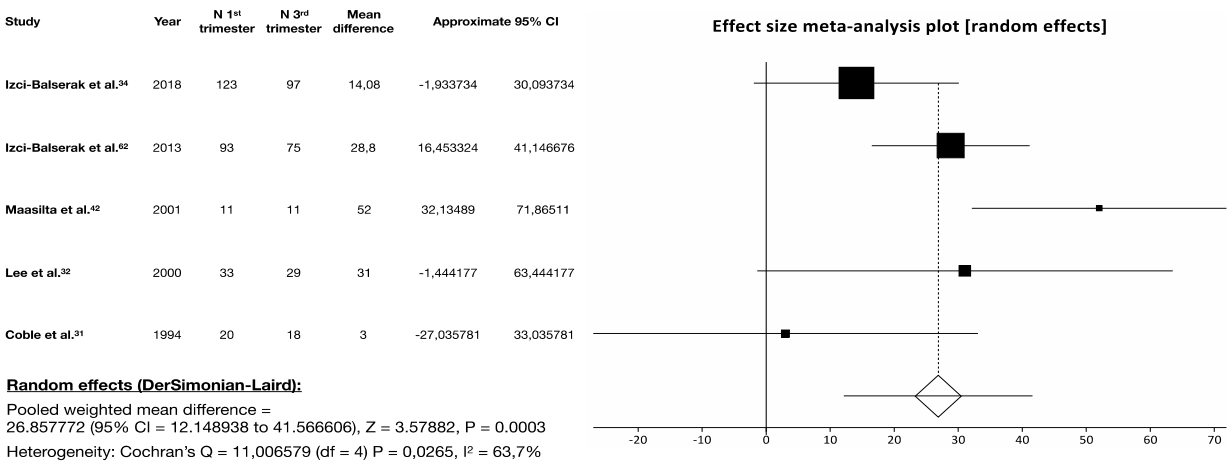

Fig. 2. Forest plot of studies reporting TST included in meta-analysis

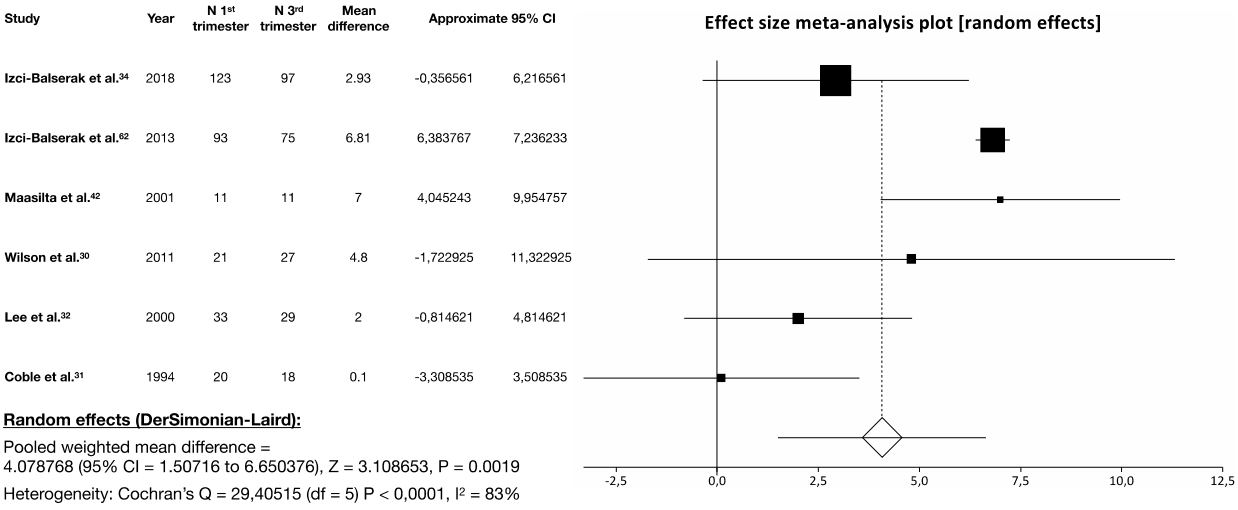

Fig. 3. Forest plot of studies reporting SE included in meta-analysis

Discussion

Changes in sleep structure during pregnancy, as objectively measured by PSG, mainly consist in a reduction of sleep duration (TST), due to an increase of WASO, and in a transition from N3 and REM sleep to more superficial NREM sleep stages (N1, N2) [28,29]. As a result, mean SE is diminished and sleep is perceived as non- restorative across gestation [30].

These findings become particularly evident in the third trimester and are confirmed both by studies comparing pregnant with age-matched non-pregnant women, and by a recent large analysis of PSG data collected among the same mothers during early and late pregnancy [34].

Hormonal variations can only partially explain these alterations, which should instead be ascribed to a series of concurrent factors, including anatomical/mechanical changes and psychological variables [31].

Objective sleep alterations occurring during pregnancy are precisely detected by PSG and might be relevant in guiding appropriate therapeutic strategies for women reporting poor sleep quality and insomnia symptoms across gestation. Previous research has shown that, in untreated women, actigraphy- assessed sleep variables tend to worsen from pregnancy to postpartum [76] and that cognitive behavioral therapy for insomnia (CBT-I) can significantly reduce insomnia symptoms and improve objectively measured sleep variables, such as SE, SOL, and TIB in pregnant women [77]. However, since objective TST seems to be not significantly modified by CBT-I [77], the benefits of using this treatment during pregnancy need to be further studied and evaluated.

According to the PSG studies published so far, there is poor evidence of an increased occurrence of SDB among healthy, normal-weight pregnant women without risk factors, suggesting that pregnancy per se does not necessarily predispose to major changes in sleep-related respiratory parameters. However, a deterioration of the respiratory pattern during pregnancy, with a higher AHI, ODI, snoring time and incidence of OSA, particularly in the third trimester, is generally a common finding in studies analyzing SDB in at-risk pregnant women. Besides gestational age, some pre- existing conditions, such as a BMI in the range of obesity, a larger neck circumference, as well as higher maternal age at pregnancy onset, should be carefully considered as possible risk factors for the development of OSA during pregnancy [33,34,75].

Also, in most studies, the classical PSG parameters considered for diagnosing OSA in the non-pregnant population, such as AHI and ODI, show no significant differences or are only slightly increased, without reaching a pathological threshold (i.e., AHI>5) in pregnant women [38]. This raises the question whether the current diagnostic criteria for OSA also apply to pregnancy, and whether other respiratory markers, such as airflow limitations and snoring, may be more reliable in identifying possible borderline pathological conditions, which may predispose to pregnancy-related adverse cardiovascular or other health outcomes [40]. Future research should be therefore focused on better defining normative PSG values for SDB during pregnancy based on large datasets.

The frequency and characteristics of PLMS during pregnancy are clearly underinvestigated, but the available studies did not show a relevant increase of PLMS-Index in women across gestation or compared to non-pregnant controls. This is a surprising finding, considering the high prevalence of RLS during pregnancy [78] and that up to 80% of patients with RLS also have increased PLMS [79]. In fact, the only small PSG study examining pregnant women with RLS confirmed these to have more PLMS before and after delivery than healthy pregnant controls [45].

Subjective tools to evaluate sleep characteristics or to screen for SDB in pregnant women must be carefully interpreted, due to their generally lower accuracy compared to PSG. Some of these instruments may be implemented by adding information provided by the women themselves or their bed partners, which may critically improve the sensibility of the tools [47,48]. This suggests that the creation and

validation of new questionnaires specifically targeting the pregnant population are recommended for future research studies.

Actigraphy represents a valid objective alternative to PSG for assessing some fundamental sleep parameters, such as TST, SE or WASO. However, its accuracy in comparison to PSG seems to be clearly influenced by the basic settings of the devices used, which would require to be validated during pregnancy [23], paying particular attention to the late GA, when mobility is reduced.

Single validation studies of a few portable devices for detecting SDB in pregnant women have shown a good diagnostic sensibility of these instruments with respect to PSG [49,50].

Hypertensive disorder of pregnancy (HDP), independently from its nature, is associated with snoring, and women affected by both conditions are more likely to have a higher AHI and to suffer from OSA [52]. Moreover, obesity may play a significant role in predisposing pregnant women with HDP to develop SDB and BMI should be therefore carefully accounted for when evaluating pregnant hypertensive individuals.

Pregnant women affected by PE not only show alterations of sleep structure, with increased SWS and REM sleep latency, as well as reduced REM sleep percentage, but are also more likely to suffer from snoring and SDB. In particular, PE patients have a higher AHI, AI, and a lower minimum oxygen desaturation, which all positively correlate with blood pressure parameters, even after adjustment for BMI, and predispose to poor maternal and fetal outcomes [58].

Data regarding the association between gestational diabetes and altered sleep pattern or SDB are scarce and not consistent. However, the largest study on maternal hyperglycemia conducted so far showed that, also in this case, the traditional parameters used to diagnose SDB may not differ between patients and healthy control subjects, even if symptoms of respiratory disturbances during sleep may be significantly more frequent in patients with impaired glucose tolerance [62].

A few studies examined the association between OSA and severe perinatal outcomes, such as impaired fetal growth or the delivery of SGA newborns. In particular, a PSG-based diagnosis of SDB in the third gestational trimester was associated with a significantly increased odds of delivering an SGA baby [64]. However, BMI seems, once again, to critically influence the value of OSA as predictor of fetal growth restriction [80]. In general, further evidence especially regarding the role of mild OSA as risk factor for pregnancy-related complication, as well as the efficacy of CPAP therapy in preventing such complications is warranted.

To date, interventional studies evaluating the effects of CPAP on pregnancy-related OSA and PE by using PSG are lacking, but overall supporting the use of this type of non-invasive ventilation, which is generally well tolerated and remarkably contributes to improve subjective sleep quality and daytime symptoms, as well as objective sleep and hemodynamic parameters [67,68].

Some limitations of the present analysis should be considered. First, some studies only report parts of their polysomnographic results, generally those addressing the specific research question, or possibly only the positive ones. Also, main characteristics considerably differ between studies, e.g., regarding design, population, sample size, time of pregnancy and criteria used for PSG scoring. This large heterogeneity makes it difficult to draw definitive conclusions about most outcome parameters and to pool the data in order to perform a meta-analysis.

Finally, articles reporting PSG results from a sample <10 women, as well as reduced montage polygraphic studies (without EEG, EMG and EOC derivations) were excluded from the present review. Although PSG is the most accurate method for sleep depiction, its use in the clinical setting may be complicated by the limited availability, the necessary technical equipment, and the elevated costs. Also, it must be considered that PSG data obtained from a single recording might be biased by an habituation effect (also called "first night effect"), especially if the sleep study was not performed in the home environment [81].

In conclusion, a growing number of PSG studies are providing further knowledge on the intrinsic features of sleep during pregnancy, thus contributing to better describe changes in objective sleep variables occurring in pregnant women beyond subjective reports. Portable devices will help to collect large-scale data in future research, but efforts are needed in designing more homogenous and comparable studies, in order to maximize the information gained from the results and to better understand the clinical value of using PSG during pregnancy.

Practice points

Sleep disturbances during pregnancy are common and may sometimes require a full polysomnographic assessment in order to:

1. correctly identify pregnancy-related sleep disorders according to current diagnostic criteria
2. avoid under- or overestimation of self-reported sleep problems
3. establish an early treatment of pathological conditions, which represent a risk factor for the health of the fetus and the mother

Research agenda

Future research studies using polysomnography in pregnant women should be preferably aimed at:

1. evaluating changes in sleep variables within the same women at different time points before, during, and after pregnancy by adopting longitudinal study designs

2. establishing an expert consensus on the minimal polysomnographic parameters to be reported in studies on pregnancy and on the sleep scoring criteria to be adopted
3. creating large datasets in order to define normative polysomnographic values per each trimester of pregnancy
4. developing algorithms based on combined information from PSG and questionnaires, in order to better predict pregnancy-related clinical outcomes
5. further validating the accuracy of portable polygraphy devices vs standard polysomnography
6. evaluating the efficacy of CBT-I and CPAP during pregnancy for the treatment of insomnia and sleep-disordered breathing, respectively

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.101249

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* The most important references are denoted by an asterisk.

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Manuscript 2

Influence of chronotype on the incidence and severity of perinatal depression in the "Life-ON" study

Corrado Garbazza[1,2,3], Sandra Hackethal[1], Enrica Migliore[4,5], Armando D'Agostino[6], Chiara Serrati[6], Valentina Fanti[6], Silvia Riccardi[1], Simone Baiardi[7,8], Alessandro Cicolin[9], Stefan Borgwardt[10,11], Susanna Mondini[12], Fabio Cirignotta[13], Christian Cajochen[2,3], Mauro Manconi[1,14,15] and the "Life-ON" study group

1 Sleep Medicine Unit, Neurocenter of Southern Switzerland, Ospedale Civico, Lugano, Switzerland.
2 Centre for Chronobiology, University of Basel, Basel, Switzerland.
3 Transfaculty Research Platform Molecular and Cognitive Neurosciences, University of Basel, Basel, Switzerland.
4 Clinical Epidemiology Unit, University Hospital Città Della Salute e Della Scienza di Torino, Turin, Italy.
5 Cancer Epidemiology Unit, University Hospital Città Della Salute e Della Scienza di Torino, Turin, Italy.
6 Department of Mental Health and Addiction, ASST Santi Paolo e Carlo, Milan, Italy; Department of Health Sciences, Università degli Studi di Milano, Milan, Italy.
7 IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy.
8 Department of Experimental, Diagnostics, and Specialty Medicine, University of Bologna, Bologna, Italy.
9 Sleep Medicine Center, Department of Neuroscience, University of Turin, Turin, Italy.
10 Department of Psychiatry (UPK), University of Basel, Basel, Switzerland.
11 Department of Psychiatry and Psychotherapy, University of Lübeck, Lübeck, Germany.
12 Neurology Unit, Sant'Orsola-Malpighi University Hospital, Bologna, Italy.
13 University of Bologna, Bologna, Italy.
14 Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland.
15 Department of Neurology, University Hospital, Inselspital, Bern, Switzerland.

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Abstract

Background

Perinatal depression (PND) is a severe complication of pregnancy, but there are no established risk factors predicting the disease. Evening chronotype has been associated with unhealthy lifestyle habits and adverse outcomes during pregnancy. In this study, we aimed to clarify whether chronotype can predict symptoms and/or occurrence of PND.

Methods

Two hundred ninety-nine women were followed-up from the first trimester of pregnancy until 6 months postpartum. Chronotype was assessed at baseline using the MEQ, while mood was repeatedly assessed by depression rating scales (EPDS, HDRS, MADRS). The influence of time and chronotype on EPDS, HDRS and MADRS, was estimated by constructing multilevel linear mixed regression models. A Cox proportional-hazard regression model was built to evaluate the association between chronotype and incidence of depression.

Results

Chronotype modulated PND symptom severity depending on time of assessment, with evening chronotypes having a higher risk for developing PND symptoms in the immediate postpartum period. These also had less healthy lifestyle habits and were more likely to suffer from gestational diabetes mellitus and undergo caesarean delivery as compared to other chronotypes.

Limitations

Only a minority of women were classified as evening chronotypes. The long follow-up phase of the study led to missing data.

Conclusions

Pregnant evening chronotypes show unhealthy lifestyle habits and sociodemographic characteristics commonly associated with a higher risk for PND. They also have a higher risk of developing PND symptoms in the immediate postpartum period. Chronotype should therefore be routinely assessed during pregnancy to identify women potentially at risk for developing PND.

Keywords

Perinatal depression, chronotype, pregnancy, Edinburgh Postnatal Depression Scale, Morningness-eveningness questionnaire

1. Introduction

Chronotype refers to the individual self-selected timing of sleep in relation to local time (Roenneberg, 2012). Chronotypes in the general population are normally distributed, ranging from morning types (early falling asleep in the evening and early wake up in the morning) to evening types (late falling asleep in the evening/night and late wake up in the morning), with intermediate types falling between these two extremes (Roenneberg et al., 2007).

Inter-individual differences in chronotype represent an important aspect of circadian regulation, reflecting a different phase relationship between daily biological and environmental events (Martin- Fairey et al., 2019). These also depend on age, gender, genetic variants, homeostatic sleep factors, as well as on the strength of external stimuli, known as Zeitgebers (e.g. temperature, nutrition, and particularly light), which synchronize the endogenous circadian clock to the 24-hour day (Roenneberg and Merrow, 2016).

Individual chronotypes can interfere with social demands related to school times, working hours, or leisure activities, generally leading evening and, to lesser extent, morning types to accumulate sleep debt on workdays and compensate for it by sleeping longer or midday napping on free days (Roenneberg et al., 2003). The degree of misalignment between biological and social time is normally referred to as social jetlag and can be quantified as the absolute difference between the timing of midsleep on workdays and on work-free days (Wittmann et al., 2006). There is a strong correlation between later chronotype and greater social jetlag (Wittmann et al., 2006), and both conditions are associated with adverse health consequences and unhealthy habits (Parsons et al., 2015). Evening chronotypes report a higher incidence of poor sleep quality and increased daytime sleepiness (Giannotti et al., 2002; Volk et al., 1994). They also have a higher risk for depression and suicides (Kitamura et al., 2010; Levandovski et al., 2011; Merikanto et al., 2015, 2013a; Selvi et al., 2011), as well as less healthy dietary habits (Kanerva et al., 2012; Malone et al., 2016). Moreover, evening chronotypes tend to consume more alcohol, nicotine, and caffeine (Adan, 1994; Hug et al., 2019) and are more likely to suffer from arterial hypertension, type 2 diabetes (Merikanto et al., 2013b) and bronchial asthma as compared to the other chronotypes (Merikanto et al., 2014).

In a nationwide Finnish study, evening types have been estimated to represent 11–13% of the general adult population, with eveningness being slightly more prevalent among females than males (Merikanto et al., 2012). By contrast, a recent analysis of data recorded by using wearable

devices in the Chinese population (n=49,573) found no gender differences in chronotypes (Zhang et al., 2019). Another large-scale study estimating the distribution of individual chronotypes in the US population based on diary data, showed that women are on average earlier chronotypes than men until the age of 40, but later types thereafter (Fischer et al., 2017). The authors hypothesized hormonal changes in women to act as modulators for an aging circadian system, causing a shift to eveningness between 35 and 50 years. In women, chronotype also seems to modulate reproductive functions, such as the length of menstruation and the likelihood for pregnancy (Toffol et al., 2013). Furthermore, evidence suggests that, especially in women, a later chronotype might represent an unfavorable factor in the onset of physical or mental disorders (Fabbian et al., 2016) and be associated with adverse childhood experiences (Hug et al., 2019).

Very few studies examined the influence of chronotype on mood during the perinatal period. Overall, pregnant evening chronotypes reported greater seasonal variations in mood and behaviour than morning types (Merikanto et al., 2017), had a higher prevalence of insomnia and depression before and during pregnancy (Sampaio Facanha et al., 2021), and more symptoms of mania and obsessive-compulsive disorder in the postpartum period (Obeysekare et al., 2020).

In the present large-scale, prospective, cohort study on women during pregnancy and postpartum, we aimed to investigate whether chronotype is a risk factor for developing perinatal depression (PND). PND is defined as a major depressive episode occurring during pregnancy or within 4 weeks after childbirth, up to one year, and represents a severe complication of pregnancy, affecting ca. 12% of women and having relevant negative health consequences for both mothers and newborns (Dagher et al., 2021). We hypothesized that a later chronotype might be predictive of PND occurrence and symptom severity. Secondarily, we examined the association between chronotype, maternal sociodemographic characteristics and lifestyle habits, in relation to PND. We hypothesized that evening chronotypes might present unfavorable social conditions and life attitudes predisposing them to develop PND.

2. Methods

2.1. Participants

Data presented here derive from a large cohort study on sleep and mood changes during the perinatal period (the "Life-ON" study) conducted between 2016 and 2020 in three centers in Italy (Milan, Turin, and Bologna) and one in Switzerland (Lugano). A detailed description of the "Life-ON" study protocol has been published previously (Baiardi et al., 2016). In summary, participating women were recruited during the first trimester of pregnancy and received 10 follow-up visits until 12 months postpartum. The time points of the consecutive visits (V) were scheduled as follows: V1 (10-15 gestational week); V2 (20-25 gestational week); V3 (34-36 gestational week); V4 (5-12 days postpartum); V5 (19-26 days postpartum); V6 (33-40 days postpartum); V7 (47-54 days postpartum); V8 (90-105 days postpartum); V9 (180-195 days postpartum); V10 (270-285 days postpartum); V11 (12 months postpartum). Sleep and mood parameters from both self- administered questionnaires and semi-structured interviews were regularly collected at every study visit (Baiardi et al., 2016). Women screened for study participation were excluded if they had a current or previous (one year) diagnosis of depressive disorder or were treated with any antidepressant medication in the previous 12 months. Twenty-three participants who developed PND, as assessed by an EPDS total score > 12 from visit 2 to visit 10, were offered to enter a randomized, controlled trial with 6-week bright light therapy (BLT) vs. placebo dim light (substudy "Life-ON2"). Seventy-eight women with an EPDS score ≤ 12 at visit 2, thus being considered not affected by PND, were also consecutively asked to participate in an open-label trial with 6-week BLT, to test its efficacy in preventing the onset of PND during the postpartum period (substudy "Life- ON3").

2.2. Chronotype assessment

Chronotype was assessed once at study entry (V1) using the 19-item Morningness–Eveningness Questionnaire (MEQ) (Horne and Ostberg, 1976). The MEQ is a self-administered rating scale developed to assess the individual differences in the degree to which respondents are active and alert at certain times of day (e.g. morning vs. evening). Each section of the questionnaire is assigned a value of 1 through 5. The sum of each item gives a global score ranging from 16 to 86, with scores ≤ 41 corresponding to "evening types", scores between 42-58 to "intermediate types" and scores ≥ 59 to "morning types".

2.3. Psychiatric assessment

Depressive symptoms during the study period were assessed using one self-administered psychiatric scale and two semi-structured interviews:

- the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) is a 10-item self-administered screening tool used to identify women suffering from depressive symptoms during the perinatal period and was completed by participants at every study visit. Responses are scored 0, 1, 2, or 3 according to increased symptom severity. The total score ranges between 0 and 30 and a cut-off score higher than 12 was considered indicative of PND
- the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) is a semi-structured interview consisting of 21 items that are scored between 0 and 4 points and was administered at visits V1, V3, V6, V9, and V11. Total scores of 0–7 are considered as being normal, 8–16 suggest mild depression, 17–23 moderate depression and scores over 24 are indicative of severe depression.
- the Montgomery-Åsberg Depression Rating Scale (MADRS) is a semi-structured interview including 10 items aimed at evaluating symptoms of depression (Montgomery and Asberg, 1979). It was administered at the same time points as the HDRS, but differently from this, the MADRS does not focus predominately on the somatic symptoms of depression, but rather addresses core mood symptoms, such as sadness, tension, lassitude, pessimistic thoughts, and suicidal thoughts. MADRS items are rated on a 0–6 continuum (0 = no abnormality, 6 = severe) and total scores in relation to the severity of depression are 0–8 (remission), 9–17 (mild depression), 18–34 (moderate depression), and ≥ 35 (severe depression).

2.4. Statistical analysis

2.4.1. Descriptive statistics for sociodemographic factors

All data analysis was performed using the R statistical software (R version 3.5.2). Demographic data of the whole study population (n = 299) and outcomes from the respective depression questionnaires on an ordinal scale were tested for normality with the Shapiro-Wilk-Test and for equality of variances using the Levene's test. Between-group differences for normally

distributed data were calculated using a one-way-test of variance (ANOVA), reporting the corresponding effect size omega squared. Differences between groups for non-normally distributed data were calculated using the Kruskal-Wallis test. As the corresponding effect-size measure we chose epsilon squared (Kelley, 1935). Overall, between-group differences for demographic and questionnaire data on a categorical scale were calculated using Pearson's chi-squared test with corresponding effect size Cramér's V. The relationships between raw MEQ-values (unstratified for the different chronotypes) and depression rating-scale scores at the respective time-points of assessment were calculated using Spearman's rho (ρ) regression coefficient. As a cut-off value rejecting the null-hypothesis, $p = <0.05$ was considered statistically significant. Instead of correcting for multiple testing, we chose to report effect sizes for the respective statistical tests.

2.4.2. Multilevel linear mixed regression

We constructed multilevel linear mixed regression models with repeated measures to assess the influence of time and chronotype on the outcome of the EPDS, HDRS and MADRS on an ordinal scale, as well as divided into non-pathologic vs. pathologic values based on the respective cut-offs of the rating scales. Women entering at visit V2 the interventional substudy "Life-ON3" were excluded from this analysis, because of the possible impact of BLT on mood variables during the subsequent observation period. Data from participants of the "Life-ON2" substudy were also excluded from the beginning to preserve the longitudinal integrity of the dataset, since the time point of BLT start across the study was highly variable. The demographic characteristics of the untreated women did not differ significantly from the full sample.

We considered a list of confounding factors that might be possibly involved in the development of depression. Definitive parameter selection was performed via backwards elimination based on Akaike information criteria (AIC) assessing model fit. Only parameters significantly improving the model fit were included in the construction of the definitive regression models fitted with the restricted maximum likelihood method (see supplemental Table 1). Chronotype, time, as well as their interaction and confounding factors were considered as fixed effects, whereas participants were modeled as a random factor. To assess model performance, we calculated the conditional R^2 (R^2c) representing the variance in the data attributable to the complete regression model.

2.4.3. Survival analysis

To investigate the association between chronotype and incidence of PND, we constructed cumulative incidence curves and calculated the difference between the curves for the different chronotypes using the log-rank test. A Cox proportional-hazard regression model was additionally constructed to extend the analysis to the effect of several risk-factors on event-free survival time (time until onset of meaningful depressive symptoms defined as EPDS >12 points). Participants in the interventional substudy "Life-ON3" were excluded from this analysis to avoid BLT as a possible factor influencing depressive symptomatology.

The list of possible confounding factors on the onset of PND was identical to that used in the multilevel linear mixed regression model (see supplemental Table 1). Exhaustive model selection was performed assessing all possible regression models ranked by goodness-of-fit based on AIC, selecting the best possible model which also included chronotype as variable. We used the Schoenfeld test to examine Cox proportional hazards model assumptions.

2.5. Ethics

The "Life-ON" study has been approved by the respective ethics committee of the four participating centers in Italy and Switzerland. All participants gave a written informed consent prior to study entry.

3. Results

3.1. Chronotype distribution

A total of 438 women (age 34.1±4.2 years) were enrolled in the "Life-ON" study during the first trimester of pregnancy (week 10-15). 409 participants (93.4%) completed the MEQ at baseline visit, of which 6.36% (n=26) were classified as evening type, 55.5% (n=227) as intermediate type, and 38.14% (n=156) as morning type. After exclusion of premature dropouts and participants with insufficient data (n=110), a sample of 299 women (age 34.1±4.3 years), who provided sufficient data from visit 1 (baseline, 10-15 gestational week) to visit 9 (6 months postpartum) was considered for statistical analysis. Chronotype distribution in this sample was similar to the whole study population, with 5.68% (n=17) being classified as evening types, 56.86% (n=170) as intermediate types, and 37.46% (n=112) as morning types. The graphic

distribution of MEQ scores (chronotypes) followed a Gaussian curve, as shown in Figure 1, similar to that known of the general population (Roenneberg et al., 2007).

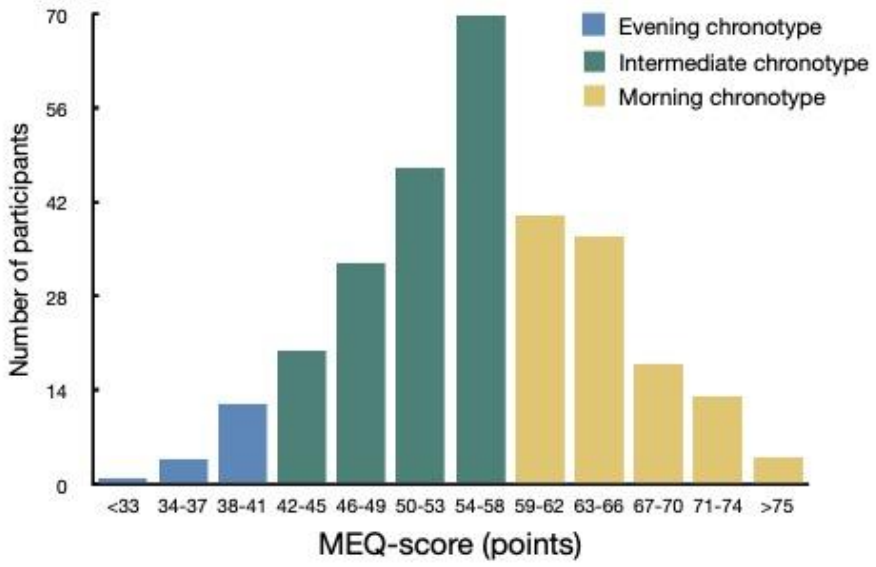

Figure 1: Distribution of chronotypes in the study population based on MEQ-score. MEQ: morningness-eveningness questionnaire.

3.2. Sociodemographic and health characteristics

Sociodemographic and health characteristics of the analyzed sample in relation to chronotype are listed in Table 1. Data showed no differences between the three chronotypes as regard to age and number of children, but only a small, non-significant, between group effect regarding weight and BMI, with no clinical relevance. Evening chronotypes were more likely to be in a relationship (64.7%) than married (35.3%) and to have a partner with restricted vs. unrestricted job, as compared to the other chronotypes. They were also more frequently smokers (p=0.005) and alcohol consumers at study entry, and had a history of chronic alcohol and medication use in the past, as compared to the other chronotypes. Concerning health status, a small effect was observed for evening types regarding suffering from gestational diabetes mellitus (GDM) at study entry, with a 3.7 times higher risk as compared to morning chronotypes. Finally, regarding adverse pregnancy outcomes, evening type women were twice as likely to receive a cesarean section at delivery, as compared to morning chronotypes.

	Morning Chronotype (n=112)		Intermediate Chronotype (n=170)		Evening Chronotype (n=17)		ANOVA			Kruskal-Wallis		
	n	mean (SD) or median (IQR)	n	mean (SD) or median (IQR)	n	mean (SD) or median (IQR)	F-value	p-value	ω^2	χ^2	p-value	ε^2
Age (in years)	112	34.4 (4.3)	170	33.9 (4.2)	17	33.5 (4.8)	0.5994	0.5498	-0.0024			
Weight (in kg)	110	58 (53|65)	167	61 (56|69)	17	57 (55|65)				5.71	0.06	**0.0192§**
BMI	103	21.72 (20.23|23.5)	163	22.35 (20.865|24.61)	16	21.54 (20.315|24.715)				3.06	0.22	**0.0103§**
Number of children	112	1 (0|1)	170	1 (0|1)	16	0 (0|1)				2.24	0.33	0.0075

		Morning Chronotype (n=112)		Intermediate Chronotype (n=170)		Evening Chronotype (n=17)		Pearson's Chi-squared test			
		n	n (%)	n	n (%)	n	n (%)	χ^2	df	p-value	Cramér's V
Pregnancy	Programmed	112	93 (83.0)	170	142 (83.5)	15	12 (70.6)	3.68	4	0.45	0.078
	Not programmed		19 (17.0)		26 (15.3)		5 (29.4)				
	Not desired		0 (0.0)		2 (1.2)		0 (0.0)				
Type of conception	spontaneous	111	107 (96.4)	169	162 (95.9)	17	17 (100.0)	0.75	2	0.69	0.05
	IVF		4 (3.6)		7 (4.1)		0 (0.0)				
Time of delivery	pre term	107	3 (2.8)	158	8 (5.1)	16	1 (6.3)	3.37	4	0.50	0.077
	at term		104 (97.2)		147 (93.0)		15 (93.7)				
	post term		0 (0.0)		3 (1.9)		0 (0.0)				
Type of delivery	C-section	111	24 (21.6)	168	44 (26.2)	17	8 (47.1)	5.05	2	0.08	**0.131§**
	Vaginal		87 (78.4)		124 (73.8)		9 (52.9)				
Number of kids	none	112	78 (69.6)	167	110 (65.9)	15	13 (76.5)	1.84	4	0.77	0.056
	one		25 (22.3)		37 (22.2)		3 (17.6)				
	2 or more		9 (11.9)		20 (8.0)		1 (5.8)				
Marital status	married	112	66 (58.9)	170	104 (61.2)	17	6 (35.3)	6.09	6	0.41	**0.101§**
	in a relationship		46 (41.1)		64 (37.7)		11 (64.7)				
	divorced		0 (0.0)		1 (0.6)		0 (0.0)				
	single		0 (0.0)		1 (0.6)		0 (0.0)				
Education level	College	112	82 (73.2)	170	113 (66.5)	15	10 (58.8)	4.09	4	0.39	0.083
	High school		27 (24.1)		48 (28.2)		5 (29.4)				
	Middle school		3 (2.7)		9 (5.3)		2 (11.8)				
Type of work (patient)	unrestricted	107	68 (63.5)	156	113 (72.4)	17	13 (76.5)	3.17	4	0.53	0.075
	restricted		24 (22.4)		25 (16.0)		3 (17.7)				
	unemployed		15 (14.0)		18 (11.5)		1 (5.9)				
Type of work (partner)	unrestricted	103	87 (84.5)	149	132 (88.6)	15	11 (73.3)	4.71	4	0.32	0.094
	restricted		13 (12.6)		15 (10.0)		4 (26.7)				
	unemployed		3 (2.9)		2 (1.3)		0 (0.0)				
Living situation	own property	110	80 (72.7)	169	120 (71.0)	16	11 (68.8)	0.16	2	0.92	0.023
	rent		30 (27.3)		49 (29.0)		5 (31.3)				
Perceived poverty	no	108	106 (98.2)	169	168 (99.4)	16	16 (100.0)	1.21	2	0.55	0.064
	yes		2 (1.8)		1 (0.6)		0 (0.0)				
Loss of work (6 months)	no	111	103 (92.8)	169	153 (90.5)	17	16 (94.1)	0.59	2	0.74	0.045
	yes		8 (7.2)		16 (9.5)		1 (5.9)				
Move (6 months)	no	111	100 (90.1)	168	149 (88.7)	17	17 (100.0)	2.18	2	0.34	0.086
	yes		11 (9.9)		19 (11.3)		0 (0.0)				
GDM	no	111	104 (93.7)	168	155 (92.3)	17	13 (76.5)	5.94	2	0.05	**0.142§**
	yes		7 (6.3)		13 (7.7)		4 (23.5)				
Iperemesis gravidarum	no	111	109 (98.2)	168	161 (95.8)	17	17 (100.0)	1.83	2	0.40	0.079
	yes		2 (1.8)		7 (4.2)		0 (0.0)				

(continued on next page)

		Morning Chronotype (n=112)		Intermediate Chronotype (n=170)		Evening Chronotype (n=17)		Pearson's Chi-squared test			
		n	n (%)	n	n (%)	n	n (%)	χ^2	df	p-value	Cramér's V
Perceived poverty	no	108	106 (98.2)	169	168 (99.4)	16	16 (100.0)	1.21	2	0.55	0.064
	yes		2 (1.8)		1 (0.6)		0 (0.0)				
Loss of work (6 months)	no	111	103 (92.8)	169	153 (90.5)	17	16 (94.1)	0.59	2	0.74	0.045
	yes		8 (7.2)		16 (9.5)		1 (5.9)				
Move (6 months)	no	111	100 (90.1)	168	149 (88.7)	17	17 (100.0)	2.18	2	0.34	0.086
	yes		11 (9.9)		19 (11.3)		0 (0.0)				
GDM	no	111	104 (93.7)	168	155 (92.3)	17	13 (76.5)	5.94	2	0.05	**0.142§**
	yes		7 (6.3)		13 (7.7)		4 (23.5)				
Iperemesis gravidarum	no	111	109 (98.2)	168	161 (95.8)	17	17 (100.0)	1.83	2	0.40	0.079
	yes		2 (1.8)		7 (4.2)		0 (0.0)				
Family history of depression	no	111	74 (66.7)	170	110 (64.7)	17	9 (52.9)	1.22	2	0.54	0.064
	yes		37 (33.3)		60 (35.3)		8 (47.0)				
Personal history of depression	no	111	96 (86.5)	170	147 (86.5)	15	14 (82.4)	0.23	2	0.89	0.028
	yes		15 (13.5)		23 (13.5)		3 (17.6)				
Previous depression treatment	no	112	103 (92.0)	170	156 (91.8)	17	16 (94.1)	0.12	2	0.94	0.020
	yes		9 (8.0)		14 (8.2)		1 (5.9)				
History other psychiatric disorders	no	112	95 (84.8)	170	140 (82.4)	17	16 (94.1)	1.69	2	0.43	0.075
	yes		17 (15.2)		30 (17.6)		1 (5.9)				
Smoking	ex-smoker	104	28 (26.9)	163	60 (36.8)	17	8 (47.0)	14.61	4	**0.005****	**0.16§**
	smoker		2 (1.9)		13 (8.0)		3 (17.7)				
	non-smoker		74 (71.2)		90 (55.2)		6 (35.3)				
Chronic alcohol intake (current)	no	112	109 (97.3)	170	159 (93.5)	17	15 (88.2)	3.38	2	0.18	**0.106§**
	yes		3 (2.7)		11 (6.5)		2 (11.8)				
Chronic alcohol intake (past)	no	88	86 (97.9)	128	119 (89.3)	10	10 (100.0)	3.09	2	0.24	**0.117§**
	yes		2 (2.3)		9 (10.7)		0 (0.0)				
Chronic medication intake (present)	no	78	50 (64.1)	117	73 (62.3)	13	10 (76.9)	1.07	2	0.59	0.072
	yes		28 (35.9)		44 (37.6)		3 (23.1)				
Chronic medication intake (past)	no	78	53 (68.0)	116	87 (75.0)	13	7 (53.8)	3.11	2	0.21	**0.123§**
	yes		25 (31.5)		29 (25.0)		6 (46.2)				

Table 1: Sociodemographic characteristics of the study population (n = 299) stratified for chronotypes. ANOVA: analysis of variance. df: degrees of freedom. GDM: Gestational diabetes mellitus. IVF: In-vitro fertilization. IQR: Interquartile range, given as IQR (25th percentile|75th percentile). SD: standard deviation. § weak group effect for epsilon squared (ε2) or Cramér's V, respectively. ** statistically significant at the level p < 0.01.

3.3. Depression rating scales

As depicted in Figure 2, a clear change in median EPDS scores across the single follow-up visits is evident, with a peak at visits V4 and V5, directly after delivery. Within the full dataset (n = 299, Figure 2a) we found a significant, moderate group effect for chronotype at visits V4 ($\chi2$ = 15.2, p= 0.0005, ε2 = 0.05; evening vs. intermediate: p = 0.017, evening vs. morning: p = 0.001, intermediate vs. morning: p = 0.014), and V5 ($\chi2$ = 14.42, p= 0.0007, ε2 = 0.048; evening vs. intermediate: p = 0.009, evening vs. morning: p = 0.0008, intermediate vs. morning: p = 0.043), with a weak group effect at V8 ($\chi2$ = 6.81, p= 0.03, ε2 = 0.02; evening vs. intermediate: p = ns., evening vs. morning: p = n.s., intermediate vs. morning: p = 0.03).

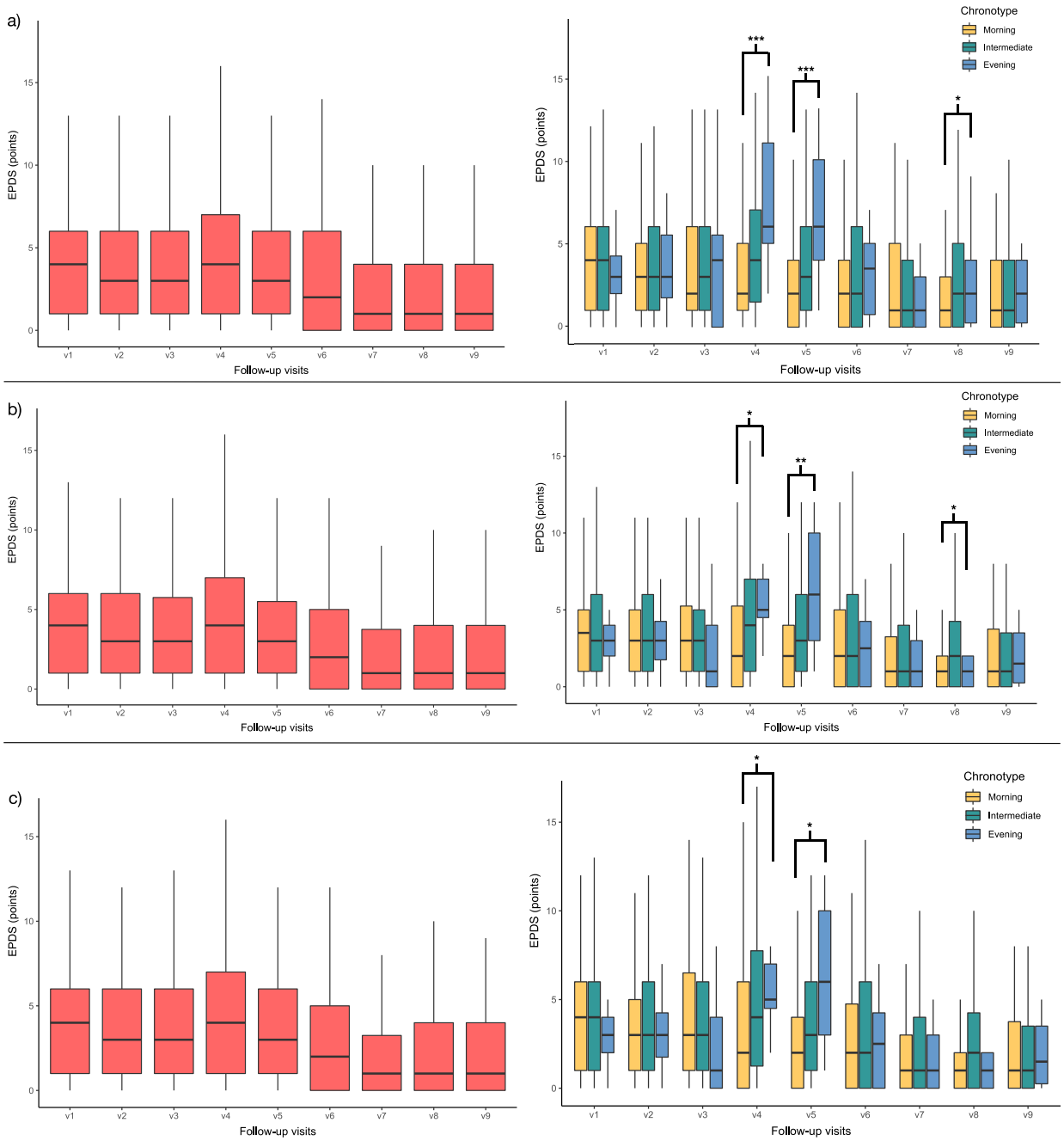

Figure 2: EPDS scores (median, IQR) during the follow-up visits, on the left-hand side unstratified for chronotype, on the right-hand side stratified for chronotype. a) Data regarding the whole study population (n = 299). b) Data from untreated women (n = 224), after exclusion of substudies "Life- ON2" and "Life-ON3" participants. c) Data from untreated women (n = 242), after exclusion of "Life- ON2" participants since start of BLT and exclusion of "Life-ON3" participants. Group effect assessed by Kruskal-Wallis test, with the respective overall p values: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The same trend was also observed when excluding data from the substudies “Life-ON2” and “Life- ON3” (n = 224, Figure 2b), with significant, weak to moderate group effects at the same time points V4 ($\chi2$ = 7.74, p= 0.02, $\varepsilon2$ = 0.03; evening vs. intermediate: p = n.s., evening vs. morning: p = n.s., intermediate vs. morning: p = 0.046), V5 ($\chi2$ = 9.96, p= 0.007, $\varepsilon2$ = 0.045; evening vs. intermediate: p = 0.05, evening vs. morning: p = 0.009, intermediate vs. morning: p = 0.05) and V8 ($\chi2$ = 6.21, p= 0.04, $\varepsilon2$ = 0.028; evening vs. intermediate: p = n.s., evening vs. morning: p = n.s., intermediate vs. morning: p = 0.048). A less pronounced but comparable association was found when additionally including data from the “Life-ON2” participants, until the start of BLT (n = 242, Figure 2c). Here, weak group effects emerged at visits V4 ($\chi2$ = 7.02, p= 0.03, $\varepsilon2$ = 0.03; post-hoc tests n.s.) and V5 ($\chi2$ = 9.01, p= 0.01, $\varepsilon2$ = 0.037; evening vs. intermediate: p = n.s., evening vs. morning: p = 0.01, intermediate vs. morning: p = n.s.), while a weak group effect not reaching statistical significance was observed at V8 ($\chi2$ = 5.93, p= 0.05, $\varepsilon2$ = 0.025).

Spearman's correlation only revealed a weak, monotonic correlation between EPDS values and MEQ for visit V4 (ρ = -0.21, p = .0014) and visit V5 (ρ = -0.21, p = .0015), while none of the other time- points or rating scales showed relevant relationships to raw MEQ values.

When fitting the multilevel linear mixed regression model predicting the values of EPDS on an ordinal scale, time, chronotype, time-chronotype interaction, total number of children, employment status, relocating (previous 6 months), family history of depression, past alcohol intake, and smoking were selected as independent parameters to achieve best model fit based on AIC. The effect of time within the final model reached statistical significance at visit 5, 7, 8 and 9, with also a significant time-chronotype interaction at visit 4, 5 and 8, as shown in Figure 3. Of the chosen confounding parameters, only relocating in the previous 6 months had a statistically significant influence on EPDS score. When examining overall model performance, 45% (R^2c=0.45) of global variation in the data was explained by the regression model.

Applying the same method to predict HDRS values on an ordinal scale, the parameters to achieve best model fit included time, total number of children, employment status, loss of employment (previous 6 months), relocating (previous 6 months), personal and family history of depression, level of education, past alcohol intake and smoking. Chronotype was not selected and therefore not included in the final model. Significant effects were found for time-restricted employment, loss of employment (previous 6 months), relocating (previous 6 months),

medium-level education and for the time point visit 3 (Figure 3). With an R^2c value of 0.42 the overall model accounted for 42% of variability within the data.

Lastly, the parameters to achieve best model fit predicting MADRS values on an ordinal scale were employment status, loss of employment (previous 6 months), smoking, past and present alcohol intake, number of children, personal history of depression and treatment, personal history of other psychiatric diseases and marital status. Chronotype and time were not selected and therefore not included in the final model. Within the final model, time-restricted employment, loss of employment in the previous 6 months, being divorced and previous treatment for depression had a significant influence predicting MADRS scores (Figure 3). With an R^2c value of 0.28 the overall model accounted for 28% of variability within the data.

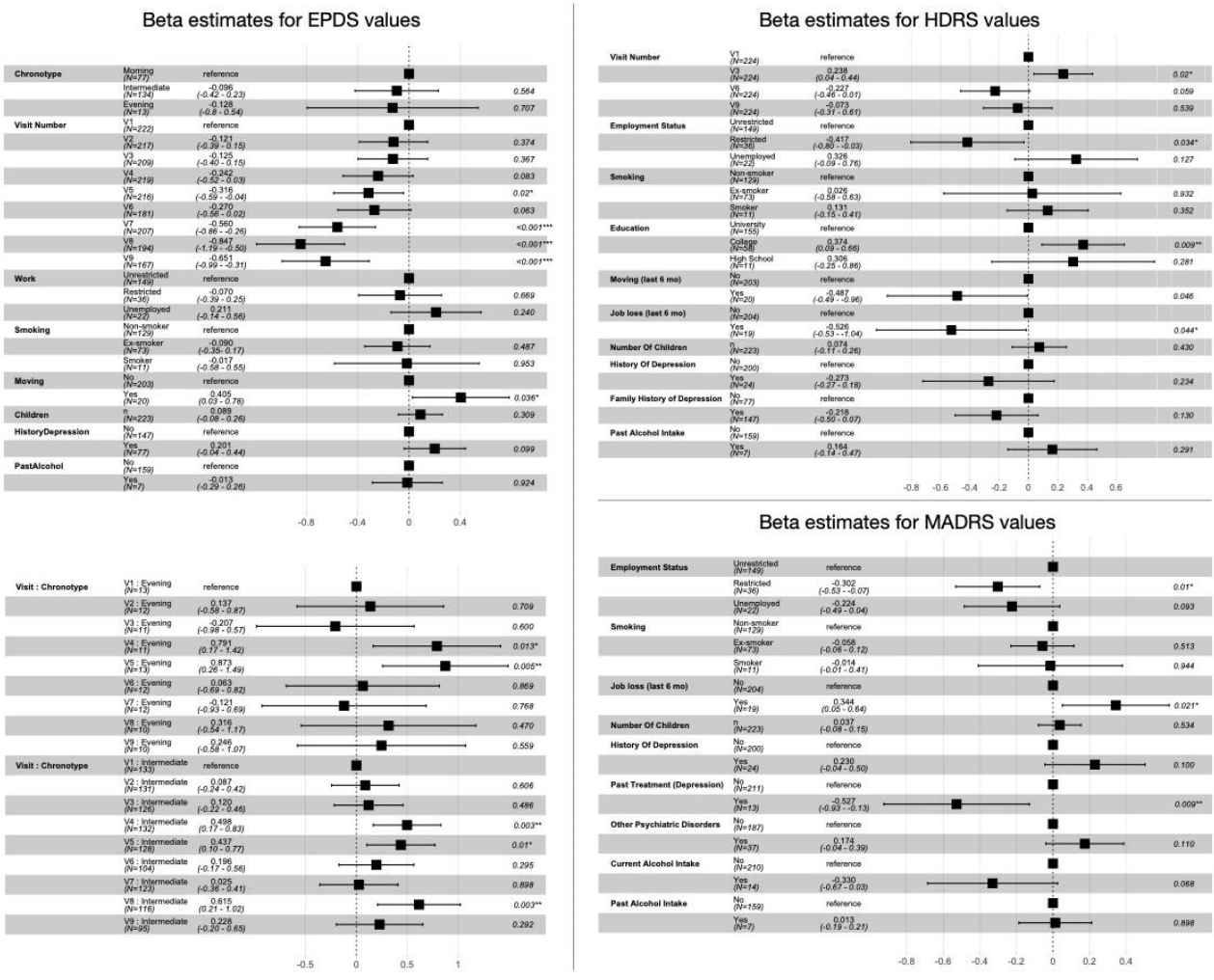

Figure 3: Beta estimate outcomes from the respective regression models predicting EPDS, HDRS and MADRS. EPDS time-chronotype interactions divided into effects for the single study visits for evening and intermediate chronotype are depicted in the bottom left-hand side. CI: confidence interval, given as 95% CI. Overall p values: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

3.4. Depression rating scales categorical

We also constructed a multilevel linear mixed regression model predicting non-pathologic vs. pathologic values of EPDS (cut-off for PND >12 points), HDRS (cut-off for "mild depression" >7 points) and MADRS (cut-off for "mild depression" >8 points) at the different follow-up time points, again using AIC based backwards elimination to select independent parameters for optimal model fit. Among our principal parameters of interest, chronotype was only selected for the model predicting HDRS and time for predicting MADRS, while those parameters were not included in the model predicting EPDS. None of the effect estimates of the selected parameters reached statistical significance when evaluating the different final models.

3.5. Overall depression incidence stratified for chronotype

During the follow-up period from inclusion to 6 months postpartum, out of 242 women considered in the survival analysis, 35 were classified as suffering from PND, corresponding to a cumulative incidence of 14.5%. Evening chronotypes (20%) showed a slightly higher percentage of cases compared to morning (13%) and intermediate chronotypes (15%), not reaching statistical significance ($\chi 2 = 0.36531$, df = 2, p-value = 0.8331, Cramer's V = 0.036).

When examining the constructed overall cumulative incidence curves for depression during the follow-up observations, a slight increase in cases can be observed across the perinatal period, with a steeper increment between 150 - 200 days of follow-up, which coincides with on-term delivery in our study population (Figure 4). The same trend is observable when stratifying for chronotypes, with overall higher depression incidence among evening chronotypes, not reaching statistical significance (log-rank test, p=0.86; Figure 4). When only considering chronotype as predictor, being an evening chronotype is associated with a 30% risk increase of developing PND (HR 1.30, CI 0.37 - 4.52), and being an intermediate chronotype with a 7% risk reduction (HR 0.93, CI 0.48 - 1.82) compared to morning chronotypes, neither of the associations reaching statistical significance.

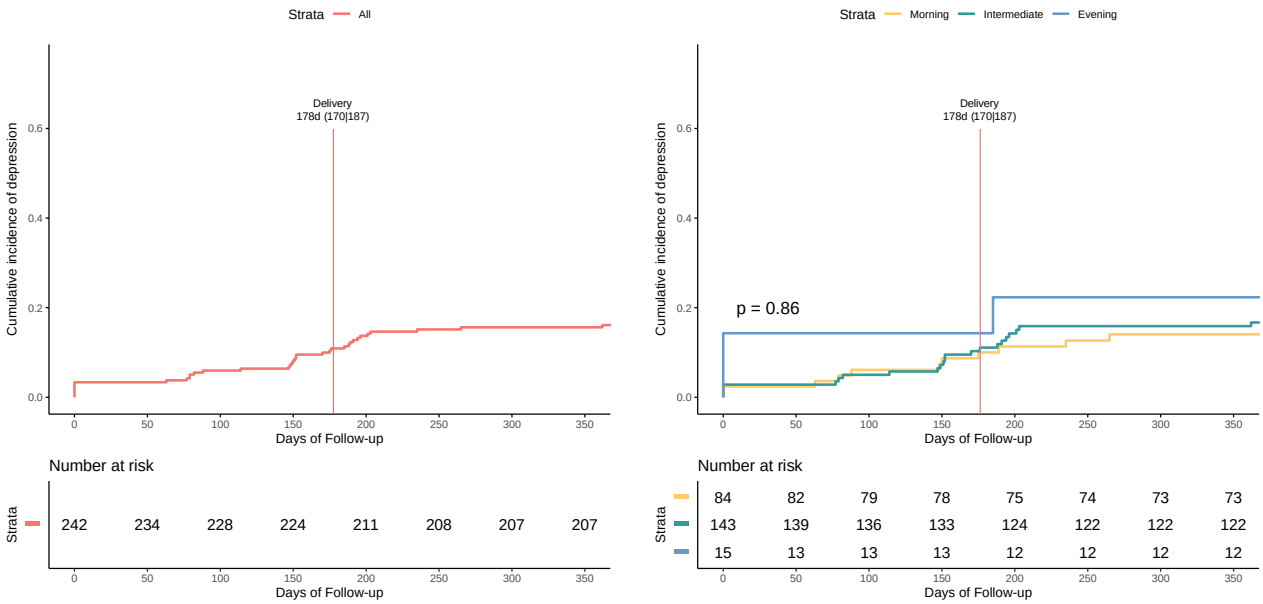

Figure 4: Cumulative incidence curve for depression (EPDS > 12) in the follow-up period (days after study inclusion) in the untreated dataset, overall (left-hand side) and stratified for chronotype (right- hand side). Time of delivery is given in days after inclusion in the study with median (red line) and IQR (red transparent rectangle, given as IQR (25th percentile|75th percentile).

Out of all possible Cox proportional-hazard models fitted when including the above mentioned confounding factors, the model with the lowest AIC, but still containing the variable "chronotype", also included total number of children, employment status, having relocated within the previous 6 months, loss of work within the previous 6 months, past history of depression, family history of depression and smoking, closely resembling the parameters already selected in the regression model predicting EPDS values on an ordinal scale (Figure 3).

Among the selected parameters, being an ex-smoker, having relocated within the previous 6 months, having more than one child, and having a previous diagnosis of depression yielded statistically significant results (Figure 5). The overall model reached statistical significance (Score (log-rank) test = 32.11 on 11 df, p=0.001). With a HR of 1.67 (CI 0.40 - 4.29), being an evening chronotype entails a 67% increased risk of developing a manifest depressive episode compared to morning chronotype, whereas, with an HR of 0.69 (CI 0.33 - 1.47), being an intermediate chronotype is associated with a 31% risk reduction. Based on this model, the factors with the greatest influence on development of depression were relocation within the previous 6 months with a two-fold risk increase (HR 3.09, CI 1.25 - 7.60), having more than one child (HR 3.95, CI 1.54 - 10.18) and previous diagnosis of depression with an approximately three-fold risk increase (HR 4.21, CI 1.66 - 10.71).

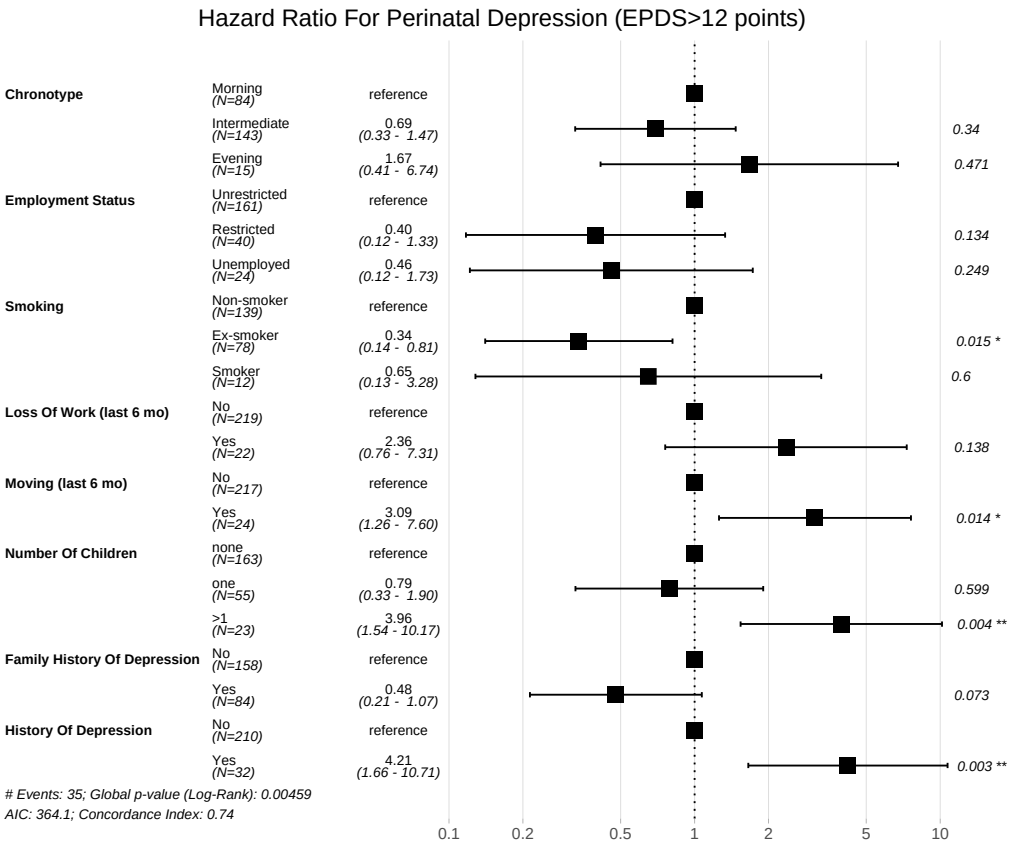

Figure 5: Hazard ratio (CI) estimation for PND (EPDS > 12) from the Cox proportional-hazard model. CI: Confidence-interval, given as 95% CI. Overall p values: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

4. Discussion

In our large cohort of pregnant women from the Life-ON study, chronotype was associated with PND symptom severity in the immediate postpartum period. A higher incidence of PND after delivery than during pregnancy is well-described in the literature and has been attributed to the complex interplay between genetic, hormonal, and psychosocial factors related to childbirth (Niel and Payne, 2020). However, even after constructing a regression model which carefully accounts for several, possible confounding factors in our sample, we found a statistically significant time- chronotype interaction for visits V4 and V5, scheduled in the first month postpartum. In particular, at these time points, both evening and intermediate chronotypes had significantly higher EPDS scores on an ordinal scale in respect to morning types. Evening chronotypes showed the most pronounced effect on EPDS values directly after delivery, suggesting that there is a time window during which they may be more vulnerable to PND compared to the other chronotypes. A weaker group effect was also observed at visit V8, corresponding to three months postpartum, when most women in our study returned to work

and probably experienced further stress in addition to childcare, which may have resulted in a worsening of mood. By contrast, chronotype was not predicting HDRS and MADRS values on an ordinal scale according to the multilevel linear mixed regression model. This should be interpreted taking into account that the EPDS is considered the most accurate tool to assess PND symptoms, as compared to other questionnaires (Levis et al., 2020). Moreover, HDRS and MADRS in our study were not administered in the immediate postpartum or at three months after delivery, which makes it difficult to compare the influence of chronotype on the values of the respective scales at the same time points. Among other variables with a significant influence on the EPDS, HDRS and MADRS scores, some conditions emerged as risk factors for developing depressive symptoms during the perinatal period. This corroborates earlier reports, that residential mobility in the previous 6 months (Grussu and Quatraro, 2009), restricted employment or loss of employment (Aochi et al., 2021), marital status (Urquia et al., 2013) and previous treatment for depression (Lancaster et al., 2010) are all associated with a higher risk for the onset of depression during the perinatal period.

The survival analysis did not show a statistically significant influence of chronotype on the overall risk of PND. However, a trend towards a risk increase for PND in evening chronotypes and a reduced risk for intermediate types, as compared to morning types, was observed. As regards the sociodemographic characteristics of the study participants, evening chronotypes were significantly more often smokers than the other chronotypes, while small, non-significant effects were also found for chronic current and past alcohol consumption, as well as chronic past medication use. In the largest population-based study conducted so far on the association between chronotype, sociodemographic, socioeconomic and health-related characteristics in a cohort of 1,646 pregnant women, evening-types were also more often smokers and had more illnesses or disabilities as compared to the other women (Merikanto et al., 2017). Other studies highlighted that pregnant women with an evening chronotype tend to have a poor diet quality (Gontijo et al., 2019), food craving traits, and to gain weight in the early gestational period (Teixeira et al., 2019) than other chronotypes. Our findings are therefore in line with the literature and confirm unhealthy lifestyle habits among evening chronotypes to be not only present in the general population (Roenneberg et al., 2019), but also in pregnant women, representing a serious risk for the health of the mothers and the fetus.

Finally, concerning the general health status of our participants and the risk of pregnancy complications, we found a small, yet non-significant effect in evening chronotypes for having

GDM at study entry and undergoing cesarean section at delivery, as compared to the other chronotypes. Interestingly, a recent study conducted in 53 pregnant women with GDM showed that evening chronotypes have a more unstable marital status, a higher prevalence of insomnia and depression before and during pregnancy, and are more likely to develop adverse pregnancy outcomes, such as pre-eclampsia and neonatal ICU admission (Sampaio Facanha et al., 2021).

Overall, one of the strengths of our study is to analyze the influence of chronotype on mood not only during pregnancy, but at 9 consecutive time points during 12 months across the perinatal period, including both the pre- and postpartum. Moreover, our work provides data from a large sample of women from 4 different participating centers, located in two countries, thus reducing the risk of recruitment bias. Also, having adopted a more conservative cutoff value of the EPDS > 12, rather than smaller, has the advantage to increase specificity in identifying "real" cases of PND and distinguishing them from milder forms of mood disturbances with common onset in the postpartum, sometimes referred to as "baby blues".

Some limitations must be considered in the interpretation of the reported findings. First, a relatively high drop-out or lost to follow-up rate led to missing data from a proportion of women in respect to the whole study sample. This is frequently observed in prospective studies with a long follow-up phase. Also, women participating in the randomized controlled trial with BLT "Life-ON2" were not considered in the regression analysis, thus excluding part of the women developing PND, which may have influenced our results as regards the identification of potential risk factors for PND.

Chronotype assessment was performed using only the MEQ, which in chronobiological research has been questioned for its intrinsic property of evaluating the sleep-wake preferences of the individuals screened, rather than the effective time of sleeping (Roenneberg, 2015). Finally, only 17 women (5.68%) among 299 participants were classified as evening chronotypes, representing a minority of cases, which may have influenced our findings. A recent investigation on chronotype, hormonal factors and activity levels changes during pregnancy in women and female mice, as measured by wrist actigraphy and running wheel activity respectively, showed that both groups had an earlier timing of sleep onset during the first and second gestational trimesters than before pregnancy and returned to the pre-pregnant state during the third trimester (Martin-Fairey et al., 2019). As a possible explanation, the authors suggested a conserved mechanism among species based on coordinated increases in estrogen

and/or progesterone during early pregnancy. Thus, considering that chronotype assessment in our study was performed during the first gestational trimester, it can even be hypothesized that the distribution of chronotypes in our sample, with a clearly higher prevalence of morning types over evening types, may have been influenced by the time of assessment.

In conclusion, pregnant women with evening chronotype in the Life-ON study present sociodemographic characteristics and lifestyle attitudes that are commonly associated with a higher risk for PND. Moreover, they are more likely subject to health problems and adverse pregnancy outcomes than the other chronotypes. Independently from all these factors, evening chronotype is significantly associated with more severe PND symptoms depending on time, with a higher incidence especially in the immediate postpartum, which is confirmed as the most vulnerable period for the mental health of new mothers. Overall, these findings urge clinicians to increase attention towards the circadian phenotype of pregnant women, by routinely assessing chronotype during pregnancy using a simple screening questionnaire. This might help to preventively identify women who are more prone to develop PND and to support them with targeted psychological, sleep hygiene or chronotherapeutic strategies, in order to prevent negative health consequences for mothers and newborns.

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Manuscript 3

Sustained remission from perinatal depression after bright light therapy: a randomized, placebo-controlled trial

Corrado Garbazza[1,2,3], Fabio Cirignotta[4], Armando D'Agostino[5], Alessandro Cicolin[6], Sandra Hackethal[3], Christian Cajochen[1,2*], Mauro Manconi[3,7,8*] and the "Life-ON" study group

[1] Centre for Chronobiology, University of Basel, Basel, Switzerland.

[2] Transfaculty Research Platform Molecular and Cognitive Neurosciences, University of Basel, Basel, Switzerland.

[3] Sleep Medicine Unit, Neurocenter of Southern Switzerland, Ospedale Civico, Lugano, Switzerland.

[4] University of Bologna, Bologna, Italy.

[5] Department of Mental Health and Addiction, ASST Santi Paolo e Carlo, Milan, Italy; Department of Health Sciences, Università degli Studi di Milano, Milan, Italy.

[6] Sleep Medicine Center, Department of Neuroscience, University of Turin, Turin, Italy.

[7] Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland.

[8] Department of Neurology, University Hospital, Inselspital, Bern, Switzerland.

*These authors should be considered joint senior author

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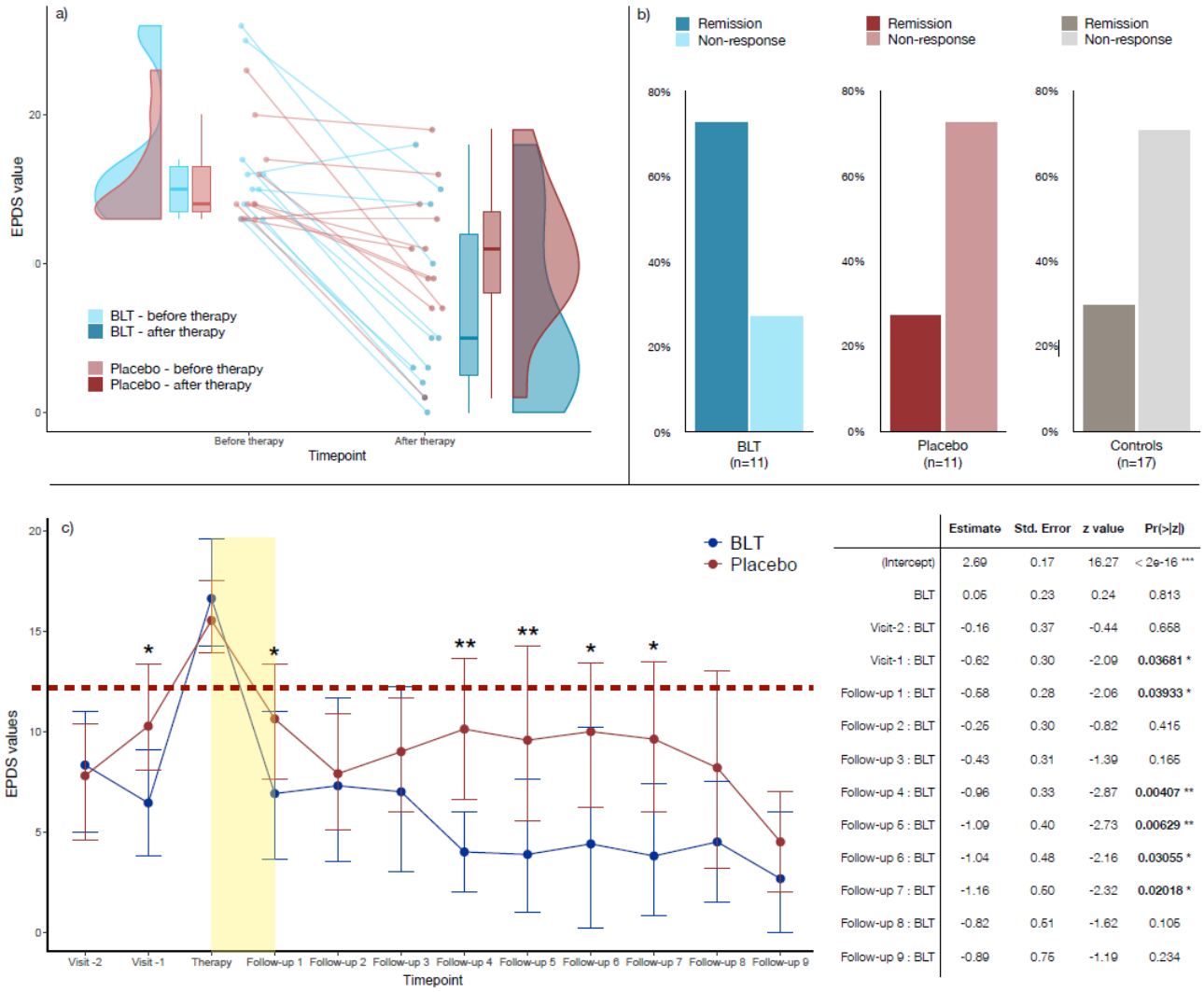
Perinatal depression (PND) is a serious complication of pregnancy, affecting ca. 12% of women during the peripartum, with potentially dramatic consequences for mothers, newborns and their families[1]. Since the identified risk factors fall into broad categories, and the safety profile of antidepressant drugs during pregnancy and breastfeeding is still debated, PND remains challenging to predict and treat, representing a major public mental health problem[2]. Bright light therapy (BLT) is a non-pharmacological intervention based on circadian science, which has been consistently proven effective and safe for treating seasonal and non-seasonal affective disorders[3]. Only a few studies have used BLT in either antenatal or postnatal depression, with overall promising but partly divergent findings[4]. Here, we present the results of the first randomized, placebo-controlled trial (RCT) aimed at testing the efficacy and safety of BLT for PND over a 12-month period.

This study is part of the "Life-ON" project, a multicenter, prospective, cohort investigation on sleep and mood changes during the perinatal period[5]. Participants without a current or recent psychiatric disorder or psychopharmacological medication, were enrolled during the first trimester of gestation and followed-up until six months postpartum. A single-blind RCT was conducted in a subsample of women with an Edinburgh Postnatal Depression Scale (EPDS) score >12 at any time point from the second trimester of pregnancy. Participants received either BLT (10'000 lux) or dim red light (DRL, 19 lux) for 6 weeks, 30 minutes in the morning, within 20 minutes after wake-up, and at a distance of 30 cm from the light box. Between-group differences were calculated using the Kruskal-Wallis and Mann-Whitney U tests for ordinal/numeric data, while the Pearson's Chi-squared and Fisher's exact tests were used for categorical data. We constructed multilevel linear models to test for the influence of time and treatment group on EPDS values and log-linear models to test for socioeconomic factors influencing PND remission, such as marital status, educational level, working and housing condition, smoking, perception of poverty, job loss or relocation in the previous six months, type of pregnancy, number of children, family and personal history of depression, previous treatment for depression, other psychiatric disorders, current and past (pre-pregnancy) alcohol consumption. Definitive parameter selection was performed via exhaustive model testing based on Akaike information criteria. Only parameters significantly improving the model were included in the construction of the definitive regression models, fitted with the restricted maximum likelihood method. The study received approval from the local ethics committees. All participants gave a written informed consent.

A total of 47 women were proposed to participate in the trial, of which 25 accepted (53%), with three participants lost to follow-up. Twenty-two women were randomized to either an active light group (BLT, n=11, median age: 33 yrs) or a placebo light group (DRL, n=11, median age: 32 yrs). Among the 22 women who developed PND during the "Life-ON" main study, but declined to be included in the RCT, five were lost to follow-up and the remaining participants were considered as an untreated control group (n=17, median age: 35 yrs). At baseline, the BLT, DRL and control groups did not differ in demographic and mood parameters, with a median (IQR) EPDS of 15.0 (13.5|16.5) vs. 14.0 (13.5|16.5) vs. 15.0 (14.0|16.0) points, respectively. After treatment, EPDS score dramatically dropped to 5.0 (2.5|12.0) points in the BLT group vs. 11.0 (8.0|13.5) points in the DRL group (Fig. 1a, p=0.15) while median EPDS values in the control group were 10.0 (7.0|13.0) points at the next follow-up visit. Among women receiving active BLT, 73% achieved remission (improvement ≥ 50%, EPDS score ≤ 12) at the next follow-up visit, in contrast to 27% in the placebo DRL group (p=0.04) and to 29% in the untreated control group (Fig. 1b). The multilevel linear model revealed a significant influence of time on EPDS score and group-time interaction, with a greater, sustained reduction in the BLT-group across the whole follow-up period (Fig. 1c). Simple log-linear regression showed a significant effect of BLT on response to treatment (β=1.96, z-value=2.05, p=0.04). When controlling for other influencing factors, best model fit was achieved including EPDS at study entry (β=-1.1, z-value=-1.8, p=0.07), BLT (β=0.6, z-value=0.2, p=0.8), loss of work in the previous 6 months (β=-2.5, z-value=-0.4, p=0.7), unplanned pregnancy (β=-3.97, z-value=-1.1, p=0.3) and positive history of depression (β=2.7, z-value=0.95, p=0.3) with Tjur's R^2=0.75. No women reported major side effects by both BLT and DRL, as assessed by the Systematic Assessment for Treatment Emergent Events at 3 and 6 weeks of treatment.

In conclusion, morning BLT induced a significant remission from PND compared to morning DRL. Remarkably, this effect was also maintained across the perinatal period, with sustained mood improvement in the months following treatment. Psychosocial stressors indicative of a more fragile living condition at baseline reduced the overall likelihood of a positive response to treatment. In contrast to previous studies, which used placebo lights in a range between 70 and 600 lux[4,5], while illuminance levels as low as 30 lux has been recently demonstrated to affect the human circadian system, we adopted a rather low-intensity control light, likely further differentiating the neurobiological effects of the experimental light interventions. Finally, BLT showed an excellent safety profile and was well-tolerated in perinatal women, thus

representing a valid therapeutic strategy in this vulnerable population. Our positive results give reason for the launch of larger RCTs including even longer observation periods.



	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	2.69	0.17	16.27	< 2e-16 ***
BLT	0.05	0.23	0.24	0.813
Visit-2 : BLT	-0.16	0.37	-0.44	0.658
Visit-1 : BLT	-0.62	0.30	-2.09	**0.03681** *
Follow-up 1 : BLT	-0.58	0.28	-2.06	**0.03933** *
Follow-up 2 : BLT	-0.25	0.30	-0.82	0.416
Follow-up 3 : BLT	-0.43	0.31	-1.39	0.165
Follow-up 4 : BLT	-0.96	0.33	-2.87	**0.00407** **
Follow-up 5 : BLT	-1.09	0.40	-2.73	**0.00629** **
Follow-up 6 : BLT	-1.04	0.48	-2.16	**0.03055** *
Follow-up 7 : BLT	-1.16	0.50	-2.32	**0.02018** *
Follow-up 8 : BLT	-0.82	0.51	-1.62	0.105
Follow-up 9 : BLT	-0.89	0.75	-1.19	0.234

Figure 1: Remission and non-response among the different light conditions and influence of time and intervention group on EPDS values across the follow-up period. a) Raincloud-plot with density plot, boxplot and individual EPDS values per patient pre- and post-treatment intervention. b) Percentage of remission and non-response to treatment stratified for the groups exposed to experimental light conditions and the untreated control group. c) EPDS values across the follow-up period relative to the beginning of therapy (yellow vertical bar) stratified for experimental light conditions. Mean time-intervals between the different follow-up visits were 55 days (min. 6 days, max. 132 days). The red dotted vertical line represents the cut-off value of EPDS=12. Right hand side: Results of the multilevel linear regression model predicting EPDS values by intervention group, time (not shown), and group-time interaction. BLT: bright light therapy. Std. Error: Standard error. Pr(>|z|): p-value. * P<0.05. ** P<0.01. *** P<0.001 (group-time interaction).

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GENERAL DISCUSSION

Summary of research findings

In our systematic review and meta-analysis of studies using PSG during pregnancy, we provided evidence that the subjective experience of sleep deterioration, that many women report during pregnancy, is related to objective alterations in sleep architecture, particularly during late gestation. These mainly consists in a reduction of sleep duration and a fragmentation of sleep continuity, with an increased number of awakenings and superficial sleep stages (N1, N2), and a simultaneous decrease of slow-wave sleep (SWS), rapid eye movement (REM) sleep, and sleep efficiency (SE). Through a quantitative analysis (meta-analysis), we calculated a significant reduction in total sleep time (TST) by 26.8 min (pooled weighted mean difference - WMD, 95% CI = 12.14-41.56) between the first and third trimester of pregnancy, as well as a reduction of SE by 4% (pooled WMD, 95% CI = 1.50-6.65) within the same time frame.
We also found that, despite several physiological factors, such as hormonal fluctuations, anatomical changes, and psychological variables, may play a role in the subjective worsening of sleep quality across gestation, is not pregnancy per se, that causes major PSG-assessed sleep disorders in healthy and normal-weight women. Rather, it is likely the combination of predisposing factors, such as obesity, higher maternal age or hypertension, and physiological changes occurring during pregnancy, that may contribute in particular to the development of obstructive sleep apnea (OSA) in at-risk pregnant women.

Chronotype has emerged as a factor associated with a time-dependent, greater severity of PND symptoms, which may help identifying women who are more likely to experience a worsening of mood during the perinatal period. Evening chronotypes, as compared to the other chronotypes, seem to be particularly vulnerable to PND. This occurs especially in the immediate postpartum, which normally also corresponds to peak in PND incidence, as well as three months after childbirth, when many women return to work and must therefore cope with both work commitments and those related to the care of the newborn. Although the survival analysis did not show a statistically significant influence of chronotype on the overall risk of PND, a trend towards an increased risk for PND in evening chronotypes and a reduced risk for intermediate types, as compared to morning types, was observed. Furthermore, in line with the literature, pregnant women with evening chronotype in the Life-ON study were more likely subject to

health problems and negative pregnancy outcomes, such as gestational diabetes mellitus and caesarean delivery, than the other chronotypes, and presented adverse sociodemographic characteristics and lifestyle attitudes, that are commonly associated with a higher risk for PND. However, after carefully controlling for all these factors, evening chronotype remained significantly associated with more severe PND symptoms depending on time of assessment.

Finally, in a classical RCT testing 6-week morning BLT (10'000 lux) vs. a low illuminance DRL (19 lux) for treating PND, the active light intervention (BLT) showed a remarkable efficacy in inducing PND remission compared to the inactive DRL. The multilevel linear model revealed a significant influence of time on EPDS score and group-time interaction, with a greater and sustained reduction in the BLT-group across the whole follow-up period. Furthermore, BLT was found to be safe and well tolerated by women with PND, thus proving to be a valid therapeutic option in these patients.

Discussion

Perinatal depression represents a major public mental health problem and a serious burden for women, their children, and families, as well as for society as a whole. The etiology of PND is likely multifactorial and future research should particularly focus on the gene-environment interaction model to better characterize women at risk for developing PND. In these individuals, in fact, it is likely that a certain genetic background combined with environmental factors, such as stressful life events, low socioeconomic status, and pregnancy complications, may predispose to PND[221]. In addition, given the large variation in global prevalence rates of PND, which is mainly related to income disparities, poverty, and maternal/infant mortality, future studies should investigate which factors are associated with different risk levels across various racial/ethnic and income groups, in order to early identify and assist women at highest risk[29].

There has been a growing interest in the last few decades in researching biomarkers of PND by using different methods and approaches[222]. However, while the characterization of especially (epi)genetic and hormonal predictors and biomarkers of PND seems promising, none of these is currently eligible for clinical use, as research findings are so far inconsistent[223].

Sleep and circadian rhythm disruption are common findings in women during the perinatal period and may have an important, still underestimated and -investigated, role in the

pathogenesis of PND. Thus, the identification of specific sleep and circadian risk factor for PND may critically contribute to the implementation of preventive strategies and therapeutic approaches for the affected women.

There is evidence that different trajectories in subjective sleep quality across the perinatal period can be identified, and that women with the worst sleep quality during pregnancy are more likely to experience severe depressive symptoms after delivery[224]. Similarly, poor sleep quality in the early postpartum period has been suggested to be an independent predictor of later PPD[225].

However, most studies on sleep disturbances in the peripartum period are based on subjective assessment methods, typically self-administered questionnaires to assess sleep quality and insomnia. In contrast, there is a lack of research on changes in objective sleep and rest-activity parameters in perinatal women, which can be recorded using PSG and actigraphy.

By systematically reviewing the available studies reporting PSG variables during pregnancy, we found that sleep disturbances are common and that a full polysomnographic evaluation is sometimes preferable to self-report methods. This is, in fact, the most accurate method for sleep evaluation and may provide relevant information that is necessary to make a correct diagnosis of sleep disorders according to the international guidelines, and to overcome the bias due to under- or overestimation of subjective sleep problems.

Overall, research studies using PSG in pregnant women to date are scarce. In particular, there is a lack of longitudinal investigations exploring changes in sleep variables in the same individuals at different timepoints, e.g., before, during, and after pregnancy. This would help creating large datasets in order to define normative PSG values for each trimester of pregnancy and the postpartum. Also, it would be desirable to establish an expert consensus on the minimal parameters to be reported and on the sleep scoring criteria to be adopted in PSG studies on pregnancy. Finally, the information obtained by PSG recordings should be integrated with that of questionnaires by using specific algorithms, in order to better predict pregnancy-related clinical outcomes and initiate early treatment for pathological conditions, which represent a risk factor for the health of the mother and the fetus. Ultimately, PSG may also be a useful tool for evaluating the efficacy of therapeutic interventions for sleep disorders during pregnancy, such as cognitive-behavioral therapy for insomnia (CBT-I) and continuous positive airway Pressure (CPAP) for the treatment of sleep-disordered breathing, respectively.

Early prevention and treatment remain the cornerstones in the clinical management of PND. Both, however, present challenges in their implementation in everyday practice.

On the preventive side, as recently stated by the US Preventive Services Task Force (USPSTF), "there is no accurate screening tool for identifying women at risk of perinatal depression and who might benefit from preventive interventions"[226]. Furthermore, it is sometimes difficult to clearly distinguish women at risk vs. those suffering from PND[227]. Although research findings indicate that particularly women with a history of depression, subthreshold depressive symptoms, and a range of unfavorable socioeconomic and demographic factors may be considered at risk of developing perinatal mood disorders, it is complex to perform a risk assessment based on information from the clinical or sociodemographic anamnesis, as it is unclear to what degree these factors predict PND occurrence[227]. Future research may provide new, validated, and easy-to-use screening tools that may help detecting women who should be referred to treatment. Moreover, new biomarkers of stress, inflammation, or genetic polymorphisms will probably be identified, that may indicate women who are particularly vulnerable to PND.

As for the screening tools, these should preferably not burden the clinical pathway of pregnant women, which already includes multiple visits before and after childbirth. Also, it must be considered that clinicians providing gynecological/obstetrical care may not have the time or adequate training to assess maternal mental health and identify women who should be referred for further psychiatric/psychological evaluation.

In this regard, we found that administering a quick and easy questionnaire for chronotype assessment during early pregnancy may provide valuable information about the circadian phenotype of women and their likelihood of experiencing more severe PND symptoms during the perinatal period. Although there are insufficient data on the interaction between chronotype and mood in the peripartum period to conclude that, in particular, evening chronotype is a risk factor for PND, we found that, in our large sample of about 300 pregnant women from the "Life-ON" study, evening types had a time-dependent, higher risk for developing PND symptoms in the immediate postpartum period than the other chronotypes. Moreover, they showed less healthy lifestyle habits and were more likely to suffer from gestational diabetes mellitus, as well as to undergo caesarean delivery as compared to other chronotypes.

Thus, in line with a broader literature existing on the association between chronotype and health outcomes[228], our findings confirmed that evening circadian preference is a trait

commonly linked to adverse physical and mental health factors, both in pregnant women and in the general population, which should therefore be considered and detected. Given that chronotype can be easily assessed by using questionnaires such as the MEQ and MCTQ and in light of the results of our study, we recommend to routinely screen for chronotype in early pregnancy and to pay particular attention in the follow-up visits to mood changes in women with an evening chronotype. Since the MEQ and MCTQ allow the immediate computation of a final score corresponding to a specific chronotype, this information could also be inserted in the records of pregnant women and be available to any clinician reviewing the clinical history of the patients.

The knowledge of chronotype could be even more valuable if combined with an objective assessment of the rest-activity rhythm by means of actigraphy for at least one week. In fact, it is well-known that evening chronotypes, due to their biological predisposition to fall sleep late in the evening and wake up late in the morning, tend to accumulate sleep debt during the week, since they have to set an alarm clock early in the morning in order to fulfill social or work obligations. This is also true for pregnant women, as in our society the maternity leave is increasingly shortened, and it is not infrequent that women in late gestation are still actively working. There is also evidence that sleep deprivation is an underlying mechanism that leads to a deterioration of mental health in evening chronotypes[229] and actigraphic recordings provide a good estimate of the amount of sleep deficit that an individual undergoes in a certain time frame. Therefore, the combined assessment of chronotype and rest-activity rhythms may deliver a relevant clinical information to set up a tailored early intervention based, for example, on cognitive-behavioral and/or chronotherapeutic (light therapy) approaches for sleep-deprived pregnant women with late chronotype.

On the therapeutic side, pharmacological approaches to PND still present many barriers related to the safety and acceptance of medications during pregnancy and lactation. As a consequence, only a few studies have rigorously evaluated pharmacological treatments, because perinatal women are general excluded from drugs trials, and no conclusion was ultimately made regarding their efficacy and safety due to a lack of data[230]. Only recently, the first drug for the treatment of PPD (brexanolone) has been approved by the Food and Drug Administration (FDA)[231], while an additional compound is currently undergoing clinical trials (zuranolone)[232]. A further, relevant gap is represented by the substantial absence of studies evaluating the long-term consequences in children of mothers who were taking antidepressants during

breastfeeding. This especially applies to SSRIs, that are currently prescribed as fist-line therapy for PND[191], despite the lack of longitudinal studies with adequate follow-up assessment of child health outcomes[20].

The antidepressant effects of BLT for affective disorders are well established, and there are several reasons for implementing BLT in clinical practice as a standard treatment for PND. Apart from the advantages of an affordable, easy-to-use, home-based, and essentially safe therapy, from a physiological point of view, we have extensively discussed how BLT may exert its beneficial effects on mood and behavior in perinatal women *(see pages 18-21).* These include the potential counterbalance of insufficient light exposure, the modulation of hormonal levels, the improvement of pregnancy-related sleep disturbances and fatigue, and the adjustment of serotonergic dysregulation. However, the studies published so far on the efficacy of BLT for PND are few, with partly divergent results, and characterized by numerous limitations[210].
First, only four out of six studies are RCTs. Second, the placebo light used in studies involving a control group has generally a too high illuminance level to rule out its possible impact on the circadian system, making it difficult to compare the effects of the active light vs. the placebo light intervention. Third, the sample sizes are small, probably due to the difficulties in recruiting pregnant women for clinical trials and to the scarce compliance, related to objective logistic problems, that is common in this population. Furthermore, all studies focus on depression with antenatal or postpartum onset, although this dichotomy is no longer present according to the current DSM-V definition of PND. Also, none of them includes a sufficient long follow-up to assess the long-term effects of BLT on mood, perhaps assuming that these would vanish once the protocol for daily BLT is terminated.

We here presented new findings from the first RCT aimed at testing the efficacy of 6-week morning BLT vs. morning DRL for the treatment of PND occurring at any time during a 12-month observation period across delivery. We found that not only BLT can induce a rapid and significant remission from PND compared to DRL, but, interestingly, that mood improvement can last even long after treatment completion. We believe that, considering new evidence that illuminance levels as low as 30 lux can have an impact on the human circadian system[233], the use of a rather low-intensity control light in our study helped to clearly distinguish the neurobiological effects of the two experimental light interventions.
Thus, on the one hand our positive results provide new evidence that BLT may be an effective therapeutic strategy in patients suffering from PND with antenatal and/or postnatal onset, who may prefer a chronotherapeutic approach to another type of pharmacological or

psychotherapeutic treatment. On the other hand, they open the way to larger RCTs with even longer observation periods, which may elucidate the short- and long-term effects of BLT for perinatal mood disorders. Further research should also investigate the mechanisms underlying the therapeutic action of BLT for PND and the feasibility of mixed modality treatments (e.g. integrated chronotherapy[234], combination of CBT-I and light/dark therapy[235]), which should be adequately tested in comparative effectiveness trials. Finally, also in our study we faced the problem of a low participation, which is common to many interventional trials, especially in the perinatal period, and resulted in a reduced sample size. However, in our experience, unlike pharmacotherapy (which raises understandable concerns about the risks for the fetus and the newborn) or psychotherapy (which may be expensive and poorly accessible), in the case of BLT the major barrier for women was represented by the logistical difficulty of sitting for half an hour in the morning and for 6 weeks in front of a light box. Therefore, there was no a priori distrust or rejection of BLT as a therapeutic tool per se, which was instead well accepted and tolerated by patients, but rather an issue of time compatibility with the morning commitments of women during pregnancy (working hours or care of other children at home), as well as in the postpartum (nursing of the newborn). In this regard, new possibilities are emerging from portable light therapy devices (glasses), that could allow women to be more mobile during the light therapy sessions. There is still no solid evidence that these devices are as effective as the traditional lamps for BLT, as only few of them have been accurately tested and validated for clinical use so far. However, new studies are currently ongoing and some of them specifically target depression in women during the perinatal period[236].

Strengths and limitations

The major strengths of our review manuscript on polysomnographic studies of pregnancy are represented by its novelty and its rigorous systematic approach. We identified a gap in the literature, due to the lack of a comprehensive and methodologically sound overview of investigations using PSG, as the most accurate method for sleep assessment, in pregnant women. We carefully followed the PRISMA guidelines and the indications of the target journal (Sleep Medicine Reviews), which has the highest impact factor in the sleep medicine field (IF 2020: 11.6) and only publishes review manuscripts, to write the first systematic review on this subject. In addition, we were able to perform a quantitative analysis (meta-analysis) of the

data collected on two relevant sleep variables (TST and SE), which corroborated the results of our review by providing an objective estimation of sleep deterioration across pregnancy.

The main limitation of this work is related to the large heterogeneity of the reviewed studies, which considerably differ in design, population examined, sample size, time of pregnancy and PSG scoring criteria. This prevents from drawing definitive conclusions about most outcome parameters and from pooling the data to perform a broader meta-analysis. We can also not exclude a reporting bias for some studies, due to a general tendence to underreport the entire polysomnographic results, selecting those that address the specific research question, or possibly only the positive ones. We excluded PSG studies conducted on very small samples (<10 women), as well as reduced montage polygraphic studies (without EEG, EMG and EOC derivations), although these are increasingly used in clinical practice for their practicality and cost sustainability, compared to PSG. Finally, most reviewed studies report PSG data from a single night, although a habituation effect (also called "first night effect") is well known in sleep research and should always be considered, especially if the sleep recording was not performed in the home environment[237].

The second and third manuscripts presented in this thesis base their strengths on the general framework of the Life-ON project. This multicenter, large-scale, cohort study was designed as a comprehensive, longitudinal investigation of numerous factors influencing the perinatal period, in order to address several questions concerning PND, including epidemiology, pathophysiology, prevention, and treatment. It included a long observation period, from the first trimester of pregnancy to 12 months postpartum, for a total of 18 months, which, while representing a significant commitment to participants and investigators, added considerable value to the data collected, and the analyses carried out so far.

Thus, for example, our analysis of the influence of chronotype on maternal mood was the first to focus not only on either pregnancy or the postpartum period, but to examine data collected at 9 consecutive timepoints across the perinatal period, in 4 participating centers, therefore reducing the risk of recruitment bias. Moreover, to avoid the common overlap between the diagnoses of PND and "baby blues" *(see page 3-4),* we adopted a more conservative cutoff value of the EPDS (> 12), which likely allowed us to identify the "real" cases of PND and distinguish them from milder forms of postpartum mood disturbances.

Our RCT on the efficacy of BLT for treating PND (substudy Life-ON 2) also shares the same strengths of the Life-ON main study in terms of the large population examined and the extended

observation period across both pregnancy and the postpartum. This made it possible to detect and report for the first time the long-term effects of BLT on PND with onset at any time before and/or after childbirth. A significant value of this study, differently from previous trials, was also the use of a low-illuminance placebo light in the control group, which likely maximized the differences in neurobehavioral effects of the two light interventions.

As for the study limitations, the Life-ON project was affected in its course by a relatively high drop-out or lost to follow-up rate, which led to missing data from a proportion of women in respect to the whole study sample. This was expected, as it is a commonly observed issue in prospective studies with a long follow-up phase, in particular if they target a population of perinatal women, who are burdened by objective logistic problems. Moreover, chronotype was assessed only using the MEQ, which in chronobiological research has been questioned for its intrinsic property of evaluating the sleep-wake preferences of the individuals screened, rather than the effective time of sleeping[238]. Finally, only 17 women (5.68%) among 299 participants were classified as evening chronotypes, representing a minority of cases, which may have influenced our findings.

Our RCT on BLT for PND was mainly limited by the low participation rate, which links it to the trials already present in the literature on BLT for either pregnancy or postpartum depression. As discussed above, the need to test BLT in larger samples of patients, in order to validate its efficacy in a more robust way, often clashes with the practical difficulty, especially for women in the perinatal period, to find the time to sit in front of a light box in the morning for 30 minutes and for 6 weeks. Thus, a future research goal should be to find alternative solutions to foster light exposure and its therapeutic properties, e.g., by more carefully using daylight, implementing lighting systems in the domestic environment, or developing portable light therapy devices.

Conclusion and outlook

Perinatal depression is a severe mental disorder with disruptive consequences on the health and well-being of mothers, children, and their families. Despite a growing body of research over the past few decades has considerably increased the knowledge of this disease, there is general consensus that PND is still prevalent, underrecognized and undertreated. Therefore, experts agree that the greatest contribution to reducing the burden of this condition on society in the

future will come from the spread of universal screening and the implementation of accessible and affordable treatments for every woman.

With this in mind, for the purpose of this thesis, we decided to investigate some specific aspects related to PND, that is the intrinsic features and objective changes characterizing sleep during pregnancy and their relationship with perinatal health outcomes, the role of circadian factors (chronotype) on mood in the perinatal period, and the efficacy and safety of BLT for treating PND.

The significance of this work as a whole therefore lies in having addressed some of the most urgent issues regarding PND, by:

1) conducting the first methodologically rigorous systematic review and meta-analysis of polysomnographic studies during pregnancy, which provides an exhaustive overview of how sleep architecture modifies across gestation in healthy women and in pregnancy-relates complication; this likely represents a milestone of background information for any researcher wishing to further explore this subject in the future
2) showing that inter-individual differences in circadian preferences should be considered and early assessed during pregnancy, as information about "eveningness" might help identifying a subgroup of women, who are more likely to develop PND symptoms, especially in the immediate postpartum, and who should be therefore more closely followed-up, also from a psychological point of view, across the perinatal period; this ultimately led us to suggest a systematic evaluation of chronotype in all pregnant women through the administration of a quick and easy screening tool, such as a chronotype questionnaire, in order to early recognize mothers potentially at risk of PND, as recommended by the public mental health prevention strategies
3) providing new evidence that BLT is an effective and safe treatment for women with PND, with even long-lasting effects; this supports the addition of this chronotherapeutic based on solid scientific rationales, well-tolerated and home-based, to the equipment available to clinicians for the treatment of PND, thus responding to the need for affordable, easy-to-use, and accessible therapies for patients

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The large number of variables collected during the Life-ON study allows to predict that, by looking at the data, many of which have not yet been analyzed, several other research questions can still be formulated and answered. For example, as a part of this project, a biobank of blood samples repeatedly collected from the participating women during the perinatal period was created, which may represent an important resource for future analyses aimed at examining the role of genetic, hormonal, and neuroinflammatory factors in the pathophysiology of PND.

Here we would like to provide an outlook on further analyses of the Life-ON data that are currently underway and on the findings that have emerged so far:

1) as part of the Life-ON 3 substudy *(see page 29),* 75 pregnant women with no severe symptoms of PND (EPDS < 12) at visit 2 (20^{th}-25^{th} gestational week) participated in an open-label study with morning BLT for preventing PND. The basic hypothesis was that light exposure during the second trimester of pregnancy might be protective against the later occurrence of PND during the third trimester of gestation or the postpartum. The light therapy protocol was identical to that used in the Life-ON 2 substudy, but since the Life-ON 3 was essentially designed as a proof of concept study, no control group with placebo dim light was included. However, women who were enrolled in the Life-ON main observational study, but did not participate in any substudy with light therapy, were considered as control group for the data analysis.
   Preliminary results showed that BLT administration during the second trimester of pregnancy did not influence the overall occurrence of depression during the following perinatal period in the treatment group, as compared to the control group. Based on these findings and in light of the results of the Life-ON 2 substudy, it might be concluded that BLT is an effective treatment for women affected by PND, but does not provide any substantial protection to healthy women against a later occurrence of depression, and can therefore not be suggested as preventive strategy for PND.

   ***Garbazza** et al. "Bright light therapy to prevent perinatal depression, an open-label study" (manuscript in preparation)*

2) one of the aims of the Life-ON main study was to objectively assess sleep and sleep disorders during the perinatal period. Participating women underwent a home-based PSG between the 20^{th}-25^{th} gestational week and completed several sleep questionnaires at 11 time points during pregnancy and up to one year postpartum (see Table 6). At the

end of the study, full-night polysomnographic data were available from 353 women, which represents the largest database of PSG recordings on pregnancy obtained from a single study. Poor sleep quality was reported by 34% of women in the first trimester of pregnancy, 46% in the third trimester, and 71% in the first month after delivery. A similar trend was seen for insomnia. Daytime sleepiness peaked in the first trimester, affecting 30% of women, and decreased in the third trimester to 22%. The incidence of restless legs syndrome (RLS) during pregnancy was 27%, with a peak in the third trimester. Sleep-disordered breathing had instead a low incidence (4.2%). A periodic limb movements during sleep (PLMS) index > 4 was found in 55% of women, while 24% had a TST < 6 hours, and 30.6% a SE < 80%.

In summary, the Life-ON study, as the largest polysomnographic investigation in pregnant women to date, also involving a thorough longitudinal subjective assessments of sleep quality, showed that insomnia, sleepiness and RLS are highly frequent during pregnancy, with insomnia and daytime sleepiness often persisting into the first months postpartum. Sleep-disordered breathing was infrequent at time of PSG recording (second trimester of pregnancy), while high PLMS scores were found, which were associated with a higher incidence of RLS.

M Manconi, LC van der Gaag, F Mangili, L Clivio, ***C Garbazza****, S Riccardi, S Mondini, F Furia, E Zambrelli, A D'Agostino, A Cicolin, F Cirignotta, and the Life-ON Study Group. "Sleep and Sleep Disorders During Pregnancy and Postpartum: The Life-ON Study" (manuscript in preparation).*

3) several tools for depression assessment were used in the Life-ON study, that differ in the type of administration, with some of them being semi-structured interviews (HDRS, MADRS) and other self-report scales (EPDS, VAS). A direct comparison between these instruments and their validation against a structured, clinician-rated, psychiatric interview (MINI) in a large sample of women at risk or suffering from PND is currently lacking. This, however, would help define an optimal selection of assessment tools for PND. Moreover, given the current high variability of PND prevalence rates found in the literature (9%-20%), that likely reflects the disparate methodologies employed over time and across cultural contexts, such analysis may even indicate which is the most appropriate tool to measure PND prevalence. An ongoing, preliminary data analysis in collaboration with the Swiss AI Lab IDSIA (Istituto Dalle Molle di Studi sull'Intelligenza

Artificiale) showed that: the best model predicting EPDS > 9 is given by the combination of the MADRS and VAS scale; the role of HDRS in prediction of other scales is limited and this instrument can be discarded without losing prediction power; there are changes in scales correlation between pre- and postpartum; patients who have higher depression scores at study entrance are more prone to drop-out in the follow-up.

Garbazza *et al. "Measuring perinatal depression: psychometric properties of assessment instruments in the Life-ON study" (manuscript in preparation)*

Finally, we would not like to conclude this work by giving the impression that, after the Life-ON study, most of the research efforts on PND are behind us. On the contrary, this vast and intensive project has allowed us to understand the numerous and multifaceted aspects of this challenging mental disorder and the multiple research areas that remain to be explored.
Some of these include, for example, the evaluation of racial/ethnic disparities in accessing PND screening and treatment services[25]. In this regard, more studies on the impact of the existing mental health policies on mothers, especially from underserved populations as racial/ethnic minorities and low-income women, are warranted[25].
Future research efforts should also be aimed at conducting safe and rigorous trials of pharmacologic treatments for PND, and longitudinal studies on the long-term neurodevelopmental consequences in children of mothers with PND, who were treated (or not) with psychotropic medications during pregnancy and the breastfeeding period.
In general, it is still not clear which mediating and moderating mechanisms determine the long-lasting effects of PND on children, and there is a gap in translational research investigating the role of neuroinflammation and microbiome in the pathophysiology of mother-infant interaction, which could also pave the way to complementary health approaches (probiotics) in comparison to conventional therapies.

As regards the field of sleep research, future studies should implement objective tools for recording sleep-wake parameters and include control groups in the analysis of depressive symptoms during the perinatal period. This would help to better understand the relationship between sleep deprivation/disruption and PND, and the underlying physiological mechanisms. Finally, interventions to prevent or treat PND should be studied, that also target the improvement of sleep quality by providing patients with cognitive-behavioral strategies to cope with stress, defuse repetitive negative thoughts and manage symptoms of insomnia.

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Declaration of own contributions to the PhD project

I declare that I have written the thesis "Sleep and chronotype during pregnancy, and the bright light treatment of perinatal depression" in full autonomy and independence, and that I have not submitted it to other universities or faculties of the University of Basel.

I also declare that I have made substantial contributions to the manuscripts that constitute this thesis, with the help of the co-authors specified therein, in the conception and design, acquisition, analysis and interpretation of data, drafting and revision of the articles.

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