Depression during Pregnancy

Light, seasons and sleep

Babette Bais

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The lines on the front of this thesis represent the wavelength of white light, the seasonality of depressive symptoms and a polysomnogram of REM-sleep.

The studies described in this thesis were performed at the Department of Psychiatry, Erasmus University Medical Center, Rotterdam, the Netherlands.

Depression during Pregnancy

light, seasons and sleep

Depressie tijdens de zwangerschap

licht, seizoenen en slaap

Proefschrift

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam

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Prof.dr. R.C.M.E. Engels

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Promotor: Prof.dr. W.J.G. Hoogendijk

Overige leden: Prof.dr. A. Franx

Prof.dr. G.T.J. van der Horst

Dr. Y. Meesters

Copromotoren: Dr. M.P. Lambregtse-van den Berg

Dr. A.M. Kamperman

Voor alle zwangerschappen die niet verlopen zoals je had gehoopt.

Contents

Chapter 1

Introduction

This thesis focuses on depression during pregnancy (or antepartum depression), with a special focus on the effects of light, seasons and sleep. In the next paragraphs of this introduction, a brief overview of depression and depression specifically during pregnancy will be provided, followed by the focus of the different parts of this thesis, study populations, outline and aims of this thesis.
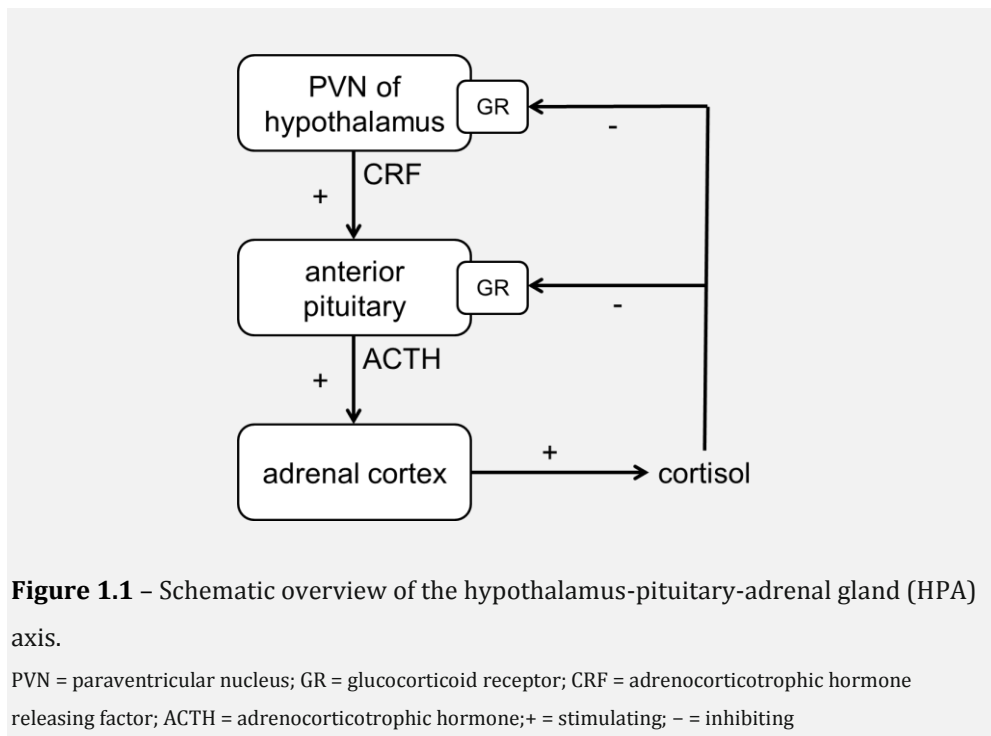
Depression

Depression is a serious mood disorder with the highest disease burden worldwide, according to the World Health Organization [1]. It is estimated that 4.4% of the global population suffers from depression, with females being more often affected than men [1]. According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), depression is characterized by a depressed mood and/or anhedonia, for a minimal duration of two weeks. In addition, patients experience at least three or four of the following symptoms: significant weight loss or gain or significant changes in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness and/or guilt, diminished ability to think and/or concentrate or recurrent thoughts of death with potential suicidal ideation or even attempts [2].

The cause of depression is largely unknown. Since hyperactivity of the hypothalamus-pituitary-adrenal gland (HPA) axis is associated with depression, it is thought that this axis plays a crucial role in the pathophysiology – as cause or consequence. Depression is thought to be related to a reduced inhibition of the HPA axis feedback loop by cortisol, due to impaired functioning of the glucocorticoid receptor (GR) [3]. Figure 1.1 shows a schematic overview of the feedback loop of cortisol.

The HPA axis regulates secretion of cortisol in response to stress [4]. HPA axis activity is controlled by the corticotropin-releasing factor (CRF) secreted by the paraventricular nucleus (PVN) of the hypothalamus. CRF activates the anterior pituitary to produce and secrete adrenocorticotrophic hormone (ACTH), which in turn stimulates the production and release of cortisol from the adrenal cortex [3, 4]. Cortisol inhibits both CRF and ACTH through the GR [3, 4]. In patients with

depression, this feedback loop is dysregulated, resulting in increased basal cortisol levels [3].

Figure 1.1 – Schematic overview of the hypothalamus-pituitary-adrenal gland (HPA) axis.

PVN = paraventricular nucleus; GR = glucocorticoid receptor; CRF = adrenocorticotrophic hormone releasing factor; ACTH = adrenocorticotrophic hormone;+ = stimulating; – = inhibiting

Depression during pregnancy

Contrary to earlier beliefs, pregnancy does not protect the mother from depression. A systematic review of 96 articles showed that approximately 12% of pregnant women suffer from depression [5]. Women who suffer from antepartum depression have a higher risk of postpartum depression as well [6]. According to the DSM-5, postpartum depression (often incorrectly stated as 'postnatal depression') has an onset within four weeks after delivery [2], but clinicians often use a broader definition in practice, such as six months or even a year postpartum [7]. However, a considerable proportion of women with postpartum depression has an onset during pregnancy or even before conception [8].

Many risk factors for antepartum depression have been identified, such as history of depression, fear of childbirth, lack of social support and low socio-economic status [9, 10].

Maternal depression during pregnancy has been associated with various adverse birth outcomes, such as prematurity and being small for gestational age [11, 12]. Additionally, children show more often cognitive, emotional and behavioral problems in childhood, adolescence and adulthood [13] and they are more at risk of suffering from depression themselves [14]. How intra-uterine child development is influenced by maternal depression has yet to be determined. Possible mechanisms are maternal cortisol crossing the placenta, placental secretion of CRF, which stimulates both maternal and fetal cortisol, and reduced blood flow to the fetus, causing fetal growth restriction [11, 15-18]. Increased maternal levels of cortisol might program the intra-uterine developing HPA axis of the child, making it susceptible to increased stress reactivity in future life [13, 19]. Moreover, maternal cortisol can directly influence fetal brain development, such as that of the amygdala and the hippocampus [20-23]. Additionally, other intra-uterine factors that are indirectly associated with maternal depression, such as unhealthy nutrition [24] and substance use [25], may affect fetal development. Finally, genetic factors and postpartum environmental factors could contribute to the higher risk of cognitive, emotional and behavioral problems in offspring [26, 27].

The peripartum period is thus a critical time period, in which fetal development determines not only the health of the (unborn) infant, but also that of following generations [28]. Therefore, early detection and treatment of antepartum depression is critical for both mother and infant.

Light therapy

In non-pregnant patients, guidelines propose psychotherapy, antidepressant medication or a combination of both as treatment for depression. However, clinical practice shows limited relevance of these guidelines for the treatment of depression during pregnancy, as psychotherapists are not always directly available, postponing treatment for several months or more, which may result in the child not benefitting from the maternal treatment. Other limitations with psychotherapy are motivation to reflect on behavior and emotions and good language skills, which both limits the applicability of psychotherapy in these patients, considering the majority of these women have a lower socioeconomic background and other problems that interfere

with compliance [29]. Therefore, women may be treated with antidepressant medication. In the Netherlands, approximately 2-3% of pregnant women use antidepressants [30-32]. In the United States, this prevalence is approximately 6-7% [33-35], but this could even be as high as 15% in some states [36]. However, the use of antidepressants is still controversial, due to potential harmful fetal effects [37, 38]. For example, increased risks have been found for cardiovascular malformations [39], persistent pulmonary hypertension of the neonate [40] and preterm delivery and low birth weight [41]. Additionally, international guidelines in the pharmacological treatment of antepartum depression are not always consistent [42] and adherence to national guidelines is low [43], which could possibly result in unwanted variation in current practice. Despite this, antidepressant use during pregnancy is increasing. Not only in the Netherlands [32, 44], but in other European countries and the United States as well [45-47]. Therefore, it is urgent to investigate alternative approaches to treat antepartum depression, such as bright light therapy (BLT). The efficacy of light therapy in treating non-seasonal depression has been shown by a Cochrane review [48] and more recent systematic reviews and meta-analyses [49-52]. An open trial of BLT in pregnant women showed improvement of mean depression ratings by 49% [53]. Two small randomized controlled trials (RCTs) showed significant improvement of depressive symptoms among pregnant women exposed to BLT compared to placebo [54, 55]. Although these studies provide evidence for the effectiveness of BLT for depression during pregnancy, their sample size is small and follow up was limited to the end of the intervention period.

In this thesis, we aimed at studying a larger sample size to study whether BLT is an effective and safe treatment for antepartum depression. Additionally, women were followed up until eighteen months postpartum.

So how does light therapy work? Light is the most powerful environmental stimulus, or 'zeitgeber', that synchronizes the suprachiasmatic nucleus (SCN), also known as the 'biological clock', with the environmental day-night rhythm [56]. Light hits the retina and intrinsically photosensitive retinal ganglion cells (ipRGCs), which are the output neurons of the retina, project via the retino-hypothalamic tract to the SCN, and thus influencing circadian rhythm [56-58], which may indirectly benefit depressive symptoms [59]. However, not only do ipRGCs project to the SCN, they also project to other brain regions, such as the medial amygdala and the lateral

habenula, which are important brain regions in the regulation of mood, and thus directly influencing depressive symptoms [56-58].

The SCN controls the HPA axis, which is seen in the association between decreased inhibitory control of the SCN and HPA axis hyperactivity [60]. Light synchronizes the SCN with the environmental day-night rhythm, influencing the HPA axis and thus cortisol levels. Next to cortisol, light also influences the circadian rhythm of melatonin [61-63].

Seasons

The effects of BLT have been shown in non-seasonal depression [48-52], but was first used as a treatment for seasonal affective disorder (SAD), a condition of reoccurring depressions during fall and winter, with remissions in spring and summer [64, 65]. In 1984, the first cases of SAD have been described by Rosenthal and colleagues, together with preliminary findings on treatment with light therapy [66]. However, in contrast, some SAD cases are not characterized by depressive episodes during autumn and winter, but during spring and summer [67, 68].

Seasonal variability has also been found in depressive symptoms during pregnancy [69] and after pregnancy in the postpartum period [70-75]. However, seasonality in postpartum depressive symptoms has not been shown by all studies [76-78]. These different findings may be explained by geographical location (and with that latitude), method of assessment (such as the use of specific questionnaires) and other characteristics of the study.

Since SAD and light therapy are intertwined to a high extent, we studied the seasonality of depressive symptoms during pregnancy in this thesis. We hypothesized that if seasons influence depressive symptoms during pregnancy, it might possibly influence the treatment effect of light therapy in the Bright Up study.

Sleep

As mentioned earlier, there are many risk factors for antepartum depression. Additionally, pregnant women typically show disturbed, desynchronized circadian rhythms, resulting in disturbed sleep patterns, which put them at risk for depression [79]. This is partly due to various hormonal changes. Increased estrogen and

progesterone levels during pregnancy influence normal sleep patterns: the increase in estrogen levels reduces rapid eye movement (REM) sleep, whereas progesterone increases non-REM sleep [80, 81]. Cortisol levels increase in pregnancy, which may affect sleep as well [81, 82]. Additionally, women may find it difficult to find a comfortable sleeping position as the pregnancy progresses [83]. Moreover, restless leg syndrome is common during pregnancy and may also contribute to sleep problems [80, 84]. Finally, frequent nocturnal bathroom visits may affect sleep as well [80].

Poor sleep quality during pregnancy is associated with both antepartum and postpartum depressive symptoms [85-89], although a causal relation is difficult to prove due to the reciprocal relation of depression and sleep. However, evidence suggests that sleep problems precede depressive symptoms in the peripartum period [90-92].

Light has not only a major direct effect on mood as discussed earlier, but also on sleep, which may indirectly benefit mood as well [57]. The ipRGCs also project to the ventrolateral preoptic area and the lateral hypothalamus, which are important brain regions in the regulation of sleep [57, 58]. Moreover, these brain regions receive input from the SCN as well [57]. Further, the SCN, which is influenced by light, controls the circadian rhythm of melatonin, which is important in sleep [63]. Light therapy may therefore be effective in treating sleep problems [93].

Due to this reciprocal relation between mood and sleep and due to the tremendous effects of BLT on sleep [57], we dedicated a part of this thesis to sleep. In this part, we studied the effects of sleep during pregnancy and the use of benzodiazepines during pregnancy, which are often prescribed for sleep problems.

Study populations

Women who were included in the studies described in this thesis originated from the following cohorts:

The Bright Up study

This RCT studies the effectiveness of BLT for pregnant women with a depressive disorder. The inclusion criteria were 12-32 weeks of pregnancy and a DSM-5

diagnosis of major depressive disorder. The exclusion criteria were amongst others primary anxiety disorder, earlier treatment with BLT and multiple pregnancy. Participants were either referred by midwives, gynecologists, general practitioners or mental health care workers or they signed up themselves without referral from a professional. Recruitment took place in The Netherlands from November 2016 to March 2019.

After inclusion, women were randomized in two treatment arms: BLT or dim red light therapy (DRLT). Although it is not known which of these two are more effective, we hypothesize that the DRLT condition can be considered as placebo. After receiving the lamps, participants commenced their daily treatment with light for 30 minutes within 30 minutes of habitual wake up time for six weeks. Follow up took place until eighteen months postpartum. Primarily, we collected data on the effects of BLT and DRLT on depressive symptoms during pregnancy. Secondly, we collected data on the effects on sleep quality and melatonin and cortisol levels. Finally, we collected data on various birth and child outcomes.

The complete protocol for the Bright Up study can be found in **Chapter 2**. **Chapter 3** discusses the results regarding the primary research question.

The Mind2Care study

This study is an observational cohort aimed at identifying women with psychopathology, psychosocial problems and substance abuse in routine obstetric care. Women attending an antenatal check-up at one of the participating midwifery practices and obstetric units were invited to fill out a digital screener, the Mind2Care questionnaire [94]. Women were eligible when they were pregnant. Exclusion criteria were having a miscarriage at the time of screening, insufficient proficiency in Dutch and insufficient mental capability to complete the questionnaire independently. Data collection for the study in this thesis took place mainly in rural and urban regions in the southwest of the Netherlands and in two cities in the south and east part of The Netherlands between April 2011 and December 2015.

The findings of this study are discussed in **Chapter 4**.

The DAPPER study (Daycare Alternative Psychiatric Pregnant women Efficiency Research)

This RCT aimed to evaluate the effectiveness of a group-based multicomponent psychotherapy intervention, developed and performed at the Erasmus University Medical Center in Rotterdam, The Netherlands, for pregnant women with a psychiatric disorder, compared to individual counseling (care as usual). Recruitment for this study took place between January 2010 and January 2013 at the tertiary outpatient clinic for perinatal psychiatry of the Department of Psychiatry, Erasmus University Medical Center. Women were eligible when they were diagnosed with a mental disorder and when they were 12-33 weeks pregnant. Exclusion criteria were an indication for hospital admission, inability to function in a group due to severe behavioral problems, insufficient proficiency in Dutch and being unable to visit the outpatient clinic.

A subset of participants was recruited between 24 and 29 weeks of pregnancy for the study in this thesis, which is discussed in **Chapter 5**.

National Centre for Register-based Research (Aarhus, Denmark)

This population-based cohort study studies the prescription patterns of benzodiazepines and benzodiazepine-related drugs before, during and after pregnancy from 1997 to 2015 in Denmark. Here, all Danish individuals are registered in the Danish Civil Registration System through a unique personal civil registration number that enables individual-level linkage of information across nation-wide registries, such as the Medical Birth Registry and the National Prescription Registry. A major advantage of population-based cohort studies is that all residents are eligible for participation, which eliminates the risk of selection bias.

The findings of the analyses in this population are discussed in **Chapter 6**.

Outline and aims of this thesis

This thesis aims to extend existing knowledge on depression during pregnancy, with a special focus on light, seasons and sleep.

In **Part I** of this thesis, we focus on the effects of light therapy for antepartum depression. We present the extensive study protocol of the Bright Up study in

Chapter 2. Here, we will provide a study design of an RCT, studying the effectiveness of light therapy for depression during pregnancy. In **Chapter 3**, we present the findings of the primary research question of this study, namely whether BLT is effective for treating antepartum depression.

Part II focuses on the seasonality of depressive symptoms during pregnancy, which will be discussed in **Chapter 4**. The aim of this study is to evaluate the seasonal influences of depressive symptoms in pregnancy.

The aim of **Part III** is to gain more insight in the effects of sleep during pregnancy. **Chapter 5** investigates the effects of sleep on depressive symptoms during pregnancy. Here, we will study both objective and subjective sleep quality and the effects on the course of antepartum depressive symptoms in psychiatric patients. Many pregnant women suffer from sleep problems, which may be treated with benzodiazepines or benzodiazepine-related drugs. Therefore, we also focus on these medications in this part of the thesis. In **Chapter 6**, we study the prescription patterns of benzodiazepines and benzodiazepine-related drugs in the peripartum period. The aim of this chapter is to gain insight in the usage of these drugs before, during and after pregnancy in a population-based cohort in Denmark. Since these findings may not be representative for other countries, we aimed to compare different countries in **Chapter 7**. This chapter studies the international usage of benzodiazepines before, during and after pregnancy in a meta-analysis.

In **Chapter 8**, we present a general discussion of the main conclusions, methodological consideration, clinical implications and implications for future research. Finally, we give a final conclusion of this thesis.

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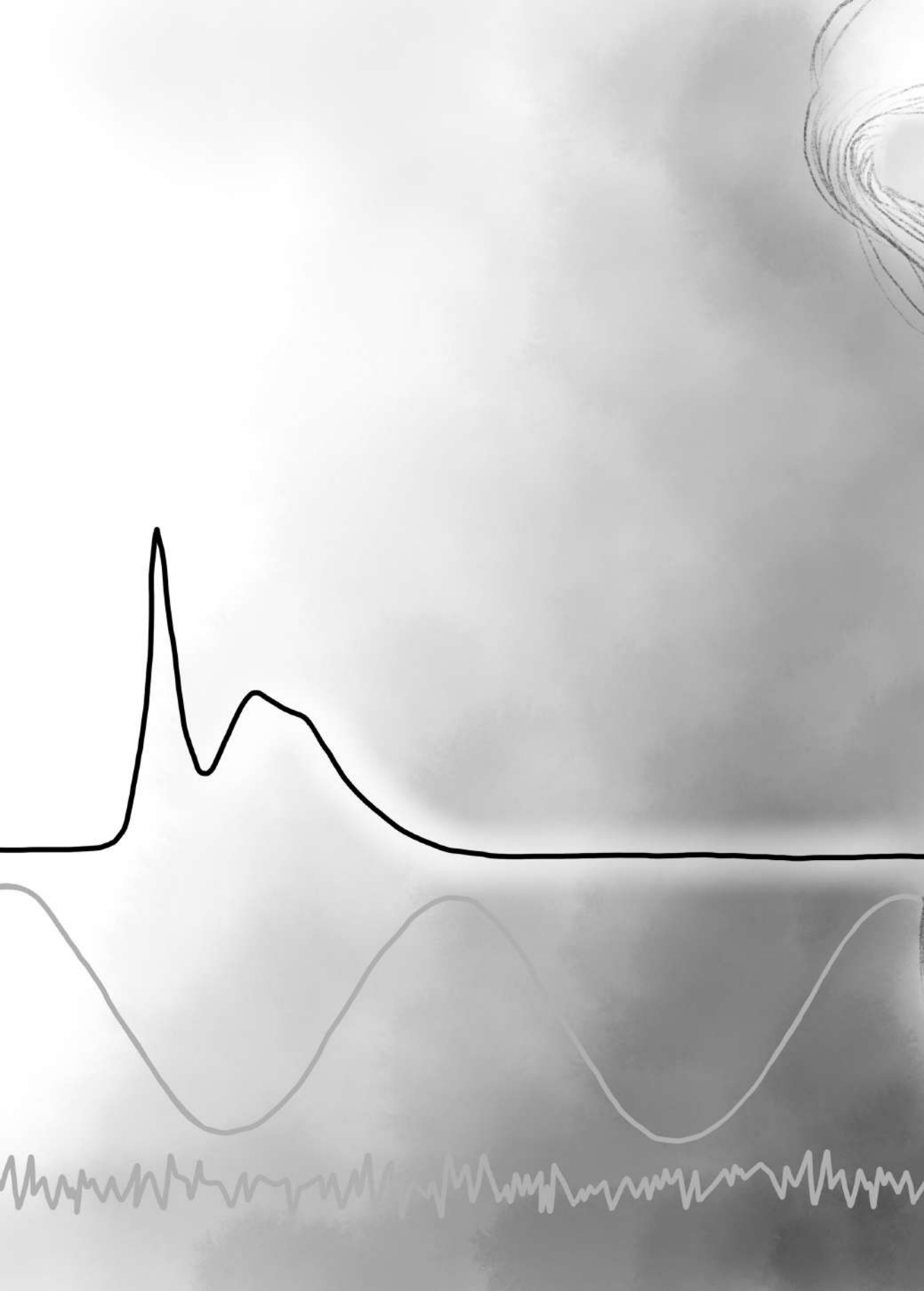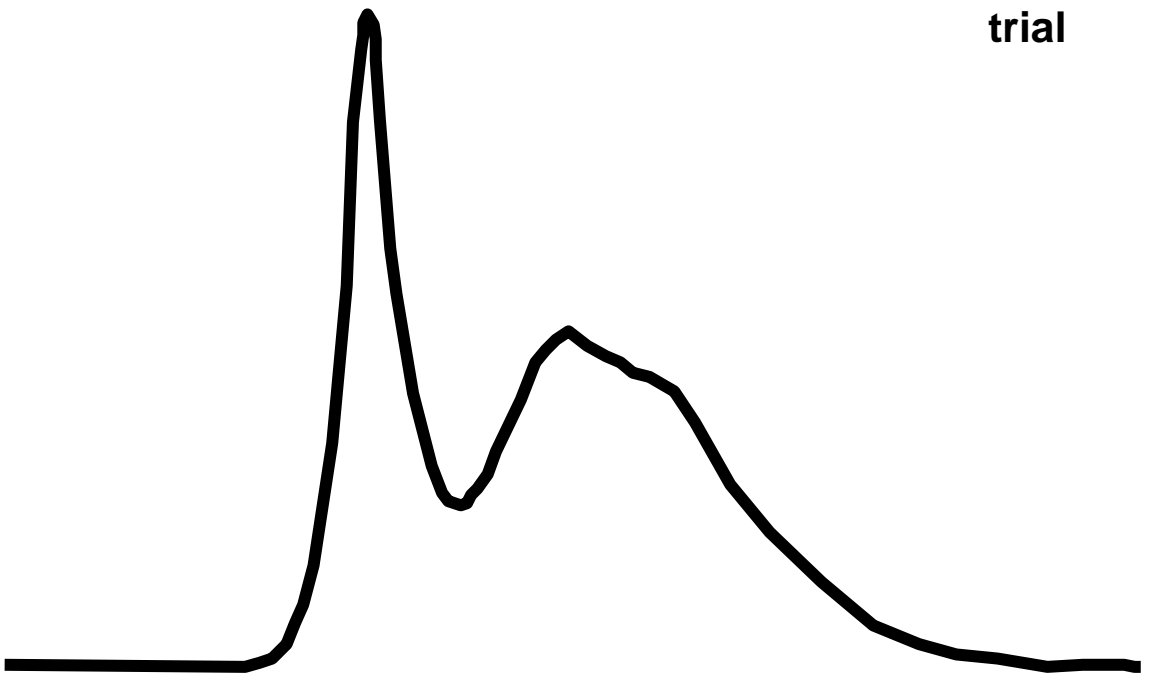
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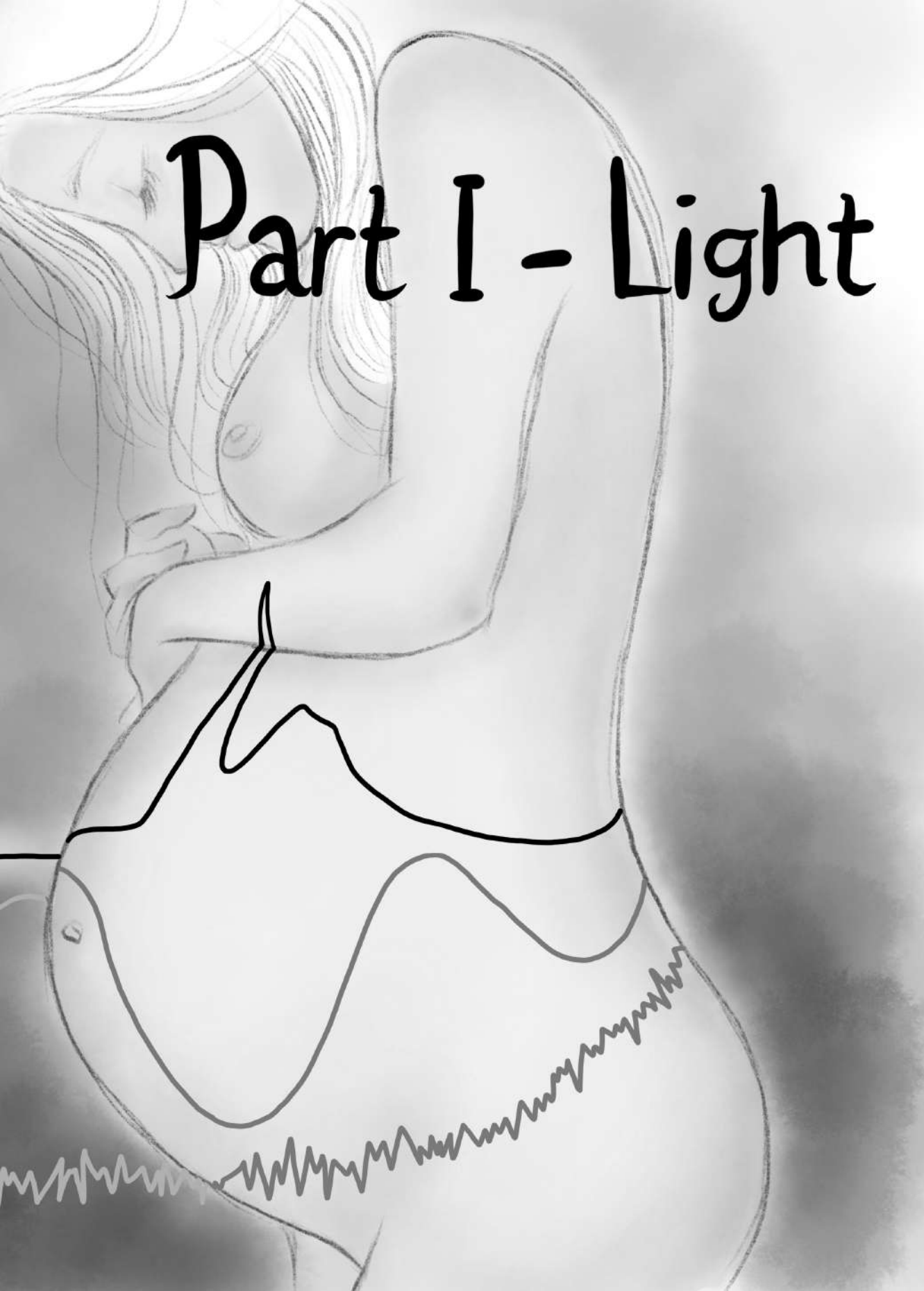
Chapter 2

Bright light therapy in pregnant women with major depressive disorder: study protocol for a randomized, double-blind, controlled clinical trial

Babette Bais, Astrid M. Kamperman, Marjolein D. van der Zwaag, Gwen C. Dieleman, Hanneke W. Harmsen van der Vliet-Torij, Hilmar H. Bijma, Ritsaert Lieverse, Witte J.G. Hoogendijk, Mijke P. Lambregtse-van den Berg

Abstract

Background: Depression during pregnancy is a common and high impact disease. Generally, 5-10% of pregnant women suffer from depression. Children who have been exposed to maternal depression during pregnancy have a higher risk of adverse birth outcomes and more often show cognitive, emotional and behavioural problems. Therefore, early detection and treatment of antepartum depression is necessary. Both psychotherapy and antidepressant medication, first choice treatments in a non-pregnant population, have limitations in treating depression during pregnancy. Therefore, it is urgent and relevant to investigate alternative treatments for antepartum depression. Bright light therapy (BLT) is a promising treatment for pregnant women with depressive disorder, for it combines direct availability, sufficient efficacy, low costs and high safety, taking the safety for the unborn child into account as well.

Methods: In this study, 150 pregnant women (12-18 weeks pregnant) with a DSM-V diagnosis of depressive disorder will be randomly allocated in a 1:1 ratio to one of the two treatment arms: treatment with BLT (9.000 lux) or treatment with dim red light therapy (100 lux). Both groups will be treated for 6 weeks at home on a daily basis for 30 minutes, within 30 minutes of habitual wake-up time. Follow-up will take place after 6 weeks of therapy, 3 and 10 weeks after end of therapy, at birth and 2, 6 and 18 months postpartum. Primary outcome will be the average change in depressive symptoms between the two groups, as measured by the Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder version and the Edinburg Postnatal Depression Scale. Changes in rating scale scores of these questionnaires over time will be analysed using generalized linear mixed models. Secondary outcomes will be the changes in maternal cortisol and melatonin levels, in maternal sleep quality and gestational age, birth weight, infant behaviour, infant cortisol exposure and infant cortisol stress response.

Discussion: If BLT reduces depressive symptoms in pregnant women, it will provide a safe, cheap, non-pharmacological and efficacious alternative treatment for psychotherapy and antidepressant medication in treating antepartum depression, without any expected adverse reactions for the unborn child.

Trial registration: Netherlands Trial Register NTR5476. Registered 5 November 2015.

Background

Depression during pregnancy is a common and high impact disease. Approximately 5-10% of pregnant women suffers from depression [1], which has been confirmed by a study in Rotterdam, the second largest city in the Netherlands [2]. Children who are exposed to maternal depression during pregnancy have a higher risk of adverse birth outcomes, such as low birth weight, and more often show cognitive, emotional and behavioural problems [3-6]. The perinatal period is a critical period, in which epigenetic programming determines not only the perinatal health, but also that of following generations [7]. Therefore, early detection and prompt treatment of depression during pregnancy can benefit both mother and child.

In non-pregnant women, guidelines propose psychotherapy, antidepressant medication or a combination of both as treatment for depression. However, clinical practice shows limited relevance of these guidelines during pregnancy, as the direct availability of psychotherapists is poor, postponing treatment for several months or more. In pregnancy, the window of opportunity is small and from the perspective of the child postponement is in fact non-treatment. Other limitations of psychotherapy are its dependence on good language skills, absence of problems that limit access to therapy and a strong motivation to reflect on ones emotions, cognition and behaviour. These factors limit the applicability of psychotherapy in a majority of pregnant women with depression, who share a socioeconomic deprived background and often have coexisting problems interfering with compliance [8]. Therefore, women with depression during pregnancy may be treated with antidepressants. In North America, use of antidepressants during pregnancy is reported by 5-13% of pregnant women [9, 10]. In the Netherlands, 2-3% of pregnant women use antidepressant medication [11, 12]. However, the safety of these medications during pregnancy is controversial [13, 14].

Therefore, investigating non-pharmacological approaches to treating depression during pregnancy is urgent and relevant, for both mother and child. Bright light therapy (BLT) is a promising treatment for pregnant women with depression based on several theoretical and clinical considerations, which will be discussed below.

BLT and depression

BLT is the first choice treatment for seasonal affective disorder (SAD) [15], a condition of reoccurring depressions during fall and winter, with remissions in spring and summer [16].

The effects of BLT have not only been consistently shown on SAD [16-19], but also on other diseases, such as non-seasonal depression [17], adult attention-deficit/hyperactivity disorder [20] and bulimia nervosa [21, 22]. The effects of BLT on non-seasonal depression have been shown in various populations, like elderly residents of group care facilities and patients with Alzheimer's disease [23-25].

BLT has been shown to synchronize the biological clock with the environmental day-night rhythm and to shift the circadian rhythm [15, 16]. Evidence suggests that this mediates the effects of BLT on depression, which has been indirectly supported by enhanced sleep and rhythms of melatonin and cortisol [23].

Hypothalamus-pituitary-adrenal axis

The hypothalamus-pituitary-adrenal gland (HPA) axis is involved in the synchronization of the biological clock by BLT. This axis regulates the secretion of cortisol in response to stress [26]. HPA-axis activity is controlled by the corticotropin-releasing factor (CRF) secreted by parvocellular neurosecretory cells in the paraventricular nucleus (PVN) of the hypothalamus, which activates the secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which in turn stimulates the production and release of cortisol from the adrenal cortex [26, 27]. CRF and ACTH are both inhibited by cortisol through the glucocorticoid receptor (GR) [26, 27]. Figure 2.1 shows a schematic overview of this feedback loop.

The cause of depression is largely unknown. However, the HPA-axis is thought to play a crucial role in the pathophysiology – as cause or consequence, since hyperactivity of this axis is associated with depression. More specifically, depression is thought to be related to reduced inhibition by cortisol, due to impaired GR function [27]. This is supported by a post-mortem study among depressed patients, which showed hyperactivity of CRF neurons of the hypothalamic PVN [28]. Second, increased basal cortisol levels are commonly found in patients with depression [27].
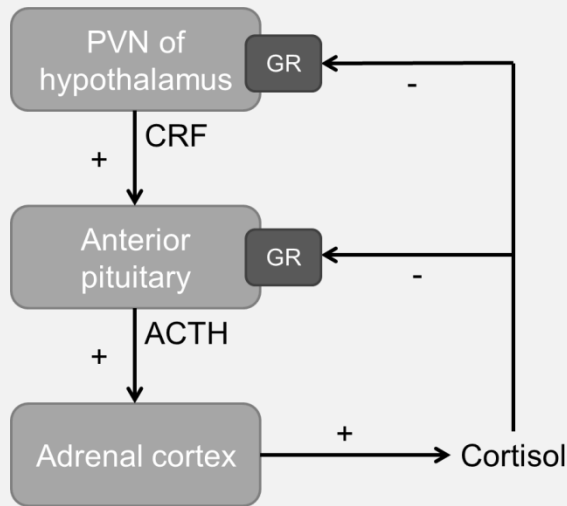
Figure 2.1 – Schematic diagram of the hypothalamus-pituitary-adrenal gland (HPA) axis.

Shown are the different structures and hormones involved in the HPA-axis. CRF, produced and released by the hypothalamus, stimulates the anterior pituitary to produce and release ACTH, which in turn stimulates the production and release of cortisol by the adrenal cortex. Cortisol inhibits both the hypothalamus and pituitary through the GR.

PVN = paraventricular nucleus; GR = glucocorticoid receptor; CRF = adrenocorticotrophic hormone releasing factor; ACTH = adrenocorticotrophic hormone; + = stimulating; - = inhibiting.

Suprachiasmatic nucleus

The suprachiasmatic nucleus (SCN), known as the 'biological clock', controls the HPA-axis: decreased inhibitory control of the SCN on the HPA-axis has been shown to be associated with HPA-axis hyperactivity [29]. The SCN is located in the hypothalamus on top of the optic chiasm and is the central pacemaker of all physiological and behavioural rhythms [15, 30]. Light is the most powerful environmental signal that synchronizes the SCN with the environmental day-night rhythm (also known as 'zeitgeber'). Environmental light versus darkness is signalled to the SCN by melanopsin-containing retinal ganglion cells through the retino-hypothalamic tract in the optic nerve (Figure 2.2) [15, 31]. The SCN is able to

maintain circadian rhythms, even in the absence of zeitgebers [15, 30]. This central control function of circadian rhythms is lost when the SCN is damaged or obliterated. Mice studies have shown that ablation of the SCN results in arrhythmicity [32, 33]. A case report of a patient with hypothalamic damage demonstrated disturbances in the sleep-wake cycle, body temperature and cognitive and behavioural functioning [34].
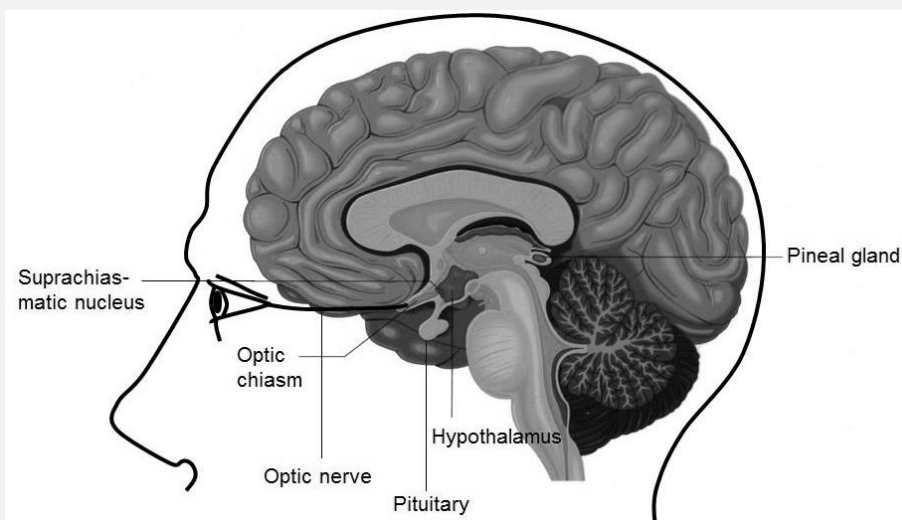
Figure 2.2 – Sagittal view of the brain.

This figure shows a sagittal view of the suprachiasmatic nucleus, the optic chiasm, the optic nerve, the hypothalamus, the pituitary and the pineal gland.

Melatonin

Melatonin is, next to cortisol, influenced by light. Melatonin is produced and secreted by the pineal gland and, like other circadian rhythms, its rhythm is controlled by the SCN (Figure 2.2) [35, 36]. Typically, melatonin levels rise in the evening, peak at early morning hours and drop to baseline at awakening [26]. Light inhibits the production of melatonin [26].

Different studies showed a change in melatonin secretion in psychiatric diseases, such as a reduction of melatonin secretion in depression [35, 37]. Earlier, BLT in

the morning has been shown to normalize saliva melatonin evening levels in elderly patients with a depressive disorder [23].

Melatonin concentrations increase during the course of pregnancy [36]. However, a study showed that nocturnal melatonin levels were lower in depressed pregnant women, compared to healthy controls [38]. In this study, we want to explore the effects of BLT on evening and morning melatonin levels.

BLT and depression during pregnancy

The SCN generates the circadian rhythms in physiology and behaviour, including reproductive hormones. Pregnant women typically show disturbed, desynchronised circadian rhythms, resulting in disturbed sleep patterns, which puts them at risk for depression [39]. Moreover, disturbed sleep and decreased physical condition put pregnant women at risk for decreased activity and less exposure to daylight [40], which might further enhance their risk for depression.

Two small (n=10 and n=27) randomized controlled trials among pregnant women with non-seasonal depression showed significant improvement of depression among women exposed to BLT compared to placebo [41, 42]. Treatment effect in terms of mean improvement of depressive symptoms was comparable with the effects of antidepressant medication (effect size around 0.45), making it a competitive treatment for antepartum depression, but without the possible adverse effects of medication to the unborn child. Although these studies provide evidence for the effectiveness of BLT for depression during pregnancy, their sample size is small.

While in previous studies among elderly patients cortisol and melatonin rhythms normalized after BLT treatment [23], the question is whether improvement of depressive symptoms after BLT in pregnant women is also mediated through improved endocrine functioning or whether these symptoms are primarily determined by the physiology of pregnancy itself. Therefore, we will also examine the circadian rhythms and hormone levels of the pregnant women, to study whether BLT also effects endocrine functioning during pregnancy.

From previous research, we know that maternal depression during pregnancy negatively influences intra-uterine and postnatal child development [3-6, 43-47]. How intra-uterine child development is influenced by maternal depression has yet

to be determined. Possible mechanisms are maternal cortisol crossing the placenta, placental secretion of CRH – which has a positive feedback loop with maternal and foetal cortisol – and reduced blood flow to the foetus, causing foetal growth restriction [5, 43-45, 47]. Increased maternal levels of cortisol, as a cause and/or consequence of maternal depression during pregnancy, might program the intra-uterine developing HPA-axis of the child, making it susceptible to increased stress reactivity in future life [3, 4, 48], which has also been confirmed in animal studies [49]. Therefore, where the earlier conducted studies on antepartum depression and BLT only studied the effects of BLT on mood [41, 42], it will be interesting to examine the effects on infant stress reactivity, long-term cortisol exposure and infant behaviour.

Aims

In this study, we will primarily study the effects of BLT on depression during pregnancy, including adverse effects. Second, we will study whether this clinical improvement is accompanied by improved sleep quality and normalized melatonin and cortisol levels during pregnancy. Third, we will study the effects of BLT on gestational age, birth weight, infant behaviour, infant cortisol stress response and long-term cortisol exposure of the infant.

Methods/Design

Hypotheses

Primary hypothesis: Daily treatment with 6 weeks of morning BLT improves depressive symptoms during pregnancy.

Secondary hypotheses:

1. Clinical improvement of depressive symptoms is accompanied by improved sleep patterns, lower basal cortisol levels and normalized melatonin concentrations during pregnancy.

2. Treatment with BLT during pregnancy improves birth and child outcomes: higher gestational age, higher birth weight, less regulation problems in infants and lower cortisol stress response. In addition, infants will show lower long-term cortisol exposure.
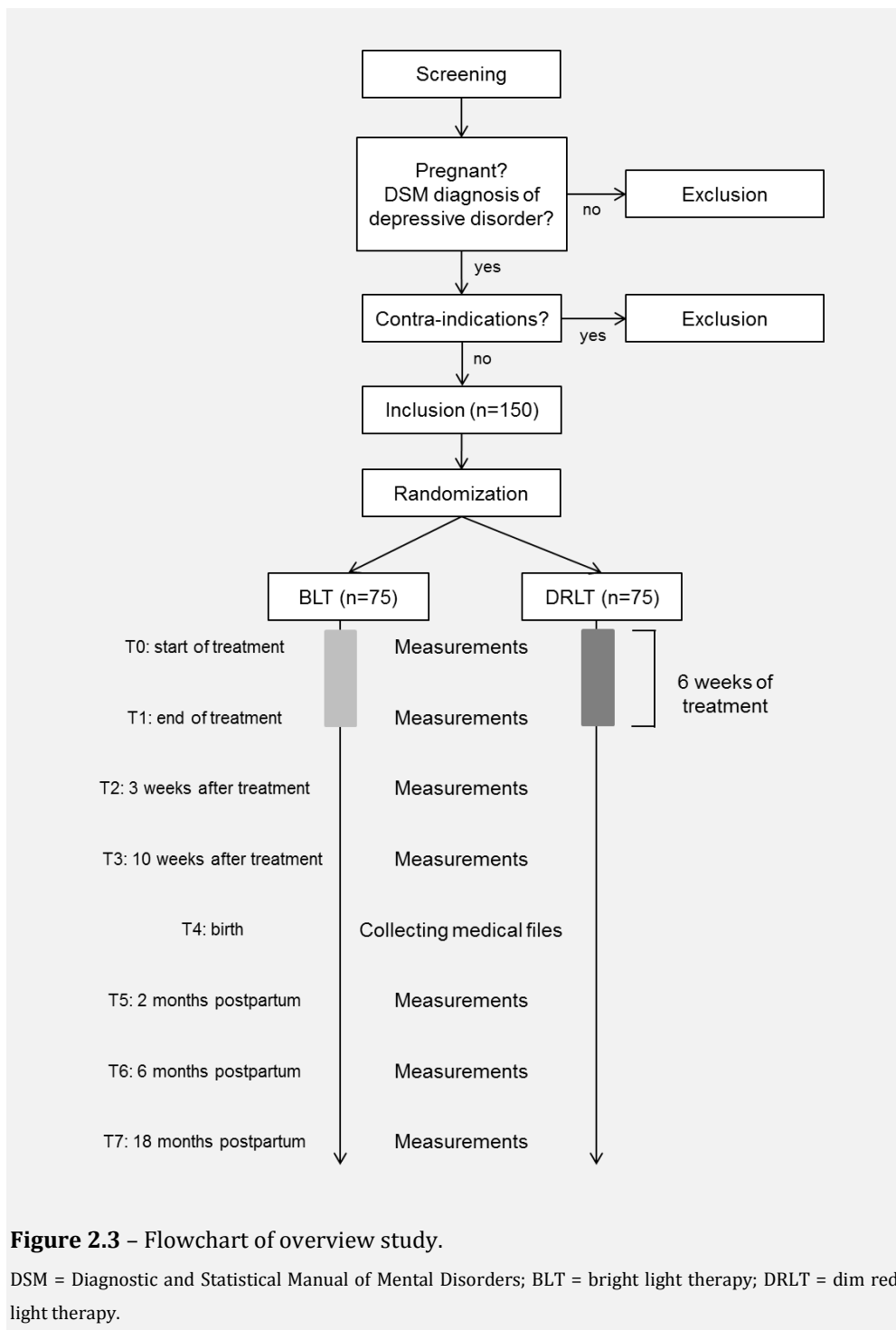
Figure 2.3 – Flowchart of overview study.

DSM = Diagnostic and Statistical Manual of Mental Disorders; BLT = bright light therapy; DRLT = dim red light therapy.

Study overview

This study is a randomized, double-blind, placebo-controlled clinical trial. After baseline measurements (T0), the participants will be randomly allocated to either receive active BLT or dim red light therapy (DRLT) in a 1:1 ratio. Subsequently, they will commence their daily treatment with light, which takes place at the participants' home for 6 weeks. After treatment, follow-up will take place at the following time points:

- after 6 weeks of treatment, which marks the end of treatment (T1);
- 3 weeks after end of treatment (T2);
- 10 weeks after end of treatment (T3);
- at birth (T4);
- 2 months postpartum (T5);
- 6 months postpartum (T6);
- 18 months postpartum (T7).

At these time points, questionnaires, body material and information from medical files will be collected (Table 2.1). A flowchart of this study is shown in Figure 2.3.

Participants

In this study, pregnant women with a depressive disorder will be eligible for participation. The specific inclusion and exclusion criteria of the study are listed in Table 2.2.

Recruitment

In the Netherlands, maternity care for low-risk pregnancies is provided in primary care, which is midwife-led. High-risk pregnancies are cared for in a general hospital (secondary care) or foetal-maternal medicine unit (tertiary care).

In this study, women will be mainly recruited through both midwifery practices and hospitals participating in the South West Consortium in the Netherlands. This is a unique consortium in which almost all parties involved in perinatal care in the South West region of the Netherlands are united: midwives, obstetricians, paediatrician, and several public health institutes. The consortium covers both urban areas (such as the city Rotterdam) and rural areas. Previous studies in this consortium involved

screening for psychosocial risk factors, psychiatric disease and the impact of structuring psychosocial care. Rotterdam is the second largest city in the Netherlands with more than 620.000 inhabitants [50]. It has a high number of deprived neighbourhoods, defined as 10% of pregnant women having a low socio-economic status (<20th percentile) [51].

Table 2.1 – Overview assessment of questionnaires and collection of body material and medical files per time point.

	T0	IP [a]	T1	T2	T3	T4	T5	T6	T7
Questionnaires									
SIGH-SAD	X	X	X	X	X		X	X	X
EPDS	X	X	X	X	X		X	X	X
Life events	X	X	X	X	X		X	X	X
PSQI	X	X	X	X	X		X		
User expectations	X								
User experiences			X				X		
MABS							X		
CBCL									X
Body material									
Urine cortisol	X		X	X			X		
Saliva cortisol/melatonin	X		X	X			X		
Hair cortisol	X				X		X		
Saliva cortisol (infant)							X		
Hair cortisol (infant)							X		
Actigraphy	X [b]				X [c]		X [c]		
Collecting medical files						X			

[a] In the intervention period, the questionnaires will be assessed weekly.

[b] The actiwatch needs to be worn for 8 weeks at T0.

[c] At T3 and T5, the actiwatch needs to be worn for 9 days.

T0 = baseline (start of treatment); T1 = after 6 weeks of treatment (end of treatment); T2 = 3 weeks after treatment; T3 = 10 weeks after treatment; T4 = birth; T5 = 2 months postpartum.

IP = intervention period; SIGH-SAD = Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder version; EPDS = Edinburgh Postnatal Depression Scale; PSQI = Pittsburgh Sleep Quality Index; MABS = Mother and Baby Scales; CBCL = Child Behaviour Checklist.

Table 2.2 – Inclusion and exclusion criteria.

Inclusion criteria	Women 18-45 years of age 12-18 weeks pregnant DSM-V diagnosis of depressive disorder (as assessed by the Structured Clinical Interview for DSM disorders)
Exclusion criteria	Insufficient proficiency in Dutch or English Multiple pregnancy The use of antidepressants shorter than 2 months Bipolar I or II disorder Any psychotic episode Substance abuse Primary anxiety disorder Recent history of suicide attempt Shift-work Somatic and/or obstetric conditions that override study participation Previous treatment with BLT Eye condition (macular degeneration, eye diseases, recent eye surgery)

Women will be routinely screened on psychopathology and psychosocial problems during their first prenatal visit in midwifery practices and hospitals by a screening model, the Mind2Care [2]. During this screening, women are asked to fill out a web-based questionnaire, consisting of 33 items, covering four domains: a socio-demographic, obstetric, psychiatric and psychosocial domain, including the Edinburgh Postnatal Depression Scale (EPDS) [52]. A cut-off score of 9 or above of the EPDS is used by the Mind2Care, in order to refer a woman towards tailored mental health care. Sensitivity and specificity of the EPDS are respectively 86% and 78% [52].

In addition, women who visit our outpatient psychiatric clinic – a centre of excellence in perinatal psychiatry – at the Erasmus University Medical Centre in Rotterdam for their depressive symptoms will be offered to participate in our study when they are not fully remitted from depressive symptoms after 2 months of treatment with antidepressant medication and/or other psychiatric treatment.

Third, pregnant women who visit their general practitioner (GP) for depressive symptoms may be referred to the study by their GP.

Finally, women will be recruited via (social) media, such as press releases, so women with depressive symptoms can enrol in the study without referral from their midwife, gynaecologist, GP or mental health care worker.

Ethics

This study will be conducted in accordance with the Helsinki Declaration, meaning that participation is voluntary and written informed consent will be obtained. Before entering the study, subjects will receive information about the study and its risks and benefits, verbal and in writing. Subjects will have a reflection period of one week. Participants can leave the study at any time for any reason without consequences with regard to their current or future treatment. Also, the investigator can decide to withdraw a participant from the study for urgent medical reasons.

The study has been approved by the medical ethical committee of the Erasmus University Medical Centre, Rotterdam, The Netherlands (registration number MEC-2015-731). A Data Safety Monitoring Board has been installed, which monitors the safety of this research.

In case of adverse effects, a treatment protocol will be effective.

Randomization and blinding

We will randomly assign 150 participants in a 1:1 allocation ratio to either receive BLT or DRLT. Randomization will be done with the web-based computer-generated randomization schedule ALEA (software for randomization in clinical trials, version 2.2) using random block sizes of 2 to 6. Stratification factors will be the use of any antidepressant medication and the number of previous depressive episodes. This will be dichotomized to 3 or less previous depressive episodes versus 4 or more [53].

Participants will be blinded for their allocation. They will be informed that this study examines the efficacy of light therapy with two different colours.

Participants will be asked to guess to which treatment group they are allocated to after treatment, as suggested by the Cochrane's Collaboration's tool for assessing risk of bias in randomized trials [54].

Blinded, independent assessors will be involved in the outcome ratings and will conduct the interviews at T1, T2, T3, T5, T6 and T7 and on a weekly base during

the intervention period. The participants are asked not to share any details about their treatment towards the assessors. In case information is shared, the assessor will be replaced. After each interview, the assessors will be asked to guess the allocation of the participant.

The researcher who will perform the primary statistical analysis (AK) will be blinded for allocation.

The field researcher (BB) will install the lamps and will provide the participants with instructions. Also, the field researcher will answer any questions asked by participants. For this, we will use protocolled answers, to maintain the blindness of the participants. Moreover, the field researcher will ask the participants about side-effects at T1 and on a weekly base during the intervention, keeping the independent assessors blinded for adverse effects that might break the blinding, e.g. strained eyes. For these practical reasons, the field researcher will not be blinded.

Intervention

Participants will be randomly allocated to BLT (9.000 lux) or DRLT (100 lux). Treatment will take place daily at home for 6 weeks, starting at 12-18 weeks pregnancy. Participants will be asked to commence the treatment within 30 minutes of habitual wake-up time with a duration of 30 minutes. Participants will sit in front of two light boxes with a distance of approximately 40 cm. The light boxes will be placed in a custom-made scaffolding. In this way, the height of the light boxes can be adjusted per person, ensuring the same distance. Also, the scaffolding ensures lighting from above, which avoids glare [42]. This makes the treatment more comfortable, enhancing treatment adherence.

The active dose was found effective in other studies [23, 41, 42]. Dim red light can be considered to be biologically inactive [55]. Although a Cochrane review of studies in BLT in non-seasonal depression showed that BLT may be effective in as little as 1 week [55], we will choose 6 weeks of daily light exposure, since the 2 studies among pregnant women with non-seasonal depression showed significant effects of BLT from 5 weeks treatment [41, 42].

All participants in both treatment arms will receive treatment as usual. Women are always free to visit their GP, whenever they are in need of this. The GP is always free to start treatment if he/she feels necessary.

When depressive symptoms increase and/or in the case of suicidal ideation, an action plan is set up and appropriate measures will be taken.

Different measures have been taken to enhance treatment adherence:

- A sensor that measures the amount of lux perceived is installed in the actiwatches, which will monitor the therapy adherence.
- Since the lamps will be installed into a custom-made scaffolding that ensures lighting from above, treatment will be more comfortable, which enhances treatment adherence.

Outcome measures

The primary outcome measure will be the average change in depressive symptoms between the two groups, as measured by the Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder version (SIGH-SAD) and the EPDS at different time points. Second, we will study responders vs. non-responders, where response is defined as a ≥50% decrease to a final score of ≤ 8 on the 17-item Hamilton scale and ≤ 5 on the EPDS.

The secondary outcome measures of this study will be the changes in maternal cortisol and melatonin levels (1), in maternal circadian rhythm (2) and in birth and child outcomes (3).

1. Morning and evening cortisol levels in saliva will be measured as a measure for HPA-axis activity. Morning and evening melatonin levels in saliva will be measured as measure of a participant's circadian phase position. Outcome measures will be the changes in cortisol and melatonin saliva levels between the two groups.

   Total 24-hour cortisol excretion will be determined from urine. Outcome measure will be the changes in cortisol levels within and between the two groups.

   Hair will be used as a long-term measure for cortisol excretion. Changes in levels between the two groups will be used as outcome measure.

2. Through actiwatches and a structured questionnaire (the Pittsburgh Sleep Quality Index – PSQI), information will be obtained regarding total sleep time, sleep efficiency and sleep onset latency, as well as circadian estimates from the rest activity rhythm such as intradaily and interdaily variability and rhythm amplitude.

3. Differences in birth and child outcomes between the two groups will be used as outcome measures: pregnancy duration, birth weight, child behaviour, long-term cortisol exposure and cortisol stress response at a routine vaccination.

Finally, we will ask about user expectations and user experiences.

Complete follow-up will be pursued. In case of discontinuing or deviating from the intervention, we will collect outcomes of EPDS and SIGH-SAD assessment.

Sample size

Based on previous literature [23, 41, 56], we expect a small to moderate response (time x treatment interaction on depressive symptoms). This corresponds to a 10 to 15% reduction of depressive symptoms over the full course of treatment. To demonstrate this (with an α of 0.05 and a β of 0.80), we will need a sample size of 63 participants per arm (126 in total). To account for lost to follow up during and after treatment, we will aim at including 150 participants. Power calculations were performed using GLIMMPSE 2.1.5 software [57].

In case of withdrawal of a participant during the recruitment period, another participant will be recruited to obtain the aimed number of participants.

Adverse effects

At every measurement, we will ask for adverse effects. The adverse effects of BLT, such as headache and nausea, are generally mild and short-lived [58, 59]. A switch to hypomania is a more serious adverse effect, which would require effect managing. In a study exploring the side effects of short-term 10,000 lux light therapy in 70 patients suffering from SAD, 1 subject experienced hypomania [58]. In the two studies (n=10 and n=27) studying the effects of light therapy in a pregnant population, 1 subject showed hypomanic symptoms [41, 42]. If a

participant shows hypomanic symptoms, the daily treatment duration will be reduced. This enhances the clinical safety [41].

No adverse effects for the foetus will be expected [42, 56].

Inclusion

Women will be asked to provide the following baseline socio-demographic factors: age, ethnicity, level of education, marital status, parity, unplanned pregnancy, body mass index, somatic conditions (if not exclusion), medication use and substance use (smoking, alcohol, drugs).

The GP will be contacted to verify whether the participant meets any exclusion criteria. The results will be discussed with an experienced perinatal psychiatrist (ML), who will – as a safety measure – verify the diagnosis and inclusion and exclusion criteria. If there are no clinical contraindications, randomization will take place.

After a positive screening on the EPDS, eligible women will be interviewed to assess lifetime psychiatric diagnosis. This will be done with the Structured Clinical Interview for DSM disorders (SCID), a semi-structured interview that is considered to be the golden standard for making the major DSM-V axis I psychiatric diagnoses [60].

Measurements – primary outcome measures

Depressive symptoms during pregnancy will be assessed using the SIGH-SAD and the EPDS.

SIGH-SAD

The SIGH-SAD is a 29-item structured interview and consists of 21 HAM-D (Hamilton Rating Scale for Depression) items and 8 atypical items, of which 11 items can be scored with a value of 0-2, 5 items with a value of 0-3 and 13 items with a value of 0-4 [61]. The sum score ranges from 0 to 63 for the HAM-D items and from 0 to 26 for the atypical items, resulting in a total sum score of 0 to 89 [61]. We will choose the original 17-item HAM-D questionnaire as primary measure, since it is more commonly used in clinical practice and research. Interrater reliability for the 17-item HAM-D questionnaire ranges from 0.82 to 0.98 [62].

Sensitivity and specificity are respectively 0.76 and 0.91 [62]. Positive and negative predictive value are respectively 0.77 and 0.92 [62]. Next to the original 17-item HAM-D questionnaire, we will use the entire SIGH-SAD questionnaire, since this questionnaire is the current benchmark for assessment of severity of depression in light therapy trials.

EPDS

The EPDS, a structured 10-item questionnaire, will be used as a validated self-report measure of depression during pregnancy [52, 63]. Each item is scored with a value, ranging from 0 to 3, which leads to a sum score of 0 to 30 [52]. Sensitivity and specificity of the EPDS are respectively 86% and 78% [52]. Originally, the EPDS was developed for the detection of postnatal depression, but has been validated for screening depression during pregnancy as well [63]. In this study, we will use a cut-off of 9, in accordance with the screening tool, the Mind2Care [2].

Measurements – secondary outcomes (endocrine)

Endocrine levels during pregnancy will be studied measuring saliva melatonin and cortisol in urine, saliva and hair.

Urinary free cortisol

Urinary free cortisol levels during a 24-hour period provide a non-invasive valid estimation of overall daily cortisol production [64]. Urine will be collected starting after the first voided urine after awakening and will include the first voided urine on the following day. The cortisol level will be determined by radioimmunoassay. Completeness of collection will be ascertained by interviews documenting urine losses. Only complete collections, with creatinine within the normal range of 0.06 mg/dL per 24 hours will be included in the analysis.

Saliva cortisol

As a measure of HPA-axis activity, saliva cortisol will be collected using cotton dental rolls, including 4 sequential samples at 30-minutes intervals starting at awakening and 3 sequential samples at hourly intervals starting 2 hours before predicted bedtime with the last sample at bedtime. The samples will be collected

the following day and subsequently delivered to the laboratory, where they will be centrifuged and stored at -80°C. Samples will be analysed using a cortisol assay on an immunoanalyser system. For determination of the diurnal time course of saliva cortisol levels, only days with at least 6 valid samples will be included in analyses.

Hair cortisol

Hair cortisol will be assessed as a validated biomarker for long-term cortisol exposure. The maternal hair strands will be collected and processed according to existing methods [65]. With this method, cortisol levels can be retrospectively assessed depending on hair length (i.e. one month for each centimetre of hair). Norm data from healthy pregnant controls will be available through one of our other ongoing studies.

Saliva melatonin

As a measure of a participant's circadian phase position, saliva melatonin levels will be collected using cotton dental rolls at hourly intervals with 3 sequential samples, starting 2 hours before predicted bedtime with the last sample at bedtime, under dim light conditions. One sample will be taken at awakening. The samples will be collected the following day and subsequently delivered to the laboratory, where they will be centrifuged and stored at -80°C. All samples will be analysed using Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS). For determination of a rise in melatonin levels in het evening, only days with 3 valid evening samples will be included in the analyses [23].

The Dim Light Melatonin Onset (DLMO; the time point when melatonin secretion rises over a predefined threshold in the evening [66]) will be calculated after measuring the melatonin evening curve. The DLMO is a reliable estimate of circadian phase position [66].

Measurements – secondary outcome measures (circadian rhythm)

The circadian rhythm during pregnancy will be studied through actiwatches and the PSQI.

Actigraphy

Actigraphy, the continuous assessment of activity with a watch-sized non-dominant wrist-worn recorder (Actiwatch Spectrum, Philips Respironics, Pittsburgh, USA), is a validated technique to obtain estimates of sleep and rest-activity rhythms [23, 67, 68]. Sleep analyses software (Actiware 6.0, Philips Respironics, Pittsburgh, USA) will be used to obtain estimates of sleep parameters. The software will calculate end and start of sleep. Further, assumed sleep (the difference between the end and the start of sleep), actual sleep time (amount of sleep determined by algorithm), sleep onset latency (the time between lights out and sleep onset) and sleep efficiency (the percentage of actual sleep time between sleep onset and final awakening, excluding sleep onset latency) will be calculated [23]. Rest-activity rhythms will be calculated, using different actimetric variables, such as interdaily stability and intradaily variability [23].

PSQI

The PSQI, a structured 19-item self-questionnaire with 5 additional items reported by bedpartner, assesses sleep quality, including a wide variety of factors, such as sleep duration and latency [69]. The sum score ranges from 0 to 21 points, with higher values corresponding to lower sleep quality [69]. These 19 items generate 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction [69].

A cut-off of 5 will be applied, where a score of <5 indicates poor sleep and ≥5 indicates good sleep [69]. The PSQI has a sensitivity of 89.6% and a specificity of 86.5% [69].

The PSQI will be assessed on a monthly base and weekly in the intervention period.

Measurements – secondary outcome measures (infant)

As infant outcome measures, birth outcomes, infant stress response, infant long-term cortisol exposure and behaviour will be studied.

Birth outcomes

After birth (T4), information will be obtained regarding complications during delivery and childbirth from the medical records: hypertension, pre-eclampsia, delivery aspects (duration, start with or without induction, augmentation, method of pain relief if any, instrumental delivery, caesarean section, hospital admission) and first week complications after delivery.

Infant stress response

To measure the infant stress response, we will collect saliva cortisol before and 15, 30 and 45 minutes after a routine vaccination at T5. We will use the same procedures and analyses as with the mothers.

Infant long-term cortisol exposure

To measure the long-term cortisol (intra-uterine) exposure, we will collect hair samples of the infant at T5. We will use the same procedures and analyses as with the mothers.

Infant behaviour

To study infant behaviour, we will assess the questionnaires Mother and Baby Scales (MABS) and Child Behaviour Checklist (CBCL).

MABS

We ask mothers (and fathers, if available) to fill out the MABS, a questionnaire consisting of various subscales [70]. In this study, we use 3 subscales of the MABS: infant alertness-responsiveness, unsettled-irregular behaviour of the infant and lack of confidence in care-taking [70], resulting in a 36-item questionnaire.

The unsettled-irregular behaviour scale consists of 8 items (e.g. 'After feeds, I've used rocking or cuddling to settle my baby), the alertness-responsiveness scale of 15 items (e.g. 'My baby watches my face') and the lack of confidence in feeding of 13 items (e.g. 'I've felt clumsy in caring for my baby'). Parents are asked to score the various statements with a score between 0 (not at all) and 5 (very much/often), which results in a sum score of 0-180. The subscale sum scores range from 0 to 75 for infant unsettled-irregular behaviour, from 0 to 40 for infant alertness-

responsiveness and from 0 to 65 for lack of confidence in care-taking [70]. A higher score on the infant unsettled-irregular behaviour scale correlates to more irregular behaviour, whereas a higher score on the infant alertness-responsiveness scale points to more alert behaviour [71]. A higher score on the lack of confidence scale suggests that the mother is less confident in taking care of the baby. Reliability of the MABS ranges from 0.81 to 0.93 (Cronbach's α), depending on the used subscale [70].

CBCL

We ask mothers (and fathers, if available) to fill out the CBCL/1.5-5, a diagnostic 99-item questionnaire which quantifies skills and behavioural problems. The questionnaire consists of different scales: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems (Internalizing Problems), attention problems and aggressive behaviour (Externalizing Problems) [72]. Together, the Externalizing and Internalizing Problems form the Total Problems [72]. Items can be scored with 0 (not at all), 1 (a little or sometimes) or 2 (clearly or often), resulting in different sum scores for the different scales. Norms for these scales were constructed, using a large representative sample of children [72].
Reliability of the CBCL is 0.85 [73].

Chronotype
The participant's chronotype will be verified at screening, since evening types are found to be more prone to depression than morning types [74, 75]. In this study, this will be assessed with the Munich Chronotype Questionnaire (MCTQ), a structured 19-item self-report measure of an individual's chronotype, based on sleep times, self-reported light exposure and self-assessed chronotype (extreme, moderate or slight early, normal or slight, moderate or extreme late), taking rest and working days in consideration [76]. The participant can be classified to 1 of the 7 chronotypes by utilizing data on the participant's midsleep phase and sleep debt [76]. Sum score ranges from 16 to 86, with the lowest score indicating extreme late chronotypes. The MCTQ correlates well with the Horne-Östberg Morningness-Eveningness Questionnaire – especially the MCTQ-assessment of time of midsleep ($r=-0.73$ on free days and $r=-0.61$ on workdays) [77].

Statistical analysis – general

Data will be analysed using SPSS 21.0. For treatment effect analyses, we will apply an intention-to-treat procedure, since none of the participants will switch to another condition and we will include all observations of all participants until study end or withdrawal.

If necessary, skewed continuous variables will be transformed to normality prior to the analyses.

For the continuous variables and categorical variables that are assessed more than twice, we will deploy linear mixed models and generalized linear mixed models respectively. These models use all available data and account for within-subject correlation over time. They can also be used to adequately deal with possible baseline imbalances. Variables measured only once will be compared between the randomized groups using the unpaired t-test, or the Chi-Square test in case of categorical variables. All effect parameters will be supplied with a 95% confidence interval.

Primary outcome analysis will be first crude, than adjusted. If despite randomization, prognostically important factors differ between the groups, they will be adjusted for supplemental analyses.

Statistical analysis – primary outcomes

Changes in HAM-D and EPDS rating scale scores over time will be analysed using generalized linear mixed models. Differences from baseline of HAM-D and EPDS scores at every time point will be the dependent variables, time will be the within-subject factor and treatment (BLT versus DRLT) will be the between-subjects factor.

Additional analysis will use alternative definitions of change: instead of the numerical difference of scores before and after, we will use a dichotomous response variable where improvement of ≥ 50% to a final score ≤ 8 on HAM-D and ≤ 5 on EPDS is defined as success, otherwise not. Finally, we will perform sensitivity analysis to examine robustness of the findings with other methods using data imputation (last observation carried forward multiple imputation).

Statistical analysis – secondary outcomes

For saliva cortisol, areas under the curves for the morning and evening (i.e. 7 to 9 AM and 8 to 11 PM) will be calculated for subsequent analyses [23]. For saliva melatonin, areas under the curves for the evening (i.e. 8 to 11 PM) will be calculated for subsequent analyses [23].

Continuous outcomes, e.g. saliva cortisol and melatonin, will be tested with the unpaired t-test and linear mixed model. Categorical outcomes, e.g. sleep quality, will be tested with Chi-Square Test and generalized linear mixed model.

Statistical analysis – covariates

Potential covariates for the mother are psychiatric history, ethnicity, level of education, parity, gestational age (duration of pregnancy at study entry), substance use, chronotypes, duration of actual depression and other psychiatric or psychotherapeutic treatment interventions. These factors might affect depressive symptoms during pregnancy. After pregnancy, we will additionally correct for complications during delivery, breastfeeding and objective and subjective sleep parameters, since these factors might influence depressive symptoms after delivery.

Potential covariates for the infant are head circumference, congenital malformations, Apgar-score and neonatal admission at Neonatal Intensive Care Unit.

Discussion

We have presented a protocol for an RCT of light therapy for antepartum depression. Two earlier conducted RCT's have shown the effects of BLT in pregnant women with depression, but studied only a small sample size (n=10 and n=27) [41, 42]. In this trial, we will study the effects of BLT on antepartum depression in a larger sample (n=150) and in addition to the earlier conducted studies, we will not only study the effects of BLT on the mother, but on the infant as well. Moreover, we will study the effects of BLT on maternal endocrine levels and maternal circadian rhythm.

BLT will benefit pregnant women, for they will receive immediate treatment for their depressive symptoms. Psychotherapists are not always available, which would postpone treatment. Also, antidepressant medication is not immediately effective. However, BLT may be effective in as little as 1 week [55]. Moreover, the adverse effects of BLT are mild and short-lived.

The unborn child would benefit from this alternative treatment, for BLT does not cause adverse effects in the unborn child. Also, since BLT may be effective in a short time period, the risks associated with maternal depression (such as lower birth weight) may be diminished.

BLT would benefit society, since BLT has lower costs than treatment with antidepressant medication or psychotherapy.

Finally, since this RCT would be the first to study the effects of BLT in the infant, it would contribute to the understanding of the role of BLT, depression and the maternal HPA-axis in the developing foetus.

Thus, if BLT reduces depressive symptoms in pregnant women, it will provide an alternative, non-pharmalogical treatment for psychotherapy and antidepressant medication in treating antepartum depression. BLT combines direct availability, sufficient efficacy, low costs and high safety, taking the safety for the unborn child into account as well. Moreover, it does not require good language skills and it can be administered at home. These considerations make BLT for treating depression in pregnant women relevant, especially in urban multi-ethnic populations with high prevalence of depression and a low level of personal resources.

List of abbreviations

ACTH: adrenocorticotrophic hormone; BLT: bright light therapy; CRF: adrenocorticotrophic hormone-releasing factor; DLMO: Dim Light Melatonin Onset; DRLT: dim red light therapy; DSM = Diagnostic and Statistical Manual of Mental Disorders; EPDS: Edinburgh Postnatal Depression Scale; GP: general practitioner; GR: glucocorticoid receptor; HAM-D: Hamilton Rating Scale for Depression; HPA: hypothalamus-pituitary-adrenal gland; MABS: Mother and Baby Scales; MCTQ: Munich Chronotype Questionnaire; PSQI: Pittsburgh Sleep Quality Index; PVN: paraventricular nucleus; SCID: Structured Clinical Interview for DSM disorders;

SIGH-SAD: Structured Interview Guide for the Hamilton Depression Rating Scale –
Seasonal Affective Disorder version.

Ethics approval and consent to participate

This study will be conducted in accordance with the Helsinki Declaration, meaning
that participation is voluntary and written informed consent will be obtained.

The study has been approved by the medical ethical committee of the Erasmus
University Medical Centre, Rotterdam, The Netherlands (registration number MEC-
2015-731).

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The lamps used in this study are provided by Philips Lighting. Author MZ is
employed by Philips Lighting.

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ZonMw is a governmental organisation that finances research in health and is not
involved in the study. Philips Lighting is a technology company – specialised in
lighting – and is involved in analysis and interpretation of the data, the writing of the
manuscript, but has not ultimate authority over any of these activities.

Authors' contributions

BB is the project's PhD candidate and the field researcher. AK is the project's
methodologist and supervises the study. MZ is the project's researcher employed
by Philips Lighting. GD is the project's child psychiatrist. HH is as midwife and

project leader of the consortium involved in the study. HB is as gynaecologist involved in the study. WH supervises the study. ML is the project's principal investigator and initiator of the study, obtained funding, designed the study and supervises the study. BB, AK, MZ, GD, HH, HB, RL, WH and ML contributed to the concept and design of the study and to the writing of the manuscript. BB, AK, MZ, GD, HH, HB, RL, WH and ML read and approved the final manuscript.

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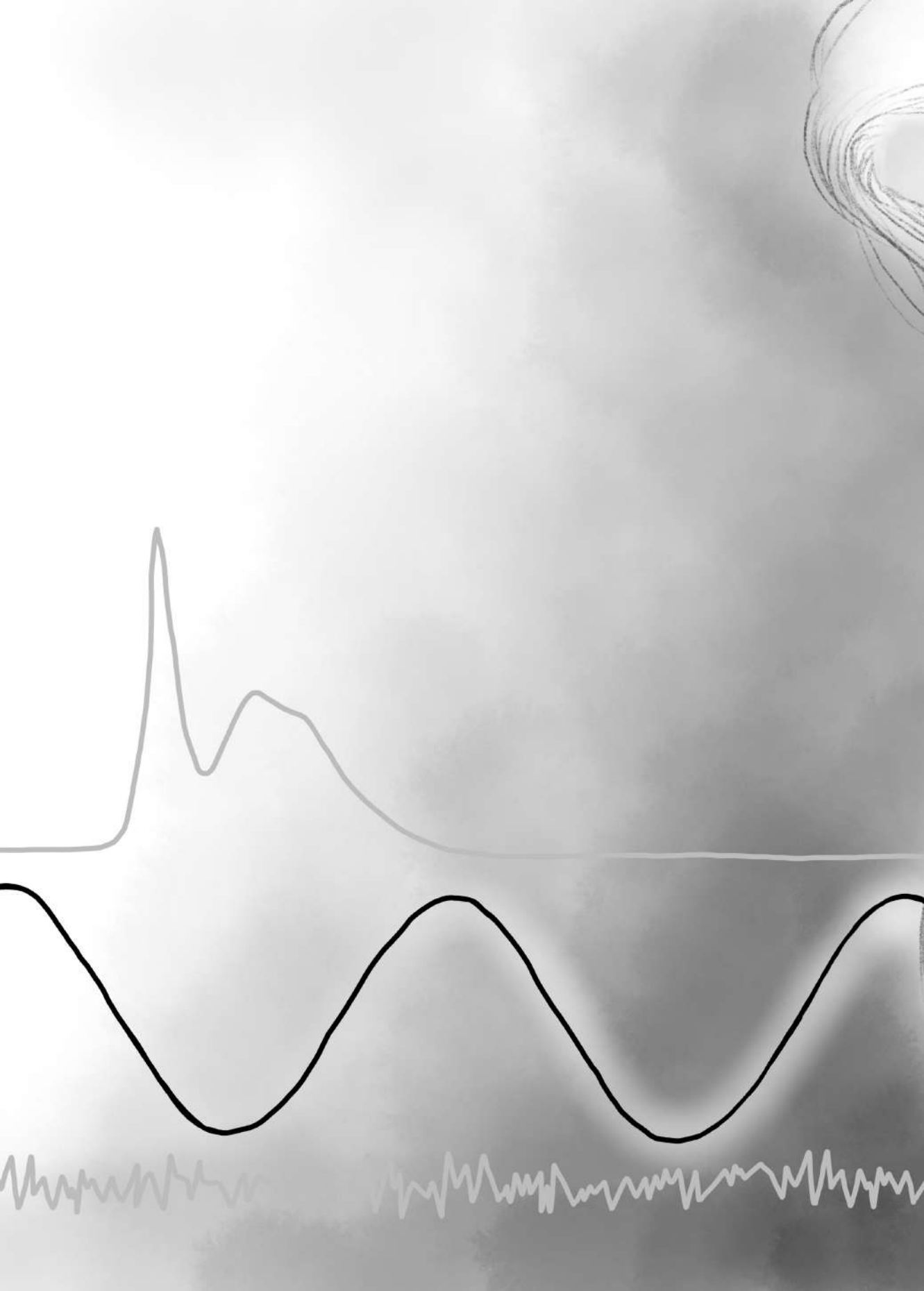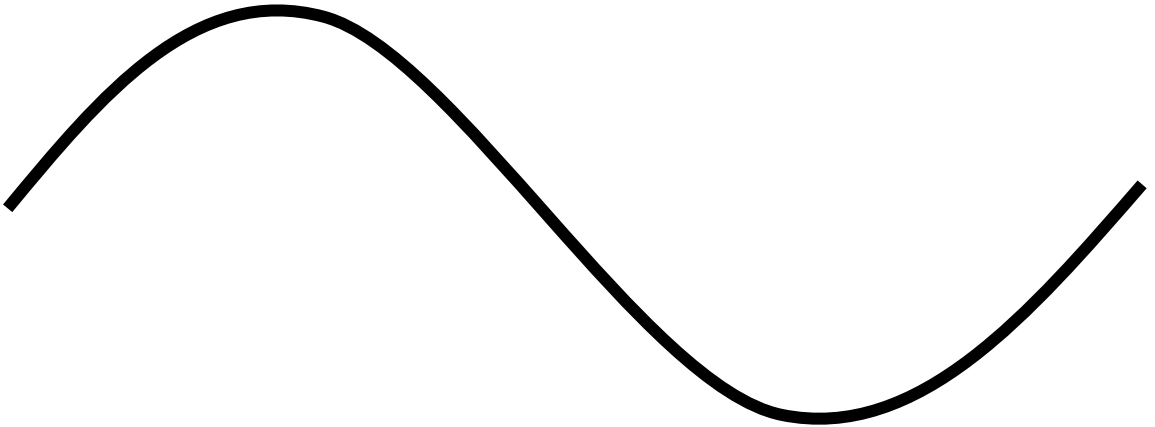
Part II - Seasons

Chapter 4

Seasonality of depressive symptoms during pregnancy

Babette Bais, Nynke de Groot, Nina H. Grootendorst-van Mil, Hanneke W. Harmsen van der Vliet-Torij, Hilmar H. Bijma, Gwen C. Dieleman, Witte J.G. Hoogendijk, Mijke P. Lambregtse-van den Berg, Astrid M. Kamperman

Abstract

Various risk factors have been identified for antepartum depression. This study evaluated seasonal influences on antepartum depressive symptoms. Data of 2,438 pregnant women on current depressive symptoms was obtained from a large-scale cross-sectional study in The Netherlands. Most women were screened during the first trimester. Depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS) and dichotomized using ≥9 as cut-off score. The seasonal relationship between antepartum depressive symptoms and the month of assessment was estimated by fitting a sinusoidal curve to the data. A total of 323 women (13.2%) scored above cut-off. In the full sample, we found no significant evidence for seasonal influences on depressive symptoms after adjusting for confounders. Additionally, we found that the seasonal influence was obscured by the modification of the effect by current treatment status. In women untreated for psychiatric complaints, we found a minimum of depressive symptomatology in September and a maximum in March. In women treated for psychiatric complaints we found a minimum of depressive symptomatology in December and a maximum in June. Thus, the effects of seasonality are apparent, but opposite in treated and untreated women. However, health professionals should be aware of depressive symptoms the whole year through.

Key words

Antepartum depression; Depression; Depressive disorder; Seasonal affective disorder; Seasons; Pregnancy

Introduction

Antepartum depression is a common and high impact disease, with major impact on both maternal and fetal health, as well as infant development [1, 2]. Women who suffer from antepartum depression are more likely to experience postpartum depression as well [3]. Children who are exposed to maternal depression during pregnancy have a higher risk of adverse birth outcomes, such as prematurity and being small for gestational age, and more often show cognitive, emotional and behavioural problems in childhood, adolescence and adulthood [4-6]. One of the possibilities to prevent these negative outcomes for mother and child is to target women at risk for antepartum depression. Possible treatment options are different forms of psychotherapy and alternative forms of therapy such as bright light therapy [7, 8]. The use of antidepressant medication in the peripartum period is still controversial and guidelines are not always consistent [9].

Several risk factors for antepartum depression have been identified, such as major life events, lack of social support, marital difficulties, low socio-economic status, young maternal age and an unplanned or unwanted pregnancy [10, 11]. In addition, a recent study showed that seasonal influences might impact the severity of antepartum depressive symptoms [12]. Seasonal influences on affective disorders have been widely recognized and are prerequisite for diagnosing seasonal affective disorder [13]. Seasonal affective disorder is characterized by recurrent depressions during fall and winter, with full remissions in spring and summer [14-16]. However, not all SAD cases are characterized by depression during fall and winter [17, 18].

Seasonal influences have been suggested in antepartum depressive symptoms [12], as well as during the postpartum period [19-24], although not consistently [25-27]. Corral *et al.* (2007) found that twice as many women with postpartum depression suffered from seasonal affective disorder compared to healthy controls. Other studies found more cases of postpartum depression in autumn and winter months, compared to summer [19-21, 23]. Weobong *et al.* (2015), who studied a population in rural Ghana, reported an associated risk of postpartum depression when giving birth in the dry season . However, Panthangi *et al.* (2009) found no consistent seasonal pattern in depressive symptoms, which was confirmed by

Jewell *et al.* (2010) and Henriksson *et al.* (2017). An explanation for these contradictory findings might be sought in geographical location, assessment method and clinical characteristics of the women, such as the presence of psychosocial risk factors or the presence and type of mental illness, moderating seasonal influences.

Here, we want to study potential seasonal influences on antepartum depressive symptoms and whether these influences differently impact subgroups of women, such as with or without a history of mental illness. The study is embedded in a population-based cross-sectional study of 2,438 pregnant women. For this purpose, we will study depressive symptoms in these women during the different months. Since seasonal influences on depressive symptoms have been found earlier both ante- and postpartum, we hypothesize that the prevalence of antepartum depressive symptoms will be higher in winter months.

Methods

Participants

Data used for this study was collected in the context of two large-scale observational research projects aimed at identifying women with psychopathology, psychosocial problems and substance use in routine obstetric care [28, 29]. Collection took place mainly in rural and urban regions in the southwest of the Netherlands and in two cities in the south and the east part of the Netherlands [28, 29]. The Netherlands is a small country located between 51-53⁰ longitude and 4-7⁰ latitude with a temperate maritime climate and high humidity (62-85%).

For this purpose, women attending an antenatal check-up at one of the participating midwifery practices and obstetric units were invited to fill out a (digital) screener, the Mind2Care questionnaire [30]. The women were informed that the questionnaire would result in an intervention suggestion, if problems would present. Answers to the questionnaire were coded. After completion of the questionnaire, a risk profile was calculated which would potentially result in an intervention advice. This advice was subsequently discussed with the caregiver, which could refer or provide the women with other specific care.

Women were eligible when they were pregnant at the time of screening. Exclusion criteria included having a miscarriage at the time of screening, insufficient proficiency in Dutch and insufficient mental capability to complete the questionnaire independently.

Most women (45.0%) were screened during the first trimester, 39.7% during the second and 15.3% during the third trimester. Screening took place between April 2011 and December 2015. Detailed information on sampling and recruitment has been published elsewhere [28, 29].

Datasets were combined (*n*=2758 and *n*=2087). Duplicate cases and cases with missing data were removed (*n*=2407). In total, we were able to include the data of 2,438 pregnant women in our analyses. The number of assessments ranged from 105 to 554 participants per month and from 419 to 1,011 per season. These differences are partially explained by the variation of birth rates throughout the year [31] and periodical differences, such as holidays.

A drop-out analysis was not possible. The data for the present study stem from an implementation study, for which the screening questionnaire was implemented in routine clinical care in midwifery clinics.

Ethics

The earlier described studies in which the present study is embedded [28, 29] have been conducted in accordance with the Helsinki Declaration. Because of the observational nature of the study, especially articles 24 (privacy and confidentially) and 25-32 (informed consent) are relevant. Written informed consent was obtained from all participants. Study protocols were approved by the medical ethical committee of the Erasmus University Medical Centre, Rotterdam, The Netherlands. The medical ethical committee deemed formal approval not necessary for the present study (registration number MEC-2016-332).

Method

The Mind2Care consists of 33 items which cover socio-demographic and obstetric factors and three symptomatology domains: psychopathology, psychosocial problems and substance use. Within the psychopathology domain, the Edinburgh Postnatal Depression Scale (EPDS) is included [32, 33]. Depressive symptoms

during pregnancy were assessed using the EPDS. This structured 10-item self-report questionnaire is developed as a screening tool for postpartum depressive symptoms [32], but is validated for the antepartum period as well [33]. Each item is scored 0-3, resulting in a sum score of 0-30 [32]. Higher scores represent more symptomatology. Depending on trimester, sensitivity and specificity of the EPDS range from 70-79% and 94-97%, respectively [32]. Since EPDS scores were non-normally distributed, with 61.4% of women scoring below 5, EPDS sum scores were dichotomized using a cut-off of 9 (indicating at least mild depressive symptoms) [34]. With this cut-off, sensitivity and specificity range from 76-97% and 92-94%, respectively [33]. A alternative cut-off of 13 (at least moderate depressive symptoms) was used for additional comparisons with other literature [34].

The month of EPDS assessment was used in this study for analyses as a measure for seasonality.

In line with literature on risk factors of antepartum depression [10, 11], the following potentially confounding factors were assessed:

- Socio-demographic: age, ethnicity, educational level, employment status, marital status.
- Obstetric: gestational age at assessment, parity.
- Psychopathology, psychosocial problems and substance use: support from partner and environment, relational problems, financial problems, housing problems, unplanned or unwanted pregnancy, smoking, alcohol use, drug use, current and past domestic violence, use of psychiatric/sleep medication, psychiatric admission in history, current (pharmacological or non-pharmacological) treatment for psychiatric problems.

Statistical analysis

We used logistic regression analysis to estimate the impact of month of assessment on antepartum depressive symptoms. For this purpose, we fitted a sinusoidal curve to the data by including a sine and cosine function to the regression model. The joint sine-cosine effect was tested using a Chi-Square Test [35]. This method is referred to as harmonic analysis and is often used to describe periodical patterns in epidemiological research [31, 36-38] and more recently, also psychiatric research [39]. Next, we tested whether the addition of a second

sinusoidal curve significantly improved the fit of the model. Analyses were repeated adjusting for confounding variables. Confounding variables were defined as having a significant univariable relationship with antepartum depressive symptoms, having an univariable relationship with month of assessment, and were not part of the causal pathway between month of assessment and antepartum depressive symptoms [40]. We report crude and adjusted odds ratio (OR) and standard error of the sine and cosine function, curve-shift and amplitude.

Finally, we explored whether the impact of month of assessment on antepartum depressive symptoms was modified by any of the assessed patient characteristics. For this purpose, we adopted the following procedure. First, we tested whether patient characteristics could be considered a risk factor of antepartum depressive symptoms using univariable logistic regression analysis. Interaction terms between significant patient characteristics with sine and cosine functions were calculated. We then added the sine and cosine interaction terms to a multivariable logistic regression model, including the sine and cosine functions, and confounding variables. For the specific aim of interpreting a significant interaction term (based on a significant Chi-Square Test of the joint sine-cosine interaction terms) and antepartum depressive symptoms, we stratified the sample in subgroups by patient characteristic, repeated the main analysis, and reported the direction and magnitude of seasonal influence within the thus formed patient subgroups. Patient characteristics between subgroups with significant interaction effect were compared using Chi-Square test.

Data was analyzed using SPSS 24.0 (IBM Corporation, Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

Results

An overview of background characteristics is shown in Table 4.1.

The median EPDS scores by month are shown in Table 4.2. The overall median EPDS score was 3 (interquartile range (IQR) 1-6; range 0-28). In this sample, 323 women (13.2%) scored EPDS ≥ 9 (at least mild depressive symptoms), of which 92 (3.8%) scored ≥ 13 (at least moderate depressive symptoms). The proportions by month of year are displayed in Figure 4.1 and Table 4.2.

Table 4.1 – Overview of background characteristics.

Characteristics	Mean (SD) or N (%)
Age:	30.0 years (± 4.6, range 15-44)
Gestational age:	17.1 weeks (± 9.0, range 2-41)
Ethnicity:	
Dutch	2158 (88.5%)
European	84 (3.5%)
Dutch Antillean	31 (1.3%)
Surinamese	28 (1.2%)
Moroccan	28 (1.2%)
Turkish	20 (0.8%)
Other	85 (3.5%)
Marital status:	
Married/cohabiting	2393 (98.2%)
Single	44 (1.8%)
Education:	
Primary education	120 (5.0%)
Secondary education	1057 (43.8%)
Higher education	1234 (51.2%)
Employment:	
Employed	2043 (84.1%)
Unemployed	386 (15.9%)
Parity:	
Primigravida	1838 (76.0%)
Multigravida	580 (24.0%)
Pregnancy intention:	
Wanted to get pregnant	2395 (98.8%)
Did not want to get pregnant (yet)	29 (1.2%)
Relationship status:	
In relationship	2393 (98.2%)
Single	44 (1.8%)

Note: variance in sample size, due to missing data.
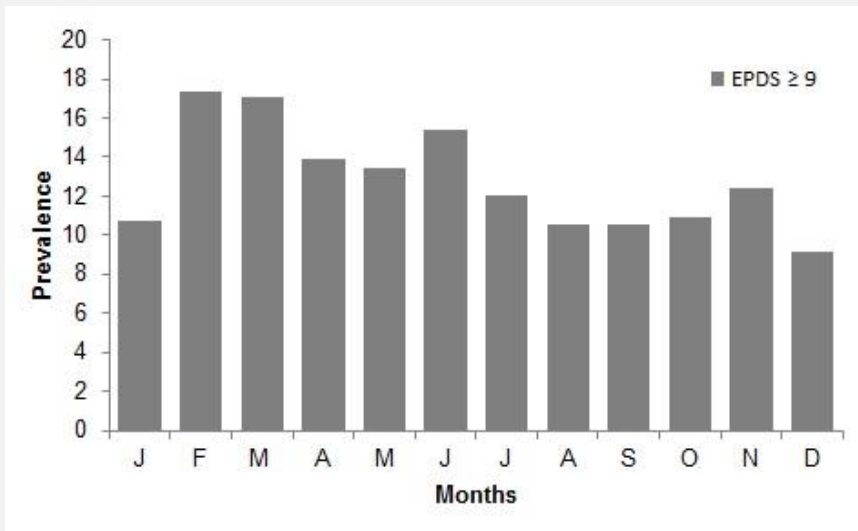
Figure 4.1 – Proportion of EPDS ≥ 9 by month.

Table 4.2 – Number of participants, median, IQR and proportions of participants with of EPDS scores of ≥ 9 by month of year.

Month	N	Median (IQR)	EPDS ≥ 9 (%)
January	140	3 (1-6)	10.7
February	138	4 (2-7)	17.4
March	305	4 (1-7)	17.1
April	554	4 (2-7)	13.9
May	201	3 (1-7)	13.4
June	156	3 (1-7)	15.4
July	200	3 (1-6)	12.0
August	170	3 (1-5)	10.6
September	171	3 (1-6)	10.5
October	156	3 (1-6)	10.9
November	105	3 (1-6)	12.4
December	142	3 (1-6)	9.2
Total	2,438	3 (1-6)	13.2

N = number of participants; IQR = interquartile range; EPDS = Edinburgh Postnatal Depression Scale.

We fitted a model with one and with two sinusoidal curves. A second curve did not further improve fit of the model. We found statistical evidence for a sinusoidal

pattern of depressive symptoms by month of assessment (sine-function β_{crude}=.224 [SE=.084], p=.007; cosine-function β_{crude}=-.014 [SE=.097], p=.888; joint sine-cosine function Chi^2 (2)=7.369, p=.025). This corresponds with a maximum of depressive symptomatology in March (estimated prevalence of 15.0%), and a minimum of depressive symptomatology in September (estimated prevalence of 10.4%). After adjustment for confounders (age, educational level, and ethnicity), we no longer found statistical evidence for a sinusoidal pattern of depressive symptoms by month of assessment (sine-function $\beta_{adjusted}$=.176 [SE=.086], p=.041; cosine-function $\beta_{adjusted}$=-.036 [SE =.099], p=.720; joint sine-cosine function Chi^2 (2)=4.377, p=.112).

Modifying factors
The risk factors that showed a significant relationship with the dichotomized EPDS score included employment status, unplanned or unwanted pregnancy, smoking, marital status, support from partner and environment, relational problems, financial problems, housing problems, present and past domestic violence, use of psychiatric/sleep medication, and current treatment for psychiatric problems. Next, we studied whether the impact of seasons on depressive symptoms might have been obscured by a modification of the effect by patient characteristics. Of all characteristics tested, one patient characteristic showed a significant moderating effect, i.e. being under current treatment for psychiatric problems (Chi^2(1)=6.431; p=.040). Adjusted for confounders, for women not receiving treatment (n=2309), we found a significant effect of seasonality (sine-function $\beta_{adjusted}$=.267 [SE=.096], p=.005; cosine-function $\beta_{adjusted}$=.070 [SE=.108], p=.516; joint sine-cosine function Chi^2(2)=8.521, p=.014), corresponding to a maximum of depressive symptomatology in March (estimated prevalence of 14.5%) and a minimum of depressive symptomatology in September (estimated prevalence of 7.8%). For women receiving treatment (n=91), we also found a significant effect of seasonality (sine-function $\beta_{adjusted}$=-.075 [SE=.312], p=.810; cosine-function $\beta_{adjusted}$=-.941 [SE=.391], p=.016; joint sine-cosine function Chi^2 (2)=6.254, p=.044). This corresponds to a maximum of depressive symptomatology in June (estimated prevalence of 73.7%) and a minimum of depressive symptomatology in December (estimated prevalence of 38.4%). The unadjusted joint sine-cosine function of

month of assessment on depressive symptoms (EPDS ≥ 9) for treated and untreated women expressed in Odds Ratio is shown in Figure 4.2.

No modifying effects were found for any of the other patient characteristics.
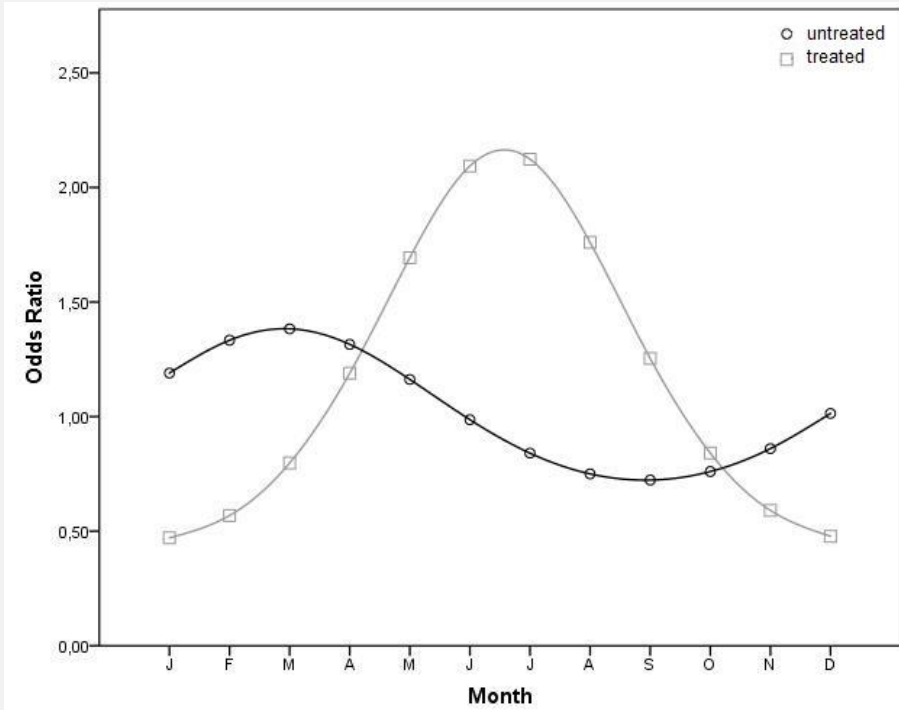
Figure 4.2 – Joint sine-cosine function of month of assessment on depressive symptoms (EPDS ≥ 9) expressed in Odds Ratio, shown for women who did not receive treatment (black) and women who did receive treatment for psychiatric problems (grey).

Function is unadjusted for confounders (age, educational level and ethnicity).

Treated versus untreated women

In order to better understand why treated women show a deviant periodical pattern of depressive symptoms, we explored the socio-demographic and clinical characteristics of this group of women. In post-hoc analyses, patient characteristics of treated women were compared to untreated women. First, as might be expected,

treated women more often than untreated women used psychiatric and/or sleep medication during pregnancy ($p<.001$; 22% versus 1.5%), and more often had a history of psychiatric admission ($p<.001$; 8% versus 1.1%). Treated women also smoked cigarettes more often during pregnancy ($p<.001$; 16% versus 5.2%). Next, they were more often single ($p=.006$; 6.5% versus 1.6%) or experienced relationship problems ($p<.001$; 21.7% versus 3.0%), including abuse ($p<.001$; 1.1% versus 0.1%). Finally, unemployment ($p<.001$; 33.0% versus 15.2%) and financial problems ($p<.001$; 20.9% versus 5.0%) were more prevalent, and they experienced less support from their environment ($p=.028$; 7.1% versus 2.3%).

Discussion

The present study used a large dataset of 2,438 pregnant women to explore seasonal differences on antepartum depressive symptoms. We found a prevalence of 13.2% of clinically relevant antepartum depressive symptoms, in agreement with previous research [2]. In the full study sample, we found no statistical evidence for a sinusoidal pattern of antepartum depressive symptoms by month of assessment, after adjusting for confounders. However, we found that the effect of month of assessment was modified by whether or not women were currently treated for psychiatric problems. Women who did not receive treatment for psychiatric problems showed a significant seasonal effect with a minimum of depressive symptomatology in September and a maximum in March, as hypothesized. Treated women also showed a significant seasonal effect, with a maximum of depressive symptomatology in June and a minimum in December.

Consistent with previous research on seasonal affective disorder [14-16], a seasonal pattern was found in women not receiving treatment for psychiatric problems. However, in a recent study in the general population, consisting of 34,294 respondents, the authors could not find a relation between depressive symptoms and latitude, season, and sunlight, thereby questioning the validity of seasonal affective disorder [41]. The findings of this study were however refuted because of several methodological and rational shortcomings, such as not including patient history and their cross-sectional approach [42].

Meliska *et al*. (2013) hypothesized that seasonal influences might contribute to worsening of already existing depressive symptoms, rather than being the cause of antepartum depressive symptoms. The findings of this study are partly in line with this hypothesis, with significant seasonal influences in women receiving treatment for psychiatric problems (both pharmacological and non-pharmacological). However, it is unexpected to find a maximum of depressive symptomatology in June and a minimum in December. Therefore, if there is a seasonal effect indeed, the seasonal effects in this subgroup of pregnant women might not be caused by light conditions, but are rather the result of other factors, such as temperature and humidity. Two earlier studies conducted in a tropical climate showed an increase in depressive symptoms in summer, due to temperature and humidity [43, 44]. However, if this would be the case, one might expect to find these effects in untreated women as well. Therefore, we do not find this hypothesis plausible. We found significant differences between treated and untreated women. However, these characteristics, such as smoking and financial problems, are often seen in psychiatric patients and are therefore not necessarily a cause for the seasonal effects in this subgroup of women. Possibly, social factors might contribute to seasonal fluctuations of self-reported depressive symptoms. For example, women might experience less social support in the summer, when family, neighbors and caregivers may be gone for vacation. Since the group of treated women shows more psychosocial problems, it may be that they are more reliant on social support. Possibly, women with a fear of delivery might have an exacerbation of their symptoms, because there are staff shortages during the summer months and they might not receive the same level of care and support. However, future research is needed to gain more insights regarding these social factors. However, one must keep in mind that patients with seasonal affective disorder are not necessarily worse in winter [17, 18].

The study by Meliska *et al*. (2013) is the only study thus far studying seasonal patterns in antepartum depression. As mentioned earlier, the results of this study are partly in line with their hypothesis. However, they only found a seasonal pattern in women suffering from antepartum depression and not in healthy controls. A possible explanation for this discrepancy with the present study might be sought in differences in study design and/or statistical analyses. In addition, the depressed

patients from the study by Meliska *et al.* (2013) were not allowed to use medication, which was not the case in our study, which might have influenced our results.

Interestingly, studies exploring seasonal effects during the postpartum period found higher prevalences of depression, compared to the present study exploring the effects during pregnancy [21, 23, 26]. An explanation might be found in the study population studied in this study: 51.2% of women attended higher education and 88.5% was native Dutch, indicating that this is a relative low risk sample, fitting with a lower prevalence of severe depressive symptoms. Also, different factors in the postpartum period might play a role in the increase of depressive symptoms, such as sleep deprivation and hormonal fluctuations.

An earlier study did not find a seasonal pattern in depressive symptoms in the general population when using a general questionnaire, as opposed to our study [45]. However, when using a specific questionnaire, the Seasonal Pattern Assessment Questionnaire, a seasonal pattern was found in the same population [46]. Therefore, we consider the possibility that our use of a general questionnaire has resulted in an underestimation of the seasonal effect.

Consistent with previous research, several risk factors were found for antepartum depressive symptoms, such as lack of social support, smoking during pregnancy and an unplanned or unwanted pregnancy [10, 11]. However, current treatment for psychiatric problems was the only risk factor showing a moderating effect between month of assessment and EPDS score. Age, educational level and ethnicity emerged as confounders of the relationship between seasonality and depressive symptoms. We hypothesize that these socio-demographic factors are related to planning of pregnancy. For example, high risk women (young, low educational level and from non-Dutch origin) might be more likely to become pregnant during the holiday.

Strengths and limitations

One of the strengths of this study is the large study sample of 2,438 respondents – with a prevalence in depressive symptomatology comparable to previous studies – which allows revealing small and modifying effects. Second, the EPDS is a validated tool for screening antepartum depression and is used worldwide. Finally,

this is one of the first studies to use a sine-cosine function to describe the relationship between seasonality and depressive symptomatology, which is specifically suited to describe periodic patterns. Also, by including confounding and modifying factors into our analysis, we were able to bring previous contradictory results into concordance.

There are limitations to this study. First, the EPDS is a self-assessment questionnaire and is not a clinical diagnosis for depression. Second, the EPDS only asks about depressive symptoms over the past week and does not assess level of impairment in daily life due to depressive symptoms. Further, a cross-sectional study may be less suitable to study the prevalence of antepartum depressive symptoms, since seasonal influences are possibly mainly experienced as an intra-individual course and as a result may be difficult to detect on a population level. Consequently, future research should study prevalence and severity of antepartum depressive symptoms in a longitudinal study, which allows following participants across seasons to determine whether they are vulnerable to seasonal influences. Because of the cross-sectional nature of the study, we have no information about the start or the length of the depressive episode or treatment. Further, we found low prevalences of EPDS ≥ 13 (3.8%) and are therefore underpowered to detect small seasonal effects in severe cases. Therefore, we conducted analyses with a lower cut-off. Finally, we might have found spurious effects. However, we were not able to perform a sensitivity analysis that could support our findings, which we suggest for future research.

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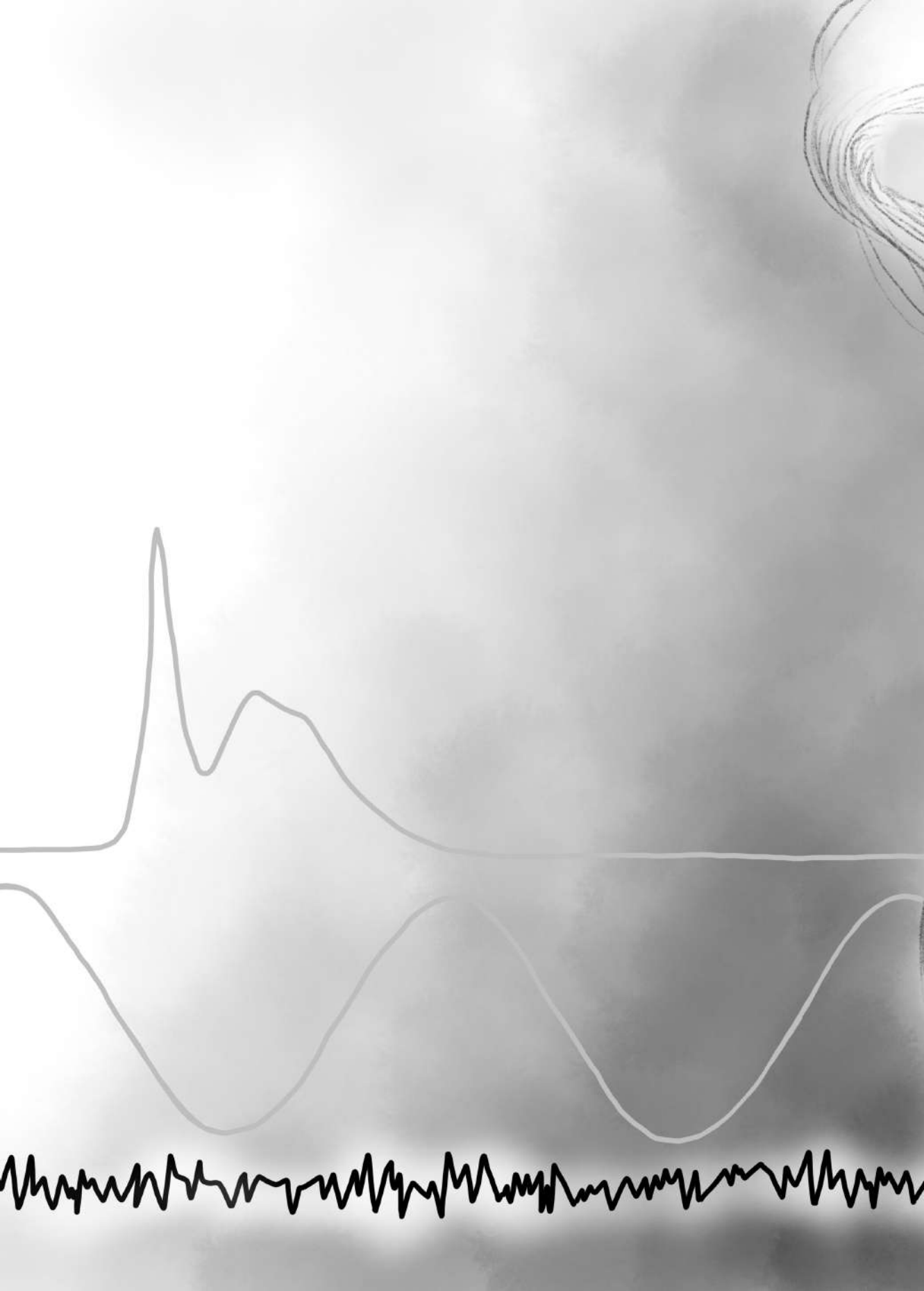
Part III - Sleep

Chapter 5

The impact of objective and subjective sleep parameters on depressive symptoms during pregnancy in women with a mental disorder: an explorative study

Babette Bais, Robert Lindeboom,, Leontien van Ravesteyn, Joke Tulen, Witte Hoogendijk, Mijke Lambregtse-van den Berg, Astrid Kamperman

Abstract

Poor sleep quality during pregnancy is associated with both antepartum and postpartum depression and adverse birth outcomes. This study evaluated both objective and subjective sleep quality and the effects on the subsequent course of antepartum depressive symptoms in psychiatric patients. This observational explorative study was embedded in an ongoing study focusing on pregnant women with a mental disorder and was performed in 18 patients (24–29 weeks pregnant). Depressive symptoms were assessed throughout pregnancy using the Edinburgh Postnatal Depression Scale (EPDS) with 5-week intervals. Sleep was assessed with actigraphy, the Pittsburgh Sleep Quality Index (PSQI) and sleep diaries at the start of the study. We studied correlations between sleep parameters and EPDS scores cross-sectionally using Spearman correlation. Next, we studied the course of antepartum EPDS scores over time per sleep parameter using generalized linear mixed modelling analysis. Objectively measured fragmentation index, total PSQI score and 4 PSQI subscales (sleep quality, sleep duration, sleep disturbances and daytime dysfunctions) were significantly correlated with EPDS scores when measured cross-sectionally at the start. Six objectively and subjectively measured sleep parameters had moderate to large effects on the course of depressive symptoms through the third trimester, but these effects were not statistically significant. More research is necessary to explore the causality of the direction between sleep problems and antepartum depressive symptoms we found in psychiatric patients.

Keywords

Introduction

Depression during pregnancy is a common and high impact disease, with a prevalence of approximately 11–13% [1]. Antepartum depression has a major impact on both maternal and fetal health, as well as infant development. Children exposed to maternal depression during pregnancy have a higher risk of adverse birth outcomes and more often show cognitive, emotional and behavioral problems [2–4].

Many risk factors for antepartum depression have been identified, such as major life events, lack of social support, marital difficulties, low socio-economic status and an unplanned or unwanted pregnancy [5,6]. Moreover, sleep problems are common in pregnancy [7,8]: pregnant women typically show disturbed, desynchronized circadian rhythms, resulting in disturbed sleep patterns, which put them at risk for depression [9]. Poor sleep quality during pregnancy is associated with both antepartum and postpartum depressive symptoms and adverse birth outcomes [10–17], although a causal relation is difficult to prove due to the reciprocal relation of depression and sleep.

The association between poor sleep quality and mental disorders has long been recognized in the general population [18,19] and has also been shown in the peripartum period. However, many studies only studied the postpartum period [20,21] and/or only studied self-reported measures [10,12,22–24]. Earlier research showed that subjective sleep quality is worse than objectively measured sleep quality in pregnant women with a mental disorder [25]. A study in healthy women showed indeed that subjective sleep quality was associated with postpartum mood disturbances, but not objectively measured sleep quality [26]. However, two other studies in healthy pregnant women found that both objective and subjective sleep parameters were significantly associated with depressive symptoms in the third trimester and postpartum [15,17]. Since these three studies were executed in healthy women, these results cannot be simply extrapolated to pregnant women with a psychiatric disorder. This is relevant, since these women are at high risk for sleep problems because of not only their pregnancy, but also because of their mental problems. Based on the reciprocal relation between depression and sleep, it is relevant for clinicians and researchers to learn whether sleep problems during

pregnancy are associated with depressive symptoms in psychiatric patients and whether these predict the longitudinal course of depressive symptoms.

Here, we explored both subjective and objective sleep parameters and their effects on the course of antepartum depressive symptoms in a sample of 18 psychiatric patients. We hypothesized that antepartum sleep quality is associated with antepartum depression symptom severity when assessed simultaneously during pregnancy and with its subsequent course. For this purpose, we studied both objectively measured sleep parameters from actigraphs and subjectively measured sleep parameters in relation to the course of depressive symptoms in pregnant women diagnosed with a mental disorder.

Materials and Methods

Participants

This study was embedded in a larger randomized controlled trial (DAPPER, NTR3015, http://www.trialregister.nl). The DAPPER study (Daycare Alternative Psychiatric Pregnant women Efficiency Research) aimed to evaluate the effectiveness of a group-based multicomponent psychotherapy intervention for pregnant women with a mental disorder, compared to individual counseling (care as usual). Both arms showed similar effects on depressive symptoms [27]. Eligible participants were pregnant women, diagnosed with a mental disorder, confirmed by the Structured Clinical Interview for DSM-IV diagnosis by one trained medical doctor [28]. A convenience subsample of participants was recruited to perform the actigraphy, PSQI and sleep diary assessments between 24 and 29 weeks of pregnancy. Participants were recruited in the second trimester, since sleep is more affected by pregnancy in the third trimester [29]. Exclusion criteria were suffering from a tremor or somatic conditions that could affect sleep, or an insufficient proficiency in Dutch.

Ethics

The study protocol of the randomized controlled trial was approved by the Medical Ethical Committee of the Erasmus University Medical Centre in Rotterdam, the Netherlands (registration number MEC-2009-370). Written informed consent was

obtained from all participants. The present study was added to the protocol after ethical approval of the amendment.

Method

The following demographic information was obtained from all participants: Age, gestational age, parity, marital status, ethnicity, educational level and employment status. Educational level was dichotomized into high and low educational level, with low educational level defined as basic vocational education or less.

Objective sleep parameters were measured using the Actiwatch Actigraphy model AW4 (Cambridge Neurotechnology Ltd, Cambridge, UK). Actigraphy, the continuous assessment of activity with a watch-sized non-dominant wrist-worn recorder, is a validated technique to obtain estimates of sleep [30–32]. The Actiwatch measured the number of movements above a threshold setting of 20 activity counts per 60 seconds epoch, and the following indices were extracted: Total sleep time, sleep latency (time until asleep), sleep efficiency (percentage of time spent asleep while in bed) and the fragmentation index (the addition of percentage time spent moving and the percentage immobility phases of 1 minute). Lower total sleep time, higher sleep latency, lower sleep efficiency and higher fragmentation index indicate more sleep problems. Sleep data were analysed using the Actiwatch Sleep Analysis program (version 1.16, Cambridge Neurotechnology Ltd, Cambridge, UK). Participants wore the Actiwatch for 7 consecutive days and nights at the start of the study. Only the weekdays (≥3 days and nights) were used for analyses because of an increase in variability during the weekends. The precision of this assessment period was better than for 7 days [25].

Subjective sleep parameters were measured at the start with the PSQI, a structured 19-item self-rating questionnaire with 5 additional items reported by bedpartner, that assesses sleep quality and disturbances of the past month [33]. The overall sum score ranges from 0–21, with higher scores corresponding to poor sleep quality [33]. A sum score of >5 indicates poor sleep quality. The PSQI has a sensitivity and specificity of respectively 89.6% and 86.5% in distinguishing good and bad sleepers [33]. The 19 self-rated items generate 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction [33].

Subscale scores range from 0–3, with higher component scores indicating more sleep problems [33].

Furthermore, we measured subjective sleep quality with sleep diaries kept by the participants. Participants kept a sleep diary during the week of the actigraphy assessments, which included questions on sleep time and sleep latency. A minimum of 3 weekday measurements of each participant were averaged, in analogy with the sleep parameters measured by the Actiwatch.

Depressive symptoms were assessed with the EPDS at the start of the study and subsequently at 5-week intervals until the end of pregnancy, thus 5, 10 and 15 weeks after the start. The EPDS is a structured 10-item self-report measure of depression during pregnancy [34]. Items are scored with a value 0–3, resulting in a sum score of 0–30 [34]. The EPDS was developed for the detection of postpartum depression, but has been validated for screening depression during pregnancy as well [35]. Using a cut-off of 10 or 11, depending on the trimester studied, sensitivity and specificity of the EPDS for screening antepartum depression range between respectively 70–79% and 94–97%, [35]. In the second and third trimester, a score above 10 indicates clinically relevant symptoms of depression [35].

Statistical analysis

With Spearman correlation coefficients, we tested whether the various sleep parameters were correlated with EPDS scores at the start of the study. A correlation of <0.3 indicates no or a very weak relationship, of 0.3–0.5 a weak, of 0.5–0.7 a moderate and of >0.7 a strong relationship [36].

We estimated the course of antepartum EPDS scores over time using generalized linear mixed models. This is a statistical technique that, especially in the context of longitudinal designs, is robust for missing data [37], particularly in case of missing at random (MAR) and missing completely at random (MCAR). In a series of random-intercept models, we included time, the standardized sleep parameter and the time x standardized sleep parameter interaction as an effect measure of a sleep parameter on the course of antepartum EPDS scores. Subsequently, we added the standardized score of EPDS measured at the start to the model, since depression severity is an important predictor for treatment outcome [38]. For the total PSQI score, we also tested the dichotomized PSQI score, using the validated

cut-off of >5 [33]. Standardized regression coefficients including the 95% Confidence Interval (CI) are reported. Regression coefficients reflect the slope of the regression line. For example, in the case of a regression coefficient of 0.15, an increase of 1 standard deviation (SD) by the sleep parameter reflects an increase of 0.15 SD on the EPDS score per measurement, thus after 5 weeks. A negative coefficient reflects a decrease in symptom severity and a positive coefficient an increase. A coefficient of <0.2 indicates a small effect, around 0.5 a moderate effect and of >0.8 a large effect [36]. By means of sensitivity analyses, we repeated our primary analysis adjusted separately one by one for medication, treatment arm, psychiatric diagnosis, age, education level, parity, work and ethnicity.

Data was checked for non-normality of distribution. Patient characteristics and sleep parameters were summarized by their median and interquartile range (IQR) for ordinal and continuous variables, since these were not normally distributed. Age and gestational age were summarized by their mean and SD. Categorical variables, such as educational level, were summarized by count and proportion. Missing data patterns were explored.

Data was analyzed using SPSS 24.0 (IBM Corporation, Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

Results

We studied 18 pregnant women. One EPDS score was missing at the start of the study, 4 at 5 weeks, 8 at 10 weeks and 13 at 15 weeks after the start. However, 5 women were at 15 weeks ≥40 weeks pregnant. Table 5.1 shows the demographic characteristics of the women at the start. Ten women were primarily diagnosed with depression, 5 women with generalized anxiety disorder, 2 with borderline personality disorder and 1 with bipolar disorder. Two participants drank alcohol and 7 participants smoked while pregnant. During the study, 4 participants used antidepressant medication, 1 used lithium and 1 methylphenidate.

Table 5.1 – Demographic characteristics of women at the start (24–29 weeks of pregnancy).

Demographics	Patients
Age in years, mean (SD)	29.5 (5.3)
Gestational age in weeks, mean (SD)	26.0 (1.7)
Parity, nulliparous	14 (78%)
Committed relationship	16 (89%)
Ethnicity, non-Western	5 (28%)
Educational level, low	13 (72%)
Unemployed	13 (72%)

Table 5.2 – Distribution of objective and subjective sleep parameters at the start (24–29 weeks of pregnancy).

Sleep parameters	Median	IQR
Objective sleep parameters		
Actiwatch total sleep time (hh:mm)	06:40	06:01–07:36
Actiwatch sleep latency (mm:ss)	21:46	12:03–41:59
Actiwatch sleep efficiency (%)	78.65	76.35–84.67
Actiwatch fragmentation index (%)	36.88	25.25–46.77
Subjective sleep parameters		
PSQI total score	7.50	4.75–11.25
PSQI sleep quality	1	1–2
PSQI sleep latency	1	0–2
PSQI sleep duration	0	0–1
PSQI sleep efficiency	1	0–3
PSQI sleep disturbances	2	1–2
PSQI sleep medication	none	none
PSQI daytime dysfunction	1	1–3
Diary total sleep time (hh:mm)	7:55	7:09–9:20
Diary sleep latency (mm:ss)	35:00	10:00–46:15

h = hour; m = minute; s = second; IQR = interquartile range.

At the start of the study, median EPDS score was 13 (IQR 8–19). Median EPDS scores were 10.5 (IQR 3.75–19.75) 5 weeks after, 13.5 (IQR 6.5–21.5) 10 weeks after and 20 (IQR 9.5–23) 15 weeks after the start.

Table 5.2 shows the objective and subjective measured sleep parameters at the start of the study.

Table 5.3 shows the correlations between the various sleep parameters and the EPDS scores at the start. A moderate relationship was found between actigraphically measured fragmentation index, PSQI sleep quality and PSQI sleep

duration and EPDS score. A strong relationship was found between total PSQI score, PSQI sleep disturbances score and PSQI daytime dysfunction score and EPDS score.

Table 5.3 – Correlations between objective and subjective sleep parameters and EPDS scores when measured cross-sectionally at the start (24–29 weeks of pregnancy).

Sleep parameters	r (SE)
Objective sleep parameters	
Actiwatch fragmentation index	−0.51* (0.22)
Actiwatch total sleep time	0.14 (0.25)
Actiwatch sleep efficiency	0.41 (0.20)
Actiwatch sleep latency	0.40 (0.26)
Subjective sleep parameters	
PSQI total score	0.79*** (0.15)
PSQI total score, dichotomized	0.78*** (0.10)
PSQI sleep quality	0.68** (0.16)
PSQI sleep latency	0.35 (0.26)
PSQI sleep duration	0.53* (0.23)
PSQI sleep efficiency	−0.38 (0.22)
PSQI sleep disturbances	0.82*** (0.13)
PSQI sleep medication	none
PSQI daytime dysfunction	0.82** (0.12)
Diary total sleep time	−0.16 (0.26)
Diary sleep latency	0.28 (0.29)

SE = standard error; $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

Sleep efficiency, total sleep time and sleep latency were not significantly associated with depressive symptoms, both objectively and subjectively measured. Table 5.4 shows the standardized regression coefficients for the course of antepartum EPDS scores for the various objectively and subjectively measured sleep parameters. None of the sleep parameters showed a significant association with the course of antepartum EPDS scores, both unadjusted and adjusted for standardized EPDS score at the start. Sensitivity analyses, in which we separately adjusted for medication, treatment arm, psychiatric diagnosis, age, education level, parity, work and ethnicity, suggested stability of the results that we found.

Though one should be careful interpreting the magnitudes of effects because of a lack of statistical significance, standardized regression coefficients differed between the studied sleep parameters. Moderate effects were found for PSQI total

score, PSQI sleep duration and sleep latency measured by diary. Large effects were found for PSQI sleep quality scores and total sleep time measured by both diary and actigraphy.

Exploring missing data patterns did not show a specific selection of women with more missing EPDS assessments.

Table 5.4 – Effects of objective and subjective sleep parameters at the start (24–29 weeks of pregnancy) on the course of depressive symptoms through the third trimester.

Sleep parameters	Standardized β (95% CI)	Standardized β$_{adj}$ (95% CI)^
Objective sleep parameters		
Fragmentation index	−0.56 (−2.39–1.28)	−0.28 (−2.01–1.47)
Total sleep time	1.23 (−0.42–2.89)	1.25 (−0.47–2.97)
Sleep efficiency	−0.03 (−1.87–1.81)	−0.36 (−2.12–1.39)
Sleep latency	−0.27 (−1.60–1.06)	−0.24 (−1.54–1.06)
Subjective sleep parameters		
PSQI total score	−0.46 (−2.29–1.38)	−0.48 (−2.12–1.17)
PSQI total score, dichotomized	−0.45 (−2.10–1.20)	−0.26 (−1.84–1.31)
PSQI sleep quality	1.73 (−2.78–6.24)	1.99 (−1.01–4.98)
PSQI sleep latency	0.41 (−1.12–1.95)	0.35 (−1.11–1.81)
PSQI sleep duration	−0.53 (−3.96–2.90)	0.72 (−1.35–2.78)
PSQI sleep efficiency	−0.19 (−1.82–1.44)	0.11 (−1.37–1.59)
PSQI sleep disturbances	0.27 (−3.26–3.79)	0.48 (−2.25–3.20)
PSQI sleep medication	none	none
PSQI daytime dysfunction	−0.36 (−4.33–3.62)	−0.15 (−2.51–2.22)
Diary total sleep time	1.12 (−0.31–2.55)	1.25 (−0.33–2.83)
Diary sleep latency	0.70 (−0.83–2.22)	0.75 (−0.84–2.33)

^Adjusted for standardized EPDS score at the start.

Discussion

The present study studied 18 pregnant women with a mental disorder to explore if and how objectively and subjectively measured sleep parameters would be associated with antepartum depressive symptoms. We found that actigraphically measured fragmentation index, total PSQI score (both continuous and dichotomous) and 4 PSQI subscales (sleep quality, sleep duration, sleep disturbances and daytime dysfunctions) were moderately to strongly correlated with depressive symptoms during pregnancy. We found that some sleep

parameters had a notable impact on the course of antepartum depressive symptoms during the third trimester (effect size > 0.8 SD), both unadjusted and adjusted for EPDS score at the start and different separate confounders (medication, treatment, psychiatric diagnosis, age, education level, parity, work and ethnicity).

Cross-sectional findings

We found a moderate to strong correlation between total PSQI score (both continuous and dichotomized) and 4 PSQI subscales and antepartum depressive symptoms, when measured cross-sectionally. Thus, women experienced more depressive symptoms when they showed more overall sleep problems, when they reported their sleep to be of poor quality, when they reported to sleep less, when they suffered from more various sleep disturbances or when they had more problems with functioning during the day.

The finding that women who report more depressive symptoms also suffer from specific sleep problems is congruent with the relation with the total PSQI score, since this sleep parameter is an overall measure of these various underlying sleep problems. With respect to daytime dysfunctioning, it is not surprising that these symptoms correlate with depressive symptoms, since daytime dysfunctioning is a symptom of depression [28].

Two previous cross-sectional studies in peripartum women using the PSQI find associations between sleep parameters and depressive symptoms, although not consistently [23,24]. However, both these studies were executed in postpartum women, who have shown to experience more sleep problems than pregnant women [39].

We found a statistically significant negative correlation between actigraphically measured fragmentation index and antepartum depressive symptoms, when measured in the second trimester at the start of the study. Thus, women reported more depressive symptoms when the Actiwatch measured a lower fragmentation index, indicating lower mobility during sleep. This is not in line with earlier studies, where a positive relation is found between depressive symptoms and fragmented sleep [13,17,22]. Depressive symptoms are common in adults with nighttime restlessness, such as (both pregnant and non-pregnant) patients with Restless

Legs Syndrome [40]. We have no explanation for this contradictory finding. We are studying a complex population where different mechanisms may be at stake. To our knowledge, sleep studies with actigraphy have not been executed earlier in a pregnant psychiatric population, so we cannot compare our findings to those from other studies. Future research should be executed to confirm our findings.

In this study, we found that the majority of the patients was suffering from sleep problems, which is common in pregnancy [7,8]. The mean PSQI score was 7.5, with 14 out of 18 patients scoring 5 or higher, an indication of clinically relevant sleep problems [33]. This score is high, but comparable to other studies peripartum. Even in studies among healthy pregnant and postpartum women without psychiatric disorders, mean PSQI scores were rather high, ranging from 6.3 to 8.3 [10,15,24,26]. A recent meta-analysis among 24 articles showed that the average PSQI score in pregnancy was 6.1 and that it increases from second to third trimester [29]. This indicates that sleep problems among pregnant women are very common. Possibly, a higher PSQI cut-off to distinguish bad sleepers is needed during pregnancy [29].

Longitudinal findings

None of the sleep parameters were significantly associated with the course of antepartum depressive symptoms. However, we did find differences in standardized regression coefficients. Though not significant, probably due to the small sample size, we found large effects for PSQI sleep quality and total sleep time measured by both diary and actigraph, which may be an indication of the direction and magnitude of the effect. However, a study with more statistical power would be necessary to confirm these findings. A post-hoc power analysis revealed that a sample size of 64 women would have been needed to show significance. Another explanation for not finding any significant effects may be the fact that all women in this study were treated for their depressive symptoms, which, as a consequence, could have positively affected the course of these symptoms. At present, such studies have not been conducted yet in a population of pregnant women diagnosed with a mental disorder. Thirdly, another explanation might be the timing of assessment. Studies with antepartum measurements studied the third trimester [10,15,17,26], a timing which is comparable to our study. However, the

third trimester is 12 weeks long and sleep may therefore be influenced differently along the trimester, since mothers have more sleep problems as the third trimester progresses, with women having more difficulty finding a comfortable sleeping position [7]. Adjustment for gestational age did not show that this influenced sleep in our patients differently. However, the effects of this may be small and a larger study sample may be necessary to find this. For these reasons, it is difficult to generalize our and other findings to the third trimester as a whole.

Strengths and limitations

One of the strengths of this study is the use of both objective and subjective sleep parameters. Many studies rely only on self-reported measures, even though these measures often show differences with objectively measured sleep parameters [25,26]. Moreover, the PSQI and actigraphs are often used in sleep research, which makes it possible to compare the findings of this study to other studies. In addition, the EPDS is a validated tool in peripartum research worldwide and is suited to measure symptoms over a period of time. Finally, to our knowledge, this is the first study that studied the effects of both objective and subjective sleep quality on depressive symptoms in pregnant women with a psychiatric disorder.

This study also has various limitations. First, we studied a relatively small number of patients and are therefore underpowered, which makes it difficult to generalize the findings of this study. Moreover, we measured sleep quality at the start of the study and did not measure this at follow up. Studying both depressive symptoms and sleep quality longitudinally might be more suited to study how these affect each other and to understand the causality. Therefore, we do not know how sleep quality changed over time and affected depressive symptoms. Third, we measured sleep quality for one week, which is a short time period and could have been influenced by external factors. A longer time period would have limited this possibility. Fourth, our data suffer from missing EPD scores. Possibly due to their mental disorder, the participants showed less motivation to fill out all questionnaires. This could have had influence on the robustness of our findings, especially regarding the final stage of pregnancy, and which could have underestimated the effect size. However, exploring missing data patterns did not show a selection of women with more missing EPDS assessments. While our

analysis did not give clear indication, we cannot rule out unmeasured factors influencing dropout. Finally, we studied a heterogeneous group of women with different mental disorders, which could have been affected differently by potential sleep problems. However, adjustment for diagnosis did not change our findings.

Future directions

For future research, it would be necessary to study more patients. In addition, it would be relevant to include pregnant women without a mental disorder as a reference group. Additionally, it would be interesting to assess sleep quality at different time points, preferably before pregnancy, in all 3 trimesters and postpartum, to gain more insight in how sleep quality changes through pregnancy and how this affects depressive symptoms in the peripartum period. In a longitudinal design, the reciprocal relation between sleep and depression may be better understood.

Conclusions

We explored if and how objectively and subjectively measured sleep parameters would be associated with antepartum depressive symptoms. Various sleep parameters were significantly correlated with EPDS scores when measured cross-sectionally at the start. A number of sleep parameters had moderate to large effects on the course of depressive symptoms through the third trimester, but these effects were not statistically significant. More research is necessary to explore the causality of the direction between sleep problems and antepartum depressive symptoms we found in psychiatric patients.

Author contribution

Conceptualization, B.B., M.L.-v.d.B. and A.K.; methodology, B.B., R.L., M.L. and A.K.; formal analysis, B.B.; data curation, L.v.R. and J.T.; writing—original draft preparation, B.B., R.L., A.K.; writing—review and editing, all auhors; supervision, R.L., W.H., M.L.-v.d.B. and A.K.

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Conflicts of interest

The authors declare no conflict of interest.

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Chapter 8

General discussion

This thesis discusses various aspects of antepartum depression, with a special focus on light, seasons and sleep.

In **Part I** of this thesis, we first outlined the design of a randomized controlled trial (RCT) for evaluating the effectiveness of light therapy for depression during pregnancy. We subsequently presented the findings regarding our primary research question. In **Part II**, we focused on the seasonality of depressive symptoms during pregnancy. In **Part III** of this thesis, we focused on sleep during pregnancy. First, we examined the impact of sleep on depressive symptoms during pregnancy in psychiatric patients. In the next two chapters, we studied prescription patterns of benzodiazepines before, during and after pregnancy, which are often prescribed for sleep problems.

Detailed descriptions on main results of the studies were discussed in the previous chapters. This chapter will provide a general discussion of all main findings, methodological considerations, clinical implications, implications for future research and a final conclusion.

Part I – Light

The Bright Up study

In **Chapter 2**, we presented the detailed protocol of the Bright Up study, where we aimed to evaluate the effectiveness of bright light therapy (BLT) for pregnant women with a depressive disorder, compared to placebo. Earlier, two small RCTs showed significant improvement of depression among pregnant women exposed to BLT compared to placebo [1, 2]. Although these studies present promising results, the sample sizes of these studies are small and therefore, these studies are at risk for chance-findings [3]. In the Bright Up study, we aimed to investigate the effects of BLT on antepartum depression in a larger study sample, including follow up postpartum.

In **Chapter 3**, we presented the findings regarding the primary research question of the Bright Up study, namely whether BLT is effective in treating depression during pregnancy. In this study, we randomized 67 pregnant women with depression to either BLT or dim red light therapy (DRLT). Although it is not known which of these two conditions is more effective, we hypothesize that the condition with DRLT could

be considered as biologically inactive and thus could be considered as placebo treatment [4]. Women received daily treatment with light of 30 minutes within 30 minutes of habitual wake-up time for six weeks. Follow up took place weekly during the intervention period, at the end of the intervention period, three and ten weeks after treatment and at two months postpartum. In this study, we did not find a statistically significant difference between the two treatment arms during the intervention period nor during the entire study. Depression rating scale scores improved with 41.2-50% during the intervention period in the BLT group and with 45-58.6% in the DRLT group.

The improvement reported in the Bright Up study is comparable to that in the open study conducted among pregnant women with depression by Oren *et al.* [5] and the RCT conducted among postpartum women by Corral *et al.* [6], who both found an improvement of 49% in depression rating scale scores. Similar to our study, Corral *et al.* did not find superiority of BLT over placebo treatment.

Effects in the Bright Up study

The mean improvement in the placebo condition in the present study may be presented by placebo effects – which could also be the case in the group treated with BLT. A meta-analysis showed that the placebo response in antidepressant trials is approximately 68% [7]. However, this response has not been studied yet in light therapy studies specifically.

Secondly, the improvement can be represented by non-specific treatment effects, such as "forcing" participants into a daily rhythm, which may benefit their symptoms [8], interaction with researchers or increased awareness and self-care by participating in a study. Noteworthy, Corral *et al.* reported that women enjoyed 30 minutes of "quiet time", which is reported by several of our participants as well. This quiet time could represent a form of relaxation or even mindfulness, which has been shown to be effective for a variety of psychological problems [9, 10]. Beneficial effects of mindfulness have also been shown for pregnant women specifically [11, 12]. Moreover, an earlier systematic review discussing studies in treating antepartum depression, which all included a control condition, showed that a considerable improvement can be observed in both treatment arms [13]. In these control conditions, women received various treatments depending on the experimental

condition, such as treatment as usual, placebo light, non-specific acupuncture or they were put on a waiting list.

Finally, the improvement in both groups may be represented by the course of pregnancy, spontaneous remission or regression to the mean. A meta-analysis has shown that untreated depressive symptoms could decrease by 10-15% over 2-20 weeks [14]. However, leaving antepartum depression untreated is not advised, since untreated antepartum depression may eventually lead to postpartum depression [15], which in its turn might negatively impact the mother-child relationship [16].

Discrepancy with earlier studies

However, our findings differ from the studies by Epperson *et al.* [1] and Wirz-Justice *et al.* [2], who both found superiority of BLT over placebo treatment among pregnant women diagnosed with depression. Wirz-Justice *et al.* included only clinical outpatients and found that BLT had more effects in severe patients in their study. However, the baseline severity of depressive symptoms in the patients in our study did not differ clinically relevant from the study by Epperson *et al.* and Wirz-Justice *et al.* Additionally, sensitivity and post-hoc analyses showed that baseline severity did not change our findings.

Both studies by Epperson *et al.* and Wirz-Justice *et al.* have a different treatment protocol from the present study. In the Bright Up study, women were instructed to have 30 minutes of light therapy within 30 minutes of habitual wake-up time. In the studies by Epperson *et al.* and Wirz-Justice *et al.*, this was one hour of light therapy within 10 minutes of habitual wake-up time. This difference in protocol may be an explanation for not finding statistical significance between the two groups in the present study, since more light exposure in the BLT group may be necessary. Thus far, no meta-analysis has been conducted yet studying the relation between different light exposure durations and depressive symptoms in non-seasonal depression. However, other studies – in non-pregnant populations – showed a statistically significant difference between the active and placebo condition with a similar treatment protocol as in the present study [4].

Future research

We intended to include 150 participants, expecting a difference of 10-15% in depressive symptoms between the two groups, which would reflect a small to medium effect. Due to a lack of resources, we decided to stop the inclusion after 67 inclusions. Despite this, we are internationally the largest RCT studying the effects of BLT on depression during pregnancy. Post-hoc power calculations showed us that this sample size would be sufficient to estimate a 15-20% difference in symptom reduction between the two conditions, which would reflect to a medium effect.

For future research, it would not only be relevant to study a larger study sample to assess more subtle effects, but also to study whether the effects found in both treatment groups represent true treatment effects, non-specific treatment effects, placebo effects or a combination hereof. This could be done by studying biological outcomes, such as melatonin and cortisol levels. In the introduction of this thesis, the hypothalamus-pituitary-adrenal gland (HPA) axis and its role in regulating cortisol has been explained. The suprachiasmatic nucleus (SCN), also known as the 'biological clock', controls the HPA axis: decreased inhibitory control of the SCN has been associated with HPA axis hyperactivity [17]. Since light synchronizes the SCN with the environmental circadian rhythm and thus influences the HPA axis, it may indirectly influence cortisol levels. The SCN does not only control the circadian rhythm of cortisol, but also that of melatonin [18-20]. Therefore, analyzing cortisol and melatonin levels may possibly show a statistically significant difference between the two treatment arms, regardless of perceived depressive symptoms. Urine, saliva and hair were collected at multiple time points in the Bright Up study, which would enable us to execute these analyses in the future. Due to limiting resources, we could not analyze these samples yet.

Clinical implications

In the Bright Up study, both treatment arms showed a major improvement in depressive symptoms. Considering this major improvement and considering the long-standing evidence on the efficacy of BLT on non-seasonal depression, amongst others shown by a Cochrane review [4] and two more recent meta-analyses [21, 22], it would be meaningful to implement light therapy in clinical practice in treating antepartum depression. Besides the beneficial effects on depressive symptoms

during pregnancy, participants experienced only mild adverse effects (e.g. headache for a maximum of three days) and found the treatment highly acceptable. Despite the fact that the placebo condition was just as effective in treating antepartum depressive symptoms as the experimental condition, light therapy would be an alternative treatment for psychotherapy and antidepressant medication, given the major improvement in a short time period, the high acceptability, the mild and short-lived side effects, the low costs and the direct availability.

Part II – Seasons

Seasons and depression

BLT has been an effective treatment for non-seasonal depression [4], but was first applied as treatment for seasonal affective disorder (SAD). In 1984, the first cases of SAD were described by Rosenthal *et al.* [23] as "a syndrome characterized by recurrent depressions that occur annually at the same time each year". Together with a description of the first SAD cases, they presented their preliminary findings on treatment with BLT. More recently, seasonal variation has also been found in pregnant [24] and postpartum women [25-30].

In order to study whether seasons might influence depressive symptoms during pregnancy and with that possibly the treatment with light therapy in the Bright Up study, we studied seasonal variability in these symptoms in a cross-sectional study in **Chapter 4**. In a large observational cohort, pregnant women were screened on psychopathology, psychosocial problems and substance use. Amongst others, data was collected on current depressive symptoms. We fitted a sinusoidal curve to the data to estimate the seasonal relationship between month of assessment and antepartum depressive symptoms. In the entire study sample, we did not find any evidence for seasonal influences on depressive symptoms during pregnancy, after adjustment for confounders. We did find that current treatment status obscured the seasonal influences. In our study, there were two distinct groups with opposite effects, which eventually resulted in not finding any effects in the total study sample. In women untreated for psychiatric complaints, a minimum of depressive symptomatology was found in September and a maximum in March. In women treated for psychiatric complaints, a minimum of depressive symptomatology was

found in December and a maximum in June. Thus, seasonal influences on depressive symptoms during pregnancy can be observed, but are different in women treated or untreated for psychiatric problems. In **Chapter 4**, we speculated on possible explanations for these findings, such as meteorological and social factors. For example, we speculated that women treated for psychiatric problems, who are possibly more in need of social support, might experience less of this support in summer, when family, neighbors and caregivers are gone for vacation, which might exacerbate their depressive symptoms.

Seasons and the Bright Up study

The findings of this part of the thesis suggested that seasons influence depressive symptoms during pregnancy and subsequently, we hypothesized that seasons might possibly influence the treatment effect in the Bright Up study. Therefore, we adjusted the analyses in the Bright Up study for when women were treated for their depressive symptoms. Possibly, treatment with BLT in winter may be more effective than treatment in summer compared to placebo treatment, for example. However, sensitivity analyses where we adjusted for when women were treated, did not change our findings (see **Chapter 3**). Thus, seasonal influences did not seem to impact the effects of light therapy in the Bright Up study.

Since the effect of current treatment status modified the seasonal influences on depressive symptoms in **Chapter 4**, we repeated the primary analyses in **Chapter 3**, adjusted for not only current treatment status, but also for any treatment intervention besides the treatment with light women received in the study. However, these sensitivity and post-hoc analyses did not change our findings in the Bright Up study as well.

One major limitation of **Part II** is that the study of **Chapter 4** is conducted in a cross-sectional design. This design may be less suitable to study the seasonality of depressive symptoms during pregnancy, since seasonal influences are possibly experienced as an intra-individual course. In the Bright Up study, it would be possible to study seasonal variations not only between women, but also within women, due to the longitudinal design. However, in these women, treatment with light therapy might change depressive symptoms and with that, any potential seasonal variation.

Future research

For future research, it is important to study the prevalence and severity of depressive symptoms during pregnancy longitudinally, which would allow to follow patients across various seasons. Since women treated for psychiatric problems showed a seasonal pattern different from the general population, it would be relevant for both researchers and clinicians to study the underlying causes for these divergent findings. Additionally, it would be important to study how seasons impact the start and the length of the depressive episode and treatment hereof. Finally, in **Chapter 4**, we found that age, ethnicity and educational level emerged as confounders in the relationship between month of assessment and depressive symptoms. Therefore, we hypothesized that these socio-demographic factors are related to the planning of pregnancy. It would be interesting for future studies to explore this hypothesis.

Clinical implications

The present study showed that depressive symptoms during pregnancy are prevalent year round. Moreover, seasonal influences may be experienced differently by different women, which may actually lead to more depressive symptoms in spring and summer for particular subgroups of women. Additionally, in the Bright Up study (**Chapter 3**), we received referrals from participants the entire year through. Therefore, health care professionals should be aware of antepartum depressive symptoms not only during autumn and winter, but also during spring and summer.

Part III – Sleep

Sleep quality and depressive symptoms

Since BLT has a great effect on sleep and with that on mood [31], we dedicated **Part III** to sleep. First, in **Chapter 5**, we studied sleep quality in pregnant women with a mental disorder. Poor sleep quality during pregnancy is associated with both antepartum and postpartum depressive symptoms [32-36]. However, many studies only studied self-reported measures, while subjective sleep quality is worse than objective sleep quality in pregnant women with a mental disorder [37]. Studies with objective measurements of sleep have thus far been conducted in healthy women only [32, 36, 38], which cannot be extrapolated to pregnant women with a mental

disorder. This is relevant, since these women are not only at risk for sleep problems because of their pregnancy, but also because of their mental problems. Therefore, we studied in **Chapter 5** the effects of both objective and subjective sleep quality on depressive symptoms in pregnant women in an explorative study of 18 psychiatric patients. Here, we found that various objective and subjective sleep parameters indicating decreased sleep quality (e.g. various subscales of the Pittsburgh Sleep Quality Index) were associated with depressive symptoms when measured cross-sectionally. A number of objective and subjective sleep parameters (e.g. total sleep time measured by diary and actigraph) had moderate to large effects on the course of depressive symptoms, both positive and negative, but these were not statistically significant.

A limitation of this study is the small sample size. Because of this small study sample, we are only powered to find large effects, which makes it difficult to draw stringent conclusions regarding the findings of this study. More research in larger study samples would be necessary to explore the causality of the direction between sleep problems and depressive symptoms in this particular group of patients. A second limitation of **Chapter 5** is that we measured sleep quality at the start of the study and did not measure this at follow up. For future studies, it would be interesting to measure both sleep quality and depressive symptoms in a longitudinal design, preferably before pregnancy, in all three trimesters and in the postpartum period, to gain more insight in how sleep quality and depressive symptoms change in the peripartum period and how these affect each other.

Clinical implications

The present study adds to the existing evidence that sleep problems during pregnancy are associated with depressive symptoms. Therefore, clinicians should be aware of potential sleep problems in pregnant patients and should make an effort in improving sleep quality during pregnancy.

Sleep quality and the Bright Up study

In the Bright Up study, we collected data on both objective and subjective sleep quality and depressive symptoms longitudinally, not only during pregnancy, but also at two months postpartum (see for more details **Chapter 2**). For this thesis, these

results have not been analyzed yet. Since sleep problems are common in pregnancy [39, 40] and depressive symptoms are associated with sleep problems both during and after pregnancy [32-36], we expect that many women experienced sleep problems in the Bright Up study. For future research, we will study the same objective and subjective sleep parameters as in **Chapter 5**, to validate these findings. In addition, we will study more objective sleep parameters, such as intradaily and interdaily variability. Since we will study these sleep parameters together with depressive symptoms in a longitudinal design, we might find different associations. Also, women will be treated for their depressive symptoms with light therapy, which might reveal different associations.

The Bright Up study did not show a significant difference in depressive symptoms between the two treatment arms (**Chapter 3**), but since BLT has a tremendous effect on sleep [31], we may find statistically significant differences in sleep parameters between the two treatment arms. Earlier, a systematic review and meta-analysis showed that light therapy may be effective in treating sleep problems in general [41]. If would BLT alleviate sleep problems during pregnancy, it would provide a non-pharmacological alternative treatment for sleep medication, without adverse effects for the fetus.

Sleep medication in the peripartum period

Sleep problems are very common during pregnancy [39, 40] and may be treated pharmacologically with benzodiazepines [42]. In a population-based cohort study (**Chapter 6**), we found that the majority of benzodiazepines prescriptions in the peripartum period were prescribed for sleeping problems. The use of benzodiazepines during pregnancy is approached with caution, considering the potential harmful (fetal) effects on one hand, but also considering maternal health on the other hand. Despite this caution, the use of benzodiazepines [43] and benzodiazepine-related drugs [44] has increased in the past decades, a trend we have observed with prescription drugs in general [45-47].

In this part of the thesis, we studied, next to the effects of sleep quality on depressive symptoms during pregnancy, the use of benzodiazepines before, during and after pregnancy. In **Chapter 6**, we studied prescription patterns of benzodiazepines and benzodiazepine-related drugs in a population-based study cohort in Denmark, where

we studied 1,154,817 pregnancies from 1997 to 2015. Here, we found a prevalence of 1.9% before pregnancy, of 0.6% during pregnancy and of 1.3% after pregnancy. In women with a psychiatric history before pregnancy, the prevalence of benzodiazepine prescriptions was five to six times higher, compared to women with no psychiatric history. We found that, contrary to earlier studies [43-47], prescription prevalence rates of benzodiazepines before, during and after pregnancy decreased in the past years. Additionally, a higher percentage of women discontinuing benzodiazepines during pregnancy was observed from 1997 to 2015.

Possibly, these observations are caused by changed treatment guidelines. Next to sleep problems, benzodiazepines are often prescribed for the treatment of anxiety disorders [42], which was also shown in **Chapter 6**. Patients suffering from anxiety disorders were often treated with benzodiazepines, but recent guidelines advise against that [48]. Therefore, these patients are treated more often with antidepressants instead of benzodiazepines [49, 50], which could explain the decrease in benzodiazepine prescriptions we have observed in this study. Additionally, the observed decrease in the past years may be driven by various studies reporting on the adverse fetal effects following benzodiazepine exposure in utero [51-54], which may have increased awareness among women and their physicians.

International exposure to sleep medication

The study of **Chapter 6** was conducted in Denmark and may therefore not be representative for other countries. Therefore, in **Chapter 7**, we conducted a systematic review and meta-analysis where we studied the prevalence of benzodiazepine exposure before, during and after pregnancy worldwide. Here, studying 7,343,571 pregnancies from 28 countries, we found a prevalence of 0.9% before pregnancy, of 1.9% during pregnancy and of 0.5% after pregnancy. We found that the prevalence was highly dependent on trimester, the type of benzodiazepine and country. For example, the highest prevalence of benzodiazepine use was found in Eastern Europe (14.0%), whereas the lowest prevalence was found in Asia (0.9%). Additionally, the prevalence was greatly influenced by study characteristics. Among the different studies, substantial heterogeneity was found.

When we pooled all prevalence data on benzodiazepine use during pregnancy in Northwestern Europe, a higher prevalence was found in this meta-analysis (1.2%), compared to the population-based study we conducted in Denmark (0.6%). A major difference between these two studies is the definition of benzodiazepine exposure. In the systematic review and meta-analysis, we included all studies reporting on benzodiazepine prevalence, including prescription studies as in **Chapter 6**, but also including studies determining prevalence from self-report and body samples. Sensitivity analyses in the meta-analysis showed a significant difference in benzodiazepine prevalence when using different definitions for benzodiazepine exposure. We found that the pooled prevalence of benzodiazepine use was lower when studies used prescription records as a proxy for benzodiazepine use, compared to when women reported their benzodiazepine use. This is in accordance with the lower prevalence in the Danish population-based study in **Chapter 6**, which is based on registry data. Still, registry data may overestimate actual medication use due to non-compliance. A higher prevalence reported by self-report compared to prescription data may be explained by the fact that women sporadically use medication from others. A Dutch study among the general population showed that approximately 13% obtained prescription drugs through non-formal channels, with sleeping medication being one of the most frequently obtained [55]. However, underestimation could still play a role here, when women do not admit to or are ashamed of using prescription drugs during pregnancy [56].

Change over time in exposure

As earlier mentioned, we found a decrease in benzodiazepine prescription rates from 1997 to 2015 in **Chapter 6**, which is in contrast to two earlier studies, reporting an increase in benzodiazepine and benzodiazepine-related drug exposure in the past years [43, 44]. In **Chapter 7**, we tried to study the prevalence rates over time. Here, we could not find a significant change over time during pregnancy. There were unfortunately not enough studies to conduct these analyses in the year before pregnancy or the year following pregnancy. Therefore, we cannot draw stringent conclusions regarding the prevalence rates over time in the systematic review and meta-analysis.

Use of sleep medication in this thesis

In **Chapter 5**, where we studied the effects of sleep on depressive symptoms during pregnancy, none of the participants reported any benzodiazepines or benzodiazepine-related drugs. Therefore, we cannot study the effects of these drugs on their sleep or depressive symptoms. In the Bright Up study (**Chapter 3**), we collected information on the use of any sleep-promoting medications and supplements. However, only four women reported on the sporadic use of benzodiazepines. Sensitivity analyses, where we could study the effects of the use of benzodiazepines on depressive symptoms during pregnancy, were therefore not justified.

Future research

From **Chapters 6** and **7**, we can conclude that the use of benzodiazepines during pregnancy is prevalent, despite the considerable heterogeneity among studies. Given the substantial proportion of children exposed to benzodiazepines in utero, it is relevant for future studies to continue to focus on the safety of maternal benzodiazepine use during pregnancy. Most studies have focused on short-term effects of fetal exposure to benzodiazepines [51-54], long-term effects are however not entirely clear [57]. Studies of sound methodological quality are necessary in order to provide reliable and evidence-based information in complex treatment decisions. However, women and clinicians should carefully weigh both the maternal health and the potential teratogenic risk known from recent literature when considering benzodiazepine treatment, a decision that is different for every individual. Further, future studies should continue to explore non-pharmacological alternative treatments, such as light therapy [41].

Clinical implications

Both **Chapter 6** and **Chapter 7** showed that benzodiazepine use is relatively common during pregnancy, with large variations across countries. Considering the relatively common prevalence with potential risks for both mother and (unborn) infant, this is worrying and calls for prescription guidelines in the preconception period. Moreover, both women and clinicians should be better informed about

potential adverse outcomes, particularly as self-treatment is common among pregnant women.

Summary of clinical and research implications

The studies in this thesis provide the following clinical and research implications:

- In **Chapter 3**, we found no superiority of BLT over DRLT in pregnant women with a depressive disorder. Both groups showed improvement in depressive symptoms during six weeks of light treatment. Given the very mild and short-lived side effects, the major improvement in a short time period, the high acceptability of the participants, the low costs and the direct availability, and considering the long-standing evidence of the beneficial effects of BLT on non-seasonal depression, light therapy should be implemented in clinical practice in treating antepartum depression.

- More studies to the effectiveness of BLT during pregnancy are warranted. It is important to determine whether the responses observed in the Bright Up study (**Chapter 3**) represent true treatment effects, non-specific treatment effects or placebo effects. This may be done by studying biological measures, such as melatonin and cortisol levels.

- In the Bright Up study (**Chapter 3**), we received referrals from pregnant women with depressive symptoms all year round. **Chapter 4** showed that depressive symptoms are not only present during autumn and winter, but also during spring and summer. Also, seasonal influences are experienced differently in different groups of pregnant women, which may even lead to more depressive symptoms during summer for particular subgroups of pregnant women. These findings indicate that health professionals should be aware of antepartum depressive symptoms the whole year through.

- Women whom were treated for psychiatric problems showed a seasonal pattern different from the general population, with a peak in depressive symptoms during summer (**Chapter 4**). For future research, it would be relevant to study the underlying causes for these divergent findings.

- Clinicians should be aware of sleep problems in pregnant patients, for these are highly prevalent and they are associated with depressive symptoms (**Chapter**

5). Therefore, an effort should be made in improving sleep quality during pregnancy.

- We found that various objective and subjective sleep parameters are associated with depressive symptoms in an explorative study of pregnant women with a mental disorder (**Chapter 5**). More research would be necessary in this vulnerable group of patients to explore the causality of the direction between sleep problems and depressive symptoms. This is relevant, since these women are at risk for sleep problems, not only because of their pregnancy, but because of their mental disorder as well.

- In **Chapter 6**, we observed that prescription prevalence rates of benzodiazepines and benzodiazepine-related drugs decreased in the past decades. Additionally, more women discontinued these drugs during pregnancy. This may be due to changed treatment guidelines in the treatment of anxiety disorder. Secondly, this decrease may be driven by increased awareness due to various studies reporting on adverse effects for the fetus and the neonate.

- In our systematic review and meta-analysis (**Chapter 7**), we found that the use of benzodiazepines during pregnancy differed greatly between countries. The highest prevalence was found in Eastern Europe, whereas the lowest prevalence was found in Asia. These differences may reflect differences in the prevalence and/or severity of mental health problems, but could also be due to differences in national guidelines, prescribing behavior of physicians, available medical facilities and beliefs of the general population.

- We found in **Chapter 6** and **7** that benzodiazepine use during pregnancy is prevalent. Therefore, it is relevant for future research to focus on not only the short-term safety of maternal benzodiazepine use for the fetus, but also the long-term safety of in utero benzodiazepine exposure, which is not entirely clear at this point. More research is necessary to provide reliable and evidence-based information, which could potentially guide treatment decisions for both women and their physicians. Further, future research should continue to explore non-pharmacological alternatives for treating sleep problems during pregnancy, such as light therapy.

- Self-treatment with benzodiazepines is relatively common during pregnancy (**Chapter 7**). Considering the potential risks for both mother and infant

associated with benzodiazepine use during pregnancy, this is a worrying finding and calls for prescription guidelines in the preconception period.

Final conclusions

Depression during pregnancy is prevalent year round. A randomized controlled trial in pregnant women with a depressive disorder showed that both bright light therapy and placebo treatment improved depressive symptoms. We found that various objective and subjective sleep parameters were associated with depressive symptoms during pregnancy. Sleep problems are very common during pregnancy, which may be treated pharmacologically with benzodiazepines. International differences in benzodiazepine exposure have been observed in women before, during and after pregnancy. However, a decrease in benzodiazepine prescriptions in the last years seems to be present.

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Summary

Depression during pregnancy is common with a prevalence of around 12%. Guidelines propose psychotherapy, antidepressant medication or a combination of both as treatment. However, in clinical practice the applicability of these treatments during pregnancy is limited, which makes it urgent to investigate alternative approaches in treating antepartum depression, such as light therapy. Earlier, two studies in pregnant women suggested beneficial effects of light therapy, but the sample sizes of these studies were small. Therefore, in **Chapter 2**, we outlined the design of a randomized controlled trial (RCT) for evaluating the effectiveness of light therapy for depression during pregnancy: the Bright Up study. In the Bright Up study, we aimed at including 150 pregnant women with a gestational age of 12-18 weeks with a diagnosis of depressive disorder. Women received either treatment with bright light therapy (BLT) or dim red light therapy (DRLT). Although it is not known which of these two conditions is most effective, we hypothesize that the DRLT condition could be considered as placebo condition. Both groups were treated daily for 30 minutes upon awakening for six weeks at home. Several follow up measurements during and after pregnancy took place at fixed points in time. The primary outcome of the trial was symptoms of depression. Secondary outcomes included maternal sleep quality (both objective and subjective), maternal hormonal levels and birth and child outcomes. We hypothesized that daily treatment with BLT would improve depressive symptoms during pregnancy. Additionally, we hypothesized that this improvement would be accompanied by improved sleep quality, lower basal cortisol levels and normalized melatonin levels. Finally, we hypothesized that birth and child outcomes would be better in women treated with BLT, compared to women treated with DRLT.

In **Chapter 3**, we reported the findings regarding our primary research question of the Bright Up study. For this study, 67 pregnant women were included between 12 and 32 weeks of pregnancy. Depressive symptoms were primarily measured with the Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder (SIGH-SAD). Secondary measures were the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Edinburgh Postnatal Depression Scale (EPDS). Follow up took place weekly during the intervention period, at the end of the intervention period, three and ten weeks after treatment and at two months

postpartum. Depression rating scale scores improved with 41.2-50% during the intervention period in the BLT group and with 45.0-58.6% in the DRLT group. We did not find a statistically significant difference between the two treatment arms during the intervention period nor during the entire study. More research is needed to determine whether these responses represent true treatment effects, non-specific treatment responses, placebo effects or a combination of these.

In **Chapter 4**, we studied the seasonal influences on depressive symptoms during pregnancy. Data of 2,438 pregnant women on current depressive symptoms was collected in a large-scale cross-sectional study. Depressive symptoms were assessed using the EPDS and dichotomized using ≥ 9 as cut-off score. The relationship between depressive symptoms during pregnancy and the month of assessment was estimated by fitting a sinusoidal curve to the data. In the full sample, after adjusting for confounders, we found no significant evidence for seasonal influences on depressive symptoms. We found that the seasonal influence was obscured by current treatment status for psychiatric complaints. In untreated women, we found a minimum of depressive symptomatology in September and a maximum in March. In women treated for psychiatric symptoms, we found a minimum of depressive symptomatology in December and a maximum in June. Thus, the effects of seasonality are apparent, but opposite in women treated and untreated for psychiatric complaints. However, health professionals should be aware of depressive symptoms during pregnancy the whole year through.

We evaluated both objective and subjective sleep quality and the effects on the subsequent course of antepartum depressive symptoms in psychiatric patients in **Chapter 5**. For this study, we included 18 pregnant (24-29 weeks) patients with a mental disorder. Depressive symptoms were assessed with five-week intervals throughout pregnancy using the EPDS. Both objective and subjective sleep parameters were assessed. Various objective and subjective sleep parameters pointing at decreased sleep quality were significantly correlated with depressive symptoms when measured cross-sectionally at baseline. Six objectively and subjectively measured sleep parameters had moderate to large effects, both positive and negative, on the course of depressive symptoms through the third trimester, but

these effects were not statistically significant. More research is necessary to explore the causality of the direction between sleep problems and antepartum depressive symptoms in psychiatric patients.

In **Chapter 6**, we studied prescription patterns of benzodiazepines and benzodiazepine-related drugs before, during and after pregnancy in a population-based study in Denmark. Here, we studied 1,154,817 pregnancies between 1997 and 2015, of which 205,406 (17.8%) pregnancies in women with a psychiatric history. The prevalence of benzodiazepine prescriptions was 1.9% before pregnancy, 0.6% during pregnancy and 1.3% after pregnancy. In women with a psychiatric history, the prevalence was five to six times higher. From 1997 to 2015, we observed a significant decrease in prescriptions before, during and after pregnancy, which was more profound among women with a psychiatric history. Approximately 90% of women discontinue benzodiazepines during pregnancy, with a higher percentage of women discontinuing over time, especially women with a psychiatric history. Possibly, these observations are caused by changed treatment guidelines for the treatment of anxiety disorder.

In **Chapter 7**, we conducted a systematic review and meta-analysis, where we studied the literature to measure the worldwide use of benzodiazepine use before, during and after pregnancy. We identified 32 studies reporting on 28 countries, together reporting on 7,343,571 pregnancies. Here, we found a prevalence of 0.9% before pregnancy, of 1.9% during pregnancy and of 0.5% after pregnancy. We found that the prevalence was highly dependent on trimester, the type of benzodiazepine and country. Prevalence was highest in the third trimester. Lorazepam was most often prescribed. Highest prevalence was found in Eastern Europe. Also, the prevalence was influenced to a great extent by characteristics of the study. Despite substantial heterogeneity, our meta-analysis confirmed that benzodiazepine use before, during and after pregnancy is prevalent worldwide. We did not find a significant change over time in benzodiazepine use during pregnancy. Given the substantial proportion of children exposed to benzodiazepines in utero, future research should further study the safety of maternal benzodiazepine use during pregnancy, both on short and on long-term effects.

Main findings and conclusions of this thesis, together with methodological considerations, implications for future research and a final conclusion, are reported in **Chapter 8**. First, we concluded that light therapy should be implemented in clinical practice in treating antepartum depression. Second, more research on the effects of BLT in the treatment of depression during pregnancy is needed. Third, health professionals should be aware of depressive symptoms during pregnancy the whole year through. For future research, it would be interesting to study the underlying causes for the high prevalence of depressive symptoms in summer in specific subgroups of pregnant women. Next, we concluded that clinicians should be aware of sleep problems in pregnant patients with a mental disorder and that more research on sleep needs to be conducted in this particular group of patients. Moreover, we observed that the number of benzodiazepine prescriptions has decreased in the past years. Also, we concluded that the use of benzodiazepines differed greatly between countries. In future studies, both short-term and long-term effects of in utero benzodiazepine exposure should be studied. Finally, prescription guidelines for benzodiazepines in the preconception period are necessary.

Nederlandse samenvatting

Depressie tijdens de zwangerschap komt regelmatig voor met een prevalentie van ongeveer 12%. Richtlijnen stellen psychotherapie, antidepressieve medicatie of een combinatie voor bij de behandeling hiervan. Echter, de klinische praktijk wijst uit dat deze behandelingen hun beperkingen hebben tijdens de zwangerschap, wat de urgentie van het onderzoeken van alternatieve benaderingen in het behandelen van antepartum depressie onderstreept, zoals lichttherapie. Twee eerdere studies onder zwangere vrouwen lieten gunstige effecten van lichttherapie zien, maar de steekproefgroottes van deze studies waren klein. Daarom hebben wij in **Hoofdstuk 2** het protocol van een gerandomiseerde klinische studie geschetst, waarin de effecten van lichttherapie voor depressie tijdens de zwangerschap worden geëvalueerd: de Bright Up studie. In de Bright Up studie streefden we ernaar om 150 vrouwen te includeren met een zwangerschapsduur van 12-18 weken en gediagnosticeerd met een depressieve stoornis. Vrouwen werden ofwel behandeld met "bright light therapy" (BLT) of "dim red light therapy" (DRLT). Hoewel het niet bekend is welke van deze twee condities het meest effectief is, was onze hypothese dat de DRLT-conditie kan worden beschouwd als placebo. Beide groepen werden thuis dagelijks 30 minuten lang behandeld na het ontwaken gedurende 6 weken. Verscheidende follow-up metingen tijdens en na de zwangerschap volgden tijdens vaste momenten. De primaire uitkomst was symptomen van depressie. Secundaire uitkomsten waren maternale slaapkwaliteit (zowel objectief als subjectief), maternale hormonale spiegels en geboorte- en kinduitkomsten. Onze hypothese was dat de dagelijkse behandeling met BLT depressieve symptomen tijdens de zwangerschap zou verminderen. Daarnaast verwachtten we dat deze verbetering gepaard zou gaan met een betere slaapkwaliteit, lagere basale cortisolspiegels en genormaliseerde melatoninespiegels. Tenslotte was onze hypothese dat geboorte- en kinduitkomsten gunstiger zouden zijn in de vrouwen die behandeld waren met BLT, vergeleken met de vrouwen die behandeld waren met DRLT.

In **Hoofdstuk 3** hebben we de bevindingen van onze primaire onderzoeksvraag binnen de Bright Up studie beschreven. Voor dit onderzoek werden 67 vrouwen geïncludeerd tussen 12 en 32 weken zwangerschap. Depressieve symptomen werden primair gemeten met de Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder (SIGH-SAD). Secundaire metingen

waren de 17-item Hamilton Rating Scale for Depression (HAM-D) en de Edinburgh Postnatal Depression Scale (EPDS). Follow-up vond wekelijks plaats tijdens de interventie, aan het einde van de interventie, drie en tien weken na de interventie en twee maanden postpartum. Depressiescores verbeterden met 41,2-50% tijdens de interventie in de BLT-groep en met 45-58,6% in de DRLT-groep. We vonden in dit onderzoek geen statistisch significant verschil tussen de twee verschillende groepen gedurende de interventie noch tijdens de gehele studie. Meer onderzoek is nodig om te bepalen of deze effecten werkelijke behandelingseffecten zijn, aspecifieke behandelingseffecten, placebo-effecten of een combinatie hiervan.

In **Hoofdstuk 4** bestudeerden we de invloed van de seizoenen op depressieve symptomen tijdens de zwangerschap. Data van 2.438 vrouwen over huidige depressieve symptomen werden verzameld in een grootschalig cross-sectioneel onderzoek. Depressieve symptomen werden gemeten met de EPDS, welke werd gedichotomiseerd met ≥ 9 als drempelwaarde. De relatie tussen antepartum depressieve symptomen en de maand van dataverzameling werd geschat door een sinusvormige curve in de data te laten passen. We vonden in de complete onderzoekspopulatie geen significant bewijs voor invloed van de seizoenen op depressieve symptomen, na het corrigeren voor andere factoren die deze relatie mogelijk zouden kunnen verstoren. We vonden dat de seizoensinvloeden werden beïnvloed door de huidige behandeling van psychiatrische symptomen. We vonden bij onbehandelde vrouwen een minimum van depressieve symptomatologie in september en een maximum in maart. Bij vrouwen die behandeld werden voor psychiatrische klachten vonden we een minimum van depressieve symptomatologie in december en een maximum in juni. De effecten van seizoenen zijn dus aanwezig, maar tegengesteld in behandelde en onbehandelde vrouwen. Echter, zorgprofessionals zouden het gehele jaar bedachtzaam moeten zijn op depressieve klachten tijdens de zwangerschap.

In **Hoofdstuk 5** evalueerden we zowel objectieve als subjectieve slaapkwaliteit en de effecten hiervan op het verloop van antepartum depressieve symptomen in psychiatrische patiënten. Voor dit onderzoek includeerden we 18 zwangere (24-29 weken) patiënten met een psychiatrische stoornis. Depressieve symptomen werden

gemeten met de EPDS gedurende de zwangerschap met intervallen van vijf weken. Zowel objectieve als subjectieve slaapparameters werden gemeten. Verscheidene objectieve en subjectieve slaapparameters wijzend op lagere slaapkwaliteit waren significant gecorreleerd met depressieve symptomen, wanneer deze cross-sectioneel werden gemeten bij de start van het onderzoek. Zes objectief en subjectief gemeten slaapparameters hadden matige tot grote effecten, zowel positief als negatief, op het verloop van de depressieve symptomen tijdens het derde trimester, maar deze waren niet statistisch significant. Meer onderzoek is nodig om de causaliteit van de richting tussen slaapproblemen en antepartum depressieve symptomen te onderzoeken in psychiatrische patiënten.

In **Hoofstuk 6** hebben we voorschrijfpatronen van benzodiazepines en benzodiazepine-gerelateerde medicatie voor, tijdens en na de zwangerschap onderzocht in een populatie-gebaseerde studie in Denemarken. Hier bestudeerden we 1.154.817 zwangerschappen tussen 1997 en 2015, waarvan 205.406 (17,8%) zwangerschappen in vrouwen met een psychiatrische voorgeschiedenis. De prevalentie van benzodiazepinerecepten was 1,9% voor de zwangerschap, 0,6% tijdens de zwangerschap en 1,3% na de zwangerschap. De prevalentie was vijf tot zes keer hoger in vrouwen met een psychiatrische voorgeschiedenis. We vonden van 1997 tot 2015 een significante afname in recepten zowel voor, tijdens als na de zwangerschap, die sterker was in vrouwen met een psychiatrische voorgeschiedenis. Ongeveer 90% van de vrouwen stopt het gebruik van benzodiazepines tijdens de zwangerschap, met een hoger percentage vrouwen die stopt na verloop van tijd, voornamelijk vrouwen met een psychiatrische voorgeschiedenis. Mogelijkerwijs zijn deze observaties toe te schrijven aan veranderingen in richtlijnen in de behandeling van angststoornissen.

In **Hoofdstuk 7** voerden wij een systematische review en meta-analyse uit waarin wij de literatuur bestudeerden rond het wereldwijde gebruik van benzodiazepines voor, tijdens en na de zwangerschap. We identificeerden 32 artikelen rapporterend over 28 landen. Gezamenlijk rapporteerden deze artikelen over 7.343.571 zwangerschappen. In onze meta-analyse vonden wij een prevalentie van 0,9% voor de zwangerschap, 1,9% tijdens de zwangerschap en 0,5% na de zwangerschap. We

vonden dat de prevalentie afhankelijk was van het onderzochte trimester, het type benzodiazepine en het land. De prevalentie was het hoogst in het derde trimester. Lorazepam werd het vaakst voorgeschreven. De hoogste prevalentie werd gevonden in Oost-Europa. Ook werd de prevalentie zeer beïnvloed door studiekarakteristieken. Ondanks aanzienlijke heterogeniteit bevestigde onze meta-analyse dat het gebruik van benzodiazepines voor, tijdens en na de zwangerschap prevalent is wereldwijd. Over de tijd vonden we geen significant verschil in benzodiazepinegebruik tijdens de zwangerschap. Gezien het grote aantal kinderen dat in de baarmoeder wordt blootgesteld aan benzodiazepines, moeten toekomstige onderzoeken de veiligheid van het maternale gebruik van benzodiazepines blijven bestuderen, zowel de effecten op de korte termijn als op de lange termijn.

De belangrijkste bevindingen en conclusies van dit proefschrift zijn samen met methodologische overwegingen, implicaties voor toekomstig onderzoek en een eindconclusie gepresenteerd in **Hoofdstuk 8**. Ten eerste concludeerden wij dat lichttherapie zou moeten worden geïmplementeerd in de klinische praktijk bij de behandeling van antepartum depressie. Ten tweede is meer onderzoek naar de effecten van BLT bij de behandeling van depressie tijdens de zwangerschap nodig. Ook moeten zorgprofessionals het hele jaar bedachtzaam zijn op depressieve klachten tijdens de zwangerschap. Voor vervolgonderzoek zou het interessant zijn om de onderliggende oorzaken van de hoge prevalentie van depressieve symptomen in de zomer bij specifieke subgroepen zwangere vrouwen te onderzoeken. Vervolgens concludeerden we dat clinici alert zouden moeten op slaapproblemen bij zwangere vrouwen met een psychiatrische stoornis en dat meer onderzoek naar slaap nodig is bij deze specifieke groep van patiënten. Ook hebben we geobserveerd dat het aantal benzodiazepinerecepten in de afgelopen jaren zijn afgenomen. Daarnaast observeerden we sterke verschillen tussen landen in het gebruik van benzodiazepines. In toekomstige onderzoeken moeten zowel kortetermijn- als langetermijneffecten van blootstelling in de baarmoeder aan benzodiazepines onderzocht worden. Tenslotte, richtlijnen voor het gebruik van benzodiazepines in de preconceptie periode zijn nodig.

List of publications

Published articles

Molenaar NM, **Bais B**, Lambregtse-van den Berg MP, Mulder CL, Howell E, Fox N, Rommel A, Bergink V, Kamperman AM. The international prevalence of antidepressant use before, during, and after pregnancy: a systematic review and meta-analysis of timing, type of prescriptions and geographical variability. *Journal of Affective Disorders.* 2019. https://doi.org/10.1016/j.jad.2019.12.014

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Bais B, De Groot N, Grootendorst-van Mil NH, Harmsen van der Vliet-Torij HW, Bijma HH, Dieleman GC, Hoogendijk WJG, Lambregtse-van den Berg MP, Kamperman AM. Seasonality of depressive symptoms during pregnancy. *Psychiatry Research.* 2018;268:257-262.

De Bakker BS, De Jong KH, Hagoort J, De Bree K, Besselink CT, De Kanter FEC, Veldhuis T, **Bais B**, Schildmeijer R, Ruijter JM, Oostra RJ, Christoffels VM, Moorman AFM. An interactive three-dimensional digital atlas and quantitative database of human development. *Science.* 2016;354(6315).

Bais B, Kamperman AM, Van der Zwaag MD, Dieleman GC, Harmen van der Vliet-Torij HW, Bijma HH, Lieverse R, Hoogendijk WJG, Lambregtse-van den Berg MP. Bright light therapy in pregnant women with major depressive disorder: study protocol for a randomized, double-blind, controlled clinical trial. *BMC Psychiatry.* 2016;16(381):1-13.

Bais B, Karst WA, Kubat B, Verdijk RM. Persistent retinal iron in abusive head trauma. *Journal of Forensic Sciences.* 2016. doi: 10.1111/1556-4029.13215

Bais B, Kubat B, Motazedi E, Verdijk RM. B-amyloid precursor protein and ubiquitin immunohistochemistry aid in the evaluation of infant autopsy eyes with abusive head trauma. *American Journal of Ophthalmology.* 2015;160(6):1285-1295.

Submitted manuscripts

Bais B, Kamperman AM, Bijma HH, Hoogendijk WJG, Souman JL, Knijff E, Lambregtse-van den Berg MP. Effects of bright light therapy for depression during pregnancy: a randomized, double-blind controlled trial.

Bais B, Munk-Olsen T, Bergink V, Liu X. Prescription patterns of benzodiazepine and benzodiazepine-related drugs in the peripartum period: a population-based study

Bais B, Molenaar NM, Bijma HH, Hoogendijk WJG, Mulder CL, Luik AI, Lambregtse-van den Berg MP, Kamperman AM. Prevalence of benzodiazepines and benzodiazepine-related drugs exposure before, during and after pregnancy: a systematic review and meta-analysis

Conference abstracts

Bais B, Kamperman AM, Hoogendijk WJG, Lambregtse-van den Berg MP. A randomized, double-blind controlled clinial trial of light therapy for pregnant women with major depressive disorder. Neuropsychobiology. 2019;DOI:10.1159/000501249. [Conference abstract]

Bais B, Kamperman AM, Van der Zwaag MD, Hoogendijk WJG, Lambregtse-van den Berg MP. Proceedings of the Bright Up study: light therapy in antepartum depression. Neuropsychobiology. 2016;74:228. [Conference abstract]

Verdijk RM, **Bais B**, Karst WA, Kubat B. Acute head trauma: beta-amyloid precursor protein (beta-APP) and ubiquitin immunohistochemical staining of the retina and optic nerve in traumatic and non-traumatic pediatric deaths. European

Congress of Pathology, London, 30 August – 3 September 2014. [Conference abstract]

Bais B, Karst WA, Kubat B, Verdijk RM. Hemosiderin and histopathological dating of retinal hemorrhages in the context of abusive head trauma. EUCCAN Conference, Amsterdam, 21–23 May 2014. [Conference abstract]

PhD portfolio

Summary of PhD training and teaching

PhD student: Babette Bais

Erasmus MC department: Psychiatry

PhD period: August 2015 – October 2019

Promotor: prof. dr. W.J.G. Hoogendijk

Supervisors: dr. A.M. Kamperman & dr. M.P. Lambregtse-van den Berg

1. PhD Training	Year	Workload
Master Evidence Based Practice at the Academic Medical Centre, Amsterdam	2016-2018	97 ECTS

Courses

Epidemiology and Evidence Based Practice: concepts

Epidemiology and Evidence Based Practice: designs

Biostatistics: elementary analysis

Systematic Reviews and Clinical Guidelines

Longitudinal Module

Biostatistics and Advanced Epidemiology

Clinimetrics

Health Economics

Health Care System Evaluation

Capita Selecta

Thesis project

Other courses

SCID-I training	2015	6 hrs
Systematic literature retrieval in PubMed	2015	0.3 ECTS
Workshop Endnote	2015	0.3 ECTS
Research Integrity	2015	0.3 ECTS
Basiscursus Registratie en Organisatie voor Klinisch Onderzoekers	2015	53 hrs

Methods of Clinical Research	2015	15 hrs
BKO-workshop 'Omgaan met groepen'	2016	4 hrs
Teach the Teacher I	2016	16 hrs

Seminars and Workshops

| PhD day 2018 'A healthy PhD!' | 2018 | 5 hrs |

Presentations

Zwangerschap en depressie — 2016 — 9 hrs
Guest lecture at the symposium 'De ongelukkige moeder' organised by study association Comenius at the University of Amsterdam.

Winterdepressie en lichttherapie — 2017 — 5 hrs
Guest lecture for study association Brainwave at the University of Utrecht.

Hoe herken je PPM bij een zwangere vrouw? — 2017 — 8 hrs
Lectures for VSV. 10 and 12 May 2017. Delft and Dordrecht, the Netherlands.

Seizoensinvloeden bij antepartum depressie — 2017 — 1 ECTS
Fourth symposium Chronotherapeutics Network of the Netherlands. 12 May 2017. Leiden, the Netherlands.

Proceedings of the Bright Up study: light therapy in antepartum depression [poster] — 2017 — 1 ECTS
29th Annual Meeting of the Society for Light Treatment and Biological Rhythms. 23-25 June 2017. Berlin, Germany.

A randomized, double-blind controlled clinical trial of light therapy for pregnant women with major depressive disorder 31st Annual Meeting of the Society for Light Treatment and Biological Rhythms. 20-22 June 2019. Chicago, United States.	2019	1 ECTS

National & International Conferences

Third symposium Chronotherapeutics Network of the Netherlands. 22 April 2016. Amsterdam, the Netherlands.	2016	4 hrs
LKPZ symposium. 2 June 2017. Rotterdam, the Netherlands.	2017	8 hrs
Fifth symposium Chronotherapeutics Network of the Netherlands. 18 May 2018. Amsterdam, the Netherlands.	2018	4 hrs
30th Annual Meeting of the Society for Light Treatment and Biological Rhytms. 21-24 June 2018. Groningen, the Netherlands.	2018	1 ECTS
iPSYCH Annual Meeting. 21-23 May 2019. Korsør , Denmark.	2019	1 ECTS

Grants

Personal grant of the School of Business and Social Sciences, Department of Economy, University of Aarhus, Denmark (20.000 DKK = €2.679).	2018	

Personal travel grant of the Erasmus MC Trust fund 2019
(€350).

Personal travel grant of the Society of Light Treatment 2019
and Biological Rhythms ($500 = €440).

Other 2019
Visiting PhD student at the University of Aarhus (15
May – 15 June 2019).

2. Teaching	Year	Workload

Supervising

Students: Nemo Backx and Matthijs de Vroome. 2015-2016 20 hrs
Bachelor Medicine.
Project: systematic review.
A correlation between antepartum depression and seasonal affective disorder: a systematic review.

Students: Maartje van den Hurk, Linda Scheffers, 2015-2016 4 hrs
Eline Rompen, Anne van Huijstee and Heleen Essink.
Bachelor Medicine.
Project: Kennismaking Beroepspraktijk (KBP).

Students: Eline Rompen and Urmi Pahladsingh. 2016-2017 10 hrs
Bachelor Medicine.
Project: systematic review.
PTSD prevalence amongst patients with schizophrenia disorder and other psychotic disorders: a systematic review.

Student: Leo Genet. 2017 28 hrs
Master Psychology.
Project: master thesis.
The efficacy of antidepressant use in pregnant women.

Students: Micki Ouwerkerk and Juul Zietse. 2017-2018 5 hrs
Bachelor Medicine.
Project: systematic review.
The effect of sleep quality and duration on

antepartum depressive symptomology: a systematic review and meta-analysis.

Student: Sophie de Droog.	2017-2018	24 hrs
Master Psychology.		
Project: master thesis.		

De invloed van chronotype op depressieve symptomen tijdens de zwangerschap.

Student: Nicolle Croes.	2018	23 hrs
Master Medicine.		
Project: master thesis.		

Antidepressant exposure during pregnancy and its effect on pregnancy and birth outcomes: a population-based cohort study.

Students: Noa van Vliet and Jasmijn Vaneman.	2018-2019	5 hrs
Bachelor Medicine.		
Project: systematic review.		

Prevalence of the use of benzodiazepines or benzodiazepine-related drugs during pregnancy and adverse birth outcomes: a systematic review.

Student: Rianne Winters.	2018-2019	21 hrs
Master Medicine.		
Project: master thesis.		

Effectiveness of psychotropic medication and their relation with depressive symptoms during pregnancy.

Students: Lisanne van Kesteren and Finn Stofkoper.	2019	21 hrs
Bachelor Midwifery.		
Project: bachelor thesis.		

Een dwarsdoorsnede onderzoek naar mogelijke associaties tussen tocofobie en de demografische, psychosociale en obstetrische karakteristieken van zwangere vrouwen in Nederland.

Student: Indira Schouten. Master Medicine. Project: master thesis. *De relatie tussen empowerment en depressieve klachten tijdens de zwangerschap*	2019	20 hrs

Student: Mieke Roukema. Master Medicine. Project: master thesis. *Prenatal exposure to selective serotonin reuptake inhibitors and adverse birth outcomes: a population-based retrospective cohort study*	2019	17 hrs

Teaching

Minor 'Mystery of Creation': *Invloed van maternale stress op foetale hersenontwikkeling.*	2016	16 hrs

Minor 'Mystery of Creation': *Invloed van maternale stress op foetale hersenontwikkeling.*	2017	3 hrs

Minor 'Mystery of Creation': *Invloed van maternale stress op foetale hersenontwikkeling.*	2019	3 hrs

Curriculum Vitae

Babette Bais was born on February 20th 1990 in Zandvoort, the Netherlands. She graduated from secondary school at the lyceum Sancta Maria in Haarlem in 2008 and after taking a gap year, she started her study Biomedical Sciences at the University of Amsterdam. In 2012, she obtained her bachelor's degree and started her master Biomedical Sciences. As part of her master's degree, she did two internships.

In her first year, she studied embryology at the department of Anatomy, Embryology and Physiology at the Academic Medical Centre in Amsterdam. Specifically, she studied the heterochrony in embryonic development in human, mouse and chicken embryos. Part of this research was published in the prestigious journal Science (see List of publications).

In her second year, she did an internship at the Erasmus Medical Centre in Rotterdam and the Netherlands Forensic Institute in The Hague, where she studied fatal child abuse. This resulted in two research papers with Babette as a first author (see List of publications).

In 2014, she graduated *cum laude*.

Babette worked as a research and educational assistant at both the University of Amsterdam and the Academic Medical Centre in Amsterdam from 2013 to 2015.

In 2015, she started with her PhD project at the Erasmus Medical Centre in Rotterdam. As a PhD student, Babette was involved in various projects in the perinatal psychiatry, which resulted in various research papers (see List of publications). Amongst others, she set up a randomized controlled trial, studying the effects of light therapy for depression during pregnancy. Moreover, she conducted two meta-analyses. After obtaining a grant, she was a visiting PhD student at the University of Aarhus in Denmark for two months where she was involved in a large-scale epidemiologic study.

Besides this personal grant, she also received funding from the Society of Light Treatment and Biological Rhythms and from the Erasmus MC Trust Fund.

During her PhD project, she visited various national and international conferences, where she often presented her research results.

From 2016 onwards, Babette was a member of the Society of Light Treatment and Biological Rhythms.

During her second and third year, Babette combined her work as a PhD candidate with a second master degree in Clinical Epidemiology at the University of Amsterdam.