Depression during Pregnancy

Light, seasons and sleep

Babette Bais

Depression during pregnancy

Light, seasons and sleep

Babette Bais

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.

Financial support for the publication of this thesis was kindly provided by the Erasmus University Medical Center.

ISBN: 978-94-6375-526-9
Cover: Lorraine Jean Lauwerends
Printed by: Ridderprint | www.ridderprint.nl

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
op gezag van de
rector magnificus

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

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

woensdag 12 februari 2020 om 13.30 uur

door

Babette Bais
geboren te Zandvoort

Erasmus University Rotterdam

Promotiecommissie

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].

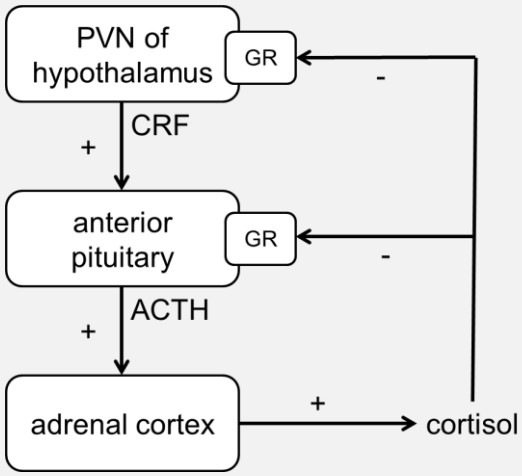


Figure 1.1 – Schematic overview of the hypothalamus-pituitary-adrenal gland (HPA) axis.

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.

References

1. (WHO), W.H.O., Depression and other common mental disorders: Global health estimates. Geneva, 2017.
2. Association, A.P., Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2013, Arlington, VA: American Psychiatric Association.
3. Pariante, C.M. and S.L. Lightman, The HPA axis in major depression: classical theories and new developments. Trends Neurosci, 2008. 31(9): p. 464-8.
4. Bear, M.F. and B. Connor, Neuroscience: exploring the brain. 3rd ed. 2007, Philadelphia: Lippincott Williams & Welkins.
5. Woody, C.A., et al., A systematic review and meta-regression of the prevalence and incidence of perinatal depression. J Affect Disord, 2017. 219: p. 86-92.
6. Milgrom, J., et al., Antenatal risk factors for postnatal depression: a large prospective study. J Affect Disord, 2008. 108: p. 147-157.
7. Wisner, K.L., E.L. Moses-Kolko, and D.K.Y. Sit, Postpartum depression: a disorder in search of a definition. Archives of Womens Mental Health, 2010. 13(1): p. 37-40.
8. Wisner, K.L., et al., Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. JAMA Psychiatry, 2013. 70(5): p. 490-8.
9. Lancaster, C.A., et al., Risk factors for depressive symptoms during pregnancy: a systematic review. Am J Obstet Gynecol, 2010. 202(1): p. 5-14.
10. Räisänen, S., et al., Risk factors for and perinatal outcomes of major depression during pregnancy: a population-based analysis during 2002-2010 in Finland. BMJ Open, 2014(11): p. DOI:10.1136/bmjopen-2014-004883.
11. Grote, N.K., et al., A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry, 2010. 67(10): p. 1012-24.
12. Jarde, A., et al., Neonatal outcomes in women with untreated antenatal depression compared with women without depression: a systematic review and meta-analysis. JAMA Psychiatry, 2016: p. DOI:10.1001/jamapsychiatry.2016.0934.
13. Talge, N.M., et al., Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? J Child Psychol Psychiatry, 2007. 48(3-4): p. 245-61.
14. Pearson, R.M., et al., Maternal depression during pregnancy and the postnatal period: risks and possible mechanisms for offspring depression at age 18 years. JAMA Psychiatry, 2013. 70(12): p. 1312-9.
15. Dierckx, B., et al., Maternal psychopathology influences infant heart rate variability: Generation R Study. Psychosom Med, 2009. 71(3): p. 313-21.
16. Goedhart, G., et al., Maternal cortisol and offspring birthweight: results from a large prospective cohort study. Psychoneuroendocrinology, 2010. 35(5): p. 644-52.
17. Henrichs, J., et al., Maternal psychological distress and fetal growth trajectories: the Generation R Study. Psychol Med, 2010. 40(4): p. 633-43.

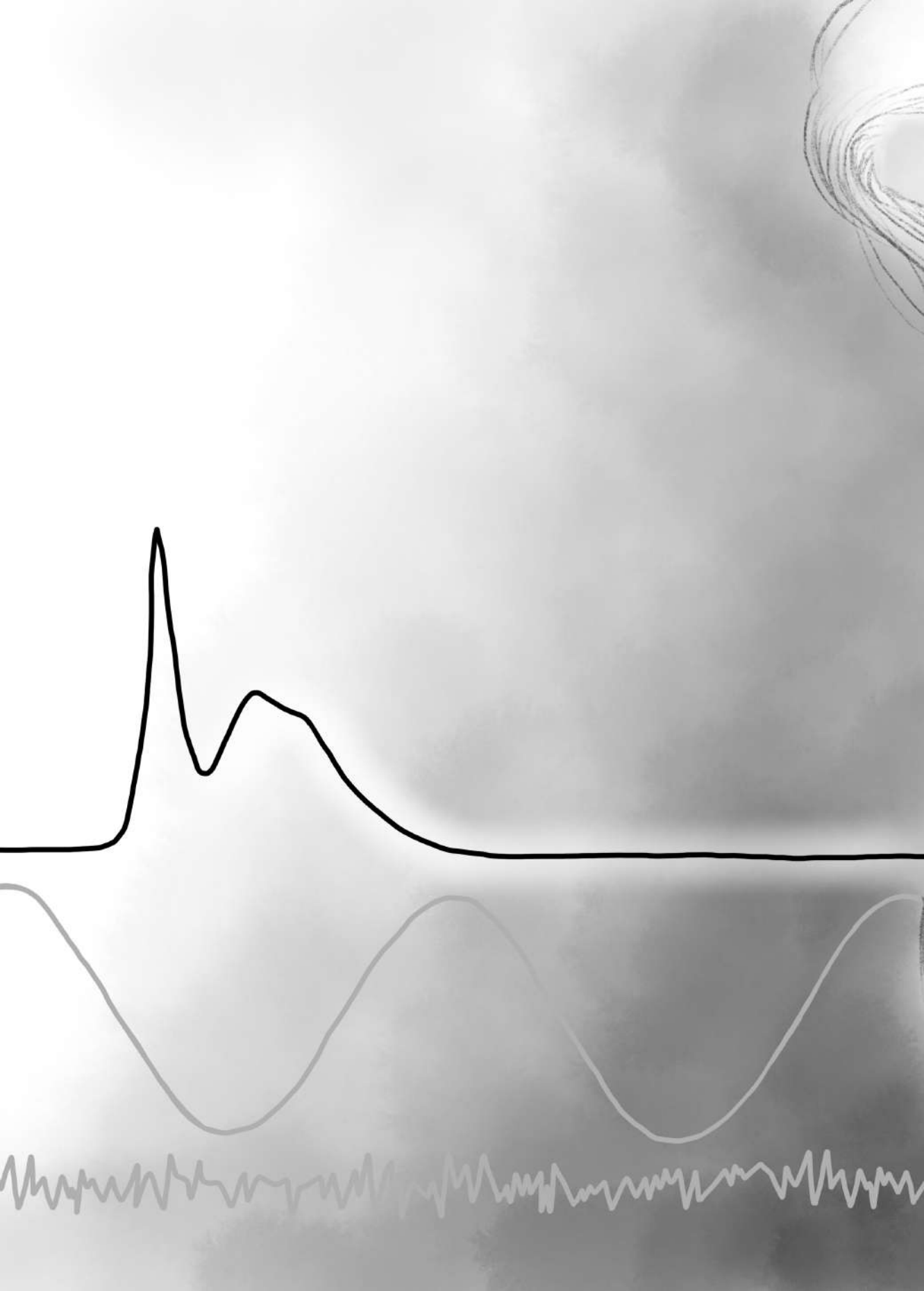
18. Zijlmans, M.A., J.M. Riksen-Walraven, and C. de Weerth, Associations between maternal prenatal cortisol concentrations and child outcomes: A systematic review. Neurosci Biobehav Rev, 2015. 53: p. 1-24.
19. Hunter, A.L., H. Minnis, and P. Wilson, Altered stress responses in children exposed to early adversity: a systematic review of salivary cortisol studies. Stress, 2011. 14(6): p. 614-26.
20. Graham, A.M., et al., Maternal Cortisol Concentrations During Pregnancy and Sex-Specific Associations With Neonatal Amygdala Connectivity and Emerging Internalizing Behaviors. Biol Psychiatry, 2019. 85(2): p. 172-181.
21. Davis, E.P., et al., Prenatal maternal cortisol concentrations predict neurodevelopment in middle childhood. Psychoneuroendocrinology, 2017. 75: p. 56-63.
22. Qiu, A., et al., Maternal anxiety and infants' hippocampal development: timing matters. Transl Psychiatry, 2013. 3: p. e306.
23. Buss, C., et al., The Role of Stress in Brain Development: The Gestational Environment's Long-Term Effects on the Brain. Cerebrum, 2012. 2012: p. 4.
24. Barker, E.D., et al., Prenatal maternal depression symptoms and nutrition, and child cognitive function. Br J Psychiatry, 2013. 203(6): p. 417-21.
25. Mesman, G.R., et al., Effects of Maternal Depression Symptoms and Alcohol Use Problems on Child Internalizing and Externalizing Behavior Problems. Journal of Child and Family Studies, 2017. 26(9): p. 2485-2494.
26. Hannigan, L.J., et al., Maternal prenatal depressive symptoms and risk for early-life psychopathology in offspring: genetic analyses in the Norwegian Mother and Child Birth Cohort Study. Lancet Psychiatry, 2018. 5(10): p. 808-815.
27. Sanger, C., et al., Associations between postnatal maternal depression and psychological outcomes in adolescent offspring: a systematic review. Arch Womens Ment Health, 2015. 18(2): p. 147-162.
28. Steegers, E.A., et al., Societal Valorisation of New Knowledge to Improve Perinatal Health: Time to Act. Paediatr Perinat Epidemiol, 2016. 30(2): p. 201-4.
29. Quispel, C., et al., Withdrawal from mental and psychosocial care during pregnancy. J Psychosom Obstet Gynaecol, 2014. 35(4): p. 140-5.
30. van Gelder, M.M.H.J., et al., Drugs associated with teratogenic mechanisms. Part I: dispensing rates among pregnant women in the Netherlands, 1998-2009. Human Reproduction, 2014. 29(1): p. 161-167.
31. Ververs, T., et al., Prevalence and patterns of antidepressant drug use during pregnancy. Eur J Clin Pharmacol, 2006. 62(10): p. 863-70.
32. Molenaar, N.M., M.P. Lambregtse-van den Berg, and G.J. Bonsel, Dispensing patterns of selective serotonin reuptake inhibitors before, during and after pregnancy: a 16-year population-based cohort study from the Netherlands. Arch Womens Ment Health, 2019.
33. Ailes, E.C., et al., Using insurance claims data to identify and estimate critical periods in pregnancy: An application to antidepressants. Birth Defects Res A Clin Mol Teratol, 2016. 106(11): p. 927-934.

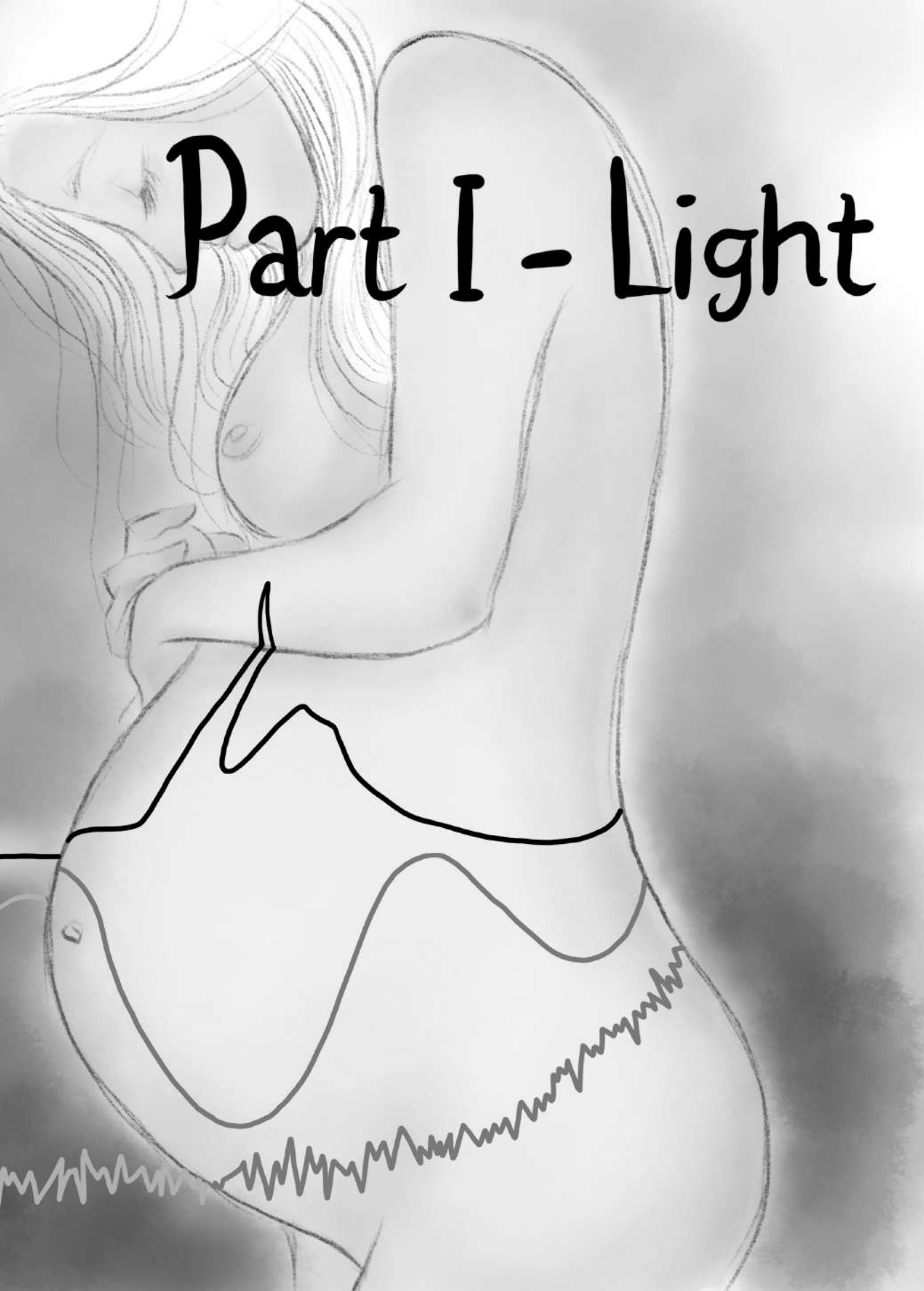
34. Andrade, S.E., et al., Use of selective serotonin reuptake inhibitors (SSRIs) in women delivering liveborn infants and other women of child-bearing age within the U.S. Food and Drug Administration's Mini-Sentinel program. Arch Womens Ment Health, 2016. 19(6): p. 969-977.
35. Taylor, L.G., et al., Development of a mother-child database for drug exposure and adverse event detection in the Military Health System. Pharmacoepidemiol Drug Saf, 2015. 24(5): p. 510-7.
36. Hanley, G.E. and B. Mintzes, Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. BMC Pregnancy Childbirth, 2014. 14: p. 242.
37. Byatt, N., K.M. Deligiannidis, and M.P. Freeman, Antidepressant use in pregnancy: a critical review focused on risks and controversies. Acta Psychiatr Scand, 2013. 127(2): p. 94-114.
38. Hanley, G.E. and T.F. Oberlander, The effect of perinatal exposures on the infant: antidepressants and depression. Best Pract Res Clin Obstet Gynaecol, 2014. 28(1): p. 37-48.
39. Simoncelli, M., B.Z. Martin, and A. Berard, Antidepressant use during pregnancy: a critical systematic review of the literature. Curr Drug Saf, 2010. 5(2): p. 153-70.
40. Kieler, H., et al., Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. BMJ, 2012. 344: p. d8012.
41. Ross, L.E., et al., Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. JAMA Psychiatry, 2013. 70(4): p. 436-43.
42. Molenaar, N.M., et al., Guidelines on treatment of perinatal depression with antidepressants: An international review. Aust N Z J Psychiatry, 2018. 52(4): p. 320-327.
43. Molenaar, N.M., et al., Antidepressants during pregnancy: Guideline adherence and current practice amongst Dutch gynaecologists and midwives. Midwifery, 2018. 61: p. 29-35.
44. Bakker, M.K., et al., Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. Br J Clin Pharmacol, 2008. 65(4): p. 600-6.
45. Charlton, R.A., et al., Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. Bjog-an International Journal of Obstetrics and Gynaecology, 2015. 122(7): p. 1010-1020.
46. Cooper, W.O., et al., Increasing use of antidepressants in pregnancy. American Journal of Obstetrics and Gynecology, 2007. 196(6): p. 544-545.
47. Jimenez-Solem, E., et al., Prevalence of Antidepressant Use during Pregnancy in Denmark, a Nation-Wide Cohort Study. Plos One, 2013. 8(4).
48. Tuunainen, A., D.F. Kripke, and T. Endo, Light therapy for non-seasonal depression. Cochrane Database Syst Rev, 2004.
49. Al-Karawi, D. and L. Jubair, Bright light therapy for nonseasonal depression: Meta-analysis of clinical trials. J Affect Disord, 2016. 198: p. 64-71.
50. Golden, R.N., et al., The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry, 2005. 162(4): p. 656-62.

51. Martensson, B., et al., Bright white light therapy in depression: A critical review of the evidence. J Affect Disord, 2015. 182: p. 1-7.
52. Perera, S., et al., Light therapy for non-seasonal depression: systematic review and meta-analysis. BJPsych Open, 2016. 2(2): p. 116-126.
53. Oren, D.A., et al., An open trial of morning light therapy for treatment of antepartum depression. Am J Psychiatry, 2002. 159(4): p. 666-9.
54. Epperson, C.N., et al., Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry, 2004. 65(3): p. 421-5.
55. Wirz-Justice, A., et al., A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. J Clin Psychiatry, 2011. 72(7): p. 986-93.
56. Blume, C., C. Garbazza, and M. Spitschan, Effects of light on human circadian rhythms, sleep and mood. Somnologie, 2019.
57. LeGates, T.A., D.C. Fernandez, and S. Hattar, Light as a central modulator of circadian rhythms, sleep and affect. Nature Reviews Neuroscience, 2014. 15(7): p. 443-454.
58. Prayag, A.S., et al., Light modulation of human clocks, wake and sleep. Clocks & Sleep, 2019. 1: p. 193-208.
59. Germain, A. and D.J. Kupfer, Circadian rhythm disturbances in depression. Hum Psychopharmacol, 2008. 23(7): p. 571-85.
60. Deuschle, M., et al., Diurnal activity and pulsatility of the hypothalamus-pituitary-adrenal system in male depressed patients and healthy controls. J Clin Endocrinol Metab, 1997. 82(1): p. 234-8.
61. Claustrat, B., J. Brun, and G. Chazot, The basic physiology and pathophysiology of melatonin. Sleep Med Rev, 2005. 9(1): p. 11-24.
62. Tamura, H., et al., Melatonin and pregnancy in the human. Reprod Toxicol, 2008. 25(3): p. 291-303.
63. Zisapel, N., New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. Br J Pharmacol, 2018. 175(16): p. 3190-3199.
64. Lam, R.W. and R.D. Levitan, Pathophysiology of seasonal affective disorder: a review. J Psychiatry Neurosci, 2000. 25(5): p. 469-80.
65. Magnusson, A. and D. Boivin, Seasonal affective disorder: an overview. Chronobiol Int, 2003. 20(2): p. 189-207.
66. Rosenthal, N.E., et al., Seasonal Affective-Disorder - a Description of the Syndrome and Preliminary Findings with Light Therapy. Archives of General Psychiatry, 1984. 41(1): p. 72-80.
67. Wehr, T.A., et al., Contrasts between symptoms of summer depression and winter depression. J Affect Disord, 1991. 23(4): p. 173-83.
68. Wehr, T.A., D.A. Sack, and N.E. Rosenthal, Seasonal affective disorder with summer depression and winter hypomania. Am J Psychiatry, 1987. 144(12): p. 1602-3.
69. Meliska, C.J., et al., Antepartum depression severity is increased during seasonally longer nights: relationship to melatonin and cortisol timing and quantity. Chronobiol Int, 2013. 30(9): p. 1160-1173.

70. Corral, M., A. Wardrop, and H.B. Zhang, Seasonality of symptoms in women with postpartum depression. Arch Womens Ment Health, 2007. 10(1): p. 9-13.
71. Hiltunen, P., et al., Seasonal variation in postnatal depression. J Affect Disord, 2004. 78(2): p. 111-8.
72. Sit, D., H. Seltman, and K.L. Wisner, Seasonal effects on depression risk and suicidal symptoms in postpartum women. Depress Anxiety, 2011. 28(5): p. 400-5.
73. Sylven, S.M., et al., Seasonality patterns in postpartum depression. Am J Obstet Gynecol, 2011. 204: p. 413.e1-6.
74. Weobong, B., et al., Determinants of postnatal depression in rural ghana: findings from the don population based cohort study. Depress Anxiety, 2015. 32(2): p. 108-19.
75. Yang, S.N., et al., The delivery mode and seasonal variation are associated with the development of postpartum depression. J Affect Disord, 2011. 132(1-2): p. 158-64.
76. Henriksson, H.E., et al., Seasonal patterns in self-reported peripartum depressive symptoms. Eur Psychiatry, 2017. 43: p. 99-108.
77. Jewell, J.S., et al., Prevalence of self-reported postpartum depression specific to season and latitude of birth: evaluating the PRAMS data. Matern Child Health J, 2010. 14(2): p. 261-7.
78. Panthangi, V., et al., Is seasonal variation another risk factor for postpartum depression? J Am Board Fam Med, 2009. 22(5): p. 492-7.
79. Facco, F.L., et al., Sleep Disturbances in Pregnancy. Obstetrics and Gynecology, 2010. 115(1): p. 77-83.
80. Sahota, P.K., S.S. Jain, and R. Dhand, Sleep disorders in pregnancy. Curr Opin Pulm Med, 2003. 9(6): p. 477-83.
81. Santiago, J.R., et al., Sleep and sleep disorders in pregnancy. Ann Intern Med, 2001. 134(5): p. 396-408.
82. Bublitz, M.H., et al., Maternal Sleep Quality and Diurnal Cortisol Regulation Over Pregnancy. Behav Sleep Med, 2018. 16(3): p. 282-293.
83. Mindell, J.A. and B.J. Jacobson, Sleep disturbances during pregnancy. J Obstet Gynecol Neonatal Nurs, 2000. 29(6): p. 590-7.
84. Chen, S.J., et al., Prevalence of restless legs syndrome during pregnancy: A systematic review and meta-analysis. Sleep Med Rev, 2018. 40: p. 43-54.
85. Coo Calcagni, S., et al., The relationship between sleep and mood in first-time and experienced mothers. Behav Sleep Med, 2012. 10(3): p. 167-79.
86. Kamysheva, E., et al., A prospective investigation of the relationships among sleep quality, physical symptoms, and depressive symptoms during pregnancy. J Affect Disord, 2010. 123(1-3): p. 317-20.
87. Lewis, B.A., et al., The effect of sleep pattern changes on postpartum depressive symptoms. BMC Womens Health, 2018. 18(1): p. 12.
88. Okun, M.L., et al., Sleep disturbances in depressed and nondepressed pregnant women. Depress Anxiety, 2011. 28(8): p. 676-85.

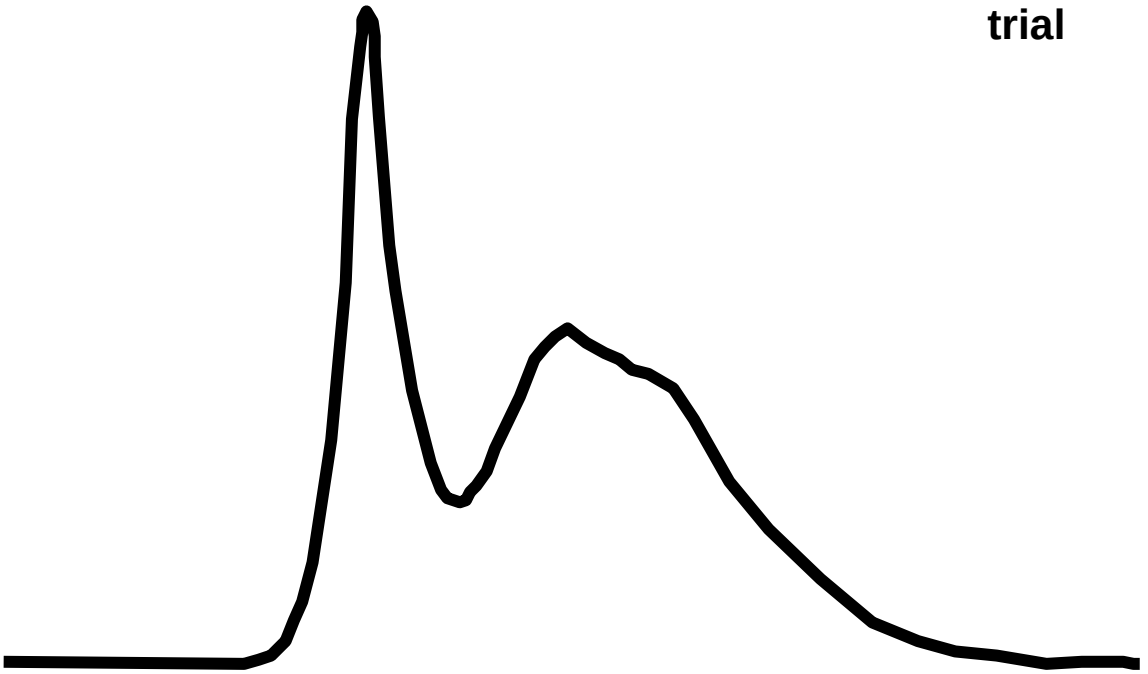
89. Park, E.M., S. Meltzer-Brody, and R. Stickgold, Poor sleep maintenance and subjective sleep quality are associated with postpartum maternal depression symptom severity. Arch Womens Ment Health, 2013. 16(6): p. 539-47.
90. Tomfohr, L.M., et al., Trajectories of Sleep Quality and Associations with Mood during the Perinatal Period. Sleep, 2015. 38(8): p. 1237-45.
91. Okun, M.L., et al., Poor sleep quality increases symptoms of depression and anxiety in postpartum women. J Behav Med, 2018. 41(5): p. 703-710.
92. Chang, J.J., et al., Sleep deprivation during pregnancy and maternal and fetal outcomes: is there a relationship? Sleep Med Rev, 2010. 14(2): p. 107-14.
93. van Maanen, A., et al., The effects of light therapy on sleep problems: A systematic review and meta-analysis. Sleep Med Rev, 2016. 29: p. 52-62.
94. Quispel, C., et al., An innovative screen-and-advice model for psychopathology and psychosocial problems among urban pregnant women: an exploratory study. J Psychosom Obstet Gynaecol, 2012. 33(1): p. 7-14.




Part I - Light

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

BMC Psychiatry 2016; 16(1):381.

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.

Keywords

Light therapy; Phototherapy; Depression; Depressive disorder; Pregnancy; Clinical trial; Circadian rhythm; Therapeutics

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].

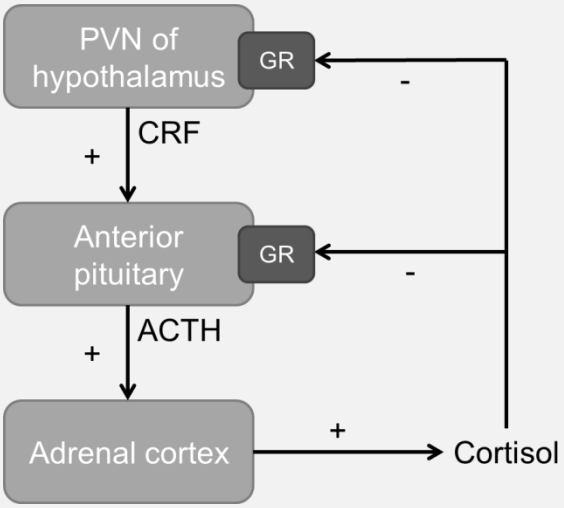


Figure 2.1 – Schematic diagram of the hypothalamus-pituitary-adrenal gland (HPA) axis.

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].

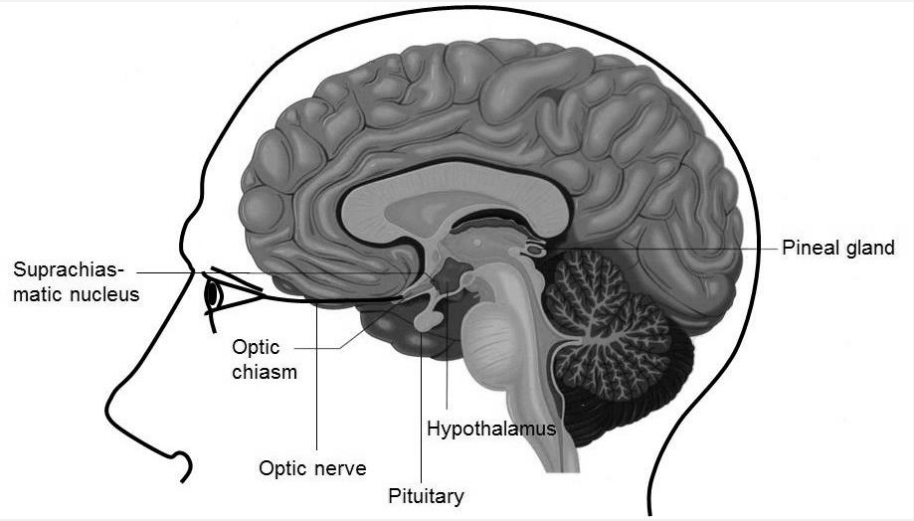


Figure 2.2 – Sagittal view of the brain.
This figure shows a sagittal view of the suprachiasmatic nucleus, the optic chiasm, the optic nerve, the hypothalamus, the pituitary and the pineal gland.

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.

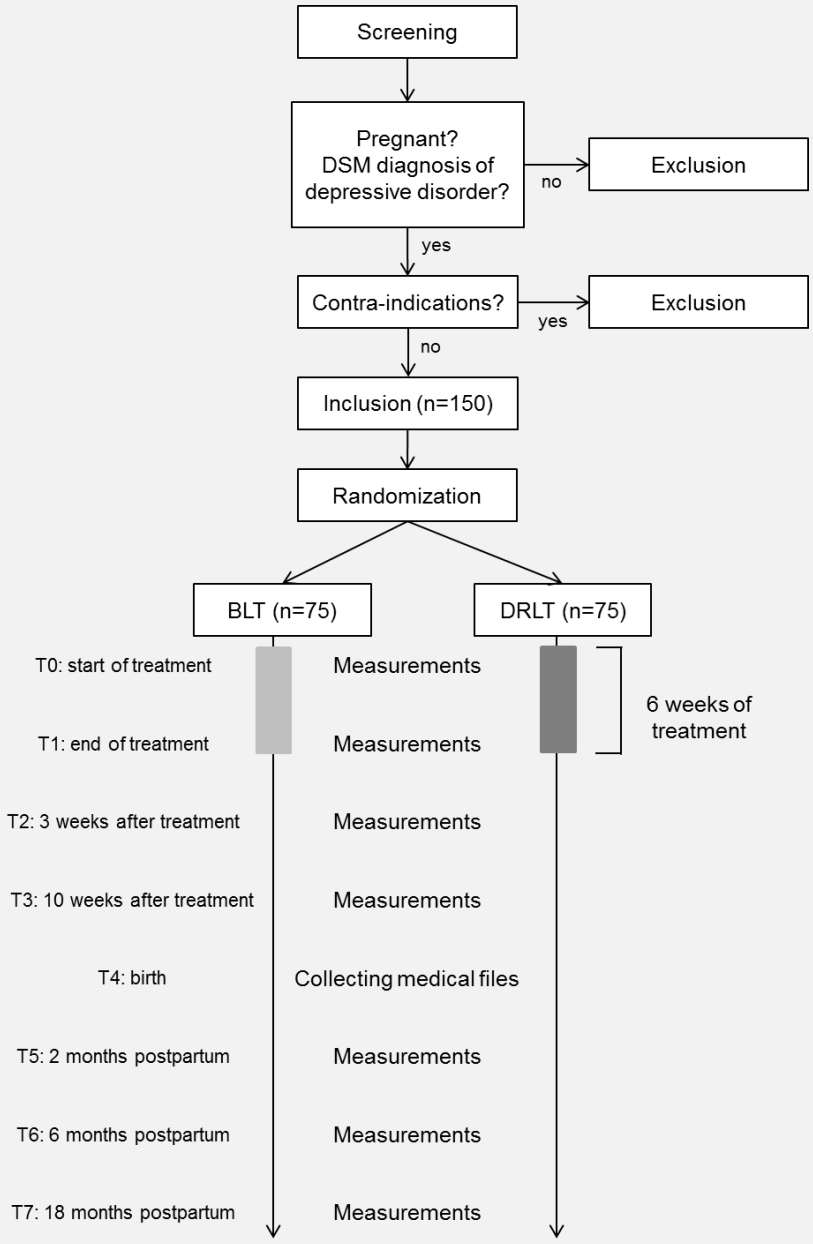


Figure 2.3 – Flowchart of overview study.

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.

Funding

The study is funded through the 'Light, Cognition, Behaviour and Health' program of The Netherlands Organization for Health Research and Development (ZonMw), in collaboration with Philips Lighting (ZonMw, grant number 058-14-003).
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.

Acknowledgements

Not applicable.

References

1. Gavin, N.I., et al., Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol, 2005. 106(5 Pt 1): p. 1071-83.
2. Quispel, C., et al., An innovative screen-and-advice model for psychopathology and psychosocial problems among urban pregnant women: an exploratory study. J Psychosom Obstet Gynaecol, 2012. 33(1): p. 7-14.
3. Field, T., Prenatal depression effects on early development: a review. Infant Behav Dev, 2011. 34(1): p. 1-14.
4. Talge, N.M., et al., Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? J Child Psychol Psychiatry, 2007. 48(3-4): p. 245-61.
5. Grote, N.K., et al., A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry, 2010. 67(10): p. 1012-24.
6. Jarde, A., et al., Neonatal outcomes in women with untreated antenatal depression compared with women without depression: a systematic review and meta-analysis. JAMA Psychiatry, 2016: p. DOI:10.1001/jamapsychiatry.2016.0934.
7. Steegers, E.A., et al., Societal Valorisation of New Knowledge to Improve Perinatal Health: Time to Act. Paediatr Perinat Epidemiol, 2016. 30(2): p. 201-4.
8. Quispel, C., et al., Withdrawal from mental and psychosocial care during pregnancy. J Psychosom Obstet Gynaecol, 2014. 35(4): p. 140-5.
9. Daw, J.R., et al., Prescription drug use in pregnancy: a retrospective, population-based study in British Columbia, Canada (2001-2006). Clin Ther, 2012. 34(1): p. 239-249.
10. Cooper, W.O., et al., Increasing use of antidepressants in pregnancy. Am J Obstet Gynecol, 2007. 196(6): p. 544.e1-e5.
11. Ververs, T., et al., Prevalence and patterns of antidepressant drug use during pregnancy. Eur J Clin Pharmacol, 2006. 62(10): p. 863-70.
12. Bakker, M.K., et al., Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. Br J Clin Pharmacol, 2008. 65(4): p. 600-6.
13. Tuccori, M., et al., Safety concerns associated with the use of serotonin reuptake inhibitors and other serotonergic/noradrenergic antidepressants during pregnancy: a review. Clin Ther, 2009. 31: p. 1426-53.
14. Chaudron, L.H., Complex challenges in treating depression during pregnancy. Am J Psychiatry, 2013. 170(1): p. 12-20.
15. Pail, G., et al., Bright-light therapy in the treatment of mood disorders. Neuropsychobiology, 2011. 64(3): p. 152-62.
16. Lam, R.W. and R.D. Levitan, Pathophysiology of seasonal affective disorder: a review. J Psychiatry Neurosci, 2000. 25(5): p. 469-80.
17. Golden, R.N., et al., The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry, 2005. 162(4): p. 656-62.

18. Partonen, T. and J. Lonnqvist, Seasonal affective disorder. Lancet, 1998. 352(9137): p. 1369-74.
19. Magnusson, A. and D. Boivin, Seasonal affective disorder: an overview. Chronobiol Int, 2003. 20(2): p. 189-207.
20. Rybak, Y.E., et al., An open trial of light therapy in adult attention-deficit/hyperactivity disorder. J Clin Psychiatry, 2006. 67(10): p. 1527-35.
21. Lam, R.W., et al., A controlled study of light therapy for bulimia nervosa. Am J Psychiatry, 1994. 151(5): p. 744-50.
22. Blouin, A.G., et al., Light therapy in bulimia nervosa: a double-blind, placebo-controlled study. Psychiatry Res, 1996. 60(1): p. 1-9.
23. Lieverse, R., et al., Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. Arch Gen Psychiatry, 2011. 68(1): p. 61-70.
24. Riemersma-van der Lek, R.F., et al., Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. JAMA, 2008. 299(22): p. 2642-55.
25. Most, E.I., P. Scheltens, and E.J. Van Someren, Prevention of depression and sleep disturbances in elderly with memory-problems by activation of the biological clock with light--a randomized clinical trial. Trials, 2010. 11: p. 19.
26. Bear, M.F. and B. Connor, Neuroscience: exploring the brain. 3rd ed. 2007, Philadelphia: Lippincott Williams & Welkins.
27. Pariante, C.M. and S.L. Lightman, The HPA axis in major depression: classical theories and new developments. Trends Neurosci, 2008. 31(9): p. 464-8.
28. Raadsheer, F.C., et al., Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. Neuroendocrinology, 1994. 60(4): p. 436-44.
29. Deuschle, M., et al., Diurnal activity and pulsatility of the hypothalamus-pituitary-adrenal system in male depressed patients and healthy controls. J Clin Endocrinol Metab, 1997. 82(1): p. 234-8.
30. Hastings, M.H., Central clocking. Trends Neurosci, 1997. 20(10): p. 459-64.
31. Buijs, R.M. and A. Kalsbeek, Hypothalamic integration of central and peripheral clocks. Nat Rev Neurosci, 2001. 2(7): p. 521-6.
32. Clark, D.D., et al., Aberrant development of the suprachiasmatic nucleus and circadian rhythms in mice lacking the homeodomain protein Six6. J Biol Rhythms, 2013. 28(1): p. 15-25.
33. Husse, J., et al., The light-dark cycle controls peripheral rhythmicity in mice with a genetically ablated suprachiasmatic nucleus clock. FASEB J, 2014. 28(11): p. 4950-60.
34. Cohen, R.A. and H.E. Albers, Disruption of human circadian and cognitive regulation following a discrete hypothalamic lesion: a case study. Neurology, 1991. 41(5): p. 726-9.
35. Claustrat, B., J. Brun, and G. Chazot, The basic physiology and pathophysiology of melatonin. Sleep Med Rev, 2005. 9(1): p. 11-24.

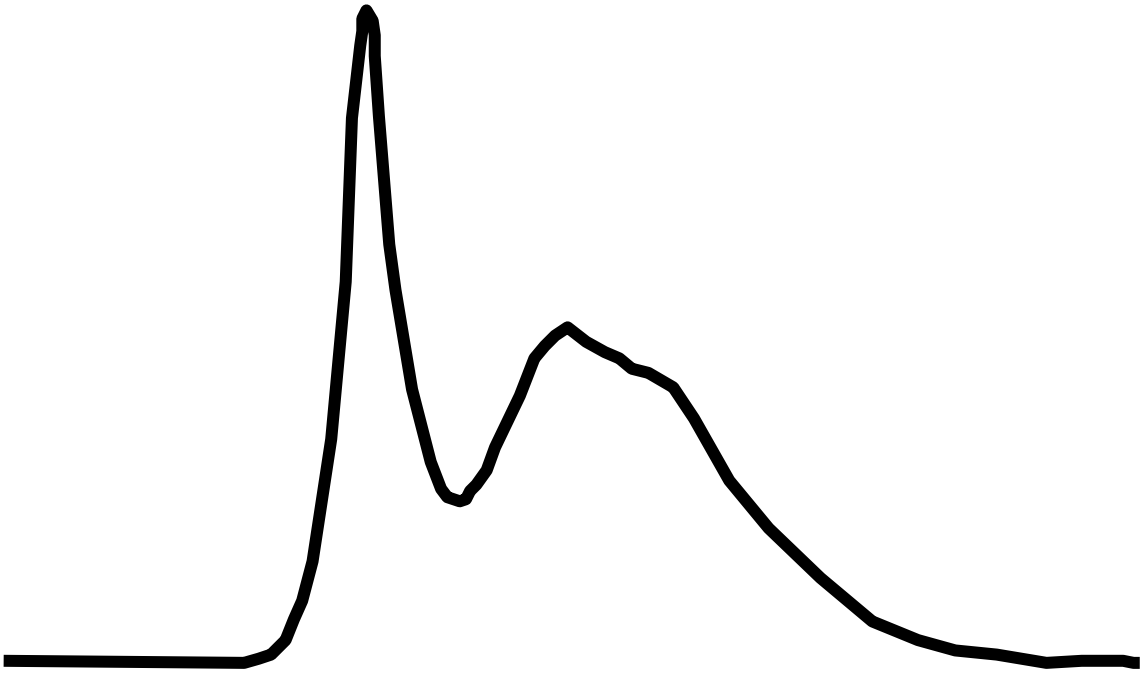
36. Tamura, H., et al., Melatonin and pregnancy in the human. Reprod Toxicol, 2008. 25(3): p. 291-303.
37. Pacchierotti C, et al., Melatonin in psychiatric disorders: a review on the melatonin involvement in psychiatry. Frontiers in Neuroendocrinology, 2011. 22: p. 18-32.
38. Parry, B.L., et al., Plasma melatonin circadian rhythm disturbances during pregnancy and postpartum in depressed women and women with personal or family histories of depression. Am J Psychiatry, 2008. 165(12): p. 1551-8.
39. Skalkidou, A., et al., Biological aspects of postpartum depression. Women's Health, 2012. 8(6): p. 659-72.
40. Robinson, M., et al., Low maternal serum vitamin D during pregnancy and the risk for postpartum depression symptoms. Arch Womens Ment Health, 2014. 17(3): p. 213-9.
41. Epperson, C.N., et al., Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry, 2004. 65(3): p. 421-5.
42. Wirz-Justice, A., et al., A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. J Clin Psychiatry, 2011. 72(7): p. 986-93.
43. Henrichs, J., et al., Maternal psychological distress and fetal growth trajectories: the Generation R Study. Psychol Med, 2010. 40(4): p. 633-43.
44. Dierckx, B., et al., Maternal psychopathology influences infant heart rate variability: Generation R Study. Psychosom Med, 2009. 71(3): p. 313-21.
45. Goedhart, G., et al., Maternal cortisol and offspring birthweight: results from a large prospective cohort study. Psychoneuroendocrinology, 2010. 35(5): p. 644-52.
46. Austin, M.P., L.R. Leader, and N. Reilly, Prenatal stress, the hypothalamic-pituitary-adrenal axis, and fetal and infant neurobehaviour. Early Hum Dev, 2005. 81(11): p. 917-26.
47. Zijlmans, M.A., J.M. Riksen-Walraven, and C. de Weerth, Associations between maternal prenatal cortisol concentrations and child outcomes: A systematic review. Neurosci Biobehav Rev, 2015. 53: p. 1-24.
48. Hunter, A.L., H. Minnis, and P. Wilson, Altered stress responses in children exposed to early adversity: a systematic review of salivary cortisol studies. Stress, 2011. 14(6): p. 614-26.
49. Kinsella, M.T. and C. Monk, Impact of maternal stress, depression and anxiety on fetal neurobehavioral development. Clin Obstet Gynecol, 2009. 52(3): p. 425-40.
50. StatLine. Central Bureau for Statistics. Population (In Dutch: Centraal Bureau voor de Statistiek. Bevolking.). [cited 2016 11 Jan 2016]; Available from: http://statline.cbs.nl/Statweb/.
51. Denktas, S., et al., Design and outline of the Healthy Pregnancy 4 All study. BMC Pregnancy Childbirth, 2014. 14: p. 253.
52. Cox, J.L., J.M. Holden, and R. Sagovsky, Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry, 1987. 150: p. 782-6.
53. Bockting, C.L., et al., A lifetime approach to major depressive disorder: The contributions of psychological interventions in preventing relapse and recurrence. Clin Psychol Rev, 2015. 41: p. 16-26.

54. Higgins, J.P., et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ, 2011. 343.
55. Tuunainen, A., D.F. Kripke, and T. Endo, Light therapy for non-seasonal depression. Cochrane Database Syst Rev, 2004.
56. Oren, D.A., et al., An open trial of morning light therapy for treatment of antepartum depression. Am J Psychiatry, 2002. 159(4): p. 666-9.
57. Kreidler, S.M., et al., GLIMMPSE: Online Power Computation for Linear Models with and without a Baseline Covariate. J Stat Softw, 2013. 54(10).
58. Kogan, A.O. and P.M. Guilford, Side effects of short-term 10,000-lux light therapy. Am J Psychiatry, 1998. 155(2): p. 293-4.
59. Oren, D.A., et al., Usage patterns of phototherapy in seasonal affective disorder. Compr Psychiatry, 1991. 32(2): p. 147-52.
60. First MB, G.M., Spitzer RL, Williams JBW, User's guide for the SCID-I. Structured clinical interview for DSM-IV TR axis I disorders (research version). 2002, New York: New York Psychiatric Institute.
61. Williams JBW, L.M., Rosenthal NE, Amira L, Terman M, Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version (SIGH-SAD). 1988, New York: New York Psychiatric Institute.
62. Bagby, R.M., et al., The Hamilton Depression Rating Scale: has the gold standard become a lead weight? Am J Psychiatry, 2004. 161(12): p. 2163-77.
63. Bergink, V., et al., Validation of the Edinburgh Depression Scale during pregnancy. J Psychosom Res, 2011. 70(4): p. 385-389.
64. Newell-Price, J., et al., The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev, 1998. 19(5): p. 647-72.
65. Staufenbiel, S.M., et al., Hair cortisol, stress exposure, and mental health in humans: a systematic review. Psychoneuroendocrinology, 2013. 38(8): p. 1220-35.
66. Even, C., et al., Efficacy of light therapy in nonseasonal depression: a systematic review. J Affect Disord, 2008. 108(1-2): p. 11-23.
67. Ancoli-Israel, S., et al., The role of actigraphy in the study of sleep and circadian rhythms. Sleep, 2003. 26(3): p. 342-92.
68. Morgenthaler, T., et al., Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep, 2007. 30(4): p. 519-29.
69. Buysse, D.J., et al., The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res, 1989. 28(2): p. 193-213.
70. Brazelton TB, N.J., Neonatal Behavioral Assessment Scale. 3rd ed. 1995, London: Max Keith Press.
71. Roza, S.J., et al., Cerebral ventricular volume and temperamental difficulties in infancy. The Generation R Study. J Psychiatry Neurosci, 2008. 33(5): p. 431-9.
72. Achenbach T.M. and Rescorla L.A., Manual for the ASEBA preschool forms and profiles. 2000, Burlington: University of Vermont.

73. Rescorla, L.A., Assessment of young children using the Achenbach System of Empirically Based Assessment (ASEBA). Ment Retard Dev Disabil Res Rev, 2005. 11(3): p. 226-37.
74. Merikanto, I., et al., Circadian preference links to depression in general adult population. J Affect Disord, 2015. 188: p. 143-8.
75. Merikanto, I., et al., Evening types are prone to depression. Chronobiol Int, 2013. 30(5): p. 719-25.
76. Roenneberg, T., A. Wirz-Justice, and M. Merrow, Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms, 2003. 18(1): p. 80-90.
77. Zavada, A., et al., Comparison of the Munich Chronotype Questionnaire with the Horne-Ostberg's Morningness-Eveningness Score. Chronobiol Int, 2005. 22(2): p. 267-78.

Chapter 3

Effects of bright light therapy for depression during pregnancy: a randomized, double-blind controlled trial



Babette Bais, Astrid M. Kamperman, Hilmar H. Bijma, Witte J.G. Hoogendijk, Jan L. Souman, Esther Knijff, Mijke P. Lambregtse-van den Berg

Submitted

Abstract

Objective: Approximately 11-13% of pregnant women suffer from depression. Bright light therapy (BLT) is a promising treatment, combining direct availability, sufficient efficacy, low costs and high safety. Here, we examined the effects of BLT on depression during pregnancy.

Methods: Sixty-seven pregnant women (12-32 weeks) with a DSM-5 diagnosis of depression were randomly allocated to treatment with BLT (9,000 lux, 5,000 K) or dim red light therapy (DRLT, 100 lux, 2,700 K), which is considered placebo. For six weeks, both groups were treated daily at home for 30 minutes upon awakening. Follow-up took place weekly during the intervention, after six weeks of therapy, three and ten weeks after treatment and two months postpartum. Depressive symptoms were measured primarily with the Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder. Secondary measures were the Hamilton Rating Scale for Depression and the Edinburgh Postnatal Depression Scale. Changes in scores of these questionnaires over time were analysed using generalized linear mixed models.

Results: Mean depression scores decreased by 41.2-50% in the BLT group and by 45.0-58.6% in the DRLT group during the intervention. We found no statistically significant difference in symptom change scores between BLT and DRLT. Sensitivity and post-hoc analyses did not change our findings.

Conclusion: BLT and DRLT were both effective in reducing depressive symptoms in pregnant women with depression. More research is necessary to determine whether these responses represent true treatment effects, non-specific treatment responses, placebo effects or a combination hereof.

Clinical Trials Registration: Bright Up, NTR5476, http://www.trialregister.nl

Keywords

Light therapy; Depression; Depressive Disorder; Pregnancy

Background

Antepartum depression is a common and high impact disease, with approximately 11-13% of pregnant women suffering from depression [1]. Women who suffer from antepartum depression are more likely to suffer from postpartum depression as well [2]. 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 [3, 4]. Additionally, children show more often cognitive, emotional and behavioral problems in childhood, adolescence and adulthood [5, 6] and they have a higher risk of suffering from depression later in life [7]. During pregnancy, fetal programming of the hypothalamus-pituitary-adrenal gland (HPA) axis takes place, which can be affected by maternal depression during pregnancy and may have long-lasting effects on stress response [8]. Possible mechanisms are 1) maternal cortisol crossing the placenta and thus increasing fetal cortisol levels, 2) placental secretion of corticotropin-releasing factor, which stimulates both maternal and fetal cortisol, and 3) reduced blood flow to the fetus, causing fetal growth restriction [3, 9-12]. In addition, epigenetic programming takes place within the antepartum period, which influences not only the health of the (unborn) infant, but also that of following generations [13]. Therefore, early detection and treatment of antepartum depression is highly important for both mother and infant.

In non-pregnant women, guidelines propose psychotherapy, antidepressant medication or a combination of both as treatment. However, psychotherapy might not be readily available and the safety of maternal use of antidepressants, which cross the placenta, still remains to be established. The use of antidepressants is controversial, because of potential teratogenicity [14, 15]. For example, increased risks has been found for persistent pulmonary hypertension of the neonate [16] and cardiovascular malformations [17]. Furthermore, pregnant women express a strong preference for non-pharmacologic treatment because of the possible harm for their unborn child [18, 19]. Moreover, current adherence to national guidelines by midwives and gynaecologists is low [20] and international guidelines on the pharmacological treatment of antepartum depression are not consistent [21], which might result in unwanted variation in practice. Despite this, antidepressant use during pregnancy is increasing, not only in the Netherlands [22, 23], but in other European

countries and the United States as well [24-26]. In the Netherlands, approximately 2-3% of pregnant women use antidepressants [23, 27, 28]. In the United States, this prevalence is approximately 6-7% [29-31], but could even be as high as 15% in some states [32]. Therefore, it is urgent and clinically relevant to investigate alternative approaches to treat antepartum depression, such as bright light therapy (BLT) [33].
Light synchronizes the suprachiasmatic nucleus (SCN), or the 'biological clock', with the environmental day-night rhythm [34]. Light hits the retina and intrinsically photosensitive retinal ganglion cells (ipRGCs) in the retina project, via the retino-hypthalamic tract to the SCN and thus influencing circadian rhythm [34-36], which may indirectly benefit depressive symptoms [37]. However, not only do ipRGCs project to the SCN, but also directly to brain regions important in the regulation of mood, such as the medial amygdala and the lateral habenula [34-36].
Although BLT is the first-choice treatment for seasonal affective disorder, a condition of reoccurring depressions during fall and winter, with remissions in spring and summer [38, 39], the effects of BLT have been shown both in seasonal affective disorder and in non-seasonal depression, which is not only shown by a Cochrane review [40], but also by more recent systematic reviews and meta-analyses [41-44]. An open trial of BLT in pregnant women showed improvement of mean depression ratings by 49% [45]. Two small randomized controlled trials showed significant improvement of depression among pregnant women exposed to BLT compared to placebo [46, 47]. Although these results seem promising, the sample sizes of these studies were small, making them at risk for chance-findings [48]. In this study, we aim to investigate the effects of BLT on antepartum depression in a larger randomized clinical trial. Moreover, we follow women until the postpartum period, to study whether treatment with light therapy during pregnancy might protect against postpartum depression. We hypothesize that daily treatment with six weeks of morning BLT will improve depressive symptoms during pregnancy.

Material and Methods

Participants

This study was a randomized, double-blind, placebo-controlled clinical trial (Bright Up, NTR5476, http://www.trialregister.nl). A detailed protocol can be found

elsewhere [49]. In short, the aim of the Bright Up study was to evaluate the effectiveness of BLT for pregnant women with a depressive disorder, compared to placebo light. Eligible participants were pregnant women (12-32 weeks of gestational age, confirmed by ultrasound) diagnosed with a depressive disorder, confirmed by a Structured Clinical Interview for DSM disorders (SCID) by one trained assessor [50]. The specific inclusion and exclusion criteria are listed in Table 3.1.

Table 3.1 – Inclusion and exclusion criteria for the Bright Up Study.

Inclusion criteria	Women
	18-45 years of age
	12-32 weeks pregnant (as confirmed by ultrasound)
	Current DSM-5 diagnosis of depressive disorder (as assessed by the SCID*)
Exclusion criteria	Insufficient proficiency in Dutch or English
	Multiple pregnancy
	Current use of antidepressants shorter than 2 months
	Lifetime diagnosis of bipolar I or II disorder
	Any psychotic episode
	Current substance abuse
	Current primary anxiety disorder
	Recent history of suicide attempt
	Current shift-work
	Somatic and/or obstetric conditions that override study participation
	Previous treatment with BLT
	Eye condition (macular degeneration, eye diseases, recent eye surgery)

* SCID = Structured Clinical Interview for DSM disorders

In the earlier published study protocol [49], we aimed to include women who were 12-18 weeks pregnant. For pragmatic reasons, in particular the fact that a substantial number of women was referred after 18 weeks of pregnancy, we later decided to widen our inclusion criteria to 12-32 weeks pregnancy.

In the Netherlands, maternity care for low-risk pregnancies is provided by midwives (primary care). High-risk pregnancies are cared for by gynaecologists in a general hospital (secondary care) or fetal-maternal medicine unit (tertiary care).

In this study, women were recruited not only via health care professionals, such as general practitioners, midwifes, gynaecologists, psychiatrists and psychologists, but also via (social) media. A complete flow-chart of the recruitment can be found in Figure 3.1.

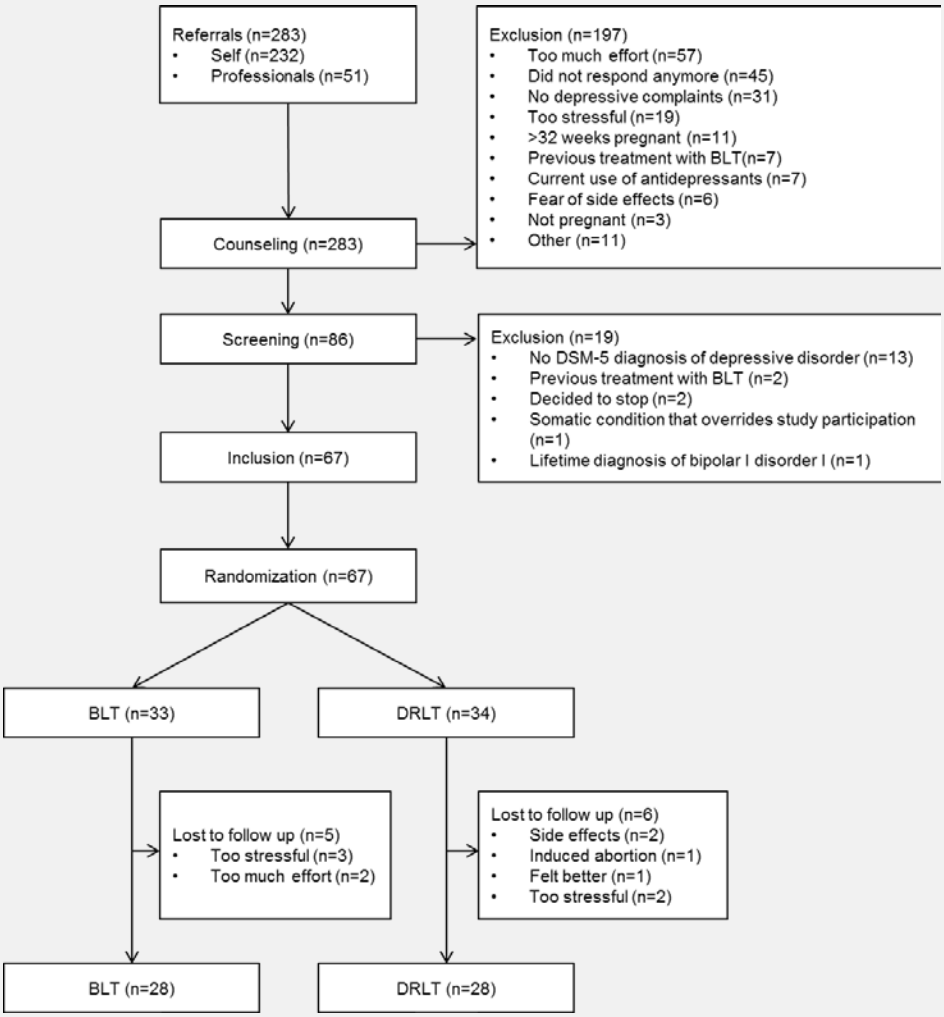


Figure 3.1 – Flow-chart of the Bright Up study.

Initially, we calculated the number of women to be included, based on the results and research methodology of previous studies [45, 46, 51]. We expected a true treatment effect in the range of a 10-15% symptom reduction over the full course of treatment, reflecting a small to medium effect size. To demonstrate this, with an α of 0.05 and a β of 0.8, a total sample size of 126 participants, 63 per arm was needed. To account for loss to follow up during and after treatment, we aimed at including 150 women. Power calculations were performed using GLIMMPSE 2.1.5. software [52]. Inclusion took place in The Netherlands and started on 9 November 2016 and lasted until 15 March 2019. By then, 67 women were included. However, due to limiting resources, we decided to stop the inclusion. Post-hoc power calculations showed that this sample size allows us to estimate a 15-20% difference in symptom reduction between the treatment conditions (e.g. a medium sized effect) with an α of 0.05 and a β of 0.8.

Ethics

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants. The study protocol and later amendments were approved by the medical ethical committee of the Erasmus University Medical Centre, Rotterdam, The Netherlands (registration number MEC-2015-731).

Blinding

Participants were blinded to allocation. Participants were informed that the study aimed to investigate the efficacy of different light colours. They were not informed that one treatment arm was considered placebo treatment. This was in accordance with approval of the medical ethical committee.

Outcome assessors were blinded to the allocation of the participants. Participants were asked not to share any details regarding their treatment towards the assessors. When blinding was broken, the assessor was replaced. The researcher performing the primary statistical analyses (AK) was blinded to the allocation. The field researcher (BB) was not blinded to the allocation for practical reasons. This

researcher made sure lamps of the correct allocation were delivered to the participants. Also, this researcher asked participants about any side effects, keeping the independent assessors blinded to any adverse effects that might break the blinding, e.g. strained eyes, and answered any questions from the participants regarding their lamps.

At baseline, we asked about any expectations concerning the treatment with regards to their depressive symptoms. Women could choose whether they expected a negative effect, a small negative effect, no effect, a small positive effect or a positive effect. After the intervention period, the participants were asked whether they were aware of their allocation.

Light therapy

Light treatment consisted of either active BLT (9,000 lux, color temperature 5,000 K) or dim red light therapy (DRLT, 100 lux, color temperature 2,700 K). The photobiological characterizations of these treatments are shown in Supplementary Table 3.1. The original lamps were adjusted in the factory where these are produced (EnergyUp HF3419/01, Philips, Eindhoven, The Netherlands). To ensure that participants are exposed to the same light intensity, the output of the lamps was fixed. For the control condition, the standard LED's in the lamp were replaced by LED's with a lower intensity and a different color temperature. The lamps in the control condition were positioned at the same distance from the participant as in the experimental condition.

The active light therapy was shown to be effective in other studies [46, 47, 51, 53]. DRLT can be considered to be biologically inactive and thus as placebo treatment [40]. In line with two previous RCT's among pregnant women, we chose six weeks of daily light exposure [46, 47].

The lamps were delivered at the participants' home by one researcher (BB) who was not blinded to the allocation of the participants. This researcher did not share anything about the allocation with the participants. After delivery of the lamps and instructions, participants commenced their daily treatment with light for 30 minutes within 30 minutes of habitual wake up time for a six weeks period. This took place at the participants' home. Participants sat in front of two lamps with a distance of approximately 40 cm (15.8 inches). They received a plastic ruler of this length to

ensure of the correct distance. The light boxes were placed in a custom-made scaffolding, so that the height of the light boxes could be adjusted per person and glare was avoided. Apart from the light treatment, participants in both treatment arms received treatment as usual: women were free to visit their general practitioner, obstetric care provider or mental health care worker and start additional treatment, whenever they felt a need for this.

During the intervention period, self-reported compliance with the light treatment was checked weekly.

Method

A baseline interview was conducted by telephone by one researcher (BB). The baseline interview collected sociodemographic information (age, ethnicity, educational level, marital status, body mass index (BMI)), obstetric information (gestational age, whether the pregnancy was planned, parity), psychiatric information (substance use (smoking, alcohol, drugs), present and past medication use, present depressive symptoms and psychiatric history) and information on somatic conditions. Also, participants were screened with the SCID for depressive disorder and various potential co-morbidities, such as generalized anxiety disorder and panic disorder. Previous depressive episodes were also assessed with the SCID. The general practitioner was contacted to verify present medication use and whether the participant met any exclusion criteria.

After baseline measurements and receiving written informed consent, the participants were randomly allocated to either receive BLT or DRLT in a 1:1 ratio. Randomization was done with the web-based computer-generated schedule ALEA (software for randomization in clinical trials, version 2.2) using random block sizes of 2-6 [54] by an independent researcher. Stratification factors were the use of any current antidepressant medication and the number of previous depressive episodes. The latter was dichotomized to three or less versus four or more [55].

Follow up took place at the following time points:

- weekly during the intervention period (T0+1, T0+2, etc.)
- after 6 weeks of treatment (T1)
- 3 weeks after end of treatment (T2)
- 10 weeks after end of treatment (T3)

- 2 months postpartum (P1)
- 6 months postpartum (P2)
- 18 months postpartum (P3)

At these time points, questionnaires were assessed and body material was collected. This paper reports the short term effectiveness, i.e. up to two months postpartum.

Primary and secondary outcome measures

The primary outcome measure was 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). Secondary outcome measures were these changes as measured by the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Edinburgh Depression Scale (EPDS).

The SIGH-SAD is a 29-item structured interview, consisting of 21 HAM-D items and 8 atypical items. We used the entire SIGH-SAD questionnaire as primary measure, since this is the current benchmark for assessment of depression severity in light therapy trials. We chose the original 17-item HAM-D questionnaire as a secondary measure, since it is more commonly used in clinical practice and research. Blinded assessors conducted the SIGH-SAD interviews (including HAM-D questions) by telephone weekly in the intervention period and at follow up.

The EPDS is a structured 10-item questionnaire and was used as a self-report measure of depression during pregnancy and postpartum [56]. Items are scored with a value 0-3, resulting in a sum score of 0-30 [56]. The EPDS was developed for the detection of postpartum depression, but has been validated for screening depression during pregnancy as well [57]. The EPDS was assessed weekly in the intervention period and at follow up. Participants received a link by e-mail to fill out the questionnaire.

Side effects, acceptability and satisfaction

During the intervention period, participants were asked weekly about any possible side effects. Acceptability was assessed by asking participants about their subjective treatment experiences after the intervention period. Women could choose whether they experienced a negative effect, a small negative effect, no effect, a small positive

effect or a positive effect. Women were asked how easy or difficult they could implement the therapy in their daily schedule and how easy or difficult the lamp was in use: very difficult, difficult, neutral, easy or very easy. Women could answer whether they found the light therapy very unpleasant, unpleasant, neutral, pleasant or very pleasant. Women were asked whether they would like to use the light therapy outside of the study (yes/no). Finally, women were asked how likely they would recommend light therapy to others on a scale of 1 to 10.

Confounders

The baseline interview collected information on various confounders, such as sociodemographic, obstetric and psychiatric information and information on somatic conditions (see Method for further specifications).

The participant's chronotype was assessed at inclusion with the Munich Chronotype Questionnaire (MCTQ), a structured 19-item self-report questionnaire [58], since evening types are more prone to depression compared to morning types [59, 60]. The participant can be classified into one of seven chronotypes: extremely, moderately or slightly early, normal or slightly, moderately or extremely late. Sum scores range from 16 to 86, with low scores indicating extremely late chronotypes.

Statistical analysis

Continuous participant characteristics were summarized by their mean and standard deviation (SD). Categorical variables, such as educational level, were summarized by count and proportion. In line with the CONSORT statement, baseline differences between the two treatment arms were not tested [61].

For treatment effect analyses, we applied an intention-to-treat procedure, since none of the participants could switch to a different condition, and we included all observations of all participants until study end or drop-out of the study.

The primary outcome was changes in SIGH-SAD rating scale scores over time. Secondary outcomes were changes in HAM-D and EPDS rating scale scores over time. Analyses were conducted using general linear mixed modelling analyses. In a series of random-intercept models, we included time, allocation and time x allocation interaction-term as an effect measure of allocation on the course of depression rating scale scores. The standardized baseline score was included in the model, since

baseline depression severity is an important predictor for treatment outcome [62]. We studied the treatment effect for both the intervention period and follow-up period (two months postpartum).

Primary analyses were first crude, then adjusted. As adjusted primary analyses, we calculated propensity scores based on patient characteristics (psychiatric history, ethnicity, level of education, an unplanned pregnancy, maternal age, parity, gestational age, duration of actual depression and other psychiatric or psychotherapeutic treatment interventions). Next, we adjusted separately for chronotype and the month of treatment. By means of sensitivity analyses, we repeated the primary analyses with last observation carried forward data imputation. As post-hoc analyses, we repeated the crude analyses for women with good compliance (<7 missed treatments) and for women with most severe depressive symptomatology (based on median split baseline SIGH-SAD scores). Effect parameters were supplied with a 95% confidence interval (CI).

Additionally, we tested responders versus non-responders with Fisher's exact test, where response was defined as a ≥50% decrease to a final score of ≤8 on the 17-item HAM-D and ≤5 on the EPDS at the end of the intervention period.

Data was analyzed using SPSS 21.0 (IBM Corporation, Chicago, IL, USA). Statistical significance was defined as $p<.05$.

Results

Demographic and clinical characteristics

Table 3.2 shows the participant characteristics at the time of inclusion. At inclusion, mean SIGH-SAD score was 26.5 (SD 7.2), mean 17-item HAM-D score was 16.9 (SD 5.3) and mean EPDS score was 16.1 (SD 4.8).

The most common comorbidity was anxiety (25.4%), followed by obsessive compulsive disorder (17.9%), PTSS (11.9%) and social phobia (11.9%). Various somatic comorbidities were reported, such as asthma, Guillain-Barré syndrome and fibromyalgia.

During the course of this study, as part of the care as usual, eleven additional women started with psychotherapy: three women in the intervention period, one after the intervention period during pregnancy and seven in the postpartum period. During the

entire study, four additional women started with psychotropic medication: one woman started with an SSRI in the intervention period and one woman in the postpartum period (both sertraline), one with an antipsychotic (quetiapine) and one with a benzodiazepine (temazepam) postpartum. Of one participant, the dose of the SSRI was increased in the postpartum period (escitalopram).

Table 3.2 – Overview of participant characteristics at inclusion.

	BLT (n=33)	**DRLT (n=34)**
Age in years, mean (SD)	31.9 (4.4)	31.9 (5.3)
Gestational age in weeks, mean (SD)	20.6 (6.2)	19.7 (6.3)
Ethnicity		
Dutch	27 (81.8%)	26 (76.5%)
Other	6 (19.2%)	8 (33.5%)
Marital status		
Married or cohabiting	33 (100%)	32 (94.1%)
Committed relationship, not cohabiting	0 (0%)	1 (2.9%)
Single	0 (0%)	1 (2.9%)
Education		
Elementary or (pre-)vocational education	11 (33.3%)	13 (38.2%)
Higher professional education	8 (24.2%)	11 (32.4%)
(Pre-) academic education	14 (42.4%)	10 (29.4%)
Parity		
Nulliparous	15 (45.5%)	20 (58.8%)
Primiparous	13 (39.4%)	9 (26.5%)
Multiparous	5 (15.2%)	5 (14.7%)
BMI in kg/m^2 or st/ft^2, mean (SD)	25.5 (4.5)	26.3 (5.4)
Planned pregnancy	22 (66.7%)	22 (64.7%)
Antidepressant medication	3 (9.1%)	5 (14.7%)
Sleep medication	3 (9.1%)	2 (5.9%)
Psychotherapy	14 (48.5%)	16 (47.1%)
Comorbidities		
0	17 (51.5%)	13 (38.2%)
1	9 (27.3%)	13 (38.2%)
>1	7 (21.2%)	8 (23.5%)
Duration of depression in weeks, mean (SD)	24.6 (16.9)	45.1 (121.9)
Depressive episodes in past		
0	12 (36.4%)	11 (32.4%)
1	9 (27.2%)	14 (41.2%)
>1	12 (36.4%)	9 (26.5%)
Chronotype		
Early (extremely, moderately and slightly)	20 (80%)	25 (92.6%)
Normal	1 (4%)	1 (3.7%)
Late (extremely, moderately and slightly)	4 (16%)	1 (3.7%)

Compliance

Self-reported compliance was somewhat higher in the BLT group, compared to the DRLT group. Amongst the women treated with BLT, eight women (24.2%) never missed a treatment, in contrast to three women (8.8%) in the DRLT group. Sixteen women (48.5%) treated with BLT missed a maximum of six treatments, where this was twenty women (58.9% in the DRLT group. In both groups, two women missed seven to thirteen treatments in the intervention period. One woman treated with BLT and two with DRLT missed fourteen or more treatments. One woman treated with BLT and two with DRLT missed the final two weeks of treatment, the first one due to complete remission of her symptoms.

Maintaining blinding

Before treatment, three women (4.8%) did not expect any effect from light therapy for their depressive symptoms. All other participants expected a (small) positive effect. After treatment, one participant treated with BLT (3.0%) and three women in the group treated with DRLT (8.8%) thought they were treated with placebo treatment. All other women had no specific ideas about their allocation.

Treatment effect

Supplementary Table 3.2 shows the observed mean SIGH-SAD, HAM-D and EPDS scores over the course of the study. In the women treated with BLT, depression scores decreased by 41.2% (SIGH-SAD), 50% (HAM-D) and 44.7% (EPDS) in the intervention period. In the DRLT group, this was respectively 49.8%, 58.6% and 45.0%. After women stopped with light treatment, mean scores continued to decrease for all questionnaires in both groups, three and ten weeks after treatment. At two months postpartum, women treated with BLT showed no increase in EPDS scores, whereas women treated with DRLT showed an increase in EPDS-scores. For both SIGH-SAD and HAM-D scores, a decrease was observed in both treatment arms.

No statistically significant difference was found between the two treatment arms for the intervention period, nor for the entire study (Figure 3.2 and Table 3.3). Adjusted primary analyses, where we repeated our primary analyses adjusted for propensity scores, and sensitivity analyses with imputed data did not show any other findings

(Table 3.3). Adjustment for chronotype and month of treatment did not change our findings as well. Post-hoc analyses, where we repeated the analyses for women with higher treatment compliance and for women with higher symptom severity at baseline, did not show a statistically significant difference between the two treatment arms (Table 3.3).

Table 3.3 – Effects of allocation on the course of depressive symptoms through the intervention period and follow-up (until two months postpartum).

	β (95% CI) of intervention*	**β (95% CI) of follow-up****
Crude analysis		
SIGH-SAD	-0.68 (-1.84 – 0.49)	-0.16 (-0.82 – 0.51)
HAM-D	-0.18 (-0.74 – 0.37)	0.04 (-0.29 – 0.37)
EPDS	0.01 (-0.51 – 0.53)	-0.05 (-0.35 – 0.24)
Adjusted analysis[a]		
SIGH-SAD	-0.24 (-1.68 – 1.20)	-0.24 (-1.68 – 1.20)
HAM-D	0.13 (-0.49 – 0.75)	0.13 (-0.49 – 0.75)
EPDS	0.25 (-0.38 – 0.89)	0.25 (-0.38 – 0.89)
Data imputation[b]		
SIGH-SAD	-0.45 (-1.44 – 0.53)	-0.08 (-0.63 – 0.46)
HAM-D	-0.09 (-0.63 – 0.44)	0.06 (-0.25 – 0.37)
EPDS	0.19 (-0.30 – 0.68)	0.04 (-0.24 – 0.32)
Post-hoc analysis: high treatment compliance[c]		
SIGH-SAD	-0.40 (-1.36 – 0.55)	-0.32 (-0.88 – 0.24)
HAM-D	-0.12 (-0.79 – 0.54)	-0.06 (-0.43 – 0.31)
EPDS	0.03 (-0.58 – 0.65)	-0.05 (-0.40 – 0.30)
Post-hoc analysis: high symptom severity[d]		
SIGH-SAD	-0.84 (-2.33 – 0.65)	-0.20 (-1.14 – 0.75)
HAM-D	-0.16 (-1.12 – 0.87)	0.13 (-0.48 – 0.73)
EPDS	-0.05 (-0.92 – 0.82)	0.20 (-0.33 – 0.74)

* Six weeks of treatment; ** Six weeks of treatment until follow-up 2 months postpartum ; [a] Propensity score composed of psychiatric history, ethnicity, level of education, an unplanned pregnancy, maternal age, parity, gestational age, duration of actual depression and other psychiatric or psychotherapeutic treatment interventions; [b] Last observation carried forward; [c] <7 missed treatments; [d] Based on median split baseline SIGH-SAD scores; DRLT group is the reference category.

For the HAM-D, 13 participants in the BLT group and 17 participants in the DRLT group were considered responders. This was respectively 11 and 9 when measured with the EPDS. When we studied responders versus non-responders, we found no statistically significant differences for both HAM-D scores (p=.46) and EPDS scores (p=.60).

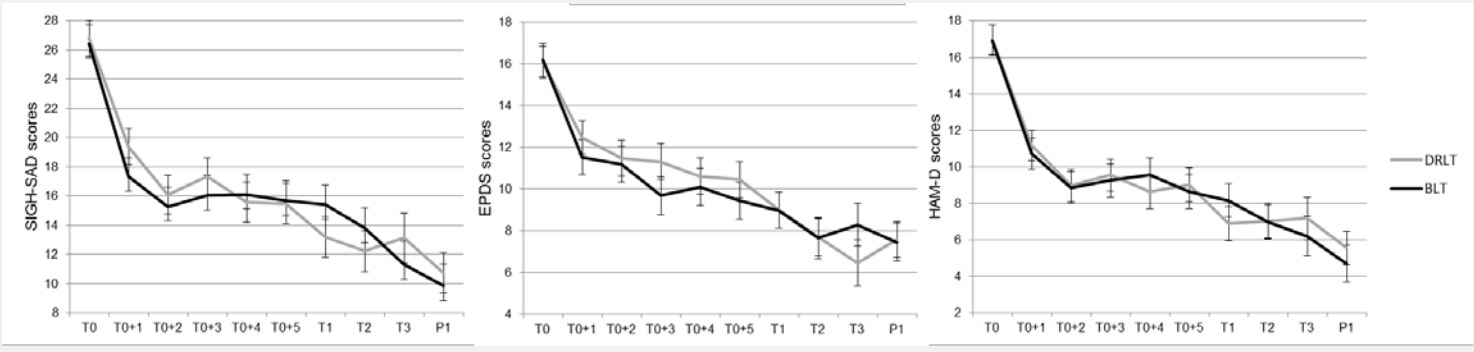


Figure 3.2 – Estimated marginal means of depression scores in women with antepartum depression until two months postpartum. Shown are SIGH-SAD, HAM-D and EPDS scores. Black lines represent treatment with BLT, gray lines with DRLT. Bars represent standard error of the mean.

T0 = baseline, before treatment; T0+1, T0+2 ... T0+5 = weeks during intervention period; T1 = end of treatment; T2 = 3 weeks after end of treatment; T3 = 10 weeks after end of treatment; P1 = 2 months postpartum

Side effects

For women treated with BLT, the most frequently reported side effect was headaches (30.3%), followed by sleep problems (12.1%) and nausea (6.1%). For women treated with DRLT, the most reported side effect was headaches (20.6%), followed by sleep problems (8.9%) and irritable eyes (5.9%). Side effects were not reported more often by women treated with BLT, compared to DRLT (p=0.52). Most side effects were experienced for a maximum of three days. None of the women suffered from any (hypo)manic symptoms. We reduced the treatment duration for five women to 20 minutes daily due to their side effects. Interestingly, two women dropped out of the study due to side effects, but only in the DRLT group.

Acceptability and satisfaction

The majority of women experienced a (small) positive effect for their depressive symptoms (78.6% BLT; 61.5% DRLT; p=0.58). All participants found the lamp (very) easy in use. Most women found the light therapy pleasant (57.1% BLT; 50% DRLT; p=0.49). Twenty-six women reported that it was (very) easy to plan the light therapy in the morning (42.9% BLT; 53.8% DRLT; p=0.43). Thirty-two women reported that they would like to use light therapy outside of the study (57.1% BLT; 61.5% DRLT; p=0.79). On average, women reported it was likely they would recommend the light therapy to others (BLT mean 8.0, SD 1.3; DRLT mean 7.0, SD 2.7; p=0.08).

Discussion

We conducted a randomized controlled trial, evaluating the effectiveness of BLT in a sample of 67 pregnant women with major depressive disorder, compared to DRLT. We found no statistically significant difference between BLT and DRLT on depressive symptoms. Mean depression scores decreased by 41.2-50% during the intervention in the women treated with BLT and by 45-58.6% in the women treated by DRLT.

Effects in the current study

This level of improvement is comparable to the studies by Oren *et al*. [45] and Corral *et al*. [63] who both found a reduction in mean depression scores of 49%. Oren *et al*.

conducted an open trial in an antepartum population, whereas Corral *et al*. conducted a randomized controlled trial among women with a postpartum depression. Similar to Corral *et al*., we did not find a statistically significant difference between the effective and placebo conditions. The mean improvement in the DRLT group can be explained by placebo effects, which could also be the case in the BLT group. A meta-analysis showed that the placebo response in antidepressant trials is approximately 68% [64], although this effect is not clear yet in light therapy trials specifically. Secondly, the improvement in both groups can be explained by non-specific treatment effects such the structure offered by the study [37], the interaction with the researchers or increased awareness and self-care resulting from participating in the study. A systematic review on various studies in treating antepartum depression with a control condition showed that these trials often show a considerable reduction in symptom scores in both treatment arms [33]. Furthermore, it might be that symptoms decrease related to the course of pregnancy, spontaneous remission or regression to the mean. A meta-analysis showed that untreated depressive symptoms could decrease by 10-15%, on average [65]. However, untreated depression during pregnancy is an important predictor for postpartum depression [66].

Corral *et al*. mentioned that several participants commented positively on having 30 minutes of “quiet time” on a daily basis. Several of our participants mentioned this as well, which could reflect sinking into a state of more relaxation or more mindfulness which may have contributed to the improvement in both groups. Two meta-analyses showed that mindfulness-based therapy is an effective treatment for a variety of psychological problems [67, 68]. An earlier pilot study and an open study of mindfulness also showed positive effects on mood specifically in pregnant women [69, 70]. Corral *et al*. mentioned that many postpartum women are motivated to access recourses, such as psychological treatment, which could have exerted non-specific treatment effects. In their study however, no participant took part in any treatment during the study. In our study, several women started psychotherapy or antidepressant medication. However, adjustment for any intervention did however not change our findings.

Differences with literature

The results of this study differ from the randomized controlled trials by Epperson *et al.* [46] and Wirz-Justice *et al*. [47], who did find superiority of bright light therapy over placebo in an antepartum population.

Wirz-Justice *et al*. included only clinical patients and found that BLT had more effects in severe patients in their study. However, mean baseline SIGH-SAD score in the Wirz-Justice et al. and Epperson et al. studies were 27.7 and 28.1, respectively, which is not clinically relevant different from the present study (26.5). Additionally, we included baseline depression scores in our model, which did not change our findings. Also, post-hoc analyses, where we repeated the analyses for women with higher baseline severity, did not show any significant findings.

Both Epperson *et al*. and Wirz-Justice *et al*. treated their patients for 1 hour a day and within 10 minutes of habitual wake-up time, which is different from the present study. Thus far, no studies have been executed comparing the effectiveness of shorter versus longer exposure to bright light in non-seasonal depression. Possibly, more light output in the BLT group would be necessary to show superiority of BLT over DRLT in a pregnant population. However, other studies that treated patients for 30 minutes also did show a statistical significant difference between the effective and the placebo intervention in non-seasonal depression [40]. One must keep in mind that these studies have been done in non-pregnant populations and different – yet unknown – underlying mechanisms may play a part during pregnancy, such as hormonal fluctuations and a shift in social role.

Our placebo condition, in which the possible effect of DRLT could be questioned, is not a plausible explanation for not finding a statistically significant effect between the treatment arms. Epperson *et al*. used a placebo condition with 500 lux white light, which is questionable as a placebo, for white light of 100 lux is able to phase-shift human circadian rhythms [71]. Since this study found a significant improvement in women treated with BLT when compared to this placebo, it is unlikely that the settings of our placebo would explain failing to achieve a significant difference between the two treatment arms.

In the study by Corral *et al*., depression scores worsened after withdrawal of treatment, indicating that spontaneous remission would be less likely. However, in the present study, mean depressions scores of all questionnaires continued to

improve after withdrawal of treatment in both groups, indicating that spontaneous remission in both groups is a possible explanation for this finding.

Strengths and limitations

Internationally, we conducted the largest randomized controlled trial studying light therapy in pregnant women with a depression. Moreover, we conducted various follow up measurements, including postpartum, to study the effects of withdrawal of treatment and to study whether treatment during pregnancy would protect against postpartum depression. Another strength is using a single assessor to diagnose depression. Moreover, the setting of treatment was within a real world setting. Finally, a strength of this study was the comprehensive assessment of side effects, as well as acceptability and satisfaction of treatment.

The main limitation of our study was that an unforeseen lack of resources prevented us from including 150 participants, as we aimed to do according to our sample size calculation [49], which enables us to find only large treatment effects [49]. Another limitation is the fact that depressive symptoms during the study are assessed by questionnaires, rather than diagnostic criteria. Moreover, various covariates are self-reported, such as BMI, substance use and medication.

Conclusions

BLT has been shown effective in treating non-seasonal depression [40] and in women with antepartum depression as well [46, 47]. In the present study, both BLT and DRLT showed improvement in pregnant women with a depressive disorder after 6 weeks of 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, more studies to the effectiveness of BLT during pregnancy are warranted. It is important to determine whether the responses observed in the present study represent true treatment effects, non-specific treatment responses, placebo effects or a combination of these. This could be done by studying biological outcomes, such as cortisol and melatonin levels, which might show a statistically significant difference between the two treatment arms irrespective of perceived symptoms of depression. Additionally, it might show an

indication of the positive effects of light therapy on the circadian rhythm and its inhibiting effects on HPA-axis hyperactivity.

Potential conflict of interests

The lamps in the study are provided by Signify Research. Author JS is employed by Signify Research.

Funding/support

MLB received funding from the 'Light, Cognition, Behaviour and Health' program of The Netherlands Organization for Health Research and Development (NWO), in collaboration with Signify Research (NWO, grant number 058-14-003) to fund the current study.

Role of the sponsors

NWO had no role in the present study. Signify Research reviewed the manuscript.

Authors' contributions

MLB is the project's principle investigator and initiator of the study, obtained funding and designed the study. BB was responsible for recruiting and counselling participants, running the study and collecting data. AK is the project's methodologist and executed the primary statistical analysis. HB and EK were involved in the recruitment of the study. JS provided support. AK, WH and MLB supervised the study. BB, AK and MLB prepared the original draft. All authors reviewed, edited and approved the final manuscript.

Acknowledgements

We would like to thank all participants for participating in the study. We would also like to thank all general practitioners, midwifes, gynaecologists, psychiatrists and psychologists for their help with the recruitment. We are grateful for all co-workers, students and assistants who contributed to the data collection in this study: Nina Molenaar, Marlies Brouwer, Leo Genet, Sophie de Droog, Sofie Koomen, Diewertje Houtman, Maria Zepeda, Nicolle Croes, Rianne Winters, Lisanne van Kesteren, Finn Stofkoper, Indira Schouten and Mieke Roukema.

References

1. Woody, C.A., et al., A systematic review and meta-regression of the prevalence and incidence of perinatal depression. J Affect Disord, 2017. 219: p. 86-92.
2. Milgrom, J., et al., Antenatal risk factors for postnatal depression: a large prospective study. J Affect Disord, 2008. 108: p. 147-157.
3. Grote, N.K., et al., A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry, 2010. 67(10): p. 1012-24.
4. Jarde, A., et al., Neonatal outcomes in women with untreated antenatal depression compared with women without depression: a systematic review and meta-analysis. JAMA Psychiatry, 2016: p. DOI:10.1001/jamapsychiatry.2016.0934.
5. Talge, N.M., et al., Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? J Child Psychol Psychiatry, 2007. 48(3-4): p. 245-61.
6. Hentges, R.F., et al., A Developmental Cascade from Prenatal Stress to Child Internalizing and Externalizing Problems. J Pediatr Psychol, 2019.
7. Pearson, R.M., et al., Maternal depression during pregnancy and the postnatal period: risks and possible mechanisms for offspring depression at age 18 years. JAMA Psychiatry, 2013. 70(12): p. 1312-9.
8. Glover, V., T.G. O'Connor, and K. O'Donnell, Prenatal stress and the programming of the HPA axis. Neurosci Biobehav Rev, 2010. 35(1): p. 17-22.
9. Dierckx, B., et al., Maternal psychopathology influences infant heart rate variability: Generation R Study. Psychosom Med, 2009. 71(3): p. 313-21.
10. Goedhart, G., et al., Maternal cortisol and offspring birthweight: results from a large prospective cohort study. Psychoneuroendocrinology, 2010. 35(5): p. 644-52.
11. Henrichs, J., et al., Maternal psychological distress and fetal growth trajectories: the Generation R Study. Psychol Med, 2010. 40(4): p. 633-43.
12. Zijlmans, M.A., J.M. Riksen-Walraven, and C. de Weerth, Associations between maternal prenatal cortisol concentrations and child outcomes: A systematic review. Neurosci Biobehav Rev, 2015. 53: p. 1-24.
13. Steegers, E.A., et al., Societal Valorisation of New Knowledge to Improve Perinatal Health: Time to Act. Paediatr Perinat Epidemiol, 2016. 30(2): p. 201-4.
14. Byatt, N., K.M. Deligiannidis, and M.P. Freeman, Antidepressant use in pregnancy: a critical review focused on risks and controversies. Acta Psychiatr Scand, 2013. 127(2): p. 94-114.
15. Hanley, G.E. and T.F. Oberlander, The effect of perinatal exposures on the infant: antidepressants and depression. Best Pract Res Clin Obstet Gynaecol, 2014. 28(1): p. 37-48.
16. Kieler, H., et al., Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. BMJ, 2012. 344: p. d8012.
17. Simoncelli, M., B.Z. Martin, and A. Berard, Antidepressant use during pregnancy: a critical systematic review of the literature. Curr Drug Saf, 2010. 5(2): p. 153-70.

18. Battle, C.L., et al., Perinatal antidepressant use: understanding women's preferences and concerns. J Psychiatr Pract, 2013. 19(6): p. 443-53.
19. Kothari, A., et al., Perceptions of pregnant women regarding antidepressant and anxiolytic medication use during pregnancy. Australas Psychiatry, 2019. 27(2): p. 117-120.
20. Molenaar, N.M., et al., Antidepressants during pregnancy: Guideline adherence and current practice amongst Dutch gynaecologists and midwives. Midwifery, 2018. 61: p. 29-35.
21. Molenaar, N.M., et al., Guidelines on treatment of perinatal depression with antidepressants: An international review. Aust N Z J Psychiatry, 2018. 52(4): p. 320-327.
22. Bakker, M.K., et al., Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. Br J Clin Pharmacol, 2008. 65(4): p. 600-6.
23. Molenaar, N.M., M.P. Lambregtse-van den Berg, and G.J. Bonsel, Dispensing patterns of selective serotonin reuptake inhibitors before, during and after pregnancy: a 16-year population-based cohort study from the Netherlands. Arch Womens Ment Health, 2019.
24. Charlton, R.A., et al., Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. Bjog-an International Journal of Obstetrics and Gynaecology, 2015. 122(7): p. 1010-1020.
25. Cooper, W.O., et al., Increasing use of antidepressants in pregnancy. American Journal of Obstetrics and Gynecology, 2007. 196(6): p. 544-545.
26. Jimenez-Solem, E., et al., Prevalence of Antidepressant Use during Pregnancy in Denmark, a Nation-Wide Cohort Study. Plos One, 2013. 8(4).
27. van Gelder, M.M.H.J., et al., Drugs associated with teratogenic mechanisms. Part I: dispensing rates among pregnant women in the Netherlands, 1998-2009. Human Reproduction, 2014. 29(1): p. 161-167.
28. Ververs, T., et al., Prevalence and patterns of antidepressant drug use during pregnancy. Eur J Clin Pharmacol, 2006. 62(10): p. 863-70.
29. Ailes, E.C., et al., Using insurance claims data to identify and estimate critical periods in pregnancy: An application to antidepressants. Birth Defects Res A Clin Mol Teratol, 2016. 106(11): p. 927-934.
30. Andrade, S.E., et al., Use of selective serotonin reuptake inhibitors (SSRIs) in women delivering liveborn infants and other women of child-bearing age within the U.S. Food and Drug Administration's Mini-Sentinel program. Arch Womens Ment Health, 2016. 19(6): p. 969-977.
31. Taylor, L.G., et al., Development of a mother-child database for drug exposure and adverse event detection in the Military Health System. Pharmacoepidemiol Drug Saf, 2015. 24(5): p. 510-7.
32. Hanley, G.E. and B. Mintzes, Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. BMC Pregnancy Childbirth, 2014. 14: p. 242.
33. van Ravesteyn, L.M., et al., Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment meta-analysis. PLoS One, 2017. 12(3): p. e0173397.

34. Blume, C., C. Garbazza, and M. Spitschan, Effects of light on human circadian rhythms, sleep and mood. Somnologie, 2019.
35. LeGates, T.A., D.C. Fernandez, and S. Hattar, Light as a central modulator of circadian rhythms, sleep and affect. Nature Reviews Neuroscience, 2014. 15(7): p. 443-454.
36. Prayag, A.S., et al., Light modulation of human clocks, wake and sleep. Clocks & Sleep, 2019. 1: p. 193-208.
37. Germain, A. and D.J. Kupfer, Circadian rhythm disturbances in depression. Hum Psychopharmacol, 2008. 23(7): p. 571-85.
38. Lam, R.W. and R.D. Levitan, Pathophysiology of seasonal affective disorder: a review. J Psychiatry Neurosci, 2000. 25(5): p. 469-80.
39. Magnusson, A. and D. Boivin, Seasonal affective disorder: an overview. Chronobiol Int, 2003. 20(2): p. 189-207.
40. Tuunainen, A., D.F. Kripke, and T. Endo, Light therapy for non-seasonal depression. Cochrane Database Syst Rev, 2004.
41. Golden, R.N., et al., The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry, 2005. 162(4): p. 656-62.
42. Al-Karawi, D. and L. Jubair, Bright light therapy for nonseasonal depression: Meta-analysis of clinical trials. J Affect Disord, 2016. 198: p. 64-71.
43. Perera, S., et al., Light therapy for non-seasonal depression: systematic review and meta-analysis. BJPsych Open, 2016. 2(2): p. 116-126.
44. Martensson, B., et al., Bright white light therapy in depression: A critical review of the evidence. J Affect Disord, 2015. 182: p. 1-7.
45. Oren, D.A., et al., An open trial of morning light therapy for treatment of antepartum depression. Am J Psychiatry, 2002. 159(4): p. 666-9.
46. Epperson, C.N., et al., Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry, 2004. 65(3): p. 421-5.
47. Wirz-Justice, A., et al., A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. J Clin Psychiatry, 2011. 72(7): p. 986-93.
48. Ioannidis, J.P., Why most published research findings are false. PLoS Med, 2005. 2(8): p. e124.
49. Bais, B., et al., Bright light therapy in pregnant women with major depressive disorder: study protocol for a randomized, double-blind, controlled clinical trial. BMC Psychiatry, 2016. 16(1): p. 381.
50. First MB, G.M., Spitzer RL, Williams JBW, User's guide for the SCID-I. Structured clinical interview for DSM-IV TR axis I disorders (research version). 2002, New York: New York Psychiatric Institute.
51. Lieverse, R., et al., Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. Arch Gen Psychiatry, 2011. 68(1): p. 61-70.
52. Kreidler, S.M., et al., GLIMMPSE: Online Power Computation for Linear Models with and without a Baseline Covariate. J Stat Softw, 2013. 54(10).

53. Meesters, Y., et al., Low-intensity blue-enriched white light (750 lux) and standard bright light (10,000 lux) are equally effective in treating SAD. A randomized controlled study. BMC Psychiatry, 2011. 11: p. 17.
54. Project, T.A.I., ALEA Randomisation Software (Version 2.2). 2006, Amsterdam: Netherlands Cancer Institute. p. http://tenalea.net/.
55. Bockting, C.L., et al., A lifetime approach to major depressive disorder: The contributions of psychological interventions in preventing relapse and recurrence. Clin Psychol Rev, 2015. 41: p. 16-26.
56. Cox, J.L., J.M. Holden, and R. Sagovsky, Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry, 1987. 150: p. 782-6.
57. Bergink, V., et al., Validation of the Edinburgh Depression Scale during pregnancy. J Psychosom Res, 2011. 70(4): p. 385-389.
58. Roenneberg, T., A. Wirz-Justice, and M. Merrow, Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms, 2003. 18(1): p. 80-90.
59. Merikanto, I., et al., Circadian preference links to depression in general adult population. J Affect Disord, 2015. 188: p. 143-8.
60. Merikanto, I., et al., Evening types are prone to depression. Chronobiol Int, 2013. 30(5): p. 719-25.
61. Schulz, K.F., et al., CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med, 2010. 8: p. 18.
62. Friedman, E.S., et al., Baseline depression severity as a predictor of single and combination antidepressant treatment outcome: results from the CO-MED trial. Eur Neuropsychopharmacol, 2012. 22(3): p. 183-99.
63. Corral, M., et al., Morning light therapy for postpartum depression. Arch Womens Ment Health, 2007. 10(5): p. 221-4.
64. Rief, W., et al., Meta-analysis of the placebo response in antidepressant trials. J Affect Disord, 2009. 118(1-3): p. 1-8.
65. Posternak, M.A. and I. Miller, Untreated short-term course of major depression: a meta-analysis of outcomes from studies using wait-list control groups. J Affect Disord, 2001. 66(2-3): p. 139-46.
66. Yazici, E., et al., Untreated depression in the first trimester of pregnancy leads to postpartum depression: high rates from a natural follow-up study. Neuropsychiatr Dis Treat, 2015. 11: p. 405-11.
67. Khoury, B., et al., Mindfulness-based therapy: a comprehensive meta-analysis. Clin Psychol Rev, 2013. 33(6): p. 763-71.
68. Hofmann, S.G., et al., The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. J Consult Clin Psychol, 2010. 78(2): p. 169-83.
69. Dimidjian, S., et al., An open trial of mindfulness-based cognitive therapy for the prevention of perinatal depressive relapse/recurrence. Arch Womens Ment Health, 2015. 18(1): p. 85-94.

70. Vieten, C. and J. Astin, Effects of a mindfulness-based intervention during pregnancy on prenatal stress and mood: results of a pilot study. Arch Womens Ment Health, 2008. 11(1): p. 67-74.
71. Zeitzer, J.M., et al., Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. J Physiol, 2000. 526 Pt 3: p. 695-702.

Supplementary Material

Supplementary Table 3.1 – Photobiological characterizations of light therapy in both treatment arms.

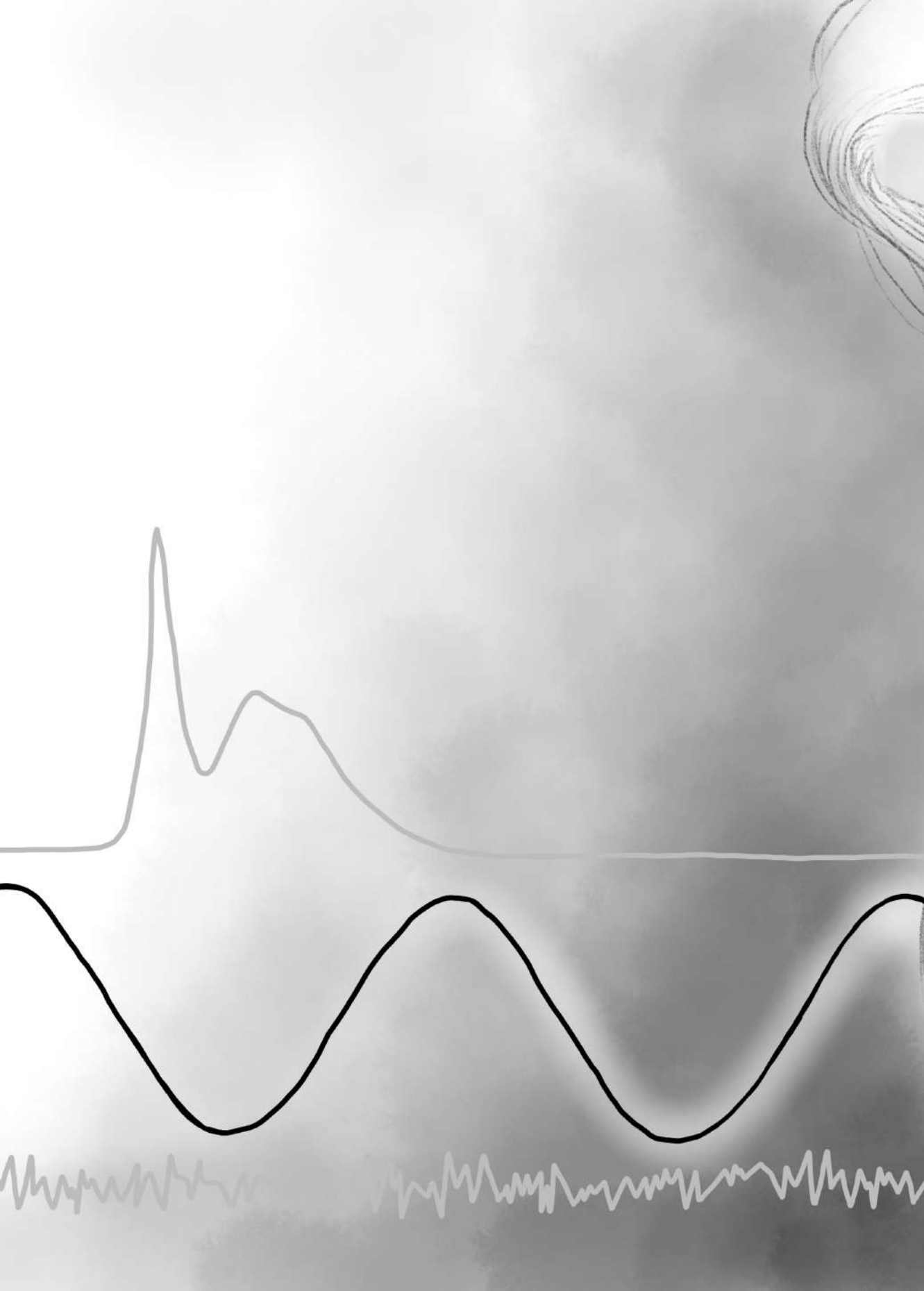
	BLT	DRLT
Cyanopic irradiance (μW · cm^{-2})	578.7	2.24
Melanopic irradiance (μW · cm^{-2})	891	5.53
Chloropic irradiance (μW · cm^{-2})	1032.3	7.23
Erythropic irradiance (μW · cm^{-2})	1212.3	11.37
Rhodopic irradiance (μW · cm^{-2})	16.61	16.61

BLT = bright light therapy; DRLT = dim red light therapy

Supplementary Table 3.2 – Observed mean SIGH-SAD, HAM-D and EPDS scores with standard deviations and number of participants over the course of the study for both treatment arms.

Measure	T0	T0+1	T0+2	T0+3	T0+4	T0+5	T1	T2	T3	P1
SIGH-SAD										
BLT (mean, S.D., N)	26.2 (7.4; 33)	17.3 (8.4; 30)	15.5 (8.6; 29)	15.6 (10.3; 25)	16.3 (9.2; 25)	16.4 (9.1; 24)	15.4 (7.9; 26)	14.0 (7.8; 25)	11.9 (8.2; 17)	8.5 (6.3; 20)
DRLT (mean, S.D., N)	26.9 (7.1; 34)	19.2 (6.6; 31)	15.9 (8.3; 27)	17.7 (7.3; 29)	15.2 (6.8; 24)	15.8 (7.8; 25)	13.5 (7.5; 25)	12.5 (7.6; 24)	10.9 (7.6; 14)	10.7 (7.7; 25)
HAM-D										
BLT (mean, S.D., N)	16.8 (5.6; 33)	10.7 (6.3; 30)	9.1 (5.9; 29)	9.0 (6.8; 25)	9.8 (6.3; 25)	9.3 (5.8; 24)	8.4 (5.4; 26)	7.4 (5.0; 25)	6.6 (5.1; 17)	4.2 (3.4; 20)
DRLT (mean, S.D., N)	16.9 (5.2; 34)	10.9 (4.5; 31)	8.9 (5.1; 27)	9.5 (5.2; 29)	8.4 (4.5; 24)	9.0 (5.7; 25)	7.0 (4.7; 25)	6.8 (5.7; 24)	5.4 (4.6; 14)	5.3 (4.9; 25)
EPDS										
BLT(mean, S.D., N)	16.2 (4.3; 31)	11.4 (5.4; 26)	11.4 (5.1; 26)	9.6 (5.2; 21)	9.8 (6.4; 23)	9.0 (5.2; 23)	9.0 (5.6; 26)	8.3 (4.8; 18)	8.9 (6.7; 16)	7.1 (4.0; 22)
DRLT (mean, S.D., N)	15.9 (5.3; 34)	12.5 (3.3; 28)	11.8 (4.3; 25)	11.4 (5.1; 24)	10.3 (4.6; 24)	10.6 (5.0; 23)	8.8 (6.3; 24)	7.7 (5.5; 23)	4.8 (2.8; 12)	7.7 (4.1; 26)

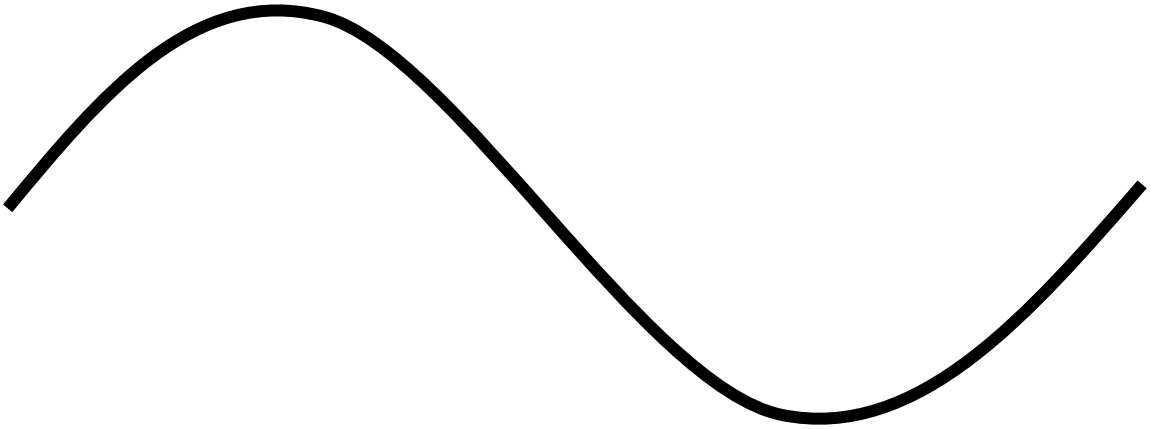
T0 = baseline, before treatment; T0+1, T0+2 ... T0+5 = weeks during intervention period; T1 = end of treatment; T2 = 3 weeks after end of treatment; T3 = 10 weeks after end of treatment; P1 = 2 months postpartum




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

Psychiatry Research 2018; 268: 257-262.

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 51-53º longitude and 4-7º 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.

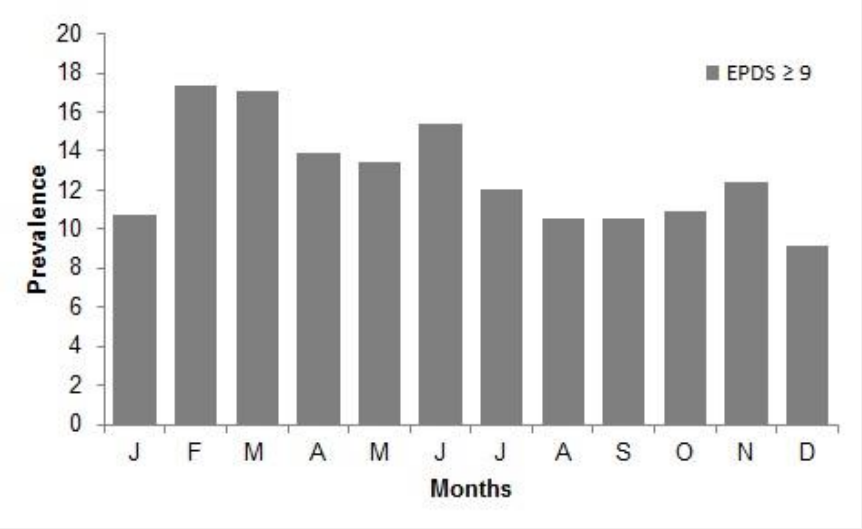


Figure 4.1 – Proportion of EPDS ≥ 9 by month.

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.

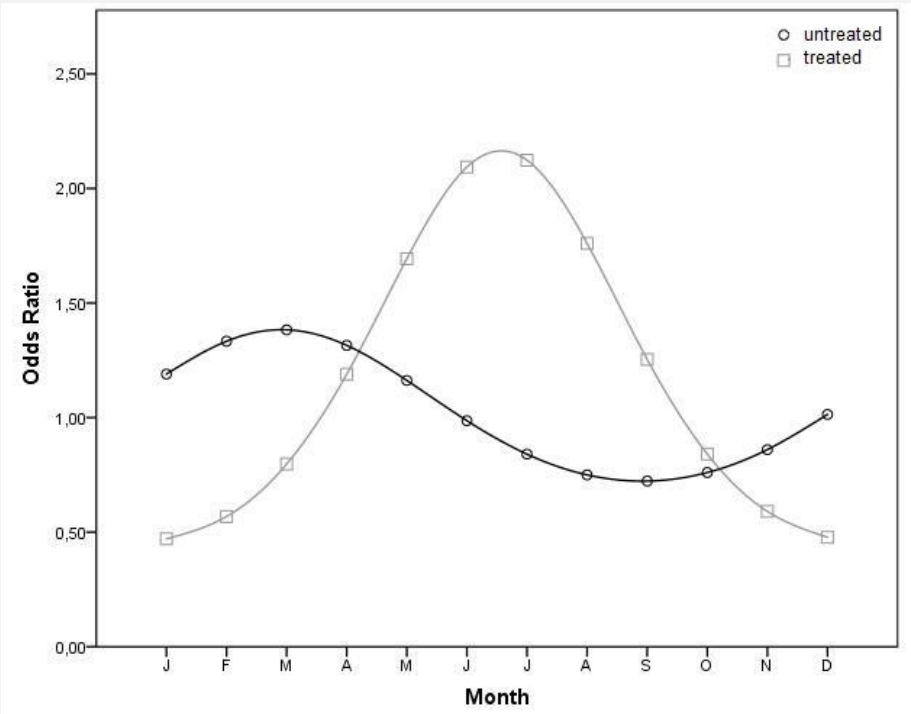


Figure 4.2 – Joint sine-cosine function of month of assessment on depressive symptoms (EPDS ≥ 9) expressed in Odds Ratio, shown for women who did not receive treatment (black) and women who did receive treatment for psychiatric problems (grey).
Function is unadjusted for confounders (age, educational 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.

Acknowledgements

We thank dr. Chantal Quispel for kindly providing the data necessary for the analysis of this study. Also, we would like to thank dr. Joost van Rosmalen for his statistical advice. We like to thank the reviewers for their valuable feedback.

Funding

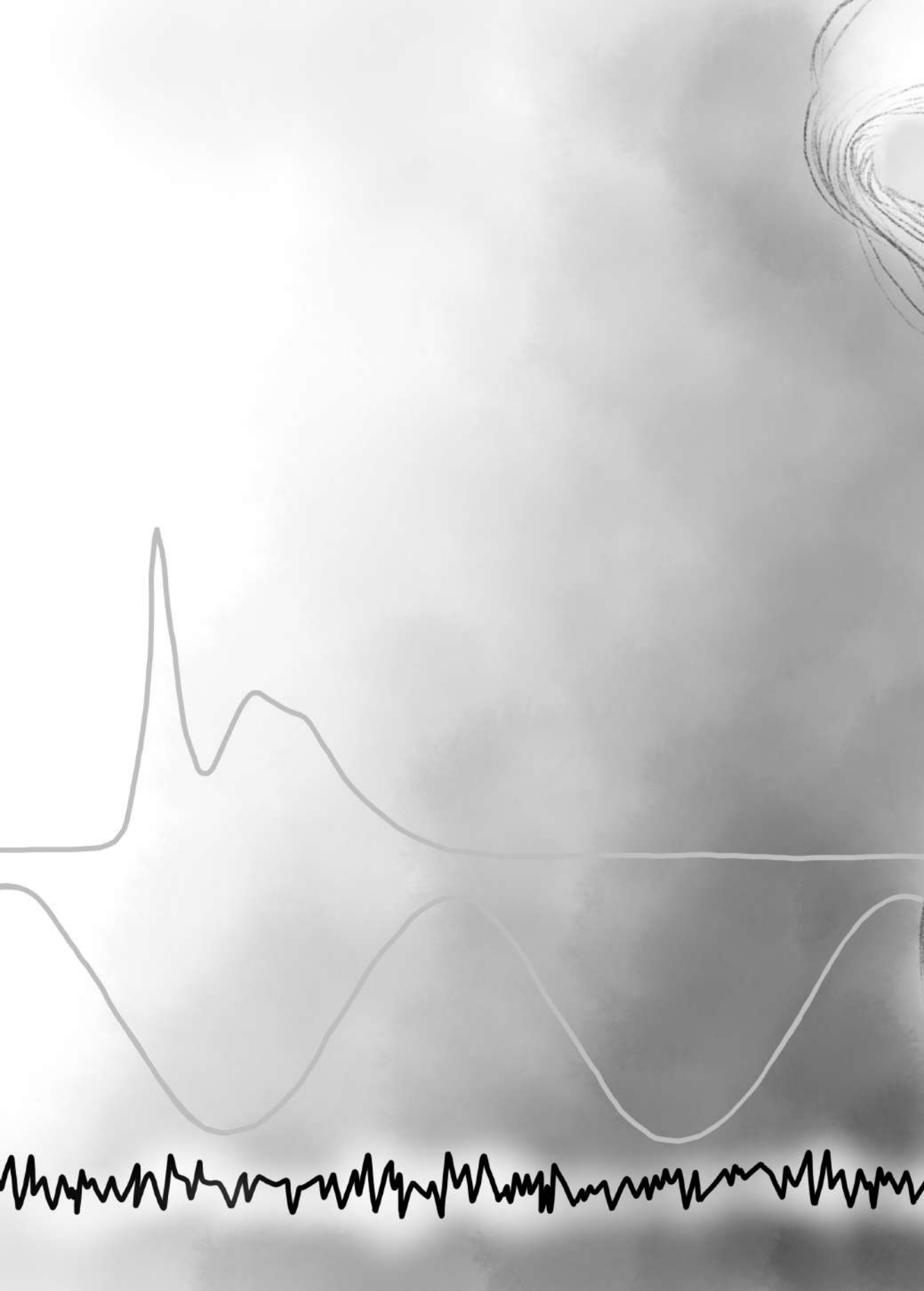
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Steegers, E.A., et al., Societal Valorisation of New Knowledge to Improve Perinatal Health: Time to Act. Paediatr Perinat Epidemiol, 2016. 30(2): p. 201-4.
2. Woody, C.A., et al., A systematic review and meta-regression of the prevalence and incidence of perinatal depression. J Affect Disord, 2017. 219: p. 86-92.
3. Milgrom, J., et al., Antenatal risk factors for postnatal depression: a large prospective study. J Affect Disord, 2008. 108: p. 147-157.
4. Talge, N.M., et al., Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? J Child Psychol Psychiatry, 2007. 48(3-4): p. 245-61.
5. Grote, N.K., et al., A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry, 2010. 67(10): p. 1012-24.
6. Jarde, A., et al., Neonatal outcomes in women with untreated antenatal depression compared with women without depression: a systematic review and meta-analysis. JAMA Psychiatry, 2016: p. DOI:10.1001/jamapsychiatry.2016.0934.
7. van Ravesteyn, L.M., et al., Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment meta-analysis. PLoS One, 2017. 12(3): p. e0173397.
8. Bais, B., et al., Bright light therapy in pregnant women with major depressive disorder: study protocol for a randomized, double-blind, controlled clinical trial. BMC Psychiatry, 2016. 16(1): p. 381.
9. Molenaar, N.M., et al., Guidelines on treatment of perinatal depression with antidepressants: An international review. Aust N Z J Psychiatry, 2018. 52(4): p. 320-327.
10. Räisänen, S., et al., Risk factors for and perinatal outcomes of major depression during pregnancy: a population-based analysis during 2002-2010 in Finland. BMJ Open, 2014(11): p. DOI:10.1136/bmjopen-2014-004883.
11. Lancaster, C.A., et al., Risk factors for depressive symptoms during pregnancy: a systematic review. Am J Obstet Gynecol, 2010. 202(1): p. 5-14.
12. Meliska, C.J., et al., Antepartum depression severity is increased during seasonally longer nights: relationship to melatonin and cortisol timing and quantity. Chronobiol Int, 2013. 30(9): p. 1160-1173.
13. Rosenthal, N.E., et al., Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry, 1984. 41(1): p. 72-80.
14. Magnusson, A. and D. Boivin, Seasonal affective disorder: an overview. Chronobiol Int, 2003. 20(2): p. 189-207.
15. Lam, R.W. and R.D. Levitan, Pathophysiology of seasonal affective disorder: a review. J Psychiatry Neurosci, 2000. 25(5): p. 469-80.
16. Partonen, T. and J. Lonnqvist, Seasonal affective disorder. Lancet, 1998. 352(9137): p. 1369-74.

17. Wehr, T.A., D.A. Sack, and N.E. Rosenthal, Seasonal affective disorder with summer depression and winter hypomania. Am J Psychiatry, 1987. 144(12): p. 1602-3.
18. Wehr, T.A., et al., Contrasts between symptoms of summer depression and winter depression. J Affect Disord, 1991. 23(4): p. 173-83.
19. Yang, S.N., et al., The delivery mode and seasonal variation are associated with the development of postpartum depression. J Affect Disord, 2011. 132(1-2): p. 158-64.
20. Sylven, S.M., et al., Seasonality patterns in postpartum depression. Am J Obstet Gynecol, 2011. 204: p. 413.e1-6.
21. Hiltunen, P., et al., Seasonal variation in postnatal depression. J Affect Disord, 2004. 78(2): p. 111-8.
22. Corral, M., A. Wardrop, and H.B. Zhang, Seasonality of symptoms in women with postpartum depression. Arch Womens Ment Health, 2007. 10(1): p. 9-13.
23. Sit, D., H. Seltman, and K.L. Wisner, Seasonal effects on depression risk and suicidal symptoms in postpartum women. Depress Anxiety, 2011. 28(5): p. 400-5.
24. Weobong, B., et al., Determinants of postnatal depression in rural ghana: findings from the don population based cohort study. Depress Anxiety, 2015. 32(2): p. 108-19.
25. Jewell, J.S., et al., Prevalence of self-reported postpartum depression specific to season and latitude of birth: evaluating the PRAMS data. Matern Child Health J, 2010. 14(2): p. 261-7.
26. Panthangi, V., et al., Is seasonal variation another risk factor for postpartum depression? J Am Board Fam Med, 2009. 22(5): p. 492-7.
27. Henriksson, H.E., et al., Seasonal patterns in self-reported peripartum depressive symptoms. Eur Psychiatry, 2017. 43: p. 99-108.
28. Quispel, C., Psychopathology, psychosocial problems and substance use during pregnancy - screening and referral towards care (doctoral thesis). 2014, Erasmus University: Rotterdam, The Netherlands.
29. De Groot, N., et al., Vulnerable pregnant women in antenatal practice: caregiver's perception of workload, associated burden and agreement with objective caseload, and the influence of a structured organisation of antenatal risk management. Midwifery, 2016. 40: p. 153-61.
30. Quispel, C., et al., An innovative screen-and-advice model for psychopathology and psychosocial problems among urban pregnant women: an exploratory study. J Psychosom Obstet Gynaecol, 2012. 33(1): p. 7-14.
31. Grootendorst-van Mil, N.H., et al., Brighter children? The association between seasonality of birth and child IQ in a population-based birth cohort. BMJ Open, 2017. 7(2): p. e012406.
32. Cox, J.L., J.M. Holden, and R. Sagovsky, Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry, 1987. 150: p. 782-6.
33. Bergink, V., et al., Validation of the Edinburgh Depression Scale during pregnancy. J Psychosom Res, 2011. 70(4): p. 385-389.
34. McCabe-Beane, J.W., et al., The identification of severity ranges for the Edinburgh Postnatal Depression Scale. J Reprod Infant Psychol, 2016: p. DOI: 10.1080/02646838.2016.1141346.
35. Stolwijk, A.M., H. Straatman, and G.A. Zielhuis, Studying seasonality by using sine and cosine functions in regression analysis. J Epidemiol Community Health, 1999. 53(4): p. 235-8.

36. Bound, J.P., P.W. Harvey, and B.J. Francis, Seasonal prevalence of major congenital malformations in the Fylde of Lancashire 1957-1981. J Epidemiol Community Health, 1989. 43(4): p. 330-42.
37. Woodhouse, P.R., et al., Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. Lancet, 1994. 343(8895): p. 435-9.
38. Weinberg, C.R., et al., Season and preterm birth in Norway: A cautionary tale. Int J Epidemiol, 2015. 44(3): p. 1068-78.
39. Murray, G., et al., Do symptoms of bipolar disorder exhibit seasonal variation? A multisite prospective investigation. Bipolar Disord, 2011. 13(7-8): p. 687-95.
40. VanderWeele, T.J. and I. Shpitser, On the definition of a confounder. Ann Stat, 2013. 41(1): p. 196-220.
41. Traffanstedt, M.K., S. Mehta, and S.G. LoBello, Major Depression With Seasonal Variation: Is It a Valid Construct? Clinical Psychological Science, 2016. 4(5): p. 825-834.
42. Winkler, D., et al., Has the existence of seasonal affective disorder been disproven? J Affect Disord, 2017. 208: p. 54-55.
43. Morrissey, S.A., et al., Seasonal affective disorder: some epidemiological findings from a tropical climate. Aust N Z J Psychiatry, 1996. 30(5): p. 579-86.
44. Srisurapanont, M. and S. Intaprasert, Seasonal variations in mood and behaviour: epidemiological findings in the north tropics. J Affect Disord, 1999. 54(1-2): p. 97-9.
45. Winthorst, W.H., et al., Seasonality in depressive and anxiety symptoms among primary care patients and in patients with depressive and anxiety disorders; results from the Netherlands Study of Depression and Anxiety. BMC Psychiatry, 2011. 11: p. 198.
46. Winthorst, W.H., et al., Self-attributed seasonality of mood and behavior: a report from the Netherlands study of depression and anxiety. Depress Anxiety, 2014. 31(6): p. 517-23.




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

International Journal of Environmental Research and Public Health 2019; 16(9): 1-10.

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

Sleep; Circadian rhythm; Depression; Depressive disorder; Antepartum depression; Pregnancy

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.

Funding

This research received no external funding.

Acknowledgments

We would like to thank all women that participated in the study. In addition, we would like to thank Monique Roggeveen and Laura Schot for their work.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Woody, C.; Ferrari, A.; Siskind, D.; Whiteford, H.; Harris, M. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. J. Affect. Disord. 2017, 219, 86–92.
2. Grote, N.K.; Bridge, J.A.; Gavin, A.R.; Melville, J.L.; Iyengar, S.; Katon, W.J. A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction. Arch. N.a. 2010, 67, 1012–1024.
3. Jarde, A.; Morais, M.; Kingston, D.; Giallo, R.; MacQueen, G.M.; Giglia, L.; Beyene, J.; Wang, Y.; McDonald, S.D. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: a systematic review and meta-analysis. JAMA Psychiatry 2016, 73, 826–37. DOI:10.1001/jamapsychiatry.2016.0934.
4. Talge, N.M.; Neal, C.; Glover, V.; Early Stress, Translational Research and Prevention Science Network: Fetal and Neonatal Experience on Child and Adolescent Mental Health. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? J. Child Psychol. Psychiatry 2007, 48, 245–61.
5. Lancaster, C.A.; Gold, K.J.; Flynn, H.A.; Yoo, H.; Marcus, S.M.; Davis, M.M. Risk factors for depressive symptoms during pregnancy: a systematic review. Am. J. Obstet. Gynecol. 2010, 202, 5–14.
6. Räisänen, S.; Lehto, S.M.; Nielsen, H.S.; Gissler, M.; Kramer, M.R.; Heinonen, S. Risk factors for and perinatal outcomes of major depression during pregnancy: a population-based analysis during 2002–2010 in Finland. BMJ Open 2014, 4, e004883.
7. Mindell, J.A.; Jacobson, B.J. Sleep Disturbances During Pregnancy. J. Obstet. Gynecol. Neonatal Nurs. 2000, 29, 590–597.
8. Mindell, J.A.; Cook, R.A.; Nikolovski, J. Sleep patterns and sleep disturbances across pregnancy. Sleep Med. 2015, 16, 483–488.
9. Facco, F.L.; Kramer, J.; Ho, K.H.; Zee, P.C.; Grobman, W.A. Sleep Disturbances in Pregnancy. Obstet. Gynecol. 2010, 115, 77–83.
10. Kamysheva, E.; Skouteris, H.; Wertheim, E.H.; Paxton, S.J.; Milgrom, J. A prospective investigation of the relationships among sleep quality, physical symptoms, and depressive symptoms during pregnancy. J. Affect. Disord. 2010, 123, 317–320.
11. Palagini, L.; Gemignani, A.; Banti, S.; Manconi, M.; Mauri, M.; Riemann, D. Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. Sleep Med. 2014, 15, 853–859.
12. Lewis, B.A.; Gjerdingen, D.; Schuver, K.; Avery, M.; Marcus, B.H. The effect of sleep pattern changes on postpartum depressive symptoms. BMC Women's Heal. 2018, 18, 12.
13. Okun, M.L.; Kiewra, K.; Luther, J.F.; Wisniewski, S.R.; Wisner, K.L. Sleep Disturbances in Depressed and Non-Depressed Pregnant Women. Depression N.a. 2011, 28, 676–685.
14. Okun, M.L.; Luther, J.F.; Wisniewski, S.R.; Sit, D.; Prairie, B.A.; Wisner, K.L. Disturbed Sleep, a Novel Risk Factor for Preterm Birth?. J. Women's Heal. 2012, 21, 54–60.

15. Calcagni, S.C.; Bei, B.; Milgrom, J.; Trinder, J. The Relationship Between Sleep and Mood in First-Time and Experienced Mothers. Behav. Sleep Med. 2012, 10, 167–179.
16. Lee, K.A.; Gay, C.L. Sleep in late pregnancy predicts length of labor and type of delivery. Am. J. Obstet. Gynecol. 2004, 191, 2041–2046.
17. Park, E.M.; Meltzer-Brody, S.; Stickgold, R. Poor sleep maintenance and subjective sleep quality are associated with postpartum maternal depression symptom severity. Arch. Women's Heal. 2013, 16, 539–547.
18. Lee, E.K.; Douglass, A.B. Sleep in Psychiatric Disorders: Where are We Now?. Can. J. N.a. 2010, 55, 403–412.
19. Regen, W.; Nanovska, S.; Spiegelhalder, K.; Baglioni, C.; Riemann, D. Comorbid Sleep Disorders in Neuropsychiatric Disorders Across the Life Cycle. N.a. Rep. 2013, 15, 364.
20. Posmontier, B. Sleep Quality in Women with and without Postpartum Depression. J. Obstet. Gynecol. Neonatal Nurs. 2008, 37, 722–737.
21. Tsai, S.-Y.; Thomas, K.A. Sleep disturbances and depressive symptoms in healthy postpartum women: A pilot study. Nurs. Heal. 2012, 35, 314–323.
22. Goyal, D.; Gay, C.; Lee, K. Fragmented maternal sleep is more strongly correlated with depressive symptoms than infant temperament at three months postpartum. Arch. Women's Heal. 2009, 12, 229–237.
23. Huang, C.-M.; Carter, P.A.; Guo, J.-L. A Comparison of Sleep and Daytime Sleepiness in Depressed and Non-Depressed Mothers During the Early Postpartum Period. J. Nurs. 2004, 12, 287–296.
24. Dørheim, S.K.; Eberhard-Gran, M.; Bjorvatn, B.; Bondevik, G.T. Sleep and Depression in Postpartum Women: A Population-Based Study. Sleep 2009, 32, 847–855.
25. Van Ravesteyn, L.M.; Tulen, J.H.; Kamperman, A.M.; Raats, M.E.; Schneider, A. (Tom); Birnie, E.; Steegers, E.A.; Hoogendijk, W.J.; Tiemeier, H.W.; Berg, M.P.L.D. Perceived Sleep Quality Is Worse Than Objective Parameters of Sleep in Pregnant Women with a Mental Disorder. J. Clin. Sleep Med. 2014, 10, 1137–1141.
26. Bei, B.; Ericksen, J.; Trinder, J.; Milgrom, J. Subjective Perception of Sleep, but not its Objective Quality, is Associated with Immediate Postpartum Mood Disturbances in Healthy Women. Sleep 2010, 33, 531–538.
27. Van Ravesteyn, L.M.; Kamperman, A.M.; Schneider, T.A.; Raats, M.E.; Steegers, E.A.; Tiemeier, H.; Hoogendijk, W.J.; Berg, M.P.L.-V.D. Group-based multicomponent treatment to reduce depressive symptoms in women with co-morbid psychiatric and psychosocial problems during pregnancy: A randomized controlled trial. J. Affect. Disord. 2018, 226, 36–44.
28. First M.B.; G. M.; Spitzer R.L.; Williams J.B.W. User's Guide for the SCID-I. Structured Clinical Interview for DSM-IV TR Axis I Disorders (Research Version). New York Psychiatric Institute: New York, NY, USA, 2002.
29. Sedov, I.D.; Cameron, E.E.; Madigan, S.; Tomfohr-Madsen, L.M. Sleep quality during pregnancy: A meta-analysis. Sleep Med. Rev. 2018, 38, 168–176.
30. Ancoli-Israel, S.; Cole, R.; Alessi, C.; Chambers, M.; Moorcroft, W.; Pollak, C.P. The Role of Actigraphy in the Study of Sleep and Circadian Rhythms. Sleep 2003, 26, 342–392.

31. Lieverse, R.; Van Someren, E.J.; Nielen, M.M.; Uitdehaag, B.M.; Smit, J.H.; Hoogendijk, W.J. Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. Arch. Gen. Psychiatry 2011, 68, 61–70.
32. Morgenthaler, T.; Alessi, C.; Friedman, L.; Owens, J.; Kapur, V.; Boehlecke, B.; Brown, T.; Chesson, A.; Coleman, J.; Lee-Chiong, T.; et al. Practice Parameters for the Use of Actigraphy in the Assessment of Sleep and Sleep Disorders: An Update for 2007. Sleep 2007, 30, 519–529.
33. Buysse, D.J.; Reynolds, C.F. 3rd; Monk, T.H.; Berman, S.R.; Kupfer, D.J., The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989, 28, 193–213.
34. Cox, J.L.; Holden, J.M.; Sagovsky, R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br. J. Psychiatry 1987, 150, 782–6.
35. Bergink, V.; Kooistra, L.; Berg, M.P.L.-V.D.; Wijnen, H.; Bunevicius, R.; Van Baar, A.; Pop, V. Validation of the Edinburgh Depression Scale during pregnancy. J. Psychosom. 2011, 70, 385–389.
36. Cohen, J. Statistical Power Analysis for the Behavioral Sciences, 2nd ed.; Lawrence Erlbaum Associates: New Jersey, NY, USA, 1988.
37. Little, R.J.A. Modeling the Drop-Out Mechanism in Repeated-Measures Studies. J. Am. Stat. Assoc. 1995, 90, 1112–1121.
38. Friedman, E.S.; Davis, L.L.; Zisook, S.; Wisniewski, S.R.; Trivedi, M.H.; Fava, M.; Rush, A.J.; CO-MED Study Team. Baseline depression severity as a predictor of single and combination antidepressant treatment outcome: results from the CO-MED trial. Eur. Neuropsychopharmacol. 2012, 22, 183–99.
39. Lee, K.A.; Zaffke, M.E.; Mcenany, G. Parity and Sleep Patterns During and After Pregnancy. Obstet. Gynecol. 2000, 95, 14–18.
40. Picchietti, D.; Winkelman, J.W. Restless Legs Syndrome, Periodic Limb Movements in Sleep, and Depression. Sleep 2005, 28, 891–8.

Chapter 6

Prescription patterns of benzodiazepine and benzodiazepine-related drugs in the peripartum period: a population-based study

Babette Bais, Trine Munk Olsen, Veerle Bergink, Xiaoqin Liu

Submitted

Abstract

Using prescription drugs during pregnancy is challenging and approached with caution. In this study, we present population-based information on prescription patterns of benzodiazepines and benzodiazepine-related drugs in the peripartum period. A population-based study of 1,154,817 pregnancies between 1997 and 2015 in Denmark, of which 205,406 (17.8%) pregnancies in women with a psychiatric history. Prescription drugs starting with Anatomical Therapeutic Chemical codes N05BA, N05CD, and N05CF from 12 months before pregnancy to 12 months following pregnancy were identified. We used generalised estimating equations to estimate the adjusted 5-year risk difference in the proportion of women redeeming benzodiazepines from one year to five years after. Logistic regression was used to analyse the association between characteristics and discontinuation of benzodiazepines during pregnancy. 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 5-6 times higher. A significant decrease in prescriptions to women with a psychiatric history was observed, which was less profound among women with no psychiatric history. Approximately 90% of women discontinue benzodiazepines during pregnancy, with a higher percentage of women discontinuing from 1997 to 2015. The observed decrease is likely explained by changing treatment guidelines.

Keywords

Benzodiazepines; Prescription drugs; Pregnancy; Postpartum period; Population

Introduction

The use of prescription drugs during pregnancy is approached with caution by both pregnant women and their health care professionals, weighting both fetal and maternal health. Despite this caution, prescribed medication use is common during pregnancy, with estimations of 27-93% of pregnant women using prescription drugs [1], including benzodiazepines. Benzodiazepines are prescribed for the treatment of anxiety disorders and also sleep problems [2]. The effects of benzodiazepines are mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [3]. Benzodiazepines have anxiolytic, hypnotic, anticonvulsant, and muscle relaxant properties, which can relieve symptoms in the short term [3, 4]. However, benzodiazepines are highly addictive and guidelines advice against long term use [5, 6].

Studies on maternal use of benzodiazepines during pregnancy mainly focused on adverse birth outcomes. A recent study showed an increased risk of spontaneous abortion with an odds ratio (OR) of 1.85 (95% confidence interval (CI) 1.61 – 2.12) [7]. An increased risk was also found for preterm birth (OR 2.03; 95% CI 1.11 – 3.69) [8], caesarean delivery (OR 2.45; 95% CI 1.36 – 4.40), low birth weight (OR 3.41; 95% CI 1.61 – 7.26), and use of neonatal ventilatory support (OR 2.85; 95% CI 1.20 – 6.90) [9]. Children exposed to benzodiazepines in utero have a higher chance to be admitted to a neonatal intensive care unit (OR 2.02; 95% CI 1.11 – 3.66) and to have small head circumferences (OR 3.89; 95% CI 1.25 – 12.03) [10]. Most studies adjusted for underlying maternal mental illness [7, 9, 10], which are also associatied with adverse birth ouctomes [11, 12]. A meta-analysis did not find increased teratogenic risks, yielding an OR of 1.07 (95% CI 0.91 – 1.25) for cohort studies and of 1.27 (95% CI 0.69 – 2.32) for case-control studies [13].

Considering the potential risks of the use of benzodiazepines, it is important to have an overview of prescription patterns of benzodiazepines and benzodiazepine-related drugs in the peripartum period, which will be helpful in estimating the prevalence of benzodiazepine usage and to explore future research priorities. This is considered relevant, as the use of prescription medication during pregnancy has increased in the past decades [14-17]. In the present study, we aimed to present population-based information on prescription patterns of benzodiazepines and

benzodiazepine-related drugs in the peripartum period over 19 years in Denmark. We further studied whether prescription prevalence rates increased in accordance with trends observed in other prescription medications.

Materials and Methods

Study population

We conducted a population-based cohort study using Danish national registers. All individuals in Denmark have a unique personal civil registration number that enables the individual-level linkage of information across nationwide registries. All pregnancies leading to live birth(s) in Denmark between 1 January 1997 and 31 December 2015 (N=1,182,529) were identified from the Danish Medical Birth Registry [18], since prescription data was available until 2016 and prevalence was studied until 12 months after delivery. The registry contains data on the mother and child, such as parity, date of birth, birth weight, length, sex, and gestational age of the offspring. We excluded 660 pregnancies by women aged <15 or >45 years. Furthermore, 27,052 pregnancies were excluded due to missing information in gestational age or if gestational age was recorded as <22 weeks or >45 weeks. Thus, 1,154,817 pregnancies were included in the analyses.

Assessment of prescription for benzodiazepine and benzodiazepine-related drugs

Information on medication prescriptions in the peripartum period was obtained from the linkage of study subjects to the National Prescription Registry [19]. The register contains individual-level data on all prescribed drugs dispensed at all pharmacies in Denmark since 1995. Registered information includes the type of drug, strength, quantity dispensed, and dispensing dates. The international Anatomical Therapeutic Chemical (ATC) classification system was used to code all medications. From April 1st, 2004 onwards, an indication variable was also added. The prescriber, e.g., a general practitioner or a hospital physician, may select an indication code from a drop-down menu containing a list of indications, or they can include the indication as free text, in which case no code is recorded [20]. Women were considered as user of benzodiazepines or benzodiazepine-related drugs (hereinafter referred to as benzodiazepines) if they claimed any drugs starting with

ATC codes N05BA, N05CD, and N05CF from 12 months prior to the pregnancy to 12 months following the pregnancy. We defined pregnancy from the first day of the last menstrual period until delivery. We estimated the start of pregnancy by subtracting gestational age from the birth date. Since 1995, ultrasound measurements have been widely used to determine gestational age in nearly all pregnancies [21].

Assessment of psychiatric history

In this study, we also focused on women with a psychiatric history, since treatment decisions are even more complex in this group [17]. We defined previous psychiatric history as at least one in- or outpatient treatment for psychiatric disorders or redeemed one prescription for psychotropic medications (ATC codes N05 and N06) at the time of 12 months before the index pregnancy. Information on psychiatric history before pregnancy was extracted from the Danish Psychiatric Central Research Register [22]. It contains data on all inpatient contacts since 1969 and from 1995 also outpatient contacts. The International Classification of Diseases (ICD) codes, version 8 (ICD-8) was used from 1977 to 1993 and ICD-10 from 1994 and onwards. The following ICD codes were used to identify psychiatric disorders: ICD-8 codes 290–315; ICD-10 codes F00–F99.

Treatment indications of benzodiazepine prescriptions

We investigated the treatment indications of benzodiazepine prescriptions in a subset of women who gave birth to children from 2007 to 2015, due to substantial missing or unspecified indication codes during 2004–2005 in the Danish National Prescription Registry. Here, the *number of prescriptions* is counted, and overall, 27,094 prescriptions dispensed before pregnancy, 6,820 during pregnancy and 16,574 after pregnancy were included. We excluded the prescriptions with missing or unspecified indications; 6,898 (25.5%) before pregnancy, 2,064 (30.3%) during pregnancy, and 3,884 (23.4%) after pregnancy.

Ethics

Registries were linked, and personal data analyzed on Statistics Denmark, where data was made available with encrypted personal information. This ensures that no

individuals can be identified. In Denmark, The Act on Processing of Personal Data does not require ethical permission or obtained written informed consent for anonymized retrospective registry studies. The present study has been approved by the Danish Data Protection Agency.

Statistical analysis

All data management and analyses were performed using Stata 15.0 (StataCorp, College Station, TX, USA). We analyzed dispensed benzodiazepine prescriptions in women during three periods: 12 months leading to pregnancy, during pregnancy, and 12 months after pregnancy. We first examined the overall prevalence of benzodiazepine prescriptions before, during, and after pregnancy. We allowed for exposure to benzodiazepines several times during the study period. For further explanation of the calculation of period prevalence, consider the following example: woman A redeemed three prescriptions from 12 months before pregnancy to 12 months after pregnancy, one before pregnancy, one during pregnancy, and another after pregnancy. She will consequently contribute information in the calculation of period prevalence before, during, and after pregnancy.

To determine whether patterns of prescribing of benzodiazepine drugs changed over time, we used generalised estimating equations with an identity link to estimate the adjusted 5-year risk difference [23], i.e., the difference in the proportion of women redeeming benzodiazepines before, during, or after pregnancy from one year to five years after. We treated calendar year as a continuous variable (in years), and adjusted for age (<25, 25–34 or ≥35 years), primiparity (yes/no), and socioeconomic status (lowest quartile, second quartile, third quartile, or highest quartile) at the time of delivery in the models. Since the pattern of benzodiazepine prescriptions may be influenced by previous psychiatric history, all the analyses were stratified by previous psychiatric history.

We defined the following seven mutually exclusive benzodiazepine groups: (1) prescriptions before pregnancy only; (2) prescriptions during pregnancy only; (3) prescriptions after pregnancy only; (4) prescriptions both before and during pregnancy; (5) prescriptions both before and after pregnancy; (6) prescriptions both during and after pregnancy; (7) prescriptions before, during, and after pregnancy. Note, the *number of women* with benzodiazepine prescriptions was counted for

these analyses. In the analysis of the association between general characteristics and discontinuation of a benzodiazepine during pregnancy, only women receiving benzodiazepine prescriptions before pregnancy (i.e., group 1, 4, 5, and 7) were included, and binary logistic regression models were used. The following characteristics were included in the models: age at delivery, primiparity, socioeconomic status, previous psychiatric history, hospital contact for psychiatric disorders, and co-dispensing of other psychotropic medication (ATC codes N05 and N06 excluding N05BA, N05CD, and N05CF; yes or no) in the year before pregnancy, and calendar year at delivery (1997–2000, 2001–2005, 2006–2010 or 2011–2015).

Results

Of 1,154,817 pregnancies, 205,406 (17.8%) pregnancies were in women with a psychiatric history 12 months before pregnancy. Table 6.1 presents the characteristics of the study subjects. Women with a psychiatric history before pregnancy were older, were less often primiparous, and had lower socioeconomic status, compared to women with no psychiatric history. Women with a psychiatric history more often used other psychotropic medications and had more often hospital contacts for psychiatric disorders in the year before pregnancy, as expected.

The prevalence of women with benzodiazepine prescriptions was 1.9% before pregnancy, 0.6% during pregnancy, and 1.3% after pregnancy. Prevalence specifically during pregnancy was 0.5% in the first trimester, 0.3% in the second trimester, and 0.2% in the third trimester. Among 6,806 women using benzodiazepines during pregnancy, 4,446 (65.3%) women did not receive benzodiazepine prescriptions in the year preceding pregnancy (Table 6.2).

Table 6.1 – Characteristics of the study population.

Characteristics	Women with psychiatric history [a]		Women with no psychiatric history		Total (N=1,154,817)
	No prescription drug (N=930,291)	With prescription drug (N=19,120)	No prescription drug (N=186,576)	With prescription drug (N=18,830)	
Age at conception (years)					
15–24	22,084 (11.8)	1934 (10.3)	124,228 (13.4)	2930 (15.3)	151,176 (13.1)
25–34	119,776 (64.2)	11,525 (61.2)	651,921 (70.1)	12,796 (66.9)	796,018 (68.9)
35–45	44,716 (24.0)	5371 (28.5)	154,142 (16.6)	3394 (17.8)	207,623 (18.0)
Primiparous (%)	81,228 (43.5)	7872 (41.8)	420,794 (45.2)	8270 (43.3)	518,164 (44.9)
Socioeconomic status at conception					
Lowest quartile	31,246 (16.8)	4763 (25.3)	146,912 (15.8)	3500 (18.3)	186,421 (16.1)
2nd quartile	43,874 (23.5)	5102 (27.1)	181,002 (19.5)	4547 (23.8)	234,525 (20.3)
3rd quartile	44,718 (24.0)	4025 (21.4)	238,100 (25.6)	4738 (24.8)	291,581 (25.3)
Highest quartile	48,731 (26.1)	3888 (20.6)	310,342 (33.4)	5656 (29.6)	368,617 (31.9)
Unknown	18,007 (9.7)	1052 (5.6)	53,935 (5.8)	679 (3.6)	73,673 (6.4)
Other psychotropic medications in the year before pregnancy	32,984 (17.7)	7751 (41.2)	10,102 (1.1)	1872 (9.8)	52,709 (4.6)
Hospital contact for psychiatric disorders in the year before pregnancy	6120 (3.3)	2075 (11.0)	2983 (0.3)	632 (3.3)	11,810 (1.0)
Calendar year of childbirth					
1997–2000	15,446 (8.3)	3386 (18.0)	227,272 (24.4)	6397 (33.5)	252,501 (21.9)
2001–2005	40,023 (21.5)	5429 (28.8)	261,328 (28.1)	5793 (30.3)	312,573 (27.1)
2006–2010	61,612 (33.0)	5587 (29.7)	238,950 (25.7)	4244 (22.2)	310,393 (26.9)
2011–2015	69,495 (37.2)	4428 (23.5)	202,741 (21.8)	2686 (14.1)	279,350 (24.2)

[a] Women with psychiatric history was defined as at least one hospital contact for psychiatric disorders or dispensing one psychotropic prescription before our study period, i.e., 12 months prior to the index pregnancy

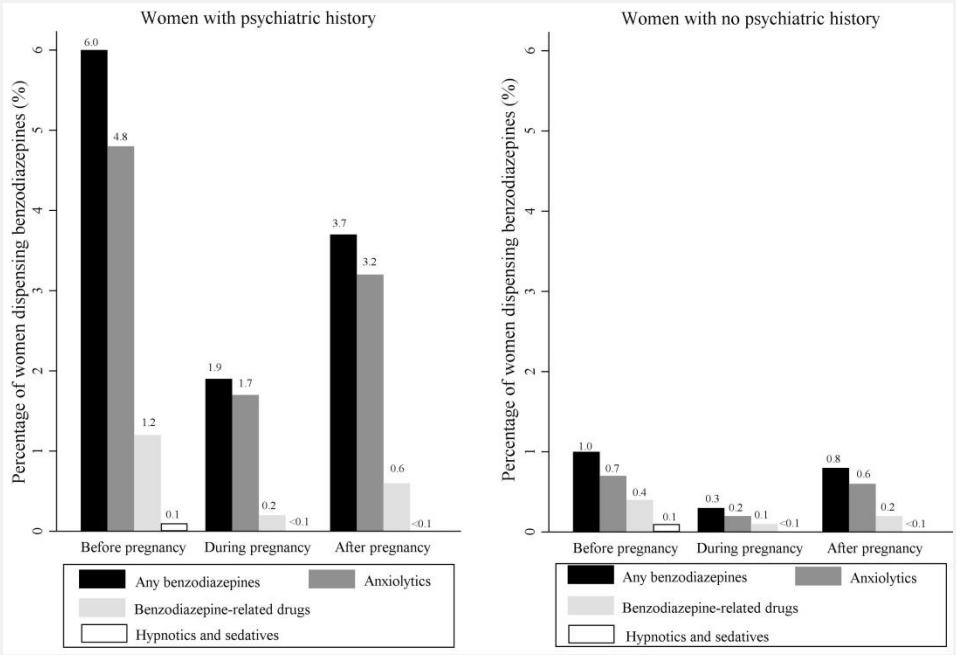


Figure 6.1 – The use of anxiolytics, hypnotics and sedatives, and benzodiazepine-related drugs in the year before, during pregnancy, or in the year following pregnancy.

Table 6.2 – Prevalence of women with benzodiazepine prescriptions before, during, and after pregnancy.

Benzodiazepine prescriptions during perinatal period	With psychiatric history (N=205,406)	With no psychiatric history (N=949,411)
Before pregnancy only	8895 (4.3)	9087 (1.0)
During pregnancy only	1578 (0.8)	2425 (0.3)
After pregnancy only	4665 (2.3)	6796 (0.7)
Both before and during pregnancy	822 (0.4)	187 (<0.1)
Both before and after pregnancy	1337 (0.7)	364 (<0.1)
Both during and after pregnancy	280 (0.1)	163 (<0.1)
Both before, during, and after pregnancy	1253 (0.6)	98 (<0.1)

Figures are numbers of women (%)

The most frequently prescribed drug was zopiclone before pregnancy, where this was oxazepam during and after pregnancy (Supplementary Table 6.1).

Benzodiazepines were most often prescribed for sleeping problems (52.3%) in the peripartum period, followed by anxiety disorder (40.6%) and panic disorder (4.7%) (Supplementary Table 6.2). In women with a psychiatric history before pregnancy, the prevalence of women with benzodiazepine prescriptions in the peripartum period was approximately five to six times higher, compared to women with no psychiatric history (Figure 6.1).

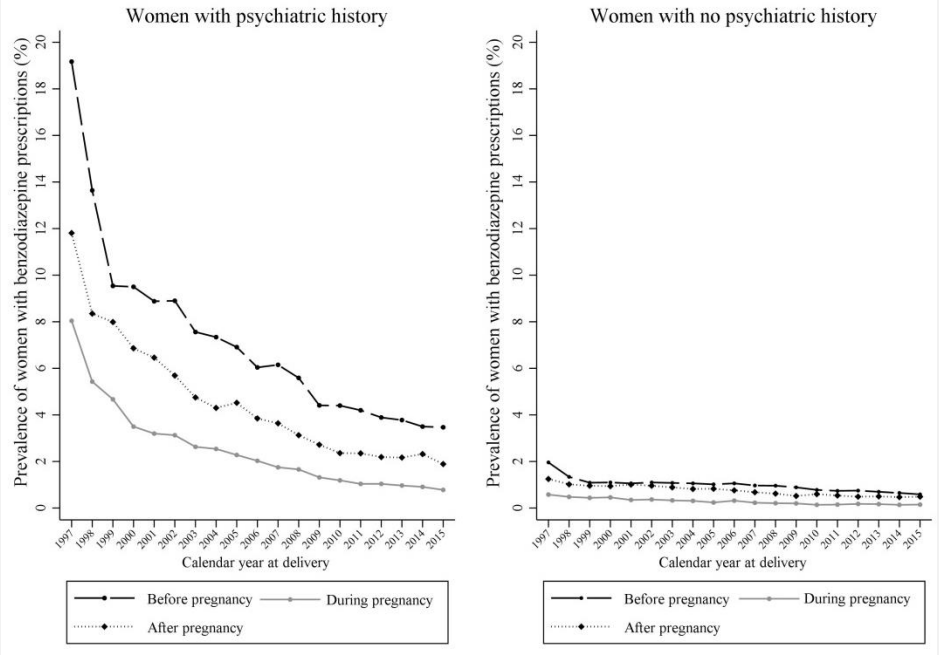


Figure 6.2 – Number of deliveries in which the women received a dispensing for benzodiazepine and benzodiazepine-related drugs in the year before, during pregnancy or in the year following pregnancy.

Figure 6.2 displays the percentage of women receiving benzodiazepine prescriptions by calendar year. From 1997 to 2015, a significant decrease in the percentage of benzodiazepines prescribed to women with a psychiatric history was observed before, during, and after pregnancy, with an adjusted 5-year risk difference of -2.3% (95% CI -2.4 – -2.2%), -0.9% (95% CI -1.0 % – -0.8%), and -

1.5% (95% CI -1.6% – -1.4%), respectively. The decrease was less profound among women with no psychiatric history, where the risk difference was -0.2 (95% CI -0.2% – -0.2%) before pregnancy, -0.1% (95% CI -0.1% – -0.1%) during pregnancy, and -0.2% (95% CI -0.2% – -0.2%) after pregnancy.

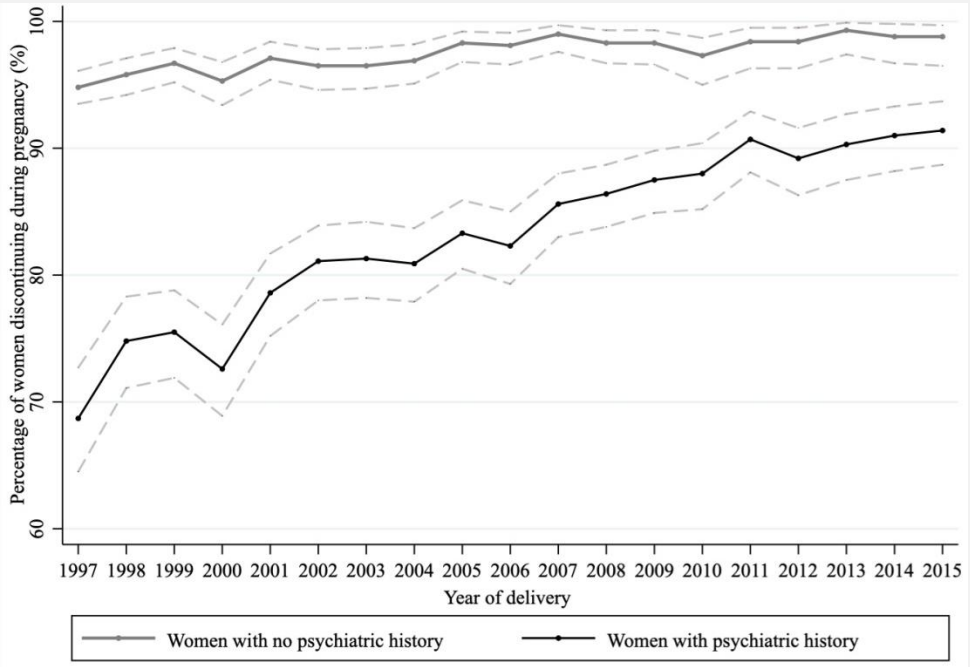


Figure 6.3 – Percentage of women with benzodiazepine dispensing in the year before pregnancy discontinuation during pregnancy in Denmark, 1997–2015.
Dotted lines represent the 95% confidence intervals.

Among 22,043 women who were prescribed benzodiazepines before pregnancy, 19,683 (89.3%) women discontinued this during pregnancy (Table 6.2). This percentage was lower in women with a psychiatric history (83.1%), compared to women with no psychiatric history (97.1%). A higher percentage of women discontinuing benzodiazepines during pregnancy was observed from 1997 to 2015. This increase was more profound among women with a psychiatric history (Figure 6.3).

Various characteristics were associated with benzodiazepine discontinuation (Figure 6.4). Primiparity, higher socioeconomic status, and a later calendar year of childbirth were associated with higher odds for discontinuation during pregnancy. A higher age, a previous psychiatric history, the use of other psychotropic medications, and hospital contacts for psychiatric disorders in the year before pregnancy were associated with lower odds for discontinuation during pregnancy.

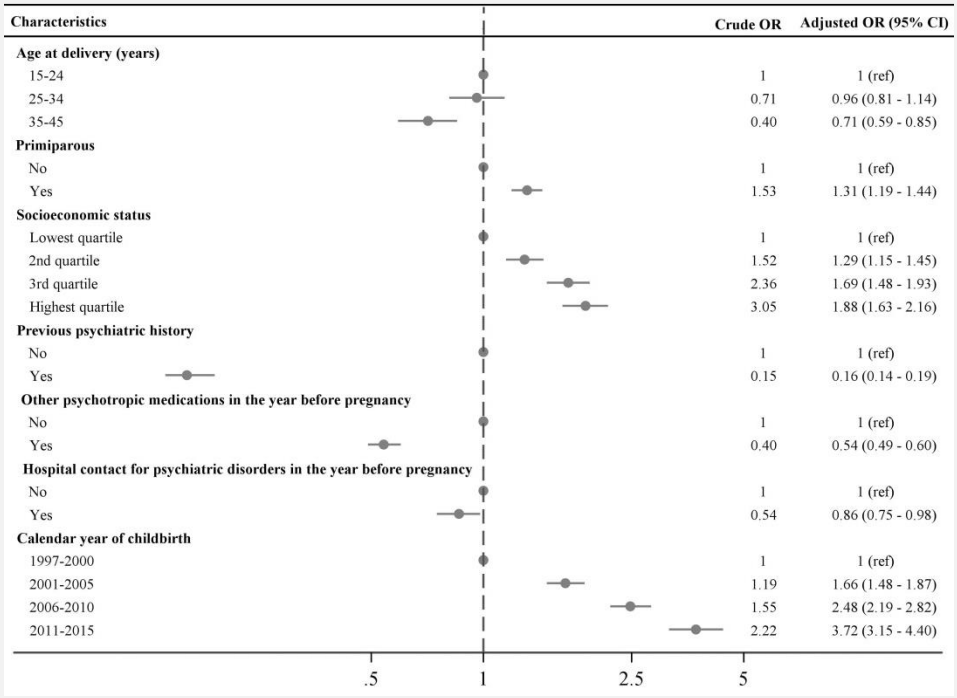


Figure 6.4 – The odds ratios of benzodiazepine discontinuation during pregnancy by characteristics (N=22,043).
All the covariates were mutually adjusted in the models.

Discussion

In this population-based study, we found that the prevalence of benzodiazepine use before pregnancy is 1.9%, during pregnancy 0.6%, and after pregnancy 1.3%.

In women with a psychiatric history before pregnancy, the prevalence was approximately five to six times higher than in women without such a history.

Prevalence comparison

Benzodiazepine use in the peripartum period has been studied worldwide, including Nordic countries. However, different time periods, definitions of medication use, study subjects, and data collection methods make it difficult to compare these findings directly. A population-based study conducted in Sweden found a prevalence of 0.16% for benzodiazepines and of 0.12% for benzodiazepine-related drugs in the first trimester [24]. A Norwegian population-based study found a prevalence of 1.8% before pregnancy, of 1.5% during pregnancy and of 0.8% after pregnancy for benzodiazepines [25]. Outside the Nordic countries, higher prevalences are observed in Europe [26-28], and particularly in North America, with prevalences ranging from 1.8% to 3.9% [29-32].

Change over time in prescriptions

Prescription drug use during pregnancy has increased over the past decades [14-17]. However, benzodiazepine use during pregnancy throughout the years has not been studied to a great extent. One population-based study in Denmark studied the prescription rates of benzodiazepine-related drugs and found an increase from 0.18% in 1997 to 0.23% in 2010 [33]. However, this study, using the same registers, studied only benzodiazepine-related drugs, which is used by only a maximum of 10% by all benzodiazepine users (Figure 6.1). The small increase of this class is obscured by the large decrease of benzodiazepines in general. A study from the United States also found an increase in benzodiazepine exposure from 0.3% in 2002 to 1.0% in 2009 [34]. This is contrary to the findings from the present study, where a decrease in the prevalence of prescriptions was observed, especially in women with a psychiatric history. Many studies have reported various adverse effects on the fetus from maternal benzodiazepine use during pregnancy [7-10], which may have increased awareness among women and their physicians, causing a decrease in prescriptions over the years. In the past, patients with anxiety disorders were often treated with benzodiazepines, but recent guidelines do not recommend benzodiazepines as first choice treatment for these indications

[35]. These patients are, therefore, treated more often with antidepressants instead of benzodiazepines [36, 37], which may contribute to the observed decrease in benzodiazepines in the past decades. We further speculate that women with a history of treatment at psychiatric facilities may get more information about the adverse effects of medication during pregnancy from health care providers than women without a psychiatric history, which would explain the differences in discontinuation between these groups.

Discontinuation of benzodiazepines during pregnancy

In the present study, approximately nine out of ten women discontinue benzodiazepines during pregnancy, a discontinuation pattern comparable to other studies [25, 33], which may be driven by not only a change in treatment guidelines [36, 37], but also by fear of potential adverse effects for the fetus [38, 39]. The percentage of women discontinuing during pregnancy increased in the past years, especially among women with a psychiatric history. High discontinuation rates during pregnancy are not shown by all studies [30-32]. These differences in prescription patterns may reflect differences in the prevalence and/or severity of mental health problems [40], but could also be due to differences in national guidelines, prescribing behavior of physicians, beliefs about medication use in the population, and available medical facilities.

Strengths and limitations

Our data were obtained from national registers, covering the entire Danish population. We studied over a million pregnancies and we are, therefore, to our knowledge, one of the largest studies studying benzodiazepine prescription patterns. However, there are some inbuilt limitations to describe use of medications using register-based data. First of all, we studied prescriptions for medication and not actual use. Non-compliance may overestimate our results, however contrarily, underestimation of the results may also have occurred, since women may sporadically use medication of family members or friends. Secondly, prescriptions are only captured from community pharmacies and not during inpatient stays, which could have underestimated our findings. However, if a woman was admitted, she would most likely be prescribed medication afterward. In this case, she would

have been captured by using the prescription register. Further, we used the date of dispensing to determine the date of use. However, it is possible that women used the medication in a different trimester or peripartum phase from when the medication was dispensed. Finally, we only included pregnancies ending in live births. A recent study showed an association between benzodiazepine exposure and risk of spontaneous abortion during early pregnancy [7]. Therefore, only including live births may have consequences for the generalizability of our findings.

Acknowledgements

This work was supported by a travel grant from Aarhus University to BB.

Funding

BB was supported by a travel grant of Aarhus University. TMO is supported by iPSYCH, the Lundbeck Foundation Initiative for Integrative Psychiatric Research (R155-2014-1724) and Fabrikant Vilhelm Pedersen og Hustrus Mindelegat. XL is supported by the Danish Council for Independent Research (DFF-5053-00156B). VB is funded by NWO and the Blavatnik Womens Health institute.

References

1. Daw, J.R., et al., Prescription drug use during pregnancy in developed countries: a systematic review. Pharmacoepidemiol Drug Saf, 2011. 20(9): p. 895-902.
2. Brunton, L.L., B.A. Chabner, and B.C. Knollmann, Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th edition ed. 2011, New York: McGraw-Hill Medicat.
3. D'Hulst, C., J.R. Atack, and R.F. Kooy, The complexity of the GABAA receptor shapes unique pharmacological profiles. Drug Discov Today, 2009. 14(17-18): p. 866-75.
4. Donoghue, J. and M. Lader, Usage of benzodiazepines: A review. Int J Psychiatry Clin Pract, 2010. 14(2): p. 78-87.
5. Nelson, J. and G. Chouinard, Guidelines for the clinical use of benzodiazepines: pharmacokinetics, dependency, rebound and withdrawal. Canadian Society for Clinical Pharmacology. Can J Clin Pharmacol, 1999. 6(2): p. 69-83.
6. Ashton, H., Guidelines for the rational use of benzodiazepines. When and what to use. Drugs, 1994. 48(1): p. 25-40.
7. Sheehy, O., J.P. Zhao, and A. Berard, Association Between Incident Exposure to Benzodiazepines in Early Pregnancy and Risk of Spontaneous Abortion. JAMA Psychiatry, 2019.
8. Ogawa, Y., N. Takeshima, and T.A. Furukawa, Maternal exposure to benzodiazepine and risk of preterm birth and low birth weight: A case-control study using a claims database in Japan. Asia Pac Psychiatry, 2018. 10(3): p. e12309.
9. Yonkers, K.A., et al., Association of Panic Disorder, Generalized Anxiety Disorder, and Benzodiazepine Treatment During Pregnancy With Risk of Adverse Birth Outcomes. JAMA Psychiatry, 2017. 74(11): p. 1145-1152.
10. Freeman, M.P., et al., Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: Results from a prospective registry of women with psychiatric disorders. Gen Hosp Psychiatry, 2018. 53: p. 73-79.
11. Grote, N.K., et al., A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry, 2010. 67(10): p. 1012-24.
12. Jarde, A., et al., Neonatal outcomes in women with untreated antenatal depression compared with women without depression: a systematic review and meta-analysis. JAMA Psychiatry, 2016: p. DOI:10.1001/jamapsychiatry.2016.0934.
13. Enato, E., M. Moretti, and G. Koren, The fetal safety of benzodiazepines: an updated meta-analysis. J Obstet Gynaecol Can, 2011. 33(1): p. 46-48.
14. Bjorn, A.M., et al., Use of prescribed drugs among primiparous women: an 11-year population-based study in Denmark. Clin Epidemiol, 2011. 3: p. 149-56.
15. Mitchell, A.A., et al., Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol, 2011. 205(1): p. 51 e1-8.

16. Smolina, K., et al., Trends and Determinants of Prescription Drug Use during Pregnancy and Postpartum in British Columbia, 2002-2011: A Population-Based Cohort Study. PLoS One, 2015. 10(5): p. e0128312.
17. Ingstrup, K.G., et al., Prescription drug use in pregnancy and variations according to prior psychiatric history. Pharmacoepidemiol Drug Saf, 2018. 27(1): p. 105-113.
18. Bliddal, M., et al., The Danish Medical Birth Register. Eur J Epidemiol, 2018. 33(1): p. 27-36.
19. Pottegard, A., et al., Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol, 2017. 46(3): p. 798-798f.
20. Denmark Statistics. Håndbog til data i Lægemiddelstatistikregisteret [Handbook for data in the Product Statistics Register]. 2013 [cited 2019 February 26]; Available from: https://docplayer.dk/2089532-Haandbog-til-data-i-laegemiddelstatistikregisteret-senest-opdateret-februar-2013.html.
21. Jorgensen, F.S., Epidemiological studies of obstetric ultrasound examinations in Denmark 1989-1990 versus 1994-1995. Acta Obstet Gynecol Scand, 1999. 78(4): p. 305-9.
22. Mors, O., G.P. Perto, and P.B. Mortensen, The Danish Psychiatric Central Research Register. Scand J Public Health, 2011. 39(7 Suppl): p. 54-7.
23. Hanley, J.A., et al., Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol, 2003. 157(4): p. 364-75.
24. Reis, M. and B. Kallen, Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects. A register study. BMJ Open, 2013. 3(2).
25. Riska, B.S., et al., Dispensing of benzodiazepines and benzodiazepine-related drugs to pregnant women: a population-based cohort study. Eur J Clin Pharmacol, 2014. 70(11): p. 1367-74.
26. Radojcic, M.R., et al., Prenatal exposure to anxiolytic and hypnotic medication in relation to behavioral problems in childhood: A population-based cohort study. Neurotoxicol Teratol, 2017. 61: p. 58-65.
27. Ban, L., et al., Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. PLoS One, 2012. 7(8): p. e43462.
28. Hurault-Delarue, C., et al., Psychomotor developmental effects of prenatal exposure to psychotropic drugs: a study in EFEMERIS database. Fundam Clin Pharmacol, 2016. 30(5): p. 476-482.
29. Bergman, U., et al., Effects of exposure to benzodiazepine during fetal life. Lancet, 1992. 340(8821): p. 694-6.
30. Daw, J.R., et al., Prescription drug use in pregnancy: a retrospective, population-based study in British Columbia, Canada (2001-2006). Clin Ther, 2012. 34(1): p. 239-249 e2.
31. Hanley, G.E. and B. Mintzes, Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. BMC Pregnancy Childbirth, 2014. 14: p. 242.

32. Palmsten, K., et al., The Most Commonly Dispensed Prescription Medications Among Pregnant Women Enrolled in the U.S. Medicaid Program. Obstet Gynecol, 2015. 126(3): p. 465-73.
33. Askaa, B., et al., Maternal Characteristics of Women Exposed to Hypnotic Benzodiazepine Receptor Agonist during Pregnancy. Obstet Gynecol Int, 2014. 2014: p. 945621.
34. Martin, C.E., et al., Trends in Drug-exposed Deliveries From 2002 to 2009. Addictive Disorders & Their Treatment, 2015. 14(2): p. 61-69.
35. Bandelow, B., et al., The diagnosis of and treatment recommendations for anxiety disorders. Dtsch Arztebl Int, 2014. 111(27-28): p. 473-80.
36. Offidani, E., et al., Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. Psychother Psychosom, 2013. 82(6): p. 355-62.
37. Berney, P., et al., A major change of prescribing pattern in absence of adequate evidence: benzodiazepines versus newer antidepressants in anxiety disorders. Psychopharmacol Bull, 2008. 41(3): p. 39-47.
38. Einarson, A., P. Selby, and G. Koren, Abrupt discontinuation of psychotropic drugs during pregnancy: fear of teratogenic risk and impact of counselling. J Psychiatry Neurosci, 2001. 26(1): p. 44-8.
39. Arch, J.J., Cognitive behavioral therapy and pharmacotherapy for anxiety: treatment preferences and credibility among pregnant and non-pregnant women. Behav Res Ther, 2014. 52: p. 53-60.
40. Steel, Z., et al., The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. Int J Epidemiol, 2014. 43(2): p. 476-93.

Supplementary Material

Supplementary Table 6.1. – The five most frequently prescribed benzodiazepines and benzodiazepine-related drugs before, during, and after pregnancy.

Order	12 months before pregnancy (%)	Pregnancy (%)	12 months following pregnancy (%)
1	Zopiclone (19.4%)	Oxazepam (18.7%)	Oxazepam (20.5%)
2	Oxazepam (19.3%)	Alprazolam (17.7%)	Zopiclone (18.6%)
3	Alprazolam (15.7%)	Zopiclone (16.7%)	Alprazolam (16.2%)
4	Zolpidem (15.1%)	Diazepam (15.1%)	Zolpidem (14.2%)
5	Diazepam (14.4%)	Zolpidem (12.3%)	Diazepam (13.9%)

Supplementary Table 6.2 – Indications for benzodiazepine treatment before, during or after pregnancy in Denmark, 2007–2015.

Treatment indication	12 months before pregnancy (%)	Pregnancy (%)	12 months following pregnancy (%)	Peripartum period (%)*
Sleeping problems	11,149 (55.2)	2203 (46.3)	6323 (49.8)	19,675 (52.3)
Anxiety disorder	7748 (38.4)	2145 (45.1)	5398 (42.5)	15,291 (40.6)
Panic disorder	920 (4.6)	201 (4.2)	664 (5.2)	1,785 (4.7)
Epileptic seizures	241 (1.2)	169 (3.6)	254 (2.0)	664 (1.8)
Other disorders/symptoms	138 (0.7)	38 (0.8)	51 (0.4)	227 (0.6)
Total	20,196	4,756	12,690	37,642

Figures are numbers of prescriptions (%); *Peripartum period includes 12 months before pregnancy, during pregnancy and 12 months following pregnancy

Chapter 7

Prevalence of benzodiazepines and benzodiazepine-related drugs exposure before, during and after pregnancy: a systematic review and meta-analysis

Babette Bais, Nina M. Molenaar, Hilmar H. Bijma, Witte J.G. Hoogendijk, Cornelis L. Mulder, Annemarie I. Luik, Mijke P. Lambregtse-van den Berg, Astrid M. Kamperman

Submitted

Abstract

Background: Maternal use of benzodiazepines during pregnancy is common and has increased over the last decades, even despite its potential harmful effects on both the mother and the (unborn) child. In this systematic review and meta-analysis, we studied the literature to estimate the worldwide use of benzodiazepines before, during and after pregnancy.

Methods: We systematically searched Embase, Medline Ovid, Web of Science and Cochrane Central up until July 2019 for studies reporting on benzodiazepine use before, during and after pregnancy. Random effects meta-analysis was conducted to calculate pooled prevalence estimates, as well as stratified according to substantive variables.

Results: We identified 32 studies reporting on 28 countries, together reporting on 7,343,571 pregnancies. The worldwide prevalence of benzodiazepine use/prescriptions during pregnancy was 1.9% (95% CI 1.6%-2.2%; I^2 97.48%). Highest prevalence was found in the third trimester (3.1%; 95% CI 1.8%-4.5%; I^2 99.83%). Lorazepam was the most frequently used/prescribed benzodiazepine (1.5%; 95% CI 0.5%-2.5%; I^2 99.87%). Highest prevalence was found in Eastern Europe (14.0%; 95% CI 12.1%-15.9%; I^2 0.00%).

Conclusions: Despite substantial heterogeneity, our meta-analysis confirmed that benzodiazepine use before, during and after pregnancy is prevalent worldwide. The relatively common use of benzodiazepines with possible risks for both mother and (unborn) child is worrying and calls for prescription guidelines for women in the preconception period. Given the substantial proportion of children exposed to benzodiazepines in utero, future research should continue to study the short- and long-term safety of maternal benzodiazepine use during pregnancy and to explore non-pharmacological alternative treatments.

Keywords

Benzodiazepines; Prescription drugs; Pregnancy; Postpartum period; Meta-analysis

Introduction

Maternal use of prescription drugs during pregnancy is approached with caution by both pregnant women and their health care professionals, considering the potential harmful fetal effects during pregnancy on one hand, while considering maternal health on the other hand. Nonetheless, prescribed medication use is common during pregnancy, with estimations of 27-93% of pregnant women filling at least one prescription drug during pregnancy (e.g. anti-infectives, antihypertensive agents and psychotropic drugs), with a wide range between countries [1]. In addition, the use of these medications during pregnancy has increased in the past decades [2-4], including the use of benzodiazepines [5] and benzodiazepine-related drugs [6].

Benzodiazepines are generally prescribed for the treatment of sleep problems and anxiety disorders [7, 8]. Benzodiazepines have anxiolytic, hypnotic, muscle relaxant and anticonvulsant properties and may relieve symptoms in the short-term [8-10]. However, benzodiazepines are highly addictive and guidelines advise against long-term use [11, 12], which is associated with physiological and psychological dependence and withdrawal [8]. When used during pregnancy, benzodiazepines pass readily through the placenta, with a greater placental transfer in late pregnancy, compared to early pregnancy [13]. Associations with a range of adverse birth outcomes have been observed, such as higher risk of spontaneous abortion (odds ratio (OR) 2.39, 95% confidence interval (CI) 2.10-2.73) [14] and preterm birth (OR 2.03, 95% CI 1.11-3.69) [15]. Moreover, maternal use of benzodiazepines in the third trimester is associated with floppy infant syndrome, including symptoms of hypothermia, lethargy and respiratory problems [16], which is also seen in the association between maternal benzodiazepine use and the need for neonatal ventilatory support (OR 1.81, 95% CI 1.39-2.37) [17] and neonatal intensive care unit admissions (OR 2.02, 95% CI 1.11-3.66) [18]. On top of that, withdrawal symptoms may persist for several months in the neonate [16]. However, a meta-analysis in one million pregnancies did not find increased teratogenic risks, such as cardiovascular malformations and oral cleft, yielding an OR of 1.07 (95% CI 0.91-1.25) for cohort studies and of 1.27 (95% CI 0.69-2.32) for case-control studies [19]. Unfortunately, in studies regarding the effects of benzodiazepine use during pregnancy on fetal development and birth outcomes, information on whether use is intermittent or

chronic is often lacking. These studies on maternal benzodiazepine use during pregnancy remain therefore inconclusive, especially the long-term effects are not entirely clear at this point [20].

Unfortunately, to date, clear data on the use of benzodiazepines related to pregnancy remains unknown. In light of the considerable increase of prescribed medication during pregnancy in general, and with the potential harmful (fetal) effects of benzodiazepines in particular, we assessed worldwide benzodiazepine use during the peripartum period. This could help to estimate benzodiazepine exposure and to prioritize and guide future investigations.

This systematic review and meta-analysis aims at providing data on the prevalence of benzodiazepines and benzodiazepine-related drugs in the peripartum period. We studied the use of these prescription drugs before, during and after pregnancy, in the different trimesters, in various countries and we examined prevalence rates over time.

Methods

This meta-analysis was registered in PROSPERO under number CRD42018117197.

Literature Search

A medical information specialist conducted the systematic electronic literature search on August 13th 2018. The search was conducted in Embase, Medline Ovid, Web of Science and Cochrane Central from inception onwards, using search terms describing the types of benzodiazepines (e.g. benzodiazepines, oxazepam), the target population (e.g. maternal, pregnancy) and the type of study (e.g. epidemiology, prevalence). A complete overview of the different search terms is shown in the Supplementary Material. The search was updated by a medical information specialist on July 2nd 2019.

Study criteria

PRISMA guidelines were followed for the reporting of the selection of the studies [21]. Studies were eligible for inclusion if they were peer-reviewed and written in

English. We included observational studies that described any population of women using benzodiazepines in the peripartum period, which we defined as: 12 months before pregnancy, during pregnancy and 12 months following pregnancy. We included studies that reported on use during pregnancy in general, in a specific trimester or at certain time points (e.g. first antenatal visit). We included benzodiazepines (Anatomical Therapeutic Chemical (ATC) codes N05BA and N05CD) and benzodiazepine-related drugs (ATC codes N05CF). Observational studies reporting a prevalence rate including the cohort size or reporting a numerator and denominator were included. Studies reporting on benzodiazepine use without specifying the specific peripartum phase (before, during or after pregnancy) were excluded. We excluded conference abstracts, case-control studies, case reports, case series and reviews. Studies providing data in all countries were eligible for inclusion. No restrictions were set for year of publication.

Study selection and data collection

Duplicates were screened and removed with the citation manager EndNote. Two reviewers (BB, NM) independently screened the titles and abstracts and assessed the full text of the potential eligible studies. Mismatches between reviewers' selection were resolved by discussion until consensus was reached. When multiple papers reported on the same cohort, we included the publication with the highest level of detail (e.g. a study reporting on the prevalence before, during and after pregnancy was chosen over a study from the same cohort reporting on pregnancy only).

Two reviewers (BB, NM) extracted data using a data extraction form. Prevalence rate was extracted as outcome. As numerator, we used the number of pregnancies or the number of women using benzodiazepines or benzodiazepine-related drugs in a specific peripartum phase. As denominator, we used the total number of pregnancies or total number of women of the matching peripartum phase. Additionally, we extracted information regarding study period, type of study (retrospective or prospective), methods of recruitment of participants, geographic location, additional in- and exclusion criteria and definition of benzodiazepine use (body sample, self-report and/or prescription records). We extracted whether cohorts included live births only and whether multiple pregnancies were included.

Quality assessment

The reviewers assessed the quality of the studies using the Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence data [22, 23]. Potential bias was assessed with regard to the following design elements: sample frame, sampling method, sample size, detailed description of subjects and setting, measurement method, adequate response rate and sufficient coverage.

We considered a sample frame appropriate when the sample was a valid representation of the population of that country, such as information from national registers. A sampling method was considered appropriate when in- and exclusive criteria were not restrictive, for example not excluding women with a history of a mental disorder. Given the expected prevalence rate of overall benzodiazepine use, we considered sample sizes larger than 1,000 women adequate. We considered all methods for outcome measurement valid (body samples such as urine and hair, (redemption of) prescriptions and self-reported use). Self-reported use was not considered as a standardized measurement method, all other methods (prescriptions and body samples, such as urine and hair) were regarded as standardized.

Statistical analysis

Data was analyzed using STATA (version 15, STATA Corporation, College Station, TX, USA) using *metaprop* procedures, which is able to perform meta-analyses of binomial data [24]. We used random effects estimation and a 95% CI to calculate an overall prevalence. Subgroup differences were tested using the random effects model as well. Random effects was chosen over fixed effects as substantial heterogeneity was expected [22]. We reported Cochrane's Q, I^2-statistics and significance levels. We conducted a meta-analysis when it was possible to pool data from two or more papers.

In our primary analysis, we studied the prevalence rates of benzodiazepines during pregnancy. Secondly, we studied the prevalence rates of benzodiazepines before and after pregnancy and benzodiazepine-related drugs before, during and after pregnancy. Next, to study benzodiazepine use during pregnancy into more detail, we studied the prevalence rates of benzodiazepines per trimester. We also studied prevalence rates of various specific benzodiazepines and benzodiazepine-related

drugs during pregnancy. Then, we conducted our primary meta-analysis stratified by region, as important differences were expected. We identified 8 different regions: Northwestern Europe (Denmark, Finland, France, Germany, Iceland, Ireland, The Netherlands, Norway, Sweden, United Kingdom), Southern Europe (Italy, Malta, Monaco, Spain), Eastern Europe (Croatia, Czechoslovakia, Yugoslavia), North America (Canada, United States), Central and South America (Brazil, Costa Rica, Panama), Asia (India, Japan, Sri Lanka, Taiwan) and Africa (Ghana, Togo, Zimbabwe).

Due to limited information on prevalence rates per calendar year, we qualitatively reviewed the impact of time on prevalence rates first. In addition, the time trend was analyzed using random effects meta-regression analysis. For this analysis, we included articles for which the study period was made explicit. Regression coefficients and 95% CI are reported.

Sensitivity analyses

We stratified our primary analysis for substantive and methodological variables, the latter including quality criteria. For the prevalence by definition of medication use, we assessed self-report only, self-report + medical records versus prescription/dispensing, since only one study reported on self report + hair sample. We did not stratify for prevalence by live births only, since all studies included in the primary meta-analysis included all births. We used both random and fixed effect calculation for our primary analyses to evaluate the impact of the estimation method for the use of benzodiazepines during pregnancy.

Small study effects

Funnel plots were used to visually assess the presence of small study effects, i.e. the tendency for the smaller studies in a meta-analysis to show larger outcomes. A funnel plot depicts the prevalence estimates against their standard error. In the bottom-right half, small studies with large prevalence estimates are shown. Studies in the bottom-left half are often omitted, since small studies reporting small non-significant effects are less likely to be published [25]. The presence of a small study effect was assessed formally by Egger's regression-based test [26]. Small study

effects are explored per pregnancy phase among studies reporting on benzodiazepine use.

Results

Selection of studies

The literature search produced 5,056 papers, 3,380 after de-duplication. Based on title and abstract, 3,202 articles were excluded, 178 full-text articles were thus assessed for eligibility. After this assessment, 32 articles were included in this meta-analysis for further analyses. All studies reported on one database from one country, except for the study by Marchetti *et al.*, who reported on 22 cohorts from 22 countries [27]. Figure 7.1 shows a flow-chart of the selection process. Interrater reliability was considered moderate to good (raw interrater agreement: 96%; kappa: 0.57, 95% CI 0.50-0.63) [28].

Study characteristics

Prevalence data for benzodiazepine and benzodiazepine-related drug use in the peripartum period was analyzed for a total sample of 7,343,571 pregnancies from 28 countries. Sample size per cohort ranged from 50 to 1,886,825 pregnancies. Six studies focused on the year before pregnancy, all 32 studies focused on the pregnancy period itself (either on the complete pregnancy or on one or more trimesters) and four studies focused on the first year after pregnancy. Most studies included information on benzodiazepines in general (N=23), while some studies focused on at least one specific benzodiazepine-related drug (N=7). Nine studies focused on one or more specific benzodiazepines. Prevalence rates are reported across a 37-year period (from 1980 to 2017). Seventeen studies (53.1%) were retrospective cohorts. Detailed characteristics are provided in Supplementary Table 7.1 and 7.2.

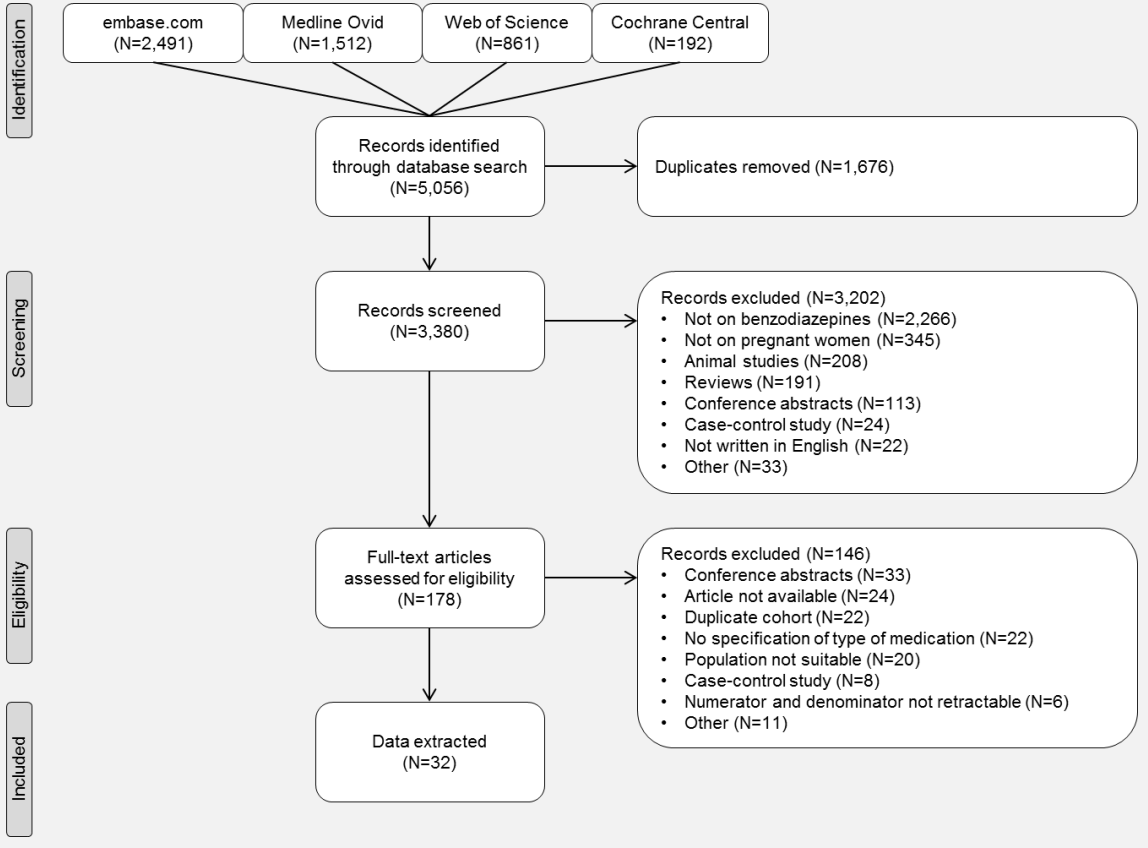


Figure 7.1 – Flow -chart of the article selection process in a meta-analysis of international use of benzodiazepine and benzodiazepine-related drugs in the peripartum period.

Prevalence of medication in the peripartum period

Table 7.1 shows the pooled prevalence estimates for benzodiazepines before, during and after pregnancy and in the specific trimesters. One study reported on benzodiazepine-related drugs before, during and after pregnancy, with a prevalence of respectively 0.4%, 0.3% and 0.2% [6]. One study reported on the prevalence of benzodiazepines and benzodiazepine-related drugs combined before and during pregnancy, with a prevalence of respectively 3.6% and 3.9% [29].

Benzodiazepine use increased from preconception to pregnancy (from 0.9% to 1.9%), with a subsequent decrease to postpartum (0.5%), which was statistically significant (Q-value=392.63; df=2; p<.01). Specifically, benzodiazepine prevalence was 0.5% in the first trimester, 0.3% in the second trimester and 3.1% in the third trimester, which differed statistically significant (Q-value=21.78; df=2; p<.01). Substantial heterogeneity was found between the different studies (>40% I^2).

Prevalence rates of benzodiazepines before, during and after pregnancy per individual cohort are shown in Supplementary Figures 7.1 to 7.3 in the online supplement.

Prevalence of specific benzodiazepines during pregnancy

Four studies reported specifically on the use of diazepam and lorazepam, three studies on temazepam and alprazolam, and two studies on oxazepam, zolpidem and clonazepam during pregnancy. All other benzodiazepines or benzodiazepine-related drugs were studied by one study only. Table 7.1 shows the pooled prevalence estimates of these specific benzodiazepines and benzodiazepine-related drugs. Considerable heterogeneity was found among the studies (>40% I^2). The highest prevalence rate was found for lorazepam (1.5%), followed by zolpidem (1.0%). The lowest prevalence rate was found for temazepam and alprazolam (both 0.1%). The difference between the specific benzodiazepines and benzodiazepine-related drugs was tested significant (Q-value=1278.42; df=6; p<.01).

Table 7.1 – Global random effects prevalence estimates of benzodiazepines in the peripartum period.

	Prevalence of benzodiazepines in the peripartum period							
	N of cohorts	N of pregnancies	N of countries	Random effects % prevalence	Forest plot of pooled random effect prevalence	95% CI	I^2 statistic (%)	Q statistic (df; p-value)
Benzodiazepines								
Year before pregnancy	2	357,317	2	0.9%		0.9%-0.9%	0.00	
During pregnancy	27	522,914	21	1.9%		1.6%-2.2%	97.48	
Year after pregnancy	2	346,218	2	0.5%		0.5%-0.6%	0.00	392.63 (2; <.01)
Benzodiazepines								
First trimester	9	2,163,124	6	0.5%		0.3%-0.7%	99.55	
Second trimester	2	357,317	2	0.3%		0.3%-0.3%	0.00	
Third trimester	5	448,680	3	3.1%		1.8%-4.5%	99.83	21.78 (2; <.01)
Pregnancy								
Lorazepam	4	418,932	3	1.5%		0.5%-2.5%	99.87	
Zolpidem	2	225,016	2	1.0%		0.9%-1.0%	0.00	
Oxazepam	2	169,322	2	0.7%		0.7%-0.7%	0.00	
Diazepam	4	172,742	4	0.3%		0.0%-0.6%	95.45	
Clonazepam	2	165,875	2	0.3%		0.3%-0.3%	0.00	
Temazepam	3	1,276,079	3	0.1%		0.1%-0.2%	96.72	
Alprazolam	3	172,115	3	0.1%	0% 3% 6%	0.0%-0.1%	73.14	1278.42 (6; <.01)

Pooled prevalence rates calculated using random effect estimation. Analyses of trimesters and of specific benzodiazepines are not sub analyses of benzodiazepines during pregnancy.

Table 7.2 – Global random effects prevalence estimates of benzodiazepines during pregnancy in different regions.

	Prevalence of benzodiazepines during pregnancy							
	N of cohorts	N of pregnancies	N of countries	Random effects % prevalence	Forest plot of pooled random effect prevalence	95% CI	I^2 statistic (%)	Q statistic (df; p-value)
Benzodiazepines								
Eastern Europe	2	1,279	2	14.0%		12.1%-15.9%	0.00	
Southern Europe	4	6,853	3	3.8%		1.4%-6.1%	93.07	
Central & South America	3	1,274	2	2.3%		0.9%-3.7%	55.10	
North America	3	118,746	2	1.8%		0.7%-2.9%	99.93	
Africa	2	840	2	1.5%		0.7%-2.3%	0.00	
Northwestern Europe	9	353,698	7	1.2%		0.8%-1.5%	61.73	
Asia	4	44,660	3	0.9%	0% 5% 15%	0.4%-1.5%	83.88	187.18 (6; <.01)

Pooled prevalence rates calculated using random effect estimation.

Table 7.3 – Global random effects prevalence estimates of benzodiazepines during pregnancy, stratified by substantive and methodological variables.

	Prevalence of benzodiazepines during pregnancy							
	N of cohorts	N of pregnancies	N of countries	Random effects % prevalence	Forest plot of pooled random effect prevalence	95% CI	I^2 statistic (%)	Q statistic (df; p-value)
Methodological factors								
Prevalence by research design								
Prospective	23	30,568	21	2.7%		2.1%-3.3%	94.85	
Retrospective	4	492,346	4	1.2%		0.6%-1.8%	99.51	11.32 (1; .01)
Prevalence by definition medication use								
Self-report + hair sample	1	209	1	11%		-	-	
Self-report	19	14,448	19	3.1%		2.2%-4.1%	94.85	
Self-report + records	4	16,157	4	1.5%		0.7%-2.3%	94.49	
Prescription/dispensing	3	492,100	3	1.2%		0.5%-1.8%	99.67	11.57 (2; <.01)
Prevalence by singletons only								
No	24	128,275	22	2.7%		2.1%-3.2%	95.37	
Yes	3	394,639	3	0.7%		0.5%-1.0%	95.91	37.65 (1; <.01)
Risk of bias criteria								
Standardized measurement method								
High risk of bias	20	14,694	19	3.1%		2.1%-4.0%	95.64	
Low risk of bias	7	508,220	6	1.4%		1.0%-1.9%	99.12	9.81 (1; .<.01)
Detailed subjects and setting description								
High risk of bias	20	118,787	20	2.8%		2.1%-3.5%	95.64	
Low risk of bias	7	404,127	7	1.1%		0.8%-1.4%	94.92	19.58 (1; .<.01)
Adequate sample size								
High risk of bias	18	7,142	17	4.0%		2.6%-5.4%	94.98	
Low risk of bias	9	516,102	8	1.4%		1.0%-1.8%	98.84	11.76 (1;<.01)
Sampling method appropriate								
Low risk of bias	23	161,300	20	2.5%		2.0%-3.0%	97.51	
Unclear	4	361,614	4	1.2%		0.8%-1.6%	94.41	13.45 (1; .01)
Appropriate sample frame								
High risk of bias	25	170,333	20	2.4%		1.9%-2.9%	97.38	
Low risk of bias	2	352,581	2	0.9%		0.9%-0.9%	0.00	35.59 (1; <.01)
					0% 6% 12%			

Pooled prevalence rates calculated using random effect estimation.

Variation in prevalence estimates per region

Table 7.2 shows the pooled prevalence estimates of benzodiazepines during pregnancy per region. Analyses revealed substantial heterogeneity between the studies (>40% I^2). The highest prevalence estimate was found in Eastern Europe (14.0%), followed by Southern Europe (3.8%) and Central and Southern America (2.3%). Lowest prevalence estimates were found in Asia (0.9%) and Northwestern Europe (1.2%). Prevalence between regions differed significantly (Q-value=187.18; df=6; p<.01).

Prevalence rates over time

No cohorts reported prevalence rates (including numerator and denominator) over a series of subsequent calendar years. Two studies mentioned prevalence rates (in percentages, therefore unsuitable for meta-regression) in the first and last year of their cohort. Askaa *et al*. mentioned an increase in the prevalence of benzodiazepine-like drugs from 0.18% in 1997 to 0.23% in 2010 [6]. Martin *et al*. reported an increase in the prevalence of benzodiazepines from 0.3% in 2002 to 1.0% in 2009, with the highest prevalence in 2005 (1.2%) [5]. Using meta-regression, we tried to quantify the development of the prevalence rates over time. Analyses were conducted including a subset of studies (N=19) reporting on benzodiazepine use during pregnancy over a limited time frame (<5 years) [27, 29-46]. Of four studies, the studied time frame was unknown or not clear, these were therefore excluded of these analyses [47-50]. Meta-regression did not show a significant increase of use over time during pregnancy (β=0.001; 95% CI -0.003-0.01; p=.62).

Risk of bias

An overview of the quality assessment can be found in Supplementary Figures 7.4 and 7.5. Overall, most included studies had a low risk of bias on at least five out of seven quality criteria (87.5%). Four studies had a high risk of bias on three out of seven quality criteria [27, 35, 39, 43], three studies had a high risk on two quality criteria and an unclear risk on one quality criterion [41, 47, 48]. Most studies used a standardized measurement method (78.1%), provided detailed descriptions of subjects and settings (75%), had an adequate sample size (62.5%) and the sampling method was appropriate (62.5%). In most studies, the sample frame was considered

inappropriate (65.6%). For example, Bergman *et al*. only included women who had Medicaid insurance [32]. Various studies, such as the study by Azadi *et* al. [30], Bosio *et al.* [47], Chaves *et al*. [35], Lendoiro *et al*. [38] and Potchoo *et al*. [41], included women who delivered at one specific hospital. Other studies, such as the study by Radojcic *et al*. [51] and Calderon-Margalit *et al.* [48] only included women who participated in a study. For all studies, risk of bias in coverage and response rate were considered low.

Sensitivity analyses

When assessing the impact of the estimation method, the overall prevalence estimates differed substantially between random and fixed effects calculations. The prevalence of benzodiazepines during pregnancy was 1.9% (95% CI 1.6%-2.2%) using random effects and 1.0% (95% CI 1.0%-1.0%) using fixed effects.

Table 7.3 shows the prevalence estimates of benzodiazepines during pregnancy, stratified by methodological variables and variables indicating risk of bias. When stratified by methodological variables, prospective studies reported a more than twice as higher prevalence (2.7%), compared to retrospective studies (1.2%; p<.01). Prevalence stratified by definition of benzodiazepine use also showed variation: exposure defined by self-report and/or hair sample in one study showed a prevalence of 11%, while exposure based on prescription or dispensing records showed a prevalence of 1.2% (p<.01). A significant difference was found between studies including singletons only (0.7%), compared to studies that did not (2.7%; p<.01).

Prevalence estimates stratified by the quality criteria all showed higher prevalences for high risk of bias, compared to low risk of bias. Studies with a standardized measurement method had a lower prevalence (1.4%), compared to studies that had unstandardized methods (3.1%; p<.01). Studies with a detailed description of subjects and settings had a lower prevalence rate (1.1%), compared to studies without (2.8%: p<.01). Studies with an adequate sample size had a lower prevalence (1.4%), compared to studies with an inadequate sample size (4.0%; p<.01). There were no studies with an inappropriate sampling method. Studies with an appropriate sampling method had a higher prevalence (2.5%), compared to studies with an unclear risk of bias (1.2%; p<.01). Prevalence estimates stratified by the quality

assessment of an appropriate sample frame indicated lower prevalence rates in appropriate sample frames (0.9%), compared to inappropriate sample frames (2.4%; p<.01).

Small study bias

The funnel plot and the accompanying Egger's test regarding benzodiazepine use during pregnancy is reported in Supplementary Figure 7.6. There were only two observations in the preconception period and two observations in the postpartum period, precluding an Egger's test. The sample sizes of the studies during pregnancy ranged from small to (very) large. However, most studies were (very) large, depicted by the majority of the studies in the upper half of the plot. The asymmetric shape of the funnel plot further suggested the presence of reporting biases and/or heterogeneity between the studies. In the lower right half of the plot, we found a few cohorts from the study by Marchetti *et al*. [27], indicative of a small studies effect. Egger's test reached significance for the included studies (β=2.40; 95% CI -0.34-5.13; p=.08), suggesting publication bias.

Discussion

In this meta-analysis, we found a global prevalence of benzodiazepine use of 0.9% (95% CI 0.9%-0.9%) before pregnancy, of 1.9% (95% CI 1.6%-2.2%) during pregnancy and of 0.5% (95% CI 0.5%-0.6%) after pregnancy. Our analyses showed that the prevalence is highly dependent on trimester, type of benzodiazepine and region. Also, the prevalence was influenced to a great extent by characteristics of the study. Among the different studies, substantial heterogeneity was found.

Changes in prevalence in the postpartum period

In this meta-analysis, we observed that the prevalence during pregnancy was approximately four times higher compared to the postpartum period. However, the pooled prevalence in the postpartum period mainly originated from one large study [52], which may not be representative. This decrease in the postpartum period differs from the prevalence of other psychotropic medication, such as antidepressant medication, where prevalence generally increases from pregnancy to the postpartum

period [53-56]. Possibly, postpartum women do not want to use benzodiazepines at night, for they want to stay alert for any nocturnal signals of their infant. Secondly, benzodiazepines are transferred to breast milk [13], which may drive the decrease in prevalence in the postpartum period.

Prevalence was highest in the third trimester (3.1%; CI 1.8%-4.5%), followed by the first (0.5%; CI 0.3%-0.7%) and second trimester (0.3%; CI 0.3%-0.3%). A meta-analysis showed that during pregnancy sleep quality decreases from the second to the third trimester [57], which may drive the increase in benzodiazepines in the third trimester. The decrease in sleep quality may be caused by increased sleeping problems as the third trimester progresses, when women have more difficulty finding a comfortable sleeping position [58]. Restless leg syndrome is common during pregnancy, with an increase to approximately 22% in the third trimester, which might also contribute to sleeping problems [59]. Gastroesophageal reflux is most common in the third trimester [60], which may be uncomfortable while laying down in bed, hence causing problems with sleep. Additionally, there is evidence suggesting that women experience more anxiety in the third trimester, which is also an indication for prescribing benzodiazepines [61, 62]. Literature is not consistent in which trimester benzodiazepine exposure would be more harmful for the fetus. On one hand, it is advised to avoid benzodiazepine use during the first trimester, due to potential teratogenic risks [63], although these risks have thus far not been demonstrated by a meta-analysis [19]. On the other hand, it is also mentioned that late third trimester use is associated with more risks for the fetus or neonate [64], including the risk of floppy infant syndrome, which could lead to hypoxia and even irreversible damage in the neonate [16].

Of note, the high prevalence in the third trimester is mostly due to the study by Bardy *et al*. [31], who reported a prevalence of 13.4% (95% CI 11.5%-15.5). This study was conducted to study the use of analgesics during labor in obstetric practice, which could explain the high prevalence.

In a study from the United States, approximately 5.2% of the general population used benzodiazepines, with use being twice as prevalent among women compared to men [65]. Among women of childbearing age, prevalence ranged from 3.6% to 7.1% [65]. This prevalence is substantially higher, compared to the prevalence of 1.8% we found in the United States and the overall prevalence of 1.9%.

Types of benzodiazepines

The most often used or prescribed benzodiazepine was lorazepam, followed by zolpidem. The US Food and Drug Administration has categorized various benzodiazepines according to their risk during pregnancy and lactation [66]. Most drugs, such as lorazepam, oxazepam and diazepam are categorized as D, indicating that there is evidence of human fetal risk [67]. Zolpidem, the second most used or prescribed benzodiazepine during pregnancy, is categorized as C, indicating that use is warranted [67], which might explain why this drug is second most used or prescribed during pregnancy. Underlying indications may explain the differences in prevalence. For example, in the United States, men are more likely to receive long-acting benzodiazepines, which are more preferred for anxiety, whereas women are more likely to receive short-acting benzodiazepines that are more preferred for insomnia [68]. However, this should be studied in future research, since we do not have information on indications.

Variance among countries

We observed a substantial difference between prevalence rates based on region. The highest prevalence estimate was found in Eastern Europa, followed by Southern Europe and Central and South America. The lowest prevalence was found in Asia. International differences in use and prescriptions may reflect differences in the prevalence and/or severity of mental health problems [69], but could also be due to differences in prescribing behavior of physicians, beliefs about medication use in the population and available medical facilities. Other studies in psychotropic medication also found large variations among countries, both in youth and adults [70-73]. However, our findings must be approached with caution, since the three regions with the highest prevalence rates had a pooled sample size of 1,279, 6,853 and 1,274, which could have biased the findings. In comparison, North America and Northwestern Europe had pooled sample sizes of 118,746 and 353,698 respectively, which may have produced more reliable findings.

Prescriptions versus use

We found different prevalence rates in our sensitivity analyses. Interestingly, when studies used prescription or dispensing records as a proxy for benzodiazepine use,

the pooled prevalence was lower than when women reported their benzodiazepine use. This finding may be explained by women sporadically using medication from family members or friends. A study in the Netherlands showed that almost 13% of the general population acquired prescribed drugs through non-formal channels, with sleeping medication being one of the most frequently illegally obtained drugs [74]. However, underestimation could still play a role here, when women are ashamed or feel guilty about medication use during pregnancy and do not admit to use benzodiazepines during pregnancy [75]. On the other hand, registry data may overestimate actual use due to non-compliance. Also, medications dispensed in the year preceding pregnancy, may actually be taken during pregnancy or even postpartum, which may under- and/or overestimate the prevalence in these peripartum phases. At this point, it is not entirely clear which method is more reliable in estimating the prevalence of benzodiazepine use. It is reported by one study that a high concordance between self-report and prescription data is indicated in a population of pregnant women, expect for medications used intermittently [76]. Since benzodiazepines are usually used sporadically, on an “as needed” basis, it is possible that self-reported use may underestimate or overestimate prevalence rates in studies.

Rates over time

Lastly, we looked at prevalence rates over time. Only two studies reported on different years in their cohort, both finding an increase of benzodiazepines or benzodiazepine-related drugs in the past years [5, 6]. Meta-regression did not show a significant change in benzodiazepine use over time during pregnancy. There were not enough studies to repeat these analyses in studies on the year preceding pregnancy or the year following pregnancy. Possibly, due to changing treatment guidelines in the treatment of anxiety disorder, where patients are more and more treated with antidepressants instead of benzodiazepines [77, 78], prevalence may decrease over time. However, due to the limited information, we cannot draw stringent conclusions on prevalence rates over time.

Limitations

Differences in study design, outcomes, time period and data collection made it difficult to pool all studies. For example, some studies only examined a specific trimester, whereas other studies reported the prevalence on the entire pregnancy. Various studies reported on benzodiazepine use during pregnancy, whereas other studies only reported on a specific drug. Additionally, all analyses revealed considerable heterogeneity. Despite using random-effects analyses, our results should therefore be interpreted with caution.

We have no information on dosing or the amount of prescriptions dispensed by women. Therefore, we have no information on intermittent and chronic users.

Only three studies had a low risk of bias on all seven quality criteria, indicating that the quality of most of the included studies is suboptimal. This is especially shown in the sample frame: approximately two third of the studies reported prevalence from an inappropriate sample frame. For future studies, it is important to conduct prospective longitudinal studies of high quality both on short-term and long-term effects, considering the high prevalence of in utero benzodiazepine exposure. Moreover, it is important to learn which measurement method of benzodiazepine use is most reliable. Methodological sound studies may be helpful in supporting the development of evidence-based guidelines, which could offer guidance in the treatment of pregnant women and potentially lowering the amount of prescriptions and use of benzodiazepines by pregnant women.

Conclusion

The use of benzodiazepines during pregnancy is relatively common, in particular during the third trimester. Considering most used or prescribed benzodiazepines are considered as high-risk by the Food and Drug Administration, with potentially severe adverse outcomes for the (unborn) child, this is a worrying finding. Women and their prescribing physicians should be better informed about potential adverse outcomes, particularly as self-treatment and stigmatization are common. Also, the found high prevalence of benzodiazepine use in particular regions, such as Eastern Europe, is of concern. Given the substantial proportion of children exposed to benzodiazepines in utero, future research should continue to study the short- and long-term safety of

maternal benzodiazepine use during pregnancy and to explore non-pharmacological alternative treatments.

Funding

This work was supported by The Netherlands Organization for Health Research and Development (NWO), in collaboration with Signify Research [grant number 058-14-003].

References

1. Daw, J.R., et al., Prescription drug use during pregnancy in developed countries: a systematic review. Pharmacoepidemiol Drug Saf, 2011. 20(9): p. 895-902.
2. Bjorn, A.M., et al., Use of prescribed drugs among primiparous women: an 11-year population-based study in Denmark. Clin Epidemiol, 2011. 3: p. 149-56.
3. Mitchell, A.A., et al., Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol, 2011. 205(1): p. 51 e1-8.
4. Smolina, K., et al., Trends and Determinants of Prescription Drug Use during Pregnancy and Postpartum in British Columbia, 2002-2011: A Population-Based Cohort Study. PLoS One, 2015. 10(5): p. e0128312.
5. Martin, C.E., et al., Trends in Drug-exposed Deliveries From 2002 to 2009. Addictive Disorders & Their Treatment, 2015. 14(2): p. 61-69.
6. Askaa, B., et al., Maternal Characteristics of Women Exposed to Hypnotic Benzodiazepine Receptor Agonist during Pregnancy. Obstet Gynecol Int, 2014. 2014: p. 945621.
7. Brunton, L.L., B.A. Chabner, and B.C. Knollmann, Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th edition ed. 2011, New York: McGraw-Hill Medicat.
8. Shyken, J.M., et al., Benzodiazepines in Pregnancy. Clin Obstet Gynecol, 2019. 62(1): p. 156-167.
9. D'Hulst, C., J.R. Atack, and R.F. Kooy, The complexity of the GABAA receptor shapes unique pharmacological profiles. Drug Discov Today, 2009. 14(17-18): p. 866-75.
10. Donoghue, J. and M. Lader, Usage of benzodiazepines: A review. Int J Psychiatry Clin Pract, 2010. 14(2): p. 78-87.
11. Ashton, H., Guidelines for the rational use of benzodiazepines. When and what to use. Drugs, 1994. 48(1): p. 25-40.
12. Nelson, J. and G. Chouinard, Guidelines for the clinical use of benzodiazepines: pharmacokinetics, dependency, rebound and withdrawal. Canadian Society for Clinical Pharmacology. Can J Clin Pharmacol, 1999. 6(2): p. 69-83.
13. Kanto, J.H., Use of Benzodiazepines during Pregnancy, Labor and Lactation, with Particular Reference to Pharmacokinetic Considerations. Drugs, 1982. 23(5): p. 354-380.
14. Sheehy, O., J.P. Zhao, and A. Berard, Association Between Incident Exposure to Benzodiazepines in Early Pregnancy and Risk of Spontaneous Abortion. JAMA Psychiatry, 2019.
15. Ogawa, Y., N. Takeshima, and T.A. Furukawa, Maternal exposure to benzodiazepine and risk of preterm birth and low birth weight: A case-control study using a claims database in Japan. Asia Pac Psychiatry, 2018. 10(3): p. e12309.
16. Bulletins--Obstetrics, A.C.o.P., ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. Obstet Gynecol, 2008. 111(4): p. 1001-20.

17. Yonkers, K.A., et al., Association of Panic Disorder, Generalized Anxiety Disorder, and Benzodiazepine Treatment During Pregnancy With Risk of Adverse Birth Outcomes. JAMA Psychiatry, 2017. 74(11): p. 1145-1152.
18. Freeman, M.P., et al., Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: Results from a prospective registry of women with psychiatric disorders. Gen Hosp Psychiatry, 2018. 53: p. 73-79.
19. Enato, E., M. Moretti, and G. Koren, The fetal safety of benzodiazepines: an updated meta-analysis. J Obstet Gynaecol Can, 2011. 33(1): p. 46-48.
20. El Marroun, H., et al., Maternal use of antidepressant or anxiolytic medication during pregnancy and childhood neurodevelopmental outcomes: a systematic review. Eur Child Adolesc Psychiatry, 2014. 23(10): p. 973-92.
21. Liberati, A., et al., The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med, 2009. 6(7): p. e1000100.
22. Munn, Z., et al., Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc, 2015. 13(3): p. 147-53.
23. Munn, Z., et al., The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. Int J Health Policy Manag, 2014. 3(3): p. 123-8.
24. Nyaga, V.N., M. Arbyn, and M. Aerts, Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health, 2014. 72(1): p. 39.
25. Sterne, J.A. and M. Egger, Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol, 2001. 54(10): p. 1046-55.
26. Egger, M., et al., Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997. 315(7109): p. 629-34.
27. Marchetti, F., et al., Use of psychotropic drugs during pregnancy. A report of the international co-operative drug use in pregnancy (DUP) study. Collaborative Group on Drug Use in Pregnancy (CGDUP). Eur J Clin Pharmacol, 1993. 45(6): p. 495-501.
28. Cohen, J., A coefficient of agreement for nominal scales. Educ Psychol Meas, 1960(20): p. 37-46.
29. Hanley, G.E. and B. Mintzes, Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. BMC Pregnancy Childbirth, 2014. 14: p. 242.
30. Azadi, A. and G.A. Dildy, 3rd, Universal screening for substance abuse at the time of parturition. Am J Obstet Gynecol, 2008. 198(5): p. e30-2.
31. Bardy, A.H., et al., Objectively measured perinatal exposure to meperidine and benzodiazepines in Finland. CLIN PHARMACOL THER, 1994. 55(4): p. 471-476.
32. Bergman, U., et al., Effects of exposure to benzodiazepine during fetal life. Lancet, 1992. 340(8821): p. 694-6.

33. Bernard, N., et al., Use of antidepressants and anxiolytics in early pregnancy and the risk of preeclampsia and gestational hypertension: a prospective study. BMC Pregnancy Childbirth, 2019. 19(1): p. 146.
34. Blotiere, P.O., et al., Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. Neurology, 2019.
35. Chaves, R.G., J.A. Lamounier, and C.C. Cesar, Self-medication in nursing mothers and its influence on the duration of breastfeeding. J Pediatr (Rio J), 2009. 85(2): p. 129-34.
36. Daw, J.R., et al., Prescription Drug Use in Pregnancy: A Retrospective, Population-Based Study in British Columbia, Canada (2001-2006). Clin Ther, 2012. 34(1): p. 239-249.e2.
37. Hurault-Delarue, C., et al., Psychomotor developmental effects of prenatal exposure to psychotropic drugs: a study in EFEMERIS database. Fundam Clin Pharmacol, 2016. 30(5): p. 476-482.
38. Lendoiro, E., et al., Maternal hair analysis for the detection of illicit drugs, medicines, and alcohol exposure during pregnancy. Ther Drug Monit, 2013. 35(3): p. 296-304.
39. Leppee, M., et al., The effects of benzodiazepines in pregnancy. Acta Neurol Belg, 2010. 110(2): p. 163-7.
40. Oga, E.A., K. Mark, and V.H. Coleman-Cowger, Cigarette Smoking Status and Substance Use in Pregnancy. Matern Child Health J, 2018. 22(10): p. 1477-1483.
41. Potchoo, Y., et al., Prescription drugs among pregnant women in Lome, Togo, West Africa. Eur J Clin Pharmacol, 2009. 65(8): p. 831-8.
42. Radojčić, M.R., et al., Prenatal exposure to anxiolytic and hypnotic medication in relation to behavioral problems in childhood: A population-based cohort study. Neurotoxicol Teratol, 2017. 61: p. 58-65.
43. Rausgaard, N.L., et al., Prevalence of substance abuse in pregnancy among Danish women. Acta Obstet Gynecol Scand, 2015. 94(2): p. 215-9.
44. Sanaullah, F., M. Gillian, and T. Lavin, Screening of substance misuse during early pregnancy in Blyth: an anonymous unlinked study. J Obstet Gynaecol, 2006. 26(3): p. 187-90.
45. Sherwood, R.A., et al., Substance misuse in early pregnancy and relationship to fetal outcome. Eur J Pediatr, 1999. 158(6): p. 488-92.
46. Wang, L.H., et al., Increased risk of adverse pregnancy outcomes in women receiving zolpidem during pregnancy. Clin Pharmacol Ther, 2010. 88(3): p. 369-374.
47. Bosio, P., et al., The prevalence of chemical substance and alcohol abuse in an obstetric population in Dublin. Ir Med J, 1997. 90(4): p. 149-50.
48. Calderon-Margalit, R., et al., Risk of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy. Am J Obstet Gynecol, 2009. 201(6): p. 579 e1-8.
49. McMillin, G.A., et al., Patterns of Drugs and Drug Metabolites Observed in Meconium: What Do They Mean? Ther Drug Monit, 2015. 37(5): p. 568-80.
50. Sloan, L.B., et al., Substance abuse during pregnancy in a rural population. Obstet Gynecol, 1992. 79(2): p. 245-8.

51. Radojcic, M.R., et al., Prenatal exposure to anxiolytic and hypnotic medication in relation to behavioral problems in childhood: A population-based cohort study. Neurotoxicol Teratol, 2017. 61: p. 58-65.
52. Riska, B.S., et al., Dispensing of benzodiazepines and benzodiazepine-related drugs to pregnant women: a population-based cohort study. Eur J Clin Pharmacol, 2014. 70(11): p. 1367-74.
53. Andrade, S.E., et al., Use of selective serotonin reuptake inhibitors (SSRIs) in women delivering liveborn infants and other women of child-bearing age within the U.S. Food and Drug Administration's Mini-Sentinel program. Arch Womens Ment Health, 2016. 19(6): p. 969-977.
54. Cooper, W.O., et al., Increasing use of antidepressants in pregnancy. American Journal of Obstetrics and Gynecology, 2007. 196(6): p. 544-545.
55. Jimenez-Solem, E., et al., Prevalence of Antidepressant Use during Pregnancy in Denmark, a Nation-Wide Cohort Study. Plos One, 2013. 8(4).
56. Molenaar, N.M., M.P. Lambregtse-van den Berg, and G.J. Bonsel, Dispensing patterns of selective serotonin reuptake inhibitors before, during and after pregnancy: a 16-year population-based cohort study from the Netherlands. Arch Womens Ment Health, 2019.
57. Sedov, I.D., et al., Sleep quality during pregnancy: A meta-analysis. Sleep Med Rev, 2018. 38: p. 168-176.
58. Mindell, J.A. and B.J. Jacobson, Sleep disturbances during pregnancy. J Obstet Gynecol Neonatal Nurs, 2000. 29(6): p. 590-7.
59. Chen, S.J., et al., Prevalence of restless legs syndrome during pregnancy: A systematic review and meta-analysis. Sleep Med Rev, 2018. 40: p. 43-54.
60. Ramu, B., et al., Prevalence and risk factors for gastroesophageal reflux in pregnancy. Indian J Gastroenterol, 2011. 30(3): p. 144-7.
61. Da Costa, D., et al., Variations in stress levels over the course of pregnancy: factors associated with elevated hassles, state anxiety and pregnancy-specific stress. J Psychosom Res, 1999. 47(6): p. 609-21.
62. Teixeira, C., et al., Anxiety and depression during pregnancy in women and men. J Affect Disord, 2009. 119(1-3): p. 142-8.
63. Iqbal, M.M., T. Sobhan, and T. Ryals, Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. Psychiatr Serv, 2002. 53(1): p. 39-49.
64. McElhatton, P.R., The effects of benzodiazepine use during pregnancy and lactation. Reprod Toxicol, 1994. 8(6): p. 461-75.
65. Olfson, M., M. King, and M. Schoenbaum, Benzodiazepine use in the United States. JAMA Psychiatry, 2015. 72(2): p. 136-42.
66. Howland, R.H., Categorizing the safety of medications during pregnancy and lactation. J Psychosoc Nurs Ment Health Serv, 2009. 47(4): p. 17-20.
67. Okun, M.L., R. Ebert, and B. Saini, A review of sleep-promoting medications used in pregnancy. Am J Obstet Gynecol, 2015. 212(4): p. 428-41.
68. Mendelson, W.B., Clinical distinctions between long-acting and short-acting benzodiazepines. J Clin Psychiatry, 1992. 53 Suppl: p. 4-7; discussion 8-9.

69. Steel, Z., et al., The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. Int J Epidemiol, 2014. 43(2): p. 476-93.
70. Balter, M.B., et al., A cross-national comparison of anti-anxiety/sedative drug use. Curr Med Res Opin, 1984. 8 Suppl 4: p. 5-20.
71. Zito, J.M., et al., A three-country comparison of psychotropic medication prevalence in youth. Child Adolesc Psychiatry Ment Health, 2008. 2(1): p. 26.
72. Zito, J.M., et al., Antidepressant prevalence for youths: a multi-national comparison. Pharmacoepidemiol Drug Saf, 2006. 15(11): p. 793-8.
73. Steinhausen, H.C., Recent international trends in psychotropic medication prescriptions for children and adolescents. Eur Child Adolesc Psychiatry, 2015. 24(6): p. 635-40.
74. Koenraadt, R. and M. De Haan, De aankoop van geneesmiddelen via internet. Een onderzoek naar het koopgedrag, de motieven, risicoperceptie en informatiebehoefte van online kopers van geneesmiddelen. , U.W.P. Institute, Editor. 2016.
75. Hafferty, J.D., et al., Self-reported medication use validated through record linkage to national prescribing data. J Clin Epidemiol, 2018. 94: p. 132-142.
76. Sarangarm, P., et al., Agreement between self-report and prescription data in medical records for pregnant women. Birth Defects Res A Clin Mol Teratol, 2012. 94(3): p. 153-61.
77. Berney, P., et al., A major change of prescribing pattern in absence of adequate evidence: benzodiazepines versus newer antidepressants in anxiety disorders. Psychopharmacol Bull, 2008. 41(3): p. 39-47.
78. Offidani, E., et al., Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. Psychother Psychosom, 2013. 82(6): p. 355-62.
79. Ban, L., et al., Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. PLoS One, 2012. 7(8): p. e43462.
80. Bardy, A.H., et al., Objectively measured perinatal exposure to meperidine and benzodiazepines in Finland. Clin Pharmacol Ther, 1994. 55(4): p. 471-6.
81. Daw, J.R., et al., Prescription drug use in pregnancy: a retrospective, population-based study in British Columbia, Canada (2001-2006). Clin Ther, 2012. 34(1): p. 239-249 e2.
82. Hurault-Delarue, C., et al., Psychomotor developmental effects of prenatal exposure to psychotropic drugs: a study in EFEMERIS database. Fundam Clin Pharmacol, 2016. 30(5): p. 476-82.
83. Leong, C., et al., Prescription medication use during pregnancies that resulted in births and abortions (2001-2013): A retrospective population-based study in a Canadian population. PLoS One, 2019. 14(3): p. e0211319.
84. Palmsten, K., et al., The Most Commonly Dispensed Prescription Medications Among Pregnant Women Enrolled in the U.S. Medicaid Program. Obstet Gynecol, 2015. 126(3): p. 465-73.
85. Reis, M. and B. Kallen, Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects. A register study. BMJ Open, 2013. 3(2).

86. Tinker, S.C., et al., Use of benzodiazepine medications during pregnancy and potential risk for birth defects, National Birth Defects Prevention Study, 1997-2011. Birth Defects Res, 2019. 111(10): p. 613-620.
87. Wang, L.H., et al., Increased risk of adverse pregnancy outcomes in women receiving zolpidem during pregnancy. Clin Pharmacol Ther, 2010. 88(3): p. 369-74.

Supplementary Material

Search terms used in the current meta-analysis

Embase:

('hypnotic sedative agent'/exp/mj OR 'anxiolytic agent'/exp/mj OR 'benzodiazepine derivative'/exp/mj OR 'benzodiazepine receptor affecting agent'/exp/mj OR (sedative* OR anxiolytic* OR antianxiolytic* OR ((sleep OR antipanic* OR anti-panic* OR hypnotic* OR serenic*) NEAR/3 (medication* OR agent* OR drug* OR pharmac*)) OR barbiturat* OR benzodiazepin* OR oxazepam* OR lorazepam* OR brotizolam OR diazepam OR valium OR flunitrazepam OR flurazepam OR loprazolam OR midazolam OR mitrazepam OR oxazepam OR temazepam OR zolpidem OR alprazolam OR bromazepam OR clobazam OR clonazepam OR clorazepin* OR prazepam* OR abecarnil OR adinazolam OR hydroxymidazolam OR alpidem OR alprazolam OR arfendazam OR benzodiazepin* OR bretazenil OR bromazepam OR brotizolam OR camazepam OR chlorazepam OR chlordiazepoxide OR cinolazepam OR clobazam OR clonazepam OR clorazepate OR clotiazepam OR cloxazolam OR dealkylflurazepam OR delorazepam OR demoxepam OR devazepide OR diazepam OR divaplon OR doxefazepam OR emapunil OR estazolam OR eszopiclone OR fasiplon OR fludiazepam OR flunitrazepam OR flurazepam OR flutoprazepam OR fosazepam OR gedocarnil OR gidazepam OR girisopam OR halazepam OR haloxazolam OR imidazenil OR ketazolam OR lirequinil OR loflazepate OR loprazolam OR lorazepam OR lormetazepam OR lotrafiban OR meclonazepam OR medazepam OR metaclazepam OR mexazolam OR midazolam OR nastorazepide OR necopidem OR nerisopam OR netazepide OR nimetazepam OR nitrazepam OR norchlordiazepoxide OR norclobazam OR nordazepam OR norfludiazepam OR norflunitrazepam OR oxazepam OR pagoclone OR persumbran OR phenazepam OR pinazepam OR prazepam OR premazepam OR quazepam OR remimazolam OR saripidem OR suproclone OR suriclone OR talampanel OR talirine OR tampramine OR taniplon OR tarazepide OR temazepam OR tetrazepam OR tifluadom OR tofisopam OR tomaymycin OR triazolam OR tuclazepam OR uxepam OR zaleplon OR zapizolam OR zolazepam OR zolpidem OR zopiclone OR abecarnil OR acecarbromal OR acetophenone OR acevaltrate OR adatanserin OR adinazolam OR adipiplon OR allobarbital OR almorexant OR alnespirone OR alpidem OR alprazolam OR amobarbital OR aprobarbital OR apronal OR atagabalin OR avizafone OR azacyclonol OR azaperone OR barbital OR barotal OR batoprazine OR bellergal OR benactyzine OR bentazepam OR benzoctamine OR binospirone OR binospirone-mesylate OR brallobarbital OR bretazenil OR bromazepam OR bromide OR bromisoval OR bromoform OR brotizolam OR buspirone OR butalbital OR butethal OR butoctamide OR camazepam OR captodiamine OR carbromal OR cartazolate OR chloral-hydrate OR chloralodol OR chloralose OR chlorazepam OR chlordiazepoxide OR chlormezanone OR clobazam OR clomethiazole OR clonazepam OR clorazepate OR cloroqualone OR clotiazepam OR cloxazolam OR cyclobarbital OR cyclopentobarbital OR dealkylflurazepam OR delorazepam OR demoxepam OR deramciclane OR detomidine OR dexmedetomidine OR diazepam OR dichloralphenazone OR didrovaltrate OR difebarbamate OR divaplon OR doxefazepam OR doxylamine OR ectylurea OR eglumetad OR eltoprazine OR emapunil OR emicerfont OR emylcamate OR enciprazine OR endixaprine OR eplivanserin OR equagesic OR esmirtazapine OR estazolam OR eszopiclone OR etazolate OR ethchlorvynol OR ethinamate OR etifoxine OR etizolam OR etoxybamide OR fabomotizole OR fasiplon OR fenobam OR filorexant OR fludiazepam OR flunitrazepam OR fluprazine OR flurazepam OR flutoprazepam OR fosazepam OR galdansetron OR gedocarnil OR gepirone OR geriforte OR gidazepam OR girisopam OR glutethimide OR halazepam OR haloxazolam OR heptabarb OR hexapropymate OR hexobarbital OR homofenazine OR hydroxyzine OR hypnorm OR imagabalin OR imidazenil OR indiplon OR indorenate OR ipsapirone OR isamoltane OR kawain OR ketazolam OR lemborexant OR lesopitron OR lirequinil OR loflazepate OR loprazolam OR lorazepam OR lorediplon OR lormetazepam OR lorpiprazole OR mafoprazine OR mandrax OR marax OR mebicar OR mecloqualone OR medazepam OR medetomidine OR menrium OR menthyl-valerate OR mephenoxalone OR meprobamate OR metaclazepam OR methaqualone OR methylpentynol OR methylphenobarbital OR methyprylon OR metomidate OR mexazolam OR midazolam OR mirisetron OR nabilone OR naluzotan OR necopidem OR nelivaptan OR nemorexant OR nerisopam OR niaprazine OR nimetazepam OR nitrazepam OR norchlordiazepoxide OR norclobazam OR nordazepam OR ocinaplon OR optalidon OR osemozotan OR oxanamide OR oxazafone OR oxazepam OR oxazolam OR pagoclone OR panadiplon OR pancopride OR paraldehyde OR pazinaclone OR pentobarbital OR phenaglycodol OR phenazepam OR phenobarbital OR pinazepam OR pipequaline OR pivagabine OR potassium-bromide OR prazepam OR pregabalin OR probarbital OR promethazine OR

propallylonal OR proxibarbal OR psyton OR pyrithyldione OR quazepam OR ramelteon OR remimazolam OR revospirone OR ricasetron OR rilmazafone OR romifidine OR saripidem OR secbutabarbital OR secobarbital OR serazapine OR siramesine OR sodium-bromide OR somnium OR sunepitron OR suproclone OR suriclone OR suvorexant OR talaglumetad OR talbutal OR tameridone OR tandospirone OR taniplon OR tasimelteon OR tedatioxetine OR teflutixol OR temazepam OR tetrabamate OR tetrazepam OR thalidomide OR tracazolate OR trazodone OR triazolam OR triclofos OR trimetozine OR tuclazepam OR umespirone OR uxepam OR valdetamide OR valepotriate OR valerian OR valnoctamide OR valtrate OR vinbarbital OR vinylbital OR vortioxetine OR xylazine OR zaleplon OR zalospirone OR zapizolam OR zolazepam OR zolpidem OR zopiclone):ab,ti) AND ('prevalence'/exp OR 'cross-sectional study'/de OR epidemiology:lnk OR 'cohort analysis'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'epidemiological data'/exp OR 'epidemiological monitoring'/de OR pharmacoepidemiology/de OR 'epidemiology'/de OR 'drug database'/de OR (('pharmacist'/de OR 'drug utilization'/de OR prescription/de OR 'drug use'/de) AND ('registration'/de OR 'register'/de OR 'data base'/de OR 'clinical practice'/de OR 'medical practice'/de)) OR 'population research'/de OR (prevalen* OR cohort* OR epidemiolog* OR ((prescri* OR practice* OR dispen* OR drug-us* OR antidepress*-us*) NEAR/6 (pattern*)) OR (pharmaceut* NEAR/3 (data* OR registr*)) OR prospectiv* OR retrospectiv* OR (population* NEAR/3 (based* OR research OR surveil*)) OR (national* NEAR/3 (stud* OR regist*)) OR cross-section* OR (Database* NEAR/3 Pharmac*)):ab,ti) AND ('pregnancy'/exp OR 'pregnant woman'/exp OR 'prenatal exposure'/exp OR 'maternal exposure'/de OR 'prenatal drug exposure'/exp OR 'prenatal period'/de OR 'perinatal period'/de OR parity/exp OR 'named groups by pregnancy'/exp OR 'perinatal depression'/exp OR 'antenatal depression'/de OR 'gestational age'/de OR 'puerperium'/exp OR (pregnan* OR prenatal* OR parit* OR nullipar* OR primipar* OR multipar* OR primigravid* OR multigravid* OR perinatal* OR antenatal* OR peri-natal* OR ante-natal* OR gestation* OR maternal* OR puerper* OR postpart* OR post-part* OR postnatal* OR post-natal*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline Ovid:
(exp "Hypnotics and Sedatives"/ OR exp Anti-Anxiety Agents/ OR exp Benzodiazepines/ OR (sedative* OR anxiolytic* OR antianxiolytic* OR ((sleep OR antipanic* OR anti-panic* OR hypnotic* OR serenic*) ADJ3 (medication* OR agent* OR drug* OR pharmac*)) OR barbiturat* OR benzodiazepin* OR oxazepam* OR lorazepam* OR brotizolam OR diazepam OR valium OR flunitrazepam OR flurazepam OR loprazolam OR midazolam OR mitrazepam OR oxazepam OR temazepam OR zolpidem OR alprazolam OR bromazepam OR clobazam OR clonazepam OR clorazepin* OR prazepam* OR abecarnil OR adinazolam OR hydroxymidazolam OR alpidem OR alprazolam OR arfendazam OR benzodiazepin* OR bretazenil OR bromazepam OR brotizolam OR camazepam OR chlorazepam OR chlordiazepoxide OR cinolazepam OR clobazam OR clonazepam OR clorazepate OR clotiazepam OR cloxazolam OR dealkylflurazepam OR delorazepam OR demoxepam OR devazepide OR diazepam OR divaplon OR doxefazepam OR emapunil OR estazolam OR eszopiclone OR fasiplon OR fludiazepam OR flunitrazepam OR flurazepam OR flutoprazepam OR fosazepam OR gedocarnil OR gidazepam OR girisopam OR halazepam OR haloxazolam OR imidazenil OR ketazolam OR lirequinil OR loflazepate OR loprazolam OR lorazepam OR lormetazepam OR lotrafiban OR meclonazepam OR medazepam OR metaclazepam OR mexazolam OR midazolam OR nastorazepide OR necopidem OR nerisopam OR netazepide OR nimetazepam OR nitrazepam OR norchlordiazepoxide OR norclobazam OR nordazepam OR norfludiazepam OR norflunitrazepam OR oxazepam OR pagoclone OR persumbran OR phenazepam OR pinazepam OR prazepam OR premazepam OR quazepam OR remimazolam OR saripidem OR suproclone OR suriclone OR talampanel OR talirine OR tampramine OR taniplon OR tarazepide OR temazepam OR tetrazepam OR tifluadom OR tofisopam OR tomaymycin OR triazolam OR tuclazepam OR uxepam OR zaleplon OR zapizolam OR zolazepam OR zolpidem OR zopiclone OR abecarnil OR acecarbromal OR acetophenone OR acevaltrate OR adatanserin OR adinazolam OR adipiplon OR allobarbital OR almorexant OR alnespirone OR alpidem OR alprazolam OR amobarbital OR aprobarbital OR apronal OR atagabalin OR avizafone OR azacyclonol OR azaperone OR barbital OR barotal OR batoprazine OR bellergal OR benactyzine OR bentazepam OR benzoctamine OR binospirone OR binospirone-mesylate OR brallobarbital OR bretazenil OR bromazepam OR bromide OR bromisoval OR bromoform OR brotizolam OR buspirone OR butalbital OR butethal OR butoctamide OR camazepam OR captodiamine OR carbromal OR cartazolate OR chloral-hydrate OR chloralodol OR chloralose OR chlorazepam OR chlordiazepoxide OR chlormezanone OR clobazam OR clomethiazole OR clonazepam OR clorazepate OR cloroqualone OR clotiazepam OR cloxazolam OR cyclobarbital OR cyclopentobarbital OR dealkylflurazepam OR delorazepam OR demoxepam OR deramciclane OR detomidine OR dexmedetomidine OR diazepam OR dichloralphenazone OR didrovaltrate OR difebarbamate OR divaplon OR doxefazepam OR doxylamine OR ectylurea OR eglumetad OR eltoprazine OR emapunil OR emicerfont OR emylcamate OR enciprazine OR endixaprine OR

eplivanserin OR equagesic OR esmirtazapine OR estazolam OR eszopiclone OR etazolate OR ethchlorvynol OR ethinamate OR etifoxine OR etizolam OR etoxybamide OR fabomotizole OR fasiplon OR fenobam OR filorexant OR fludiazepam OR flunitrazepam OR fluprazine OR flurazepam OR flutoprazepam OR fosazepam OR galdansetron OR gedocarnil OR gepirone OR geriforte OR gidazepam OR girisopam OR glutethimide OR halazepam OR haloxazolam OR heptabarb OR hexapropymate OR hexobarbital OR homofenazine OR hydroxyzine OR hypnorm OR imagabalin OR imidazenil OR indiplon OR indorenate OR ipsapirone OR isamoltane OR kawain OR ketazolam OR lemborexant OR lesopitron OR lirequinil OR loflazepate OR loprazolam OR lorazepam OR lorediplon OR lormetazepam OR lorpiprazole OR mafoprazine OR mandrax OR marax OR mebicar OR mecloqualone OR medazepam OR medetomidine OR menrium OR menthyl-valerate OR mephenoxalone OR meprobamate OR metaclazepam OR methaqualone OR methylpentynol OR methylphenobarbital OR methyprylon OR metomidate OR mexazolam OR midazolam OR mirisetron OR nabilone OR naluzotan OR necopidem OR nelivaptan OR nemorexant OR nerisopam OR niaprazine OR nimetazepam OR nitrazepam OR norchlordiazepoxide OR norclobazam OR nordazepam OR ocinaplon OR optalidon OR osemozotan OR oxanamide OR oxazafone OR oxazepam OR oxazolam OR pagoclone OR panadiplon OR pancopride OR paraldehyde OR pazinaclone OR pentobarbital OR phenaglycodol OR phenazepam OR phenobarbital OR pinazepam OR pipequaline OR pivagabine OR potassium-bromide OR prazepam OR pregabalin OR probarbital OR promethazine OR propallylonal OR proxibarbal OR psyton OR pyrithyldione OR quazepam OR ramelteon OR remimazolam OR revospirone OR ricasetron OR rilmazafone OR romifidine OR saripidem OR secbutabarbital OR secobarbital OR serazapine OR siramesine OR sodium-bromide OR somnium OR sunepitron OR suproclone OR suriclone OR suvorexant OR talaglumetad OR talbutal OR tameridone OR tandospirone OR taniplon OR tasimelteon OR tedatioxetine OR teflutixol OR temazepam OR tetrabamate OR tetrazepam OR thalidomide OR tracazolate OR trazodone OR triazolam OR triclofos OR trimetozine OR tuclazepam OR umespirone OR uxepam OR valdetamide OR valepotriate OR valerian OR valnoctamide OR valtrate OR vinbarbital OR vinylbital OR vortioxetine OR xylazine OR zaleplon OR zalospirone OR zapizolam OR zolazepam OR zolpidem OR zopiclone).ab,ti.) AND (prevalence/ OR epidemiology.fs. OR Cross-Sectional Studies/ OR exp Cohort Studies/ OR Epidemiological Monitoring/ OR Epidemiologic Studies/ OR Pharmacoepidemiology/ OR epidemiology/ OR Databases, Pharmaceutical/ OR ((pharmacists/ OR drug utilization/ OR prescriptions/) AND (Registries/ OR Databases, Factual/ OR "Practice Patterns, Physicians'")) OR Population Surveillance/ OR (prevalen* OR cohort* OR epidemiolog* OR ((prescri* OR practice* OR dispen* OR drug-us* OR antidepress*-us*) ADJ6 (pattern*)) OR (pharmaceut* ADJ3 (data* OR registr*)) OR prospectiv* OR retrospectiv* OR (population* ADJ3 (based* OR research OR surveil*)) OR (national* ADJ3 (stud* OR regist*)) OR cross-section* OR (Database* ADJ3 Pharmac*)).ab,ti.) AND (exp pregnancy/ OR pregnant women/ OR Maternal Exposure/ OR Gestational Age/ OR Depression, Postpartum/ OR Gestational Age/ OR Postpartum Period/ OR (pregnan* OR prenatal* OR parit* OR nullipar* OR primipar* OR multipar* OR primigravid* OR multigravid* OR perinatal* OR antenatal* OR peri-natal* OR ante-natal* OR gestation* OR maternal* OR puerper* OR postpart* OR post-part* OR postnatal* OR post-natal*).ab,ti.) NOT (exp animals/ NOT humans/)

Web of Science:
TS=(((sedative* OR anxiolytic* OR antianxiolytic* OR ((sleep OR antipanic* OR anti-panic* OR hypnotic* OR serenic*) NEAR/2 (medication* OR agent* OR drug* OR pharmac*)) OR barbiturat* OR benzodiazepin* OR oxazepam* OR lorazepam* OR brotizolam OR diazepam OR valium OR flunitrazepam OR flurazepam OR loprazolam OR midazolam OR mitrazepam OR oxazepam OR temazepam OR zolpidem OR alprazolam OR bromazepam OR clobazam OR clonazepam OR clorazepin* OR prazepam* OR abecarnil OR adinazolam OR hydroxymidazolam OR alpidem OR alprazolam OR arfendazam OR benzodiazepin* OR bretazenil OR bromazepam OR brotizolam OR camazepam OR chlorazepam OR chlordiazepoxide OR cinolazepam OR clobazam OR clonazepam OR clorazepate OR clotiazepam OR cloxazolam OR dealkylflurazepam OR delorazepam OR demoxepam OR devazepide OR diazepam OR divaplon OR doxefazepam OR emapunil OR estazolam OR eszopiclone OR fasiplon OR fludiazepam OR flunitrazepam OR flurazepam OR flutoprazepam OR fosazepam OR gedocarnil OR gidazepam OR girisopam OR halazepam OR haloxazolam OR imidazenil OR ketazolam OR lirequinil OR loflazepate OR loprazolam OR lorazepam OR lormetazepam OR lotrafiban OR meclonazepam OR medazepam OR metaclazepam OR mexazolam OR midazolam OR nastorazepide OR necopidem OR nerisopam OR netazepide OR nimetazepam OR nitrazepam OR norchlordiazepoxide OR norclobazam OR nordazepam OR norfludiazepam OR norflunitrazepam OR oxazepam OR pagoclone OR persumbran OR phenazepam OR pinazepam OR prazepam OR premazepam OR quazepam OR remimazolam OR saripidem OR suproclone OR suriclone OR talampanel OR talirine OR tampramine OR taniplon OR tarazepide OR temazepam OR tetrazepam OR tifluadom OR tofisopam OR tomaymycin OR triazolam OR tuclazepam OR uxepam OR zaleplon OR

zapizolam OR zolazepam OR zolpidem OR zopiclone OR abecarnil OR acecarbromal OR acetophenone OR acevaltrate OR adatanserin OR adinazolam OR adipiplon OR allobarbital OR almorexant OR alnespirone OR alpidem OR alprazolam OR amobarbital OR aprobarbital OR apronal OR atagabalin OR avizafone OR azacyclonol OR azaperone OR barbital OR barotal OR batoprazine OR bellergal OR benactyzine OR bentazepam OR benzoctamine OR binospirone OR binospirone-mesylate OR brallobarbital OR bretazenil OR bromazepam OR bromide OR bromisoval OR bromoform OR brotizolam OR buspirone OR butalbital OR butethal OR butoctamide OR camazepam OR captodiamine OR carbromal OR cartazolate OR chloral-hydrate OR chloralodol OR chloralose OR chlorazepam OR chlordiazepoxide OR chlormezanone OR clobazam OR clomethiazole OR clonazepam OR clorazepate OR cloroqualone OR clotiazepam OR cloxazolam OR cyclobarbital OR cyclopentobarbital OR dealkylflurazepam OR delorazepam OR demoxepam OR deramciclane OR detomidine OR dexmedetomidine OR diazepam OR dichloralphenazone OR didrovaltrate OR difebarbamate OR divaplon OR doxefazepam OR doxylamine OR ectylurea OR eglumetad OR eltoprazine OR emapunil OR emicerfont OR emylcamate OR enciprazine OR endixaprine OR eplivanserin OR equagesic OR esmirtazapine OR estazolam OR eszopiclone OR etazolate OR ethchlorvynol OR ethinamate OR etifoxine OR etizolam OR etoxybamide OR fabomotizole OR fasiplon OR fenobam OR filorexant OR fludiazepam OR flunitrazepam OR fluprazine OR flurazepam OR flutoprazepam OR fosazepam OR galdansetron OR gedocarnil OR gepirone OR geriforte OR gidazepam OR girisopam OR glutethimide OR halazepam OR haloxazolam OR heptabarb OR hexapropymate OR hexobarbital OR homofenazine OR hydroxyzine OR hypnorm OR imagabalin OR imidazenil OR indiplon OR indorenate OR ipsapirone OR isamoltane OR kawain OR ketazolam OR lemborexant OR lesopitron OR lirequinil OR loflazepate OR loprazolam OR lorazepam OR lorediplon OR lormetazepam OR lorpiprazole OR mafoprazine OR mandrax OR marax OR mebicar OR mecloqualone OR medazepam OR medetomidine OR menrium OR menthyl-valerate OR mephenoxalone OR meprobamate OR metaclazepam OR methaqualone OR methylpentynol OR methylphenobarbital OR methyprylon OR metomidate OR mexazolam OR midazolam OR mirisetron OR nabilone OR naluzotan OR necopidem OR nelivaptan OR nemorexant OR nerisopam OR niaprazine OR nimetazepam OR nitrazepam OR norchlordiazepoxide OR norclobazam OR nordazepam OR ocinaplon OR optalidon OR osemozotan OR oxanamide OR oxazafone OR oxazepam OR oxazolam OR pagoclone OR panadiplon OR pancopride OR paraldehyde OR pazinaclone OR pentobarbital OR phenaglycodol OR phenazepam OR phenobarbital OR pinazepam OR pipequaline OR pivagabine OR potassium-bromide OR prazepam OR pregabalin OR probarbital OR promethazine OR propallylonal OR proxibarbal OR psyton OR pyrithyldione OR quazepam OR ramelteon OR remimazolam OR revospirone OR ricasetron OR rilmazafone OR romifidine OR saripidem OR secbutabarbital OR secobarbital OR serazapine OR siramesine OR sodium-bromide OR somnium OR sunepitron OR suproclone OR suriclone OR suvorexant OR talaglumetad OR talbutal OR tameridone OR tandospirone OR taniplon OR tasimelteon OR tedatioxetine OR teflutixol OR temazepam OR tetrabamate OR tetrazepam OR thalidomide OR tracazolate OR trazodone OR triazolam OR triclofos OR trimetozine OR tuclazepam OR umespirone OR uxepam OR valdetamide OR valepotriate OR valerian OR valnoctamide OR valtrate OR vinbarbital OR vinylbital OR vortioxetine OR xylazine OR zaleplon OR zalospirone OR zapizolam OR zolazepam OR zolpidem OR zopiclone)) AND ((prevalen* OR cohort* OR epidemiolog* OR ((prescri* OR practice* OR dispen* OR drug-us* OR antidepress*-us*) NEAR/5 (pattern*)) OR (pharmaceut* NEAR/2 (data* OR registr*)) OR prospectiv* OR retrospectiv* OR (population* NEAR/2 (based* OR research OR surveil*)) OR (national* NEAR/2 (stud* OR regist*)) OR cross-section* OR (Database* NEAR/2 Pharmac*))) AND ((pregnan* OR prenatal* OR parit* OR nullipar* OR primipar* OR multipar* OR primigravid* OR multigravid* OR perinatal* OR antenatal* OR peri-natal* OR ante-natal* OR gestation* OR maternal* OR puerper* OR postpart* OR post-part* OR postnatal* OR post-natal*)))

Cochrane CENTRAL:
((sedative* OR anxiolytic* OR antianxiolytic* OR ((sleep OR antipanic* OR (anti next panic*) OR hypnotic* OR serenic*) NEAR/3 (medication* OR agent* OR drug* OR pharmac*)) OR barbiturat* OR benzodiazepin* OR oxazepam* OR lorazepam* OR brotizolam OR diazepam OR valium OR flunitrazepam OR flurazepam OR loprazolam OR midazolam OR mitrazepam OR oxazepam OR temazepam OR zolpidem OR alprazolam OR bromazepam OR clobazam OR clonazepam OR clorazepin* OR prazepam* OR abecarnil OR adinazolam OR hydroxymidazolam OR alpidem OR alprazolam OR arfendazam OR benzodiazepin* OR bretazenil OR bromazepam OR brotizolam OR camazepam OR chlorazepam OR chlordiazepoxide OR cinolazepam OR clobazam OR clonazepam OR clorazepate OR clotiazepam OR cloxazolam OR dealkylflurazepam OR delorazepam OR demoxepam OR devazepide OR diazepam OR divaplon OR doxefazepam OR emapunil OR estazolam OR eszopiclone OR fasiplon OR fludiazepam OR flunitrazepam OR flurazepam OR flutoprazepam OR fosazepam OR gedocarnil OR gidazepam OR girisopam OR halazepam OR haloxazolam OR imidazenil OR ketazolam OR lirequinil OR loflazepate OR loprazolam OR lorazepam OR lormetazepam OR

lotrafiban OR meclonazepam OR medazepam OR metaclazepam OR mexazolam OR midazolam OR nastorazepide OR necopidem OR nerisopam OR netazepide OR nimetazepam OR nitrazepam OR norchlordiazepoxide OR norclobazam OR nordazepam OR norfludiazepam OR norflunitrazepam OR oxazepam OR pagoclone OR persumbran OR phenazepam OR pinazepam OR prazepam OR premazepam OR quazepam OR remimazolam OR saripidem OR suproclone OR suriclone OR talampanel OR talirine OR tampramine OR taniplon OR tarazepide OR temazepam OR tetrazepam OR tifluadom OR tofisopam OR tomaymycin OR triazolam OR tuclazepam OR uxepam OR zaleplon OR zapizolam OR zolazepam OR zolpidem OR zopiclone OR abecarnil OR acecarbromal OR acetophenone OR acevaltrate OR adatanserin OR adinazolam OR adipiplon OR allobarbital OR almorexant OR alnespirone OR alpidem OR alprazolam OR amobarbital OR aprobarbital OR apronal OR atagabalin OR avizafone OR azacyclonol OR azaperone OR barbital OR barotal OR batoprazine OR bellergal OR benactyzine OR bentazepam OR benzoctamine OR binospirone OR binospirone next mesylate OR brallobarbital OR bretazenil OR bromazepam OR bromide OR bromisoval OR bromoform OR brotizolam OR buspirone OR butalbital OR butethal OR butoctamide OR camazepam OR captodiamine OR carbromal OR cartazolate OR chloral next hydrate OR chloralodol OR chloralose OR chlorazepam OR chlordiazepoxide OR chlormezanone OR clobazam OR clomethiazole OR clonazepam OR clorazepate OR cloroqualone OR clotiazepam OR cloxazolam OR cyclobarbital OR cyclopentobarbital OR dealkylflurazepam OR delorazepam OR demoxepam OR deramciclane OR detomidine OR dexmedetomidine OR diazepam OR dichloralphenazone OR didrovaltrate OR difebarbamate OR divaplon OR doxefazepam OR doxylamine OR ectylurea OR eglumetad OR eltoprazine OR emapunil OR emicerfont OR emylcamate OR enciprazine OR endixaprine OR eplivanserin OR equagesic OR esmirtazapine OR estazolam OR eszopiclone OR etazolate OR ethchlorvynol OR ethinamate OR etifoxine OR etizolam OR etoxybamide OR fabomotizole OR fasiplon OR fenobam OR filorexant OR fludiazepam OR flunitrazepam OR fluprazine OR flurazepam OR flutoprazepam OR fosazepam OR galdansetron OR gedocarnil OR gepirone OR geriforte OR gidazepam OR girisopam OR glutethimide OR halazepam OR haloxazolam OR heptabarb OR hexapropymate OR hexobarbital OR homofenazine OR hydroxyzine OR hypnorm OR imagabalin OR imidazenil OR indiplon OR indorenate OR ipsapirone OR isamoltane OR kawain OR ketazolam OR lemborexant OR lesopitron OR lirequinil OR loflazepate OR loprazolam OR lorazepam OR lorediplon OR lormetazepam OR lorpiprazole OR mafoprazine OR mandrax OR marax OR mebicar OR mecloqualone OR medazepam OR medetomidine OR menrium OR menthyl next valerate OR mephenoxalone OR meprobamate OR metaclazepam OR methaqualone OR methylpentynol OR methylphenobarbital OR methyprylon OR metomidate OR mexazolam OR midazolam OR mirisetron OR nabilone OR naluzotan OR necopidem OR nelivaptan OR nemorexant OR nerisopam OR niaprazine OR nimetazepam OR nitrazepam OR norchlordiazepoxide OR norclobazam OR nordazepam OR ocinaplon OR optalidon OR osemozotan OR oxanamide OR oxazafone OR oxazepam OR oxazolam OR pagoclone OR panadiplon OR pancopride OR paraldehyde OR pazinaclone OR pentobarbital OR phenaglycodol OR phenazepam OR phenobarbital OR pinazepam OR pipequaline OR pivagabine OR potassium next bromide OR prazepam OR pregabalin OR probarbital OR promethazine OR propallylonal OR proxibarbal OR psyton OR pyrithyldione OR quazepam OR ramelteon OR remimazolam OR revospirone OR ricasetron OR rilmazafone OR romifidine OR saripidem OR secbutabarbital OR secobarbital OR serazapine OR siramesine OR sodium next bromide OR somnium OR sunepitron OR suproclone OR suriclone OR suvorexant OR talaglumetad OR talbutal OR tameridone OR tandospirone OR taniplon OR tasimelteon OR tedatioxetine OR teflutixol OR temazepam OR tetrabamate OR tetrazepam OR thalidomide OR tracazolate OR trazodone OR triazolam OR triclofos OR trimetozine OR tuclazepam OR umespirone OR uxepam OR valdetamide OR valepotriate OR valerian OR valnoctamide OR valtrate OR vinbarbital OR vinylbital OR vortioxetine OR xylazine OR zaleplon OR zalospirone OR zapizolam OR zolazepam OR zolpidem OR zopiclone):ab,ti) AND ((prevalen* OR cohort* OR epidemiolog* OR ((prescri* OR practice* OR dispen* OR (drug next us*) OR (antidepres* next us*)) NEAR/6 (pattern*)) OR (pharmaceut* NEAR/3 (data* OR registr*)) OR prospectiv* OR retrospectiv* OR (population* NEAR/3 (based* OR research OR surveil*)) OR (national* NEAR/3 (stud* OR regist*)) OR (cross next section*) OR (Database* NEAR/3 Pharmac*)):ab,ti) AND ((pregnan* OR prenatal* OR parit* OR nullipar* OR primipar* OR multipar* OR primigravid* OR multigravid* OR perinatal* OR antenatal* OR (peri next natal*) OR (ante next natal*) OR gestation* OR maternal* OR puerper* OR postpart* OR (post next part*) OR postnatal* OR (post next natal*)):ab,ti)

Supplementary Table 7.1 – Overview of characteristics of included studies in the meta-analysis (N=32).

Study	Country	Data source(s)	Study design	Time frame	Pregnancy phase
Askaa 2014 [6]	Denmark	Danish Medical Birth Registry	R	1997-2010	12 weeks preconception – 12 weeks postpartum
Azadi 2008 [30]	USA	Louisiana State University obstetric database of patients that delivered at University Hospital in New Orleans	R	2005	At initial screening related to pregnancy, exact timing unknown
Ban 2012 [79]	UK	The Health Improvement Network	R	1990-2009	First trimester
Bardy 1994 [80]	Finland	National Public Health Institute and Finnish Medical Birth Registry	P	1991	After delivery
Bergman 1992 [32]	USA	Michigan's Medicaid	R	1980-1983	Entire pregnancy
Bernard 2019 [33]	Canada	The CHU de Québec-Université Laval	P	2005-2010	Entire pregnancy
Blotière 2019 [34]	France	The French national health insurance database (DCIR) and the French hospital discharge database (PMSI)	R	2011-2015	First trimester
Bosio 1997 [47]	Ireland	Rotunda hospital	P	?	At first antenatal visit and at 6 weeks postpartum
Calderon-Margalit 2009 [48]	USA	Omega study	P	1996-?	Entire pregnancy
Chaves 2009 [35]	Brazil	Maternity unit of Hospital Manoel Gonçalves de Sousa Moreira	R	2003	Entire pregnancy
Daw 2012 [81]	Canada	BC PharmaNet and Population Data BC	R	2001-2006	3 months preconception – 3 months postpartum

Hanley 2014 [29]	USA	Truven Helath Market Scan database	R	2006-2011	6 months preconception – end of pregnancy
Hurault-Delarue 2016 [82]	France	EFEMERIS	R	2004-2009	Second and/or third trimester
Lendoiro 2013 [38]	Spain	Unversity Hospital of Vigo	P	2011	Entire pregnancy
Leong 2019 [83]	Canada	Manitoba Population Research Data Repository	R	2001-2013	Entire pregnancy
Leppée 2010 [39]	Croatia	Four Zagreb hospitals	P	2004	Entire pregnancy
Marchetti 1993 [27]	22 countries	DUP study (Drug Use in Pregnancy)	P	1988-1990	Entire pregnancy
Martin 2015 [5]	USA	A single tertiary care center	R	2002-2009	After delivery
McMillin 2015 [49]	USA	ARUP National Clinical Reference Laboratory	P	?	After delivery
Oga 2018 [40]	USA	Two obstetric practices, Baltimore	P	2017	Entire pregnancy
Ogawa 2018 [15]	Japan	Japan Medical Data Center (JMDC)	R	2005-2014	Entire pregnancy
Palmsten 2015 [84]	USA	Medicaid Analytic Extract	R	2000-2007	3 months preconception – end of pregnancy
Potchoo 2009 [41]	Togo	Tokoin's University Hospital of Lome	R	2003-2006	Entire pregnancy
Radojcic 2017 [51]	Netherlands	Generation R	P	2002-2006	Entire pregnancy

Rausgaard 2015 [43]	Denmark	8 clinics in southern Denmark	P	2013	End of first trimester
Reis 2013 [85]	Sweden	Swedish Medical Birth Register	R	1995-2008	First trimester
Riska 2014 [52]	Norway	Norwegian Medical Birth Register	R	2004-2011	3 months preconception – 3 months postpartum
Sanaullah 2006 [44]	UK	Blyth and Cramlington clinics	P	2003	At an antenatal booking, exact timing unknown
Sherwood 1999 [45]	UK	King's College Hospital, London	P	1994-1995	First trimester
Sloan 1992 [50]	USA	University of Missouri Obstetrics and Gynaecology Clinic or affiliated rural clinic	P	?	First trimester
Tinker 2019 [86]	USA	The National Birth Defects Prevention Study (NBDPS)	P	1997-2011	Before pregnancy and the trimesters
Wang 2010 [87]	Taiwan	The Taiwan National Health Insurance Research Database (NHIRD) and national birth-certificate registry	R	2005	Entire pregnancy

P = prospective cohort study; R = retrospective cohort study

Supplementary Table 7.2 – Overview of specifics of included studies in the meta-analysis (N=32).

Study	N*	Age limits	Live births only	Singletons only	Additional inclusion criteria	Additional exclusion criteria	Medication reported	Outcome definition
Askaa 2014 [6]	911,017	n.a.	N	N	N	Missing gestational length; Gestational length <155 days or > 315 days	Zopiclone, zolpidem, zaleplon	≥ 1 dispensing
Azadi 2008 [30]	462	n.a.	N	N	N	N	Benzodiazepines	Positive urine test
Ban 2012 [79]	512,573	15-45	N	Y	N	Women registered at general practices in Northern Ireland; Women with evidence of bipolar disorder, schizophrenia and other psychotic disorders; Multiple classes of benzodiazepines	Benzodiazepines	≥ 1 dispensing in the first trimester
Bardy 1994 [80]	1,201	n.a.	Y	N	N	N	Benzodiazepines	Positive umbilical serum test
Bergman 1992 [32]	104,339	n.a.	N	N	N	N	Benzodiazepines	≥ 1 dispensing
Bernard 2019 [33]	6,878	> 18	N	Y	N	Women with chronic hepatic or renal disease; Lost to follow-up; Pregnancy terminations, miscarriages or fetal deaths < 20 weeks; Taking other medication for psychiatric problems such as anticonvulsant, antiepileptic, antipsychotic, stimulant or unidentified medication	Benzodiazepines	Hospital records with standardized form

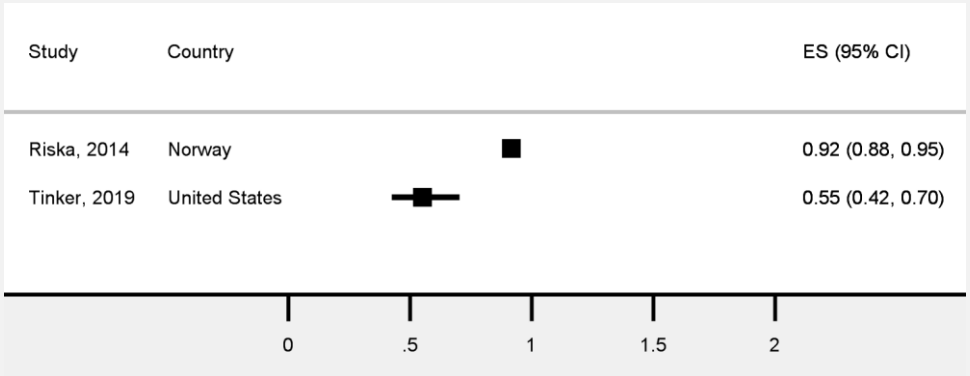
Blotière 2019 [34]	1,886,825	n.a.	Y	Y	Rolled in national health insurance general scheme for salaried workers during the penultimate year before pregnancy; ≥ 20 weeks pregnant	Pregnancies with teratogenic infections or chromosomal abnormalities	Clonazepam	≥ 1 dispensing
Bosio 1997 [47]	504 1st trimester; 515 postpartum	n.a.	N	N	N	N	Benzodiazepines	Positive urine test
Calderon-Margalit 2009 [48]	2,793	>18	N	N	Women who initiated prenatal care at < 20 weeks of gestation; English speaking; Planning to carry pregnancy to term; Planning to deliver at either 1 of the 2 study hospitals	Iatrogenic or spontaneous abortion	Benzodiazepines	Self-report and medical records
Chaves 2009 [35]	246	n.a.	N	N	N	N	Benzodiazepines	Self-report and medical records
Daw 2012 [81]	163,082	n.a.	Y	N	N	Women who did not reside in British Columbia for ≥ 275 days in the year preceding delivery and following delivery	Lorazepam, oxazepam, clonazepam, diazepam, alprazolam, temazepam, triazolam	≥ 1 dispensing
Hanley 2014 [29]	343,299	n.a.	Y	N	Missing > 3 months of enrollment; Consecutive pregnancies	N	Benzodiazepines, eazopiclone, zolpidem, zaleplon	≥ 1 dispensing

Hurault-Delarue 2016 [82]	32,796	n.a.	Y	N	Only children for whom psychomotor development data were available	Only receiving dispensations of during the first trimester	Anxiolytics, bromazepam, zolpidem, prazepam	≥ 1 dispensing; For anxiolytics: ≥ 2 dispensings
Lendoiro 2013 [38]	209	n.a.	N	N	N	Refusal to participate	Benzodiazepines	Self-report and positive hair test
Leong 2019 [83]	246,817	n.a.	N	N	Women with pregnancy outcome identified through hospital discharge records and medical claims data and continuous healthcare coverage from 365 days preconception to 90 days post-partum between 2001 and 2013	Molar or ectopic pregnancies	Lorazepam	≥ 1 dispensing
Leppée 2010 [39]	893	n.a.	N	N	N	Refusal to participate	Diazepam	Self-report and medical records
Marchetti 1993 [27]	50-5,222**	n.a.	N	N	N	N	Benzodiazepines	Self-report
Martin 2015 [5]	13,531	n.a.	Y	N	N	Only positive for methadone, amphetamines, or barbiturates	Benzodiazepines	Positive urine test
McMillin 2015 [49]	76,631	n.a.	N	N	N	N	Benzodiazepines	Positive meconium test
Oga 2018 [40]	494	>18	N	N	English speaking	N	Benzodiazepines	Positive urine test

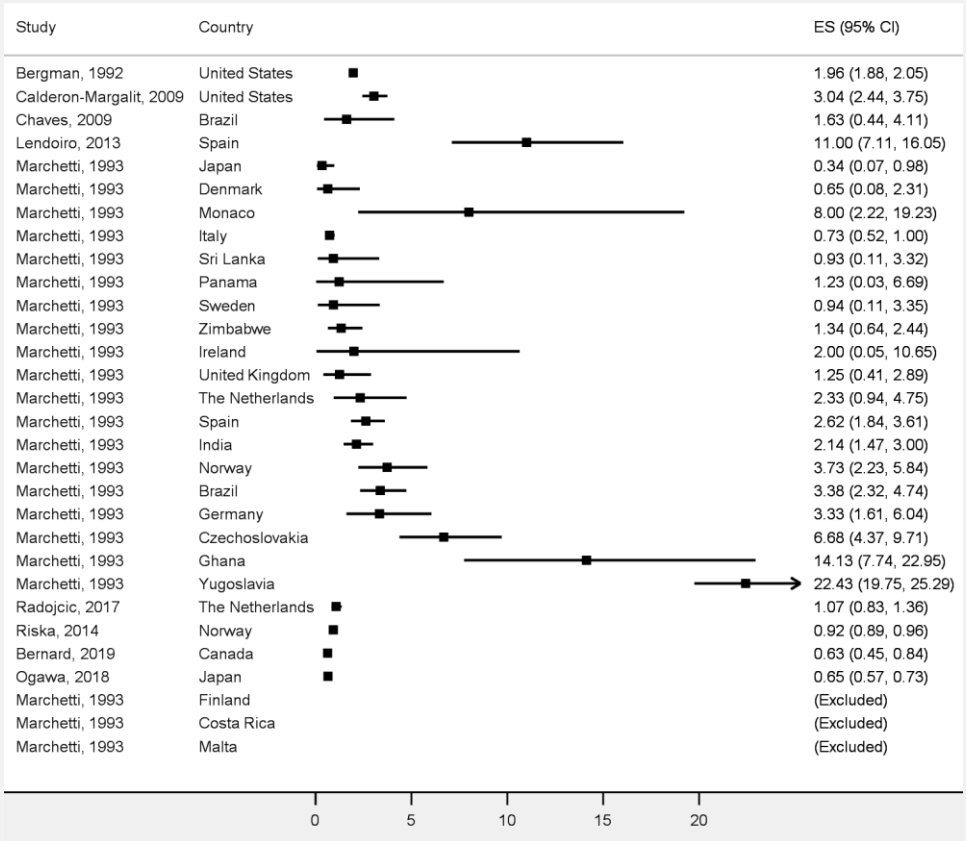
Ogawa 2018 [15]	42,058	n.a.	Y	N	Recorded in database ≥ 9 months before birth of first singleton child; Not dropped out of database prior to delivery; Estimated conception in January 2005 or later; Delivery date prior to February 2014	Alcohol or nicotine dependence	Benzodiazepines	≥ 1 dispensing
Palmsten 2015 [84]	1,106,757	12-55	Y	N	Continuous enrollment in Medicaid; No private insurance; No restricted benefits; Enrollment from 3 months before the last menstrual period through delivery	N	Temazepam	≥ 1 dispensing
Potchoo 2009 [41]	627	n.a.	N	N	Must attend all antenatal visits	N	Diazepam	Unknown
Radojcic 2017[51]	6,240	n.a.	N	N	All pregnant women in Rotterdam willing to participate; Children who participated in the prenatal and postnatal follow-up	Using medication before pregnancy, but not in pregnancy	Benzodiazepines, zolpidem, zopiclone	Self-report or prescription record from pharmacy

Rausgaard 2015 [43]	608	n.a.	N	N	Informed consent for the study	N	Benzodiazepines	Positive urine test
Reis 2013 [85]	1,290,672	n.a.	N	N	N	Children diagnosed with common and clinically less significant malformations	Benzodiazepines, hypnotic benzodiazepine receptor agonists	Self-report
Riska 2014 [52]	345,703	n.a.	Y	Y	Valid personal identity number; Place of residency in Norway at the time of delivery	Unlikely birth weight	Benzodiazepines	≥ 1 dispensing
Sanaullah 2006 [44]	149	n.a.	N	N	Women attending the clinic for an antenatal booking	N	Benzodiazepines, zopiclone	Positive urine test
Sherwood 1999 [45]	807	n.a.	N	N	Urine samples submitted for pregnancy testing with a positive result	N	Benzodiazepines	Positive urine test
Sloan 1992 [50]	181	n.a.	N	N	Women who presented for their first obstetric visit	N	Benzodiazepines	Positive urine test
Tinker 2019 [86]	11,614	n.a.	N	N	N	N	Benzodiazepines	Self-report
Wang 2010 [87]	218,776	n.a.	Y	Y	N	History of mental disorder; Diagnosis of hypertension, diabetes, or coronary heart disease prior to conceiving	Zolpidem	≥ 1 dispensing

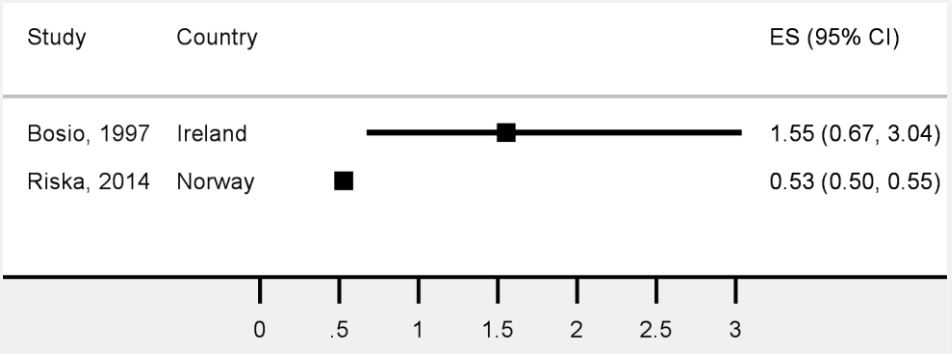
* Per study, the denominator is reported. ** Marchetti *et al.* studied 22 cohorts from 22 countries, with sample sizes varying from 50 to 5,222; N = no; Y = yes; n.a. = not applicable



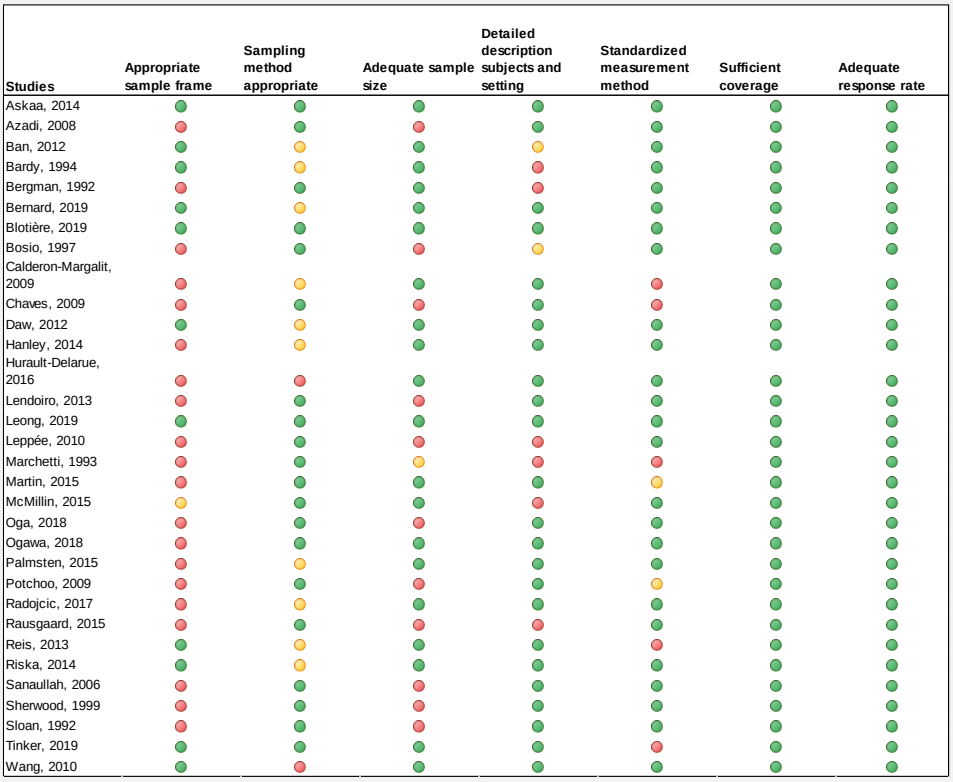
Supplementary Figure 7.1 – Prevalence estimate of benzodiazepines before pregnancy.



Supplementary Figure 7.2 – Prevalence estimate of benzodiazepines during pregnancy.

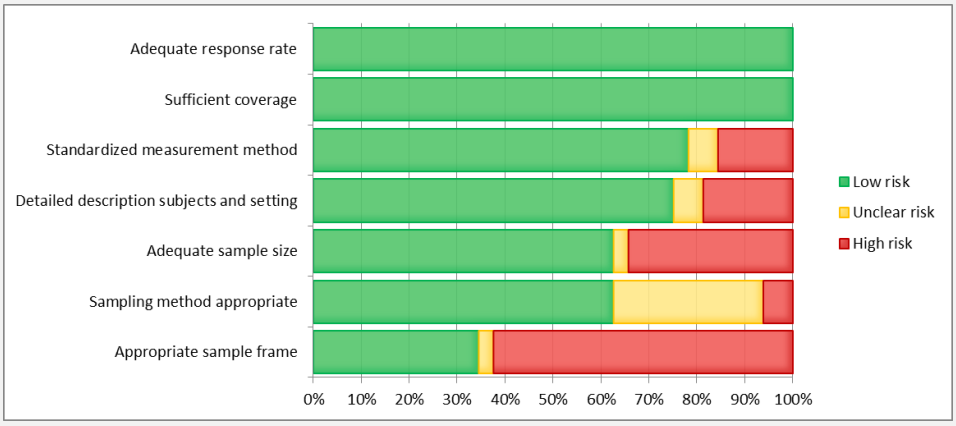


Supplementary Figure 7.3 – Prevalence estimate of benzodiazepines after pregnancy.

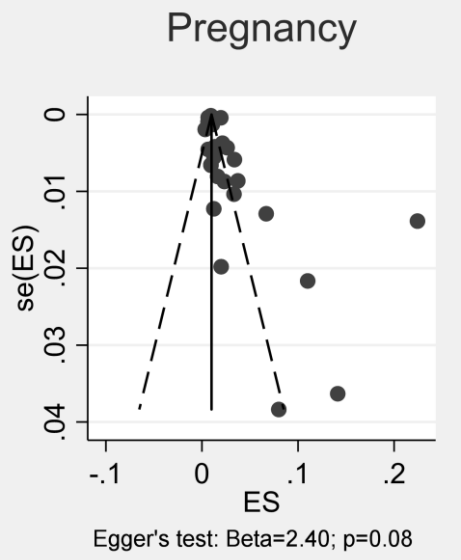


Supplementary Figure 7.4 – Risk of bias assessment per article, based on the Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence data [22, 23].

Red = high risk of bias; yellow = unclear risk of bias; green = low risk of bias.



Supplementary Figure 7.5 – Risk of bias assessment per criterion, based on the Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence data [22, 23].



Supplementary Figure 7.6 – Funnel plot of benzodiazepines during pregnancy to assess the presence of small-study effects.

Supplementary References

1. Daw, J.R., et al., Prescription drug use during pregnancy in developed countries: a systematic review. Pharmacoepidemiol Drug Saf, 2011. 20(9): p. 895-902.
2. Bjorn, A.M., et al., Use of prescribed drugs among primiparous women: an 11-year population-based study in Denmark. Clin Epidemiol, 2011. 3: p. 149-56.
3. Mitchell, A.A., et al., Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol, 2011. 205(1): p. 51 e1-8.
4. Smolina, K., et al., Trends and Determinants of Prescription Drug Use during Pregnancy and Postpartum in British Columbia, 2002-2011: A Population-Based Cohort Study. PLoS One, 2015. 10(5): p. e0128312.
5. Martin, C.E., et al., Trends in Drug-exposed Deliveries From 2002 to 2009. Addictive Disorders & Their Treatment, 2015. 14(2): p. 61-69.
6. Askaa, B., et al., Maternal Characteristics of Women Exposed to Hypnotic Benzodiazepine Receptor Agonist during Pregnancy. Obstet Gynecol Int, 2014. 2014: p. 945621.
7. Brunton, L.L., B.A. Chabner, and B.C. Knollmann, Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th edition ed. 2011, New York: McGraw-Hill Medicat.
8. Shyken, J.M., et al., Benzodiazepines in Pregnancy. Clin Obstet Gynecol, 2019. 62(1): p. 156-167.
9. D'Hulst, C., J.R. Atack, and R.F. Kooy, The complexity of the GABAA receptor shapes unique pharmacological profiles. Drug Discov Today, 2009. 14(17-18): p. 866-75.
10. Donoghue, J. and M. Lader, Usage of benzodiazepines: A review. Int J Psychiatry Clin Pract, 2010. 14(2): p. 78-87.
11. Ashton, H., Guidelines for the rational use of benzodiazepines. When and what to use. Drugs, 1994. 48(1): p. 25-40.
12. Nelson, J. and G. Chouinard, Guidelines for the clinical use of benzodiazepines: pharmacokinetics, dependency, rebound and withdrawal. Canadian Society for Clinical Pharmacology. Can J Clin Pharmacol, 1999. 6(2): p. 69-83.
13. Kanto, J.H., Use of Benzodiazepines during Pregnancy, Labor and Lactation, with Particular Reference to Pharmacokinetic Considerations. Drugs, 1982. 23(5): p. 354-380.
14. Sheehy, O., J.P. Zhao, and A. Berard, Association Between Incident Exposure to Benzodiazepines in Early Pregnancy and Risk of Spontaneous Abortion. JAMA Psychiatry, 2019.
15. Ogawa, Y., N. Takeshima, and T.A. Furukawa, Maternal exposure to benzodiazepine and risk of preterm birth and low birth weight: A case-control study using a claims database in Japan. Asia Pac Psychiatry, 2018. 10(3): p. e12309.
16. Bulletins--Obstetrics, A.C.o.P., ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. Obstet Gynecol, 2008. 111(4): p. 1001-20.

17. Yonkers, K.A., et al., Association of Panic Disorder, Generalized Anxiety Disorder, and Benzodiazepine Treatment During Pregnancy With Risk of Adverse Birth Outcomes. JAMA Psychiatry, 2017. 74(11): p. 1145-1152.
18. Freeman, M.P., et al., Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: Results from a prospective registry of women with psychiatric disorders. Gen Hosp Psychiatry, 2018. 53: p. 73-79.
19. Enato, E., M. Moretti, and G. Koren, The fetal safety of benzodiazepines: an updated meta-analysis. J Obstet Gynaecol Can, 2011. 33(1): p. 46-48.
20. El Marroun, H., et al., Maternal use of antidepressant or anxiolytic medication during pregnancy and childhood neurodevelopmental outcomes: a systematic review. Eur Child Adolesc Psychiatry, 2014. 23(10): p. 973-92.
21. Liberati, A., et al., The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med, 2009. 6(7): p. e1000100.
22. Munn, Z., et al., Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc, 2015. 13(3): p. 147-53.
23. Munn, Z., et al., The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. Int J Health Policy Manag, 2014. 3(3): p. 123-8.
24. Nyaga, V.N., M. Arbyn, and M. Aerts, Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health, 2014. 72(1): p. 39.
25. Sterne, J.A. and M. Egger, Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol, 2001. 54(10): p. 1046-55.
26. Egger, M., et al., Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997. 315(7109): p. 629-34.
27. Marchetti, F., et al., Use of psychotropic drugs during pregnancy. A report of the international co-operative drug use in pregnancy (DUP) study. Collaborative Group on Drug Use in Pregnancy (CGDUP). Eur J Clin Pharmacol, 1993. 45(6): p. 495-501.
28. Cohen, J., A coefficient of agreement for nominal scales. Educ Psychol Meas, 1960(20): p. 37-46.
29. Hanley, G.E. and B. Mintzes, Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. BMC Pregnancy Childbirth, 2014. 14: p. 242.
30. Azadi, A. and G.A. Dildy, 3rd, Universal screening for substance abuse at the time of parturition. Am J Obstet Gynecol, 2008. 198(5): p. e30-2.
31. Bardy, A.H., et al., Objectively measured perinatal exposure to meperidine and benzodiazepines in Finland. CLIN PHARMACOL THER, 1994. 55(4): p. 471-476.
32. Bergman, U., et al., Effects of exposure to benzodiazepine during fetal life. Lancet, 1992. 340(8821): p. 694-6.

33. Bernard, N., et al., Use of antidepressants and anxiolytics in early pregnancy and the risk of preeclampsia and gestational hypertension: a prospective study. BMC Pregnancy Childbirth, 2019. 19(1): p. 146.
34. Blotiere, P.O., et al., Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. Neurology, 2019.
35. Chaves, R.G., J.A. Lamounier, and C.C. Cesar, Self-medication in nursing mothers and its influence on the duration of breastfeeding. J Pediatr (Rio J), 2009. 85(2): p. 129-34.
36. Daw, J.R., et al., Prescription Drug Use in Pregnancy: A Retrospective, Population-Based Study in British Columbia, Canada (2001-2006). Clin Ther, 2012. 34(1): p. 239-249.e2.
37. Hurault-Delarue, C., et al., Psychomotor developmental effects of prenatal exposure to psychotropic drugs: a study in EFEMERIS database. Fundam Clin Pharmacol, 2016. 30(5): p. 476-482.
38. Lendoiro, E., et al., Maternal hair analysis for the detection of illicit drugs, medicines, and alcohol exposure during pregnancy. Ther Drug Monit, 2013. 35(3): p. 296-304.
39. Leppee, M., et al., The effects of benzodiazepines in pregnancy. Acta Neurol Belg, 2010. 110(2): p. 163-7.
40. Oga, E.A., K. Mark, and V.H. Coleman-Cowger, Cigarette Smoking Status and Substance Use in Pregnancy. Matern Child Health J, 2018. 22(10): p. 1477-1483.
41. Potchoo, Y., et al., Prescription drugs among pregnant women in Lome, Togo, West Africa. Eur J Clin Pharmacol, 2009. 65(8): p. 831-8.
42. Radojčić, M.R., et al., Prenatal exposure to anxiolytic and hypnotic medication in relation to behavioral problems in childhood: A population-based cohort study. Neurotoxicol Teratol, 2017. 61: p. 58-65.
43. Rausgaard, N.L., et al., Prevalence of substance abuse in pregnancy among Danish women. Acta Obstet Gynecol Scand, 2015. 94(2): p. 215-9.
44. Sanaullah, F., M. Gillian, and T. Lavin, Screening of substance misuse during early pregnancy in Blyth: an anonymous unlinked study. J Obstet Gynaecol, 2006. 26(3): p. 187-90.
45. Sherwood, R.A., et al., Substance misuse in early pregnancy and relationship to fetal outcome. Eur J Pediatr, 1999. 158(6): p. 488-92.
46. Wang, L.H., et al., Increased risk of adverse pregnancy outcomes in women receiving zolpidem during pregnancy. Clin Pharmacol Ther, 2010. 88(3): p. 369-374.
47. Bosio, P., et al., The prevalence of chemical substance and alcohol abuse in an obstetric population in Dublin. Ir Med J, 1997. 90(4): p. 149-50.
48. Calderon-Margalit, R., et al., Risk of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy. Am J Obstet Gynecol, 2009. 201(6): p. 579 e1-8.
49. McMillin, G.A., et al., Patterns of Drugs and Drug Metabolites Observed in Meconium: What Do They Mean? Ther Drug Monit, 2015. 37(5): p. 568-80.
50. Sloan, L.B., et al., Substance abuse during pregnancy in a rural population. Obstet Gynecol, 1992. 79(2): p. 245-8.

51. Radojcic, M.R., et al., Prenatal exposure to anxiolytic and hypnotic medication in relation to behavioral problems in childhood: A population-based cohort study. Neurotoxicol Teratol, 2017. 61: p. 58-65.
52. Riska, B.S., et al., Dispensing of benzodiazepines and benzodiazepine-related drugs to pregnant women: a population-based cohort study. Eur J Clin Pharmacol, 2014. 70(11): p. 1367-74.
53. Andrade, S.E., et al., Use of selective serotonin reuptake inhibitors (SSRIs) in women delivering liveborn infants and other women of child-bearing age within the U.S. Food and Drug Administration's Mini-Sentinel program. Arch Womens Ment Health, 2016. 19(6): p. 969-977.
54. Cooper, W.O., et al., Increasing use of antidepressants in pregnancy. American Journal of Obstetrics and Gynecology, 2007. 196(6): p. 544-545.
55. Jimenez-Solem, E., et al., Prevalence of Antidepressant Use during Pregnancy in Denmark, a Nation-Wide Cohort Study. Plos One, 2013. 8(4).
56. Molenaar, N.M., M.P. Lambregtse-van den Berg, and G.J. Bonsel, Dispensing patterns of selective serotonin reuptake inhibitors before, during and after pregnancy: a 16-year population-based cohort study from the Netherlands. Arch Womens Ment Health, 2019.
57. Sedov, I.D., et al., Sleep quality during pregnancy: A meta-analysis. Sleep Med Rev, 2018. 38: p. 168-176.
58. Mindell, J.A. and B.J. Jacobson, Sleep disturbances during pregnancy. J Obstet Gynecol Neonatal Nurs, 2000. 29(6): p. 590-7.
59. Chen, S.J., et al., Prevalence of restless legs syndrome during pregnancy: A systematic review and meta-analysis. Sleep Med Rev, 2018. 40: p. 43-54.
60. Ramu, B., et al., Prevalence and risk factors for gastroesophageal reflux in pregnancy. Indian J Gastroenterol, 2011. 30(3): p. 144-7.
61. Da Costa, D., et al., Variations in stress levels over the course of pregnancy: factors associated with elevated hassles, state anxiety and pregnancy-specific stress. J Psychosom Res, 1999. 47(6): p. 609-21.
62. Teixeira, C., et al., Anxiety and depression during pregnancy in women and men. J Affect Disord, 2009. 119(1-3): p. 142-8.
63. Iqbal, M.M., T. Sobhan, and T. Ryals, Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. Psychiatr Serv, 2002. 53(1): p. 39-49.
64. McElhatton, P.R., The effects of benzodiazepine use during pregnancy and lactation. Reprod Toxicol, 1994. 8(6): p. 461-75.
65. Olfson, M., M. King, and M. Schoenbaum, Benzodiazepine use in the United States. JAMA Psychiatry, 2015. 72(2): p. 136-42.
66. Howland, R.H., Categorizing the safety of medications during pregnancy and lactation. J Psychosoc Nurs Ment Health Serv, 2009. 47(4): p. 17-20.
67. Okun, M.L., R. Ebert, and B. Saini, A review of sleep-promoting medications used in pregnancy. Am J Obstet Gynecol, 2015. 212(4): p. 428-41.
68. Mendelson, W.B., Clinical distinctions between long-acting and short-acting benzodiazepines. J Clin Psychiatry, 1992. 53 Suppl: p. 4-7; discussion 8-9.

69. Steel, Z., et al., The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. Int J Epidemiol, 2014. 43(2): p. 476-93.
70. Balter, M.B., et al., A cross-national comparison of anti-anxiety/sedative drug use. Curr Med Res Opin, 1984. 8 Suppl 4: p. 5-20.
71. Zito, J.M., et al., A three-country comparison of psychotropic medication prevalence in youth. Child Adolesc Psychiatry Ment Health, 2008. 2(1): p. 26.
72. Zito, J.M., et al., Antidepressant prevalence for youths: a multi-national comparison. Pharmacoepidemiol Drug Saf, 2006. 15(11): p. 793-8.
73. Steinhausen, H.C., Recent international trends in psychotropic medication prescriptions for children and adolescents. Eur Child Adolesc Psychiatry, 2015. 24(6): p. 635-40.
74. Koenraadt, R. and M. De Haan, De aankoop van geneesmiddelen via internet. Een onderzoek naar het koopgedrag, de motieven, risicoperceptie en informatiebehoefte van online kopers van geneesmiddelen. , U.W.P. Institute, Editor. 2016.
75. Hafferty, J.D., et al., Self-reported medication use validated through record linkage to national prescribing data. J Clin Epidemiol, 2018. 94: p. 132-142.
76. Sarangarm, P., et al., Agreement between self-report and prescription data in medical records for pregnant women. Birth Defects Res A Clin Mol Teratol, 2012. 94(3): p. 153-61.
77. Berney, P., et al., A major change of prescribing pattern in absence of adequate evidence: benzodiazepines versus newer antidepressants in anxiety disorders. Psychopharmacol Bull, 2008. 41(3): p. 39-47.
78. Offidani, E., et al., Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. Psychother Psychosom, 2013. 82(6): p. 355-62.
79. Ban, L., et al., Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. PLoS One, 2012. 7(8): p. e43462.
80. Bardy, A.H., et al., Objectively measured perinatal exposure to meperidine and benzodiazepines in Finland. Clin Pharmacol Ther, 1994. 55(4): p. 471-6.
81. Daw, J.R., et al., Prescription drug use in pregnancy: a retrospective, population-based study in British Columbia, Canada (2001-2006). Clin Ther, 2012. 34(1): p. 239-249 e2.
82. Hurault-Delarue, C., et al., Psychomotor developmental effects of prenatal exposure to psychotropic drugs: a study in EFEMERIS database. Fundam Clin Pharmacol, 2016. 30(5): p. 476-82.
83. Leong, C., et al., Prescription medication use during pregnancies that resulted in births and abortions (2001-2013): A retrospective population-based study in a Canadian population. PLoS One, 2019. 14(3): p. e0211319.
84. Palmsten, K., et al., The Most Commonly Dispensed Prescription Medications Among Pregnant Women Enrolled in the U.S. Medicaid Program. Obstet Gynecol, 2015. 126(3): p. 465-73.
85. Reis, M. and B. Kallen, Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects. A register study. BMJ Open, 2013. 3(2).

86. Tinker, S.C., et al., Use of benzodiazepine medications during pregnancy and potential risk for birth defects, National Birth Defects Prevention Study, 1997-2011. Birth Defects Res, 2019. 111(10): p. 613-620.
87. Wang, L.H., et al., Increased risk of adverse pregnancy outcomes in women receiving zolpidem during pregnancy. Clin Pharmacol Ther, 2010. 88(3): p. 369-74.

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.

References

1. Epperson, C.N., et al., Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry, 2004. 65(3): p. 421-5.
2. Wirz-Justice, A., et al., A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. J Clin Psychiatry, 2011. 72(7): p. 986-93.
3. Ioannidis, J.P., Why most published research findings are false. PLoS Med, 2005. 2(8): p. e124.
4. Tuunainen, A., D.F. Kripke, and T. Endo, Light therapy for non-seasonal depression. Cochrane Database Syst Rev, 2004.
5. Oren, D.A., et al., An open trial of morning light therapy for treatment of antepartum depression. Am J Psychiatry, 2002. 159(4): p. 666-9.
6. Corral, M., et al., Morning light therapy for postpartum depression. Arch Womens Ment Health, 2007. 10(5): p. 221-4.
7. Rief, W., et al., Meta-analysis of the placebo response in antidepressant trials. J Affect Disord, 2009. 118(1-3): p. 1-8.
8. Germain, A. and D.J. Kupfer, Circadian rhythm disturbances in depression. Hum Psychopharmacol, 2008. 23(7): p. 571-85.
9. Hofmann, S.G., et al., The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. J Consult Clin Psychol, 2010. 78(2): p. 169-83.
10. Khoury, B., et al., Mindfulness-based therapy: a comprehensive meta-analysis. Clin Psychol Rev, 2013. 33(6): p. 763-71.
11. Dimidjian, S., et al., An open trial of mindfulness-based cognitive therapy for the prevention of perinatal depressive relapse/recurrence. Arch Womens Ment Health, 2015. 18(1): p. 85-94.
12. Vieten, C. and J. Astin, Effects of a mindfulness-based intervention during pregnancy on prenatal stress and mood: results of a pilot study. Arch Womens Ment Health, 2008. 11(1): p. 67-74.
13. van Ravesteyn, L.M., et al., Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment meta-analysis. PLoS One, 2017. 12(3): p. e0173397.
14. Posternak, M.A. and I. Miller, Untreated short-term course of major depression: a meta-analysis of outcomes from studies using wait-list control groups. J Affect Disord, 2001. 66(2-3): p. 139-46.
15. Yazici, E., et al., Untreated depression in the first trimester of pregnancy leads to postpartum depression: high rates from a natural follow-up study. Neuropsychiatr Dis Treat, 2015. 11: p. 405-11.
16. Reck, C., et al., The impact of maternal anxiety disorder on mother-infant interaction in the postpartum period. PLoS One, 2018. 13(5): p. e0194763.
17. Deuschle, M., et al., Diurnal activity and pulsatility of the hypothalamus-pituitary-adrenal system in male depressed patients and healthy controls. J Clin Endocrinol Metab, 1997. 82(1): p. 234-8.
18. Claustrat, B., J. Brun, and G. Chazot, The basic physiology and pathophysiology of melatonin. Sleep Med Rev, 2005. 9(1): p. 11-24.

19. Tamura, H., et al., Melatonin and pregnancy in the human. Reprod Toxicol, 2008. 25(3): p. 291-303.
20. Zisapel, N., New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. Br J Pharmacol, 2018. 175(16): p. 3190-3199.
21. Al-Karawi, D. and L. Jubair, Bright light therapy for nonseasonal depression: Meta-analysis of clinical trials. J Affect Disord, 2016. 198: p. 64-71.
22. Perera, S., et al., Light therapy for non-seasonal depression: systematic review and meta-analysis. BJPsych Open, 2016. 2(2): p. 116-126.
23. Rosenthal, N.E., et al., Seasonal Affective-Disorder - a Description of the Syndrome and Preliminary Findings with Light Therapy. Archives of General Psychiatry, 1984. 41(1): p. 72-80.
24. Meliska, C.J., et al., Antepartum depression severity is increased during seasonally longer nights: relationship to melatonin and cortisol timing and quantity. Chronobiol Int, 2013. 30(9): p. 1160-1173.
25. Corral, M., A. Wardrop, and H.B. Zhang, Seasonality of symptoms in women with postpartum depression. Arch Womens Ment Health, 2007. 10(1): p. 9-13.
26. Hiltunen, P., et al., Seasonal variation in postnatal depression. J Affect Disord, 2004. 78(2): p. 111-8.
27. Sit, D., H. Seltman, and K.L. Wisner, Seasonal effects on depression risk and suicidal symptoms in postpartum women. Depress Anxiety, 2011. 28(5): p. 400-5.
28. Sylven, S.M., et al., Seasonality patterns in postpartum depression. Am J Obstet Gynecol, 2011. 204: p. 413.e1-6.
29. Weobong, B., et al., Determinants of postnatal depression in rural ghana: findings from the don population based cohort study. Depress Anxiety, 2015. 32(2): p. 108-19.
30. Yang, S.N., et al., The delivery mode and seasonal variation are associated with the development of postpartum depression. J Affect Disord, 2011. 132(1-2): p. 158-64.
31. LeGates, T.A., D.C. Fernandez, and S. Hattar, Light as a central modulator of circadian rhythms, sleep and affect. Nature Reviews Neuroscience, 2014. 15(7): p. 443-454.
32. Coo Calcagni, S., et al., The relationship between sleep and mood in first-time and experienced mothers. Behav Sleep Med, 2012. 10(3): p. 167-79.
33. Kamysheva, E., et al., A prospective investigation of the relationships among sleep quality, physical symptoms, and depressive symptoms during pregnancy. J Affect Disord, 2010. 123(1-3): p. 317-20.
34. Lewis, B.A., et al., The effect of sleep pattern changes on postpartum depressive symptoms. BMC Womens Health, 2018. 18(1): p. 12.
35. Okun, M.L., et al., Sleep disturbances in depressed and nondepressed pregnant women. Depress Anxiety, 2011. 28(8): p. 676-85.
36. Park, E.M., S. Meltzer-Brody, and R. Stickgold, Poor sleep maintenance and subjective sleep quality are associated with postpartum maternal depression symptom severity. Arch Womens Ment Health, 2013. 16(6): p. 539-47.
37. Van Ravesteyn, L.M., et al., Perceived sleep quality is worse than objective parameters of sleep in pregnant women with a mental disorder. J Clin Sleep Med, 2014. 10(10): p. 1137-41.

38. Bei, B., et al., Subjective perception of sleep, but not its objective quality, is associated with immediate postpartum mood disturbances in healthy women. Sleep, 2010. 33(4): p. 531-8.
39. Mindell, J.A., R.A. Cook, and J. Nikolovski, Sleep patterns and sleep disturbances across pregnancy. Sleep Med, 2015. 16(4): p. 483-8.
40. Mindell, J.A. and B.J. Jacobson, Sleep disturbances during pregnancy. J Obstet Gynecol Neonatal Nurs, 2000. 29(6): p. 590-7.
41. van Maanen, A., et al., The effects of light therapy on sleep problems: A systematic review and meta-analysis. Sleep Med Rev, 2016. 29: p. 52-62.
42. Brunton, L.L., B.A. Chabner, and B.C. Knollmann, Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th edition ed. 2011, New York: McGraw-Hill Medicat.
43. Martin, C.E., et al., Trends in Drug-exposed Deliveries From 2002 to 2009. Addictive Disorders & Their Treatment, 2015. 14(2): p. 61-69.
44. Askaa, B., et al., Maternal Characteristics of Women Exposed to Hypnotic Benzodiazepine Receptor Agonist during Pregnancy. Obstet Gynecol Int, 2014. 2014: p. 945621.
45. Bjorn, A.M., et al., Use of prescribed drugs among primiparous women: an 11-year population-based study in Denmark. Clin Epidemiol, 2011. 3: p. 149-56.
46. Mitchell, A.A., et al., Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol, 2011. 205(1): p. 51 e1-8.
47. Smolina, K., et al., Trends and Determinants of Prescription Drug Use during Pregnancy and Postpartum in British Columbia, 2002-2011: A Population-Based Cohort Study. PLoS One, 2015. 10(5): p. e0128312.
48. Bandelow, B., et al., The diagnosis of and treatment recommendations for anxiety disorders. Dtsch Arztebl Int, 2014. 111(27-28): p. 473-80.
49. Berney, P., et al., A major change of prescribing pattern in absence of adequate evidence: benzodiazepines versus newer antidepressants in anxiety disorders. Psychopharmacol Bull, 2008. 41(3): p. 39-47.
50. Offidani, E., et al., Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. Psychother Psychosom, 2013. 82(6): p. 355-62.
51. Freeman, M.P., et al., Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: Results from a prospective registry of women with psychiatric disorders. Gen Hosp Psychiatry, 2018. 53: p. 73-79.
52. Ogawa, Y., N. Takeshima, and T.A. Furukawa, Maternal exposure to benzodiazepine and risk of preterm birth and low birth weight: A case-control study using a claims database in Japan. Asia Pac Psychiatry, 2018. 10(3): p. e12309.
53. Sheehy, O., J.P. Zhao, and A. Berard, Association Between Incident Exposure to Benzodiazepines in Early Pregnancy and Risk of Spontaneous Abortion. JAMA Psychiatry, 2019.
54. Yonkers, K.A., et al., Association of Panic Disorder, Generalized Anxiety Disorder, and Benzodiazepine Treatment During Pregnancy With Risk of Adverse Birth Outcomes. JAMA Psychiatry, 2017. 74(11): p. 1145-1152.

55. Koenraadt, R. and M. De Haan, De aankoop van geneesmiddelen via internet. Een onderzoek naar het koopgedrag, de motieven, risicoperceptie en informatiebehoefte van online kopers van geneesmiddelen. , U.W.P. Institute, Editor. 2016.
56. Hafferty, J.D., et al., Self-reported medication use validated through record linkage to national prescribing data. J Clin Epidemiol, 2018. 94: p. 132-142.
57. El Marroun, H., et al., Maternal use of antidepressant or anxiolytic medication during pregnancy and childhood neurodevelopmental outcomes: a systematic review. Eur Child Adolesc Psychiatry, 2014. 23(10): p. 973-92.

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

Bais B, Lindeboom R, Van Ravesteyn L, Tulen J, Hoogendijk W, Lambregtse-van den Berg M, Kamperman A. The impact of objective and subjective sleep parameters on depressive symptoms during pregnancy: an explorative study. *International Journal of Environmental Research and Public Health*. 2019; 16(9):1-10.

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 Guest lecture at the symposium 'De ongelukkige moeder' organised by study association Comenius at the University of Amsterdam.	2016	9 hrs
Winterdepressie en lichttherapie Guest lecture for study association Brainwave at the University of Utrecht.	2017	5 hrs
Hoe herken je PPM bij een zwangere vrouw? Lectures for VSV. 10 and 12 May 2017. Delft and Dordrecht, the Netherlands.	2017	8 hrs
Seizoensinvloeden bij antepartum depressie Fourth symposium Chronotherapeutics Network of the Netherlands. 12 May 2017. Leiden, the Netherlands.	2017	1 ECTS
Proceedings of the Bright Up study: light therapy in antepartum depression [poster] 29th Annual Meeting of the Society for Light Treatment and Biological Rhythms. 23-25 June 2017. Berlin, Germany.	2017	1 ECTS

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 (€350).	2019
Personal travel grant of the Society of Light Treatment and Biological Rhythms ($500 = €440).	2019
Other Visiting PhD student at the University of Aarhus (15 May – 15 June 2019).	2019

2. Teaching	Year	Workload
Supervising		
Students: Nemo Backx and Matthijs de Vroome. Bachelor Medicine. Project: systematic review. *A correlation between antepartum depression and seasonal affective disorder: a systematic review.*	2015-2016	20 hrs
Students: Maartje van den Hurk, Linda Scheffers, Eline Rompen, Anne van Huijstee and Heleen Essink. Bachelor Medicine. Project: Kennismaking Beroepspraktijk (KBP).	2015-2016	4 hrs
Students: Eline Rompen and Urmi Pahladsingh. Bachelor Medicine. Project: systematic review. *PTSD prevalence amongst patients with schizophrenia disorder and other psychotic disorders: a systematic review.*	2016-2017	10 hrs
Student: Leo Genet. Master Psychology. Project: master thesis. *The efficacy of antidepressant use in pregnant women.*	2017	28 hrs
Students: Micki Ouwerkerk and Juul Zietse. Bachelor Medicine. Project: systematic review. *The effect of sleep quality and duration on*	2017-2018	5 hrs

antepartum depressive symptomology: a systematic review and meta-analysis.		
Student: Sophie de Droog. Master Psychology. Project: master thesis. *De invloed van chronotype op depressieve symptomen tijdens de zwangerschap.*	2017-2018	24 hrs
Student: Nicolle Croes. Master Medicine. Project: master thesis. *Antidepressant exposure during pregnancy and its effect on pregnancy and birth outcomes: a population-based cohort study.*	2018	23 hrs
Students: Noa van Vliet and Jasmijn Vaneman. Bachelor Medicine. Project: systematic review. *Prevalence of the use of benzodiazepines or benzodiazepine-related drugs during pregnancy and adverse birth outcomes: a systematic review.*	2018-2019	5 hrs
Student: Rianne Winters. Master Medicine. Project: master thesis. *Effectiveness of psychotropic medication and their relation with depressive symptoms during pregnancy.*	2018-2019	21 hrs
Students: Lisanne van Kesteren and Finn Stofkoper. Bachelor Midwifery. Project: bachelor thesis.	2019	21 hrs

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.