Treatment and impact of mental disorders during pregnancy

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Colofon

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Treatment and impact of mental disorders during pregnancy

Behandeling en impact van psychiatrische stoornissen tijdens de zwangerschap

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Content

Chapter 1

General introduction and Thesis outline

General introduction and Thesis outline *

** Based on the book chapter "Groepsbehandeling voor zwangeren met ernstige psychiatrische klachten" in the "Handboek Psychiatrie en Zwangerschap" [1]*

Mental disorders are a major cause of disability among women during the perinatal period and may have consequences for her unborn child as well. A major depressive disorder (MDD) is the most common and known mental disorder during pregnancy, with prevalence rates varying between 3.1% and 11.0% [2]. Untreated or incompletely managed depression increases the risk of postpartum depression and maternal suicide, but may also impair fetal development, leading to a lower birth weight, premature birth and long term infant development [3]. Also other (co-morbid) mental disorders and psychosocial problems are important risk factors in the pathway of depression leading to adverse obstetric outcomes [4].
This introduction provides a comprehensive overview of symptoms, prevalence and specific issues of mental disorders during pregnancy, discusses the impact on a woman and her unborn child, and offers considerations for treatment. Treatment of antepartum mental disorders includes a variety of psychotherapeutic interventions and also pharmacotherapy, depending on the type and severity of the disorder, weighing potential risks for the woman and (unborn) child and individual preferences. Awareness, recognition and prompt referral are key to early intervention and prevention of long-term impairment of maternal well-being and adverse effect on the mother-child relationship and infant development.

A broad range of mental disorders and co-morbid disorders

This thesis applies to a heterogeneous group of pregnant women in different ways. First, it applies to a group of women whom are previously diagnosed with a mental disorder, or who otherwise have a history of psychiatric problems or treatment for a mental disorder. Pregnancy may potentially be a stressful period that can intensify symptoms, provoke exacerbations or give rise to associated disorders. But it also includes a group of pregnant women who experience psychiatric symptoms for the first time in their life.
Secondly, the heterogeneity of patients is also reflected by the broad range of mental disorders that are prevalent during pregnancy. The prevalence of all different mental disorders in pregnant women does not differ from outside of pregnancy. A large National Epidemiologic Survey performed among 43.094 women in the USA, showed no significant differences in the 12-month prevalence of mental disorders between past-year pregnant women (25.3% fulfilled the DSM-IV criteria, using a structured diagnostic interview "SCID" [5]), postpartum women (27.5%), and non-pregnant women of childbearing age (30.1%). Except for the significantly higher prevalence of major depressive disorder (MDD) in postpartum women (9.3%) than in non-pregnant women (8.1%) (OR=1.59, 95% CI=1.15–2.20) [6]. In other words, pregnancy seems to be neither protective nor exacerbating [7, 8].

Table 1 – Overview of mental disorders and characteristics specific to the antepartum period

Mental disorder	Prevalence in %		Symptoms of mental disorder (Increased/decreased during pregnancy or specific manifestations)	Specific issues related to the pregnancy
	General population	During pregnancy *		
Mood related				
Major depressive disorder (MDD)	8.0 – 12.0	3.1 – 11.0 [2] $1^{trim} > 2^{trim} > 3^{trim}$	- Depressed mood - Anhedonia - Feelings of worthlessness or guilt (to their unborn child) (↑) - Suicidal thoughts (↓) - Fatigue (↑) - Insomnia (↑) or hypersomnia (↑) - Change in appetite (↑) - Poor concentration (↑) - Psychomotor agitation or retardation	- Under diagnosing or late referral, due to mistaking depressive symptoms for typical "pregnancy complaints" [15] - Alertness to the possibility of bipolarity in a patient with MDD and a first-degree family member with a history of mania
Bipolar disorder [16]	1.0 – 1.1	2.8 $1^{trim} = 2^{trim} = 3^{trim}$	Periods of depression (↑), hypomania and mania: - Expansive/irritable mood - Inflated self-esteem - Decreased need for sleep - More talkative, racing thoughts and distractibility - Increase goal-directed activity - Excessive involvement in pleasurable activities	- Heredity is strong; rate is 14-fold increased for offspring who have a parent with bipolar disorder. - Pregnant women with a pre-existing bipolar disorder have a 25%-30% risk to experience an episode of depression or mania either in pregnancy or after delivery. - Alertness of discontinuation of medication during pregnancy, ≥80% of these women will experience relapse
Anxiety related				
Obsessive Compulsive Disorder (OCD)	2.0 – 3.0	3.5 $1^{trim} = 2^{trim} = 3^{trim}$	- Anxiety-provoking intrusive thoughts (obsessions) - Repetitive behaviours (compulsions) During pregnancy, OCD often manifests as a preoccupation with contamination and repetitive cleaning and checking. OCD could have its onset or be exacerbated during the antepartum period[17]. For example, a blood- and injection phobia can be exacerbated due regular checks.	MDD most common comorbid diagnosis, with a lifetime prevalence of 60-80% in non-pregnant OCD-patients Alertness that OCD during the postpartum period, may adversely affect the child, leading to insecure attachment style and inadequate care giving
Tocophobia (fear of childbirth)		6.0 – 10.0 $1^{trim} = 2^{trim} < 3^{trim}$	Continuously dreading upcoming labour and delivery, anticipation of the delivery provokes an anxiety response (such as a panic attack), attempts to avoid childbirth (elective caesarean request, pregnancy termination)	Both in primigravida women (incl. avoiding pregnancy), as in multiparous women (after a traumatic delivery) Women with tocophobia have a 6-fold increased risk of developing a PTSD

Post Traumatic Stress Disorder (PTSD)	6.8 – 12.3	0.0 – 5.9 $1^{trim} = 2^{trim} < 3^{trim}$	Severe traumatic event causing intense fear, resulting in: - Re-experiencing (↑) - Numbing and avoidance - Increased arousal	- Triggers can be a traumatic delivery or sexual abuse
Panic Disorder (PD)	2.7 – 4.7	1.3 – 2.5 [18] $1^{trim} = 2^{trim} = 3^{trim}$	Recurrent, unexpected panic attacks, following: - Worry about future - Phobic avoidance PD could be exacerbated due to more physical complaints, or improved due to increased progesterone levels and its anxiolytic effect[19].	Importance to differentiate between obstetric complaints (preeclampsia, hypertension, phaeochromocytoma) and PD, due to the overlapping symptoms
Eating Disorders (ED) - Anorexia nervosa - Bulimia nervosa - Binge eating disorder	0.3 – 1.0 1.0 – 1/5 3.5	0.6 – 0.9 $1^{trim} = 2^{trim} = 3^{trim}$	- Refusal to maintain body weight - Intense fear of gaining weight (↑) - Distorted perception of body weight and shape During pregnancy, the need to gain (not too much) weight and the closely monitored eating habits, may exacerbated ED.	Antepartum complications associated with a lifetime ED diagnosis include: - Increased risk for hyperemesis - Smoking during pregnancy - Lower birth weight, preterm delivery and caesarean section - (Impaired fertility) - Possibility of symptom remission or underreporting by patients
Schizophrenia and disorders with psychotic features and/or substance use and related disorders	1.0 – 2.0	0.4% $1^{trim} = 2^{trim} = 3^{trim}$	- Positive and negative symptoms - Cognitive impairment - Mood symptoms During pregnancy worsening of symptoms (more anxiety, interpersonal problems, panic disorders)[17]	Women with psychotic disorders have a greater likelihood of being raped and engage in a higher frequency of sexual behaviour. In combination with inadequate contraception use, it puts them at risk for STD's and unwanted pregnancies[17]. Many women are homeless or live in impoverished conditions. Attention to attachment style and parenting skills, often in cooperation with the Childcare and protection board. Alertness of co-existing health problems and suicide risks.

* Stable, increase or decrease of symptoms during each trimester in pregnancy

Thirdly, in clinical obstetrical practice prevalence of mental disorders during pregnancy seems to be similar to cohort studies but showed a high number of co-morbid mental disorders in clinical studies. At an obstetric outpatient clinic, two studies showed that 24.0% had ≥2 or more co-morbid disorders and 5.0% had ≥3 or more co-morbid mental disorders [9, 10]. Most frequent axis 1 disorders were: anxiety disorders (21.7%, including specific phobia and panic disorder), MDD (8.8%) and eating disorders (0.9%). To our knowledge, only one study focused on the prevalence of personality disorders during pregnancy, which turned out to be 6% based on a self-report measure [11].

Strikingly, most literature describing mental disorders during the antepartum period is available on MDD. Studies on other mental disorders during pregnancy are far less substantial. Emerging evidence suggests that comorbidity and psychosocial problems, including low socio-economic status are important risk factors in the pathway of depression leading to adverse obstetric outcomes [4]. We subscribe the importance of recognizing the heterogeneous group of pregnant women with co-morbid psychiatric and psychosocial problems who are not eligible for routine treatments mainly focusing on depression. The following mental disorders have specific pregnancy-related characteristics in terms of prevalence, manifestation, or treatment and are described in table 1.

During pregnancy, symptoms of a mental disorder like changes in mood, sleep, appetite and energy are often difficult to distinguish from the normal experiences of pregnancy. Although up to 70% of women report some negative mood symptoms during pregnancy, it is of key importance to check whether women meet diagnostic criteria according DSM-V [12]. The course of mental disorders during pregnancy varies: most studies report a peak of depressive symptoms during the first and second trimester and show improvement during the third trimester, in contrast to anxiety related symptoms which increase as the delivery approaches [13]. There is little information on specific phenotypes of mood disturbances in pregnant women with a mental disorder.

Mood disturbances can cause sleeping problems; on the other hand sleep disturbances are also a symptom in several mental disorders. Approximately one-third of all pregnant women report sleeping problems and the persistence of disturbed sleep is associated with less mental well-being and adverse obstetric outcomes [14]. The underlying causal pathway is unknown, whether sleep quality in pregnant women is objectively worse in a sense of reduced or fragmented sleep, or whether their perception of it is altered, possibly as a result of co-occurring psychiatric symptoms.

Impact on mother and child

Pregnant women with severe mental health problems need special care and attention. Untreated severe psychiatric symptoms have a major impact on the woman and on her partner/family. Unfortunately studies focusing on depression showed also adverse outcomes on pregnancy, delivery and the future child [3]. Direct influences of maternal stress in utero associated with depression may impair fetal development [20], leading to a lower birth weight [3], premature birth [21] and long term infants' neurodevelopment [13, 22]. Exposure to elevated intrauterine cortisol levels makes the hypothalamus-pituitary-adrenal (HPA) axis of the child already susceptible to programming during fetal life, which place children at risk for developing psychopathology and other developing problems in later life. Although the fetal programming hypothesis is the most widely investigated possible explanation of the association between maternal psychopathology and child outcomes, there are more theories on this mechanism.

There are also indirect negative effects of having a mental disorder during pregnancy [23]. Pregnant women with a severe mental disorder have a worse self-care, avoid frequent prenatal checks, smoke more often and use more alcohol and drugs [24]. These indirect effects are not only harmful to the fetus, but also for the later child development. It becomes increasingly clear from research that early fetal development determines future adult health [25]. This applies to both 'good' (protective factors) as poor health outcomes. From a clinical perspective, it would be interesting whether fluctuations in mood - as often observed in pregnant women with and without mental disorder - affect child development or maternal mood in the postpartum period. Mood fluctuations have received more attention in the postpartum period because of the phenomenon of the 'postpartum blues' and its association with postpartum depression. Women suffering from a mental disorders during pregnancy are at an increased risks of postpartum depression [26] and maternal suicide [27].

In 2001 in the UK, the Confidential Enquiries into Maternal Death (CEMD) made us aware of the impact of mental illness on maternal deaths and identified suicide as the leading cause of late maternal deaths. Recent studies highlight a history of deliberate self-harm in a significant proportion (25 - 50%) of maternal suicides [28]. Compared with the postnatal period, women who die from suicide during pregnancy are more likely to have a diagnosis of schizophrenia related disorders or bipolar disorder and less likely to have a diagnosis of depression [29]. Little is known about the prevalence and risk factors of self-harm in pregnant women with a mental disorder, even though deliberate self-harm in pregnancy is potentially harmful to the viability of the pregnancy, in addition to being a potential risk factor for suicide.

Weighing risks and benefits for treatment

The challenge for the treatment of a mental disorder during pregnancy is to offer the best and most effective treatment for the mother, with the least harm for the unborn child. Antidepressants are known to be effective in non-pregnant depressed women [30] and showed comparable effects to psychotherapy for depressive and anxiety disorders in non-pregnant women [31]. The disadvantage of pharmacotherapy are the side-effects for the mother and the largely - unknown - effects on the fetus. Many women as well as clinicians prefer not to start or continue the use of antidepressants during pregnancy [32], as long term effects of most pharmacotherapy on the fetal development are insufficiently known [33, 34]. Selective serotonin reuptake inhibitors (SSRIs) are the most frequently used pharmacotherapy in pregnant women with MDD, with an estimated 2-3% of women in Europe. The possible role of SSRIs in the prevention of relapse is also controversial [35, 36]. A recent study found that failure to use or discontinue antidepressants in pregnancy did not have a strong effect on the development of a major depressive episode [37]. Another study found that women who discontinue medication were more likely to relapse than women who continued medication (68 vs. 26%) [38]. The NICE guidelines from the UK advise clinicians to do a risk-benefit analysis, to weigh the risk of relapse against the potential risk for the fetus and encourage the use of non-pharmacological interventions [39]. Also in non-pregnant patients.

Aims of this thesis

All overall aim of the present thesis is to extend existing knowledge on the treatment and impact of a mental disorder during pregnancy. This is of paramount importance, because of the lack of evidence-based treatment algorithms due to the complicated risk-benefit analysis for both mother and her unborn child, with a special focus on non-pharmacological interventions. Therefore, we will first systematically review all pharmacological and non-pharmacological interventions to treat antepartum mental disorders. Secondly, this dissertation evaluates the effectiveness of a new group-based multicomponent treatment for pregnant women with a mental disorder. At last, it explores the impact of a mental disorder during pregnancy on sleep and mood fluctuations and on suicidal ideation and self-harm.

The aims of the thesis can be summarized as follows:

1. To review all pharmacological and non-pharmacological interventions to treat mental disorders during pregnancy
2. To evaluate the efficacy of a new group-based multicomponent therapy in pregnant women with a mental disorder
3. To assess the impact of psychopathology on sleep quality by measuring the objective and subjective sleep quality of pregnant women with a mental disorder
4. To describe phenotypes of mood fluctuations across pregnancy and associations with pregnancy outcomes and postpartum depression
5. To investigate the prevalence of suicidal ideation and deliberate self-harm in pregnant women with a severe mental disorder

Setting

All studies included in this thesis were embedded in the DAPPER-trial, except for the study on suicidal ideation and self-harm. DAPPER is an acronym for Daycare Alternative Psychiatric Pregnant women Efficiency Research. It is a randomized controlled trial (RCT) to evaluate a new group-based multicomponent therapy to reduce depressive symptoms in pregnant women with a mental disorder. Pregnant women were recruited between January 2010 and January 2013 after a diagnostic procedure at the tertiary outpatient clinic for perinatal psychiatry of the Department of Psychiatry, Erasmus University Medical Center (Erasmus MC), Rotterdam, the Netherlands. Rotterdam is the second largest city of the Netherlands and is characterized by a multi-ethnic population and large socioeconomically deprived neighbourhoods, with 10% of pregnant women having a low socio-economic status (<20th percentile). This is associated with adverse birth outcomes [40, 41], for example with 8000 newborns per year 10% being small of gestational age (<10th percentile) [42].

Patients were referred by general practitioners, midwives, gynaecologists and psychiatrists from the bigger area of Rotterdam-Rijnmond. Inclusion criteria were: a) mental and/or

personality disorder verified with the Structured Clinical Interview for DSM-IV-TR Disorders (SCID) [5] by a trained medical doctor; b) gestational age between 12 and 33 weeks; and c) written informed consent. Exclusion criteria were: a) indication for hospital admission; b) inability to function in a group due to severe behavioural problems e.g. aggression, suicidal behaviour, uncontrollable addictive behaviour; c) insufficient command of the Dutch language; or d) inability to visit the outpatient clinic.

A group-based multicomponent treatment for pregnant women

A decade ago at the Erasmus MC, in analogy with other evidence-based group treatments for mood- and personality disorders in non-pregnant patients, a group-based multicomponent therapy (GMT) for pregnant women with a mental disorder was founded. GMT aims to reduce stress, depressive and anxiety symptoms in women with co-morbid psychiatric and psychosocial problems with a special focus on emotional and practical preparation for motherhood. Pregnant women experience a stigma on having negative feelings towards their pregnancy and their unborn child. One of the major benefits of a group-based treatment is peer support; sharing problems and solutions, and reassurance by fellow patients. The medical team places the focus on reducing current psychiatric symptoms, strengthening coping strategies and increasing psycho-hygiene measures, such as avoiding stressful situations and giving practical tips on pregnancy and future motherhood.

The treatment takes place every week, covers multiple therapies and is given to an open group of maximum eight pregnant women. Before participation of the weekly therapy, a patient has to meet certain conditions: a diagnosed mental disorder, ≥12 weeks of gestation, a treatment plan and signal plan (to recognize deterioration) is composed at the outpatient clinic. Safety of the group has to be secured. In case a participant has severe suicidal or psychotic symptoms, she cannot participate. The program of the group-based multicomponent treatment includes:

- Weekly treatment evaluation and theme discussion: Led by a community psychiatric nurse (SPV) various topics related to pregnancy, the expectancy of motherhood and having a mental disorder are discussed. The goal of this therapy is that women learn how to deal with the challenging aspects of the upcoming motherhood and enhancing social support.
- Psycho-education: A perinatal psychiatrist focusses on medical topics (incl. pharmacotherapy), recognizing and interpreting psychiatric symptoms and stimulating healthy behaviour. Experts from other disciplines are invited depending on the issues raised, for example an obstetrician, anesthesiologist or lactation expert.
- Cognitive Behavioural Therapy (CBT): A perinatal psychologist helps women to replace non-functional thoughts with more realistic thoughts (G-schemes) to reduce depressive and anxiety symptoms, and also helps strengthening coping strategies and problem-solving techniques.

- Psychomotor therapy: An infant mental health-specialist encourages women to make contact with the unborn fetus and to actively learn how to relax. One of the goals is to increase maternal mentalization according to the applied-relaxation method of Ost (1987), stimulating bonding to the fetus and advises on maintaining a good sleep hygiene.
- Expressive and relaxation therapy by a creative arts therapist, who provides women several techniques and activities to find distraction and to reduce stress.

Measures

Patients were referred to the outpatient clinic of the Erasmus MC. After an intake with a psychiatrist patients are contacted for study participation. After a structured diagnostic interview ("SCID" [5]) and fulfilling inclusion criteria written informed consent was obtained. Participants of the DAPPER-trial fulfilled 3 questionnaires to assess their sleep quality and depressive symptoms every 5 weeks during treatment until delivery. Participants were asked to fill in a weekly diary to assess their mood, sleep quality and to evaluate the offered treatment. Obstetric records of all mothers were looked up in the hospitals and supplemented as required at the 6 weeks postpartum home visit.

Note: GA= gestational age, SCID = Structured Clinical Interview DSM-IV disorders, EDS = Edinburgh Depression Scale, HDRS = Hamilton Depression Rating Scale, PSQI = Pittsburg Sleep Quality Inventory.

Outline of this thesis

This thesis aims to extend existing knowledge on the treatment (Part I) and impact (Part II) of a mental disorder during pregnancy. **Chapter 2** gives a systematic review of the literature on treatments for mental disorders in pregnant women and a meta-analysis is performed to estimate the treatment effect of the interventions on the psychiatric symptoms during pregnancy. **Chapter 3** describes the DAPPER-trial, a RCT evaluating a new group-based multicomponent therapy for pregnant women to reduce depressive symptoms. **Part II** of this thesis focuses on the impact of a mental disorder on sleep, mood and suicidal ideation during pregnancy. **Chapter 4** focuses on the impact of a mental disorder on sleep quality by comparing subjective and objective sleep quality in a case-control study. **Chapter 5** explores patterns of mood fluctuations in pregnant women with a mental disorder and investigates associations with obstetric outcomes and postpartum depression. In **Chapter 6**, we describe the prevalence of suicidal ideation and deliberate self-harm events in pregnant women with a severe mental disorder in London. Implications of this thesis and recommendations for further research are discussed in **Chapter 7**. Finally, the results of this thesis are summarized in the appendices**.**

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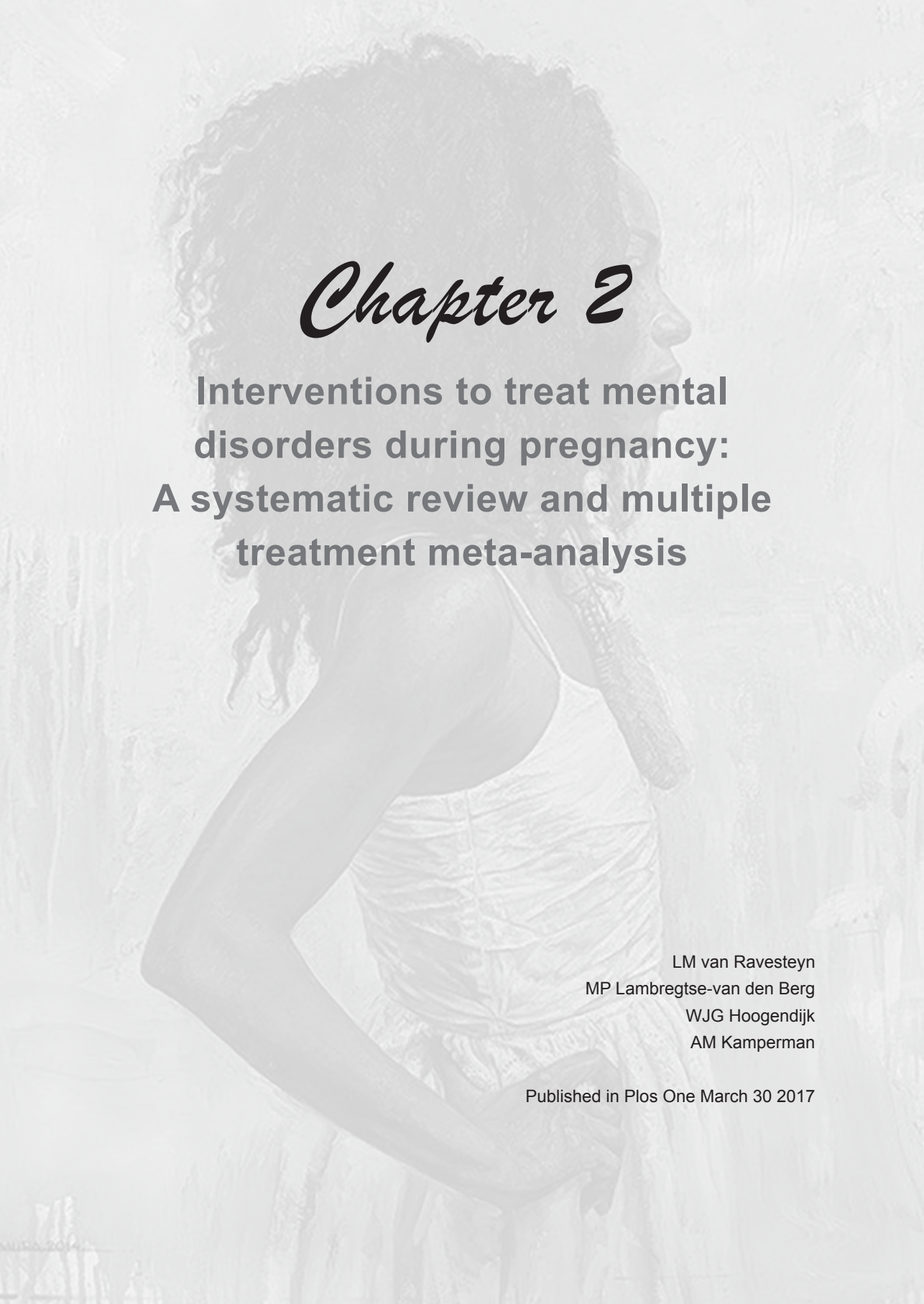
Part 1

Treatment of a mental disorder during pregnancy



Chapter 2

Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment meta-analysis

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Abstract

Background: For women suffering from an antepartum mental disorder (AMD), there is lack of evidence-based treatment algorithms due to the complicated risk-benefit analysis for both mother and unborn child. We aimed to provide a comprehensive overview of pharmacological and non-pharmacological interventions to treat AMD and performed a meta-analysis of the estimated treatment effect on the psychiatric symptoms during pregnancy.

Methods: MedLine, PsycINFO and Embase databases were searched by two independent reviewers for clinical trials with a control condition on treatment of women with AMD, i.e. major depressive (MDD), anxiety, psychotic, eating, somatoform and personality disorders. We inventoried the effect of the treatment, i.e. decrease of psychiatric symptoms at the end of the treatment or postpartum. We adhered to the PRISMA-protocol.

Findings: Twenty-nine trials were found involving 2779 patients. Trials studied patients with depressive disorders (k=28), and anxiety disorders (k=1). No pharmacological trials were detected. A form of psychotherapy, like Cognitive Behavioural Therapy (*g*=-0.61; 95%CI:-0.73 to -0.49, I^2=0%; k=7) or Interpersonal Psychotherapy (*g*=-0.67; 95%CI:-1.27 to -0.07; I^2=79%; k=4), holds robust benefit for pregnant women with MDD. Body-oriented interventions (*g*=-0.43; 95%CI:-0.61 to -0.25; I^2=17%; k=7) and acupuncture (*g*=-0.43; 95%CI:-0.80 to -0.06; I^2=0%; k=2) showed medium sized reduction of depressive symptoms. Bright light therapy (*g*=-0.59; 95%CI:-1.25 to 0.06; I^2=0%; k=2), and food supplements (*g*=-0.51; 95%CI:-1.02 to 0.01; I^2=20%; k=3) did not show significant treatment effects. One study was found on Integrative Collaborative Care.

Conclusions: This meta-analysis found a robust moderate treatment effect of CBT for MDD during pregnancy, and to a lesser extent for IPT. As an alternative, positive results were found for body-oriented interventions and acupuncture. No evidence was found for bright light therapy and food supplements. Only non-pharmacological trials on women with MDD were found. Research on a wider range of AMD is needed.

Introduction

Antepartum mental disorders (AMDs) are a major cause of disability among women during the perinatal period, and may have consequences for children's (intra-uterine) growth and development [1, 2]. To date, most reviews and treatments for antepartum mental disorders focussed on depression [3, 4] while a broader range of mental disorders is prevalent during pregnancy and psychiatric symptoms may overlap. The heterogeneity of patients is reflected by estimates from the National Epidemiologic Survey among 43094 American women, showing that the 12-month prevalence of the full range of AMDs did not differ from outside of pregnancy [5], nor resulting in lower rates [6, 7]. According to DSM-IV criteria, most prevalent AMDs were major depressive disorder (MDD), anxiety disorder and psychotic disorder in pregnant women. Prevalence rates of a mental disorder during pregnancy was 25.3%; almost equivalent among postpartum women (27.5%) and non-pregnant women (30.1%) [5].

In a hospital setting, the prevalence of AMDs is similar to cohort studies and additionally a high number of co-morbid mental disorders is found [8-11], e.g. several studies showed that 24.0% had ≥2 or more co-morbid disorders and 5.0% had ≥3 or more co-morbid mental disorders. To clinicians, a pregnant woman can present with a range of psychiatric and somatic symptoms, which sometimes overlap with typical "pregnancy complaints". For diagnostic and therapeutic purposes, it is important to verify whether a patient dysfunctions in all life domains and to determine the mental disorder(s) according to the DSM-IV criteria. For MDD, DSM-V criteria remained the same and our outcomes can be extrapolated to the current situation. In consultation with the patient, a tailored treatment should be promptly offered, because of the on-going adverse influence of AMDs on the gestation and the increased risk to harmful health behaviours of mother, e.g. smoking, substance use, poor nutrition and avoidance of obstetric care [12, 13]. It has been hypothesized that most relevant effects of AMDs on the foetus take place during mid-gestation and are associated with adverse obstetric outcomes, including preterm delivery, low birth weight, hypertension and preeclampsia [14-17]. To protect the foetus, it is necessary to weigh the potential benefit of treating the mother's AMD with psychotropic medication against the adverse effects of not treating or relapsing of AMD. There are no suitable data available to guide evidence-based decisions on pharmacological treatment of AMD during pregnancy. Selective serotonin reuptake inhibitors (SSRIs) are the most frequently used pharmacological treatment in pregnant women with MDD, with an estimated 2–3% of women in Europe. There a no studies on (dis)continuation of SSRIs during pregnancy, only two naturalistic studies investigated the preventive effect of SSRI's for MDD during pregnancy and the results are equivocal [18, 19]. It poses pregnant women and clinicians for a dilemma, what is best for foetus and mother?

From a patient and clinician perspective, there is need to explore evidence for pharmacotherapy and also alternative non-pharmacological treatments for AMDs. In case of depressive

disorders, several alternative treatment algorithms in non-pregnant women are shown to be effective [20] and Dennis et al. systematically reviewed these interventions in antenatal depression [21-23]. The authors concluded that for antenatal depression the evidence is too inconclusive to make any recommendations for depression-specific acupuncture, maternal massage, bright light therapy, and omega-3 fatty acids [21]. Various treatments for depression during pregnancy have been systematically reviewed [24-34], however, it remains unclear which non-pharmacological treatment clinicians should offer to pregnant patients with (co-morbid) mental disorders other than depression.

For clinicians it is important to know all available alternative treatments, next to pharmacotherapy, that he/she can offer to a patient with AMD. Our systematic review aimed to provide an overview of randomized or open intervention trials with a control condition that evaluated pharmacological and all non-pharmacological interventions for AMD. Subsequently, the aim of our meta-analysis is to provide an estimation of the overall effect size of a decrease of psychiatric symptoms at the end of treatment or postpartum, for each categorized intervention per mental disorder.

Materials and Methods

Eligibility criteria

To be selected for inclusion for our review, a trial was required to meet the following criteria:

1. Type of participants

We considered trials that studied pregnant women with a diagnosed mental disorder, with a focus on the following mental disorders and grouped in 7 categories: 1) depressive disorder (MDD, dysthymic disorder); 2) anxiety disorder, e.g. agoraphobia, obsessive-compulsive disorder, panic disorder, phobic disorder, stress disorder, posttraumatic stress disorder; 3) eating disorder, e.g. anorexia nervosa, binge-eating, bulimia nervosa; 4) adjustment disorder; 5) somatoform disorder; 6) schizophrenia and other disorders with psychotics features, e.g. bipolar disorder, or 7) personality disorder. We decided to exclude addiction or any substance-use related disorders, e.g. nicotine-addicts or heroin users. Studies focussing on a population with psychosocial risk factors but without a diagnosed mental disorder were excluded. A prerequisite was that the AMD was diagnosed by means of a (semi-structured) psychiatric interview during pregnancy, e.g. SCID, Mini International Neuropsychiatric Interview (MINI), Composite International Diagnostic Interview (CIDI), Clinical Interview Schedule-Revised (CIS-R) for ICD-10 criteria or Diagnostic Interview Schedule (DIS), and not using screening instruments.

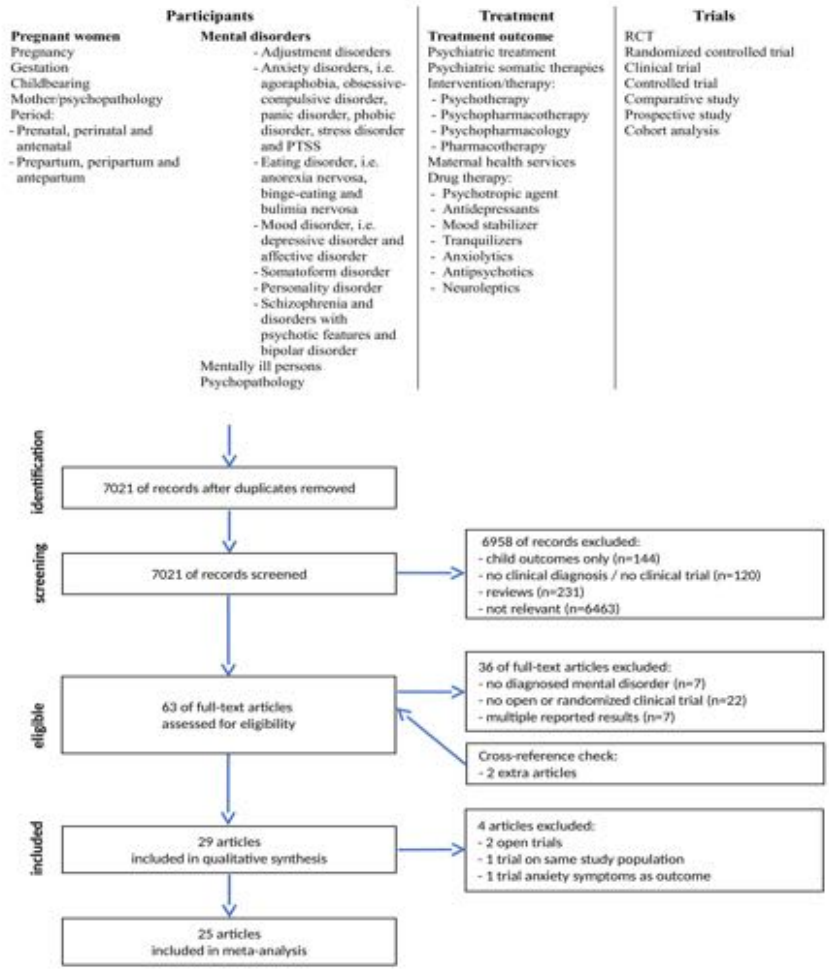
2. Type of treatment
We considered all available pharmacological treatments for AMD, including antidepressants, mood stabilizers, antipsychotics, anxiolytics/tranquilizers and neuroleptics. Also all non-pharmacological interventions for the treatment of AMD were taken into account, including all psychological, body-oriented therapies or other alternative forms of treatment, or combination of these interventions. We included trials that evaluated interventions, which had the primary aim to treat the mental disorder present during pregnancy. Interventions with the focus to prevent – or to treat risk factors for – postpartum psychopathology were excluded.
3. Type of outcome measures:
We included all trials that were performed during pregnancy and evaluated the effect of the intervention at the end of the treatment period or closest to delivery in the postpartum period. We inventoried the effect of the treatment on the mental disorder of the mother, i.e. decrease of psychiatric symptoms at the end of treatment or postpartum closest to the delivery.
4. Types of trials:
We included all studies with a randomized-controlled (RCT) or open trial design and were published in a peer-reviewed journal. For reasons of validity and quality, we decided to focus only on trials with a control condition and excluded abstracts, case-series and case reports. No language, publication date or publication status restrictions were imposed.

Search strategy, data abstraction and synthesis for systematic review

Trials were identified by searching electronic databases, scanning reference lists of articles and consultations with experts in the field. MedLine, PsychInfo and Embase were searched from their inception to June 2016 using combinations of the following terms: *Pregnancy, Mental disorders*, *Treatment* (see Fig 1 for details and flowchart). To identify other published or unpublished trials, Clinical Trial Databases were searched (clinicaltrial.gov, The ICTRP Search Portal). The last search was run on June 2th 2016. Two reviewers (LR and AK) independently screened all titles and abstracts, excluded protocols and reviews and assessed full-text articles for eligibility. Disagreement between reviewers was resolved by an independent psychiatrist (MLvdB). Results are reported according to the PRISMA-protocol [35], but there was no review protocol. We assessed inter-rater agreement by kappa statistic using GraphPad Software. A kappa value of 0.61-0.80 reflects substantial, and a kappa-value of 0.81-1.00 (almost) perfect agreement [36]. Details related to the design of the trial, the participants (mental disorder definition and sample size), the description of the treatment and control condition and the outcomes of the trial were extracted from the articles and reported in Table 1. Most trials used multiple outcomes measures and our interest was to include the outcome measure that operationalized the clinical psychiatric symptoms best, i.e. preference for the Edinburgh (Postnatal) Depression Scale (EDS) which is validated for the use of assessment of depressive symptoms during pregnancy [37]. Our preference was to use the outcome data from the Intention To Treat analysis (ITT), and otherwise data from the per

protocol analysis. In case the trial design, procedure or mental health outcomes were reported in an unusual or inconclusive format, the corresponding author of the trial was requested for additional information. Five corresponding authors were contacted and four authors gave the additional information. In situations when multiple articles were drawn from the same trial, the most complete dataset was reported in detail. In case of multiple interventions, both interventions were reviewed, but in case of multiple control conditions only the primary control condition was reported. Pilots or feasibility trials are only mentioned briefly. Subsequently, per subgroup of mental disorders (as described above) the studied interventions and their effect on the mental disorder at the end of therapy or trial, preferably the time point closest to the delivery is presented.

Figure 1 - Flow diagram of the review selection procedure, adhered to the PRISMA statement



Risk of bias in individual trials and across trials

The reviewers independently rated the risk of bias for each trial according to the Cochrane Risk of Bias Tool and reported randomization procedure, allocation concealment, blinding procedures and selective reporting in Appendices B [38, 39]. Publication bias was visually assessed with a funnel plot and formally with Egger's test, to see if the effect decreased with increasing sample size [40]. These plots should be shaped like a funnel if no publication bias is present. However, since smaller or non-significant trials are less likely to be published, trials in the bottom left-hand corner of the plot are often omitted.

Procedure for meta-analysis

For our meta-analysis, we used the same search strategy as mentioned before and included only randomized controlled trial designs. We excluded open trials. We calculated pooled estimates using bias corrected standardized mean estimates, i.e. Hedges' *g*, with 95% confidence intervals between the intervention group and the control group at the end of the trial or postpartum closest to the delivery. Hedges' *g* corrects for the differences in variances resulting from the inclusion of trials with varying sample sizes [41]. The magnitude of Hedges' *g* can be interpreted as small (0.20), moderate (0.50), or large (0.80) in line with Cohen's *d* [42]. Pooling was performed per type of intervention and per category of mental disorder over a minimum of two trials. Results for each subgroup of intervention are plotted in a forest plot. Random-effects analysis were used to estimate an overall treatment effect since it produces a more reliable estimate than fixed effect analysis in case of substantial heterogeneity. Cochran's Q-test, I^2, and T^2 statistics were used to quantify heterogeneity across trials. I^2 >40% was considered as substantial heterogeneity. Heterogeneity was further explored by conducting sensitivity analyses. For this aim, we calculated the overall treatment effect using both fixed and random effects modelling and evaluated the impact of the modelling procedure on the overall treatment effect [43]. Additionally, we created subgroups of trials based on 1) modus of intervention (group-based vs. individual therapy), 2) timing of outcome assessment (end of therapy vs. in the postpartum period), 3) randomization, i.e. secure vs. unknown, 4) allocation concealment (secure vs. unknown/insecure), 5) attrition (less vs. more than 20%), 6) overall study quality (unbiased, unknown/partially biased vs. biased), and 7) outcome measure (questionnaire used), and we evaluated the impact of these moderator variables on the overall treatment effect. Finally, we assessed the influence of the age of the patient as a continuous variable on treatment effect using random effects meta-regression analysis. Standardized effect sizes were calculated using Comprehensive Meta-Analysis (CMA) [44]. Further statistical analyses were performed using the "Metan package" in Stata 13 [45, 46].

Results

Using our search strategy, we identified 7021 articles (see Fig 1 for a flow diagram). After reviewing the title and abstract, 63 articles were assessed for eligibility and 37 articles did not meet the inclusion criteria. We included 27 articles reporting a clinical trial with a control condition evaluating a treatment for AMD. After cross checking the references, we added 2 relevant articles (A10, A18), thus we included 29 articles in our systematic review. Inter-rater reliability was very good (raw inter-rater agreement= 94%; κ=0.87). All 29 articles were published in English between 1997 and 2015 (see Table 1 for a summary of all included articles). A reference list of all included articles is presented in Appendices A. Together the articles described 28 unique studies; Burns et al. (A2) and Pearson et al. (A21) published on the same study cohort. Collectively there were a total of 2779 participants in the trials. Almost all participants were diagnosed with a depressive disorder (k=28) and, to a lesser extent diagnosed with an anxiety disorder (k=1). No trials were detected with participants diagnosed with AMDs, psychotic disorder, eating disorder, somatoform disorder or personality disorders. Included trials described the effects of a variety of different interventions, e.g. Cognitive Behavioural Therapy (CBT), Inter Personal Therapy (IPT), bright light therapy, body-oriented interventions, acupuncture, food supplements and Integrative Collaborative Care (ICC). The treatment period ranged from 2 to 16 weeks and number of sessions varied between 2 to 32 sessions. Assessment of outcome differed in timing, e.g. end of treatment period (k=25) or postpartum period (k=4), and type of questionnaire frequently used were EPDS (k=9), CES-D (k=7) and BDI (k=4). The majority of the trials randomly allocated participants to an intervention or control condition (k=27), except for two trials with an open design. In the following paragraphs, the results of the different interventions per diagnostic subgroup are described.

Depressive disorder

In general, the results from 28 unique trials focusing on the treatment of a depressive disorder in pregnant women indicated beneficial effects in relation to a decrease of depressive symptoms at the end of treatment or in the postpartum period. These trials included participants that fulfilled the criteria for MDD according to DSM-IV or ICD-10 criteria. Participants were diagnosed with the SCID (k=16), MINI (k=3), DIS (k=2), CIS-R (k=2) or other clinical (semi-structured) psychiatric interview (k=5), often combined with a screening instrument. The majority of the studies were conducted in a Western country (Australia, Sweden, Switzerland, UK, USA) and three trials were conducted in a low-resource country (Pakistan, Korea and Taiwan). The majority of the sample sizes of the included trials were small, varying from 10 to 903 participants and covered in total 2703 participants. Except for one open trial, all trials were (partly) randomized controlled trials.

In total, 8 trials evaluated CBT, 4 trials evaluated IPT, 3 trials examined the use of bright light therapy, 7 trials were on body-oriented therapies, 2 trials on acupuncture, 3 trials on food supplements and one trial on ICC. Participants were individually exposed to the intervention (k=21) or the treatment was delivered to a group (k=7). Reduction of depressive symptoms was expressed in scores on the EPDS (k=9), CES-D (k=7), BDI (k=4), HDRS (k=3), SIGH-SAD (k=3), CIS-R (k=2), SCL-20 (k=1) at the end of treatment (k=23) or postpartum (k=3).

Cognitive behavioural therapy (CBT)

Austin et al. conducted one of the first large RCTs to demonstrate the superiority of CBT over a booklet and provided weekly 2-hour CBT group sessions for 6 weeks (A1). Per protocol analyses showed that both groups symptomatically improved over time but there was no difference between the two groups. Cho et al. conducted a pilot randomized controlled trial to compare CBT with psycho-education with twenty-seven depressed patients. The intervention group received 9 sessions of individual CBT and had significantly lower rates of depression one month after childbirth (A3). In a low-resource setting, Rahman et al. conducted a large cluster-randomized controlled trial and trained community health workers to provide a CBT-like intervention at home. Although the primary outcome was infant weight and height at 6 months postpartum, less mothers met criteria for major depression in the intervention group than in the control group (OR 0.22 95%CI: 0.14 to 0.36, p<0.001) (A22). Also in another setting, Hayden studied pregnant women with diabetes and with depression (n=34) and without depression (n=68), but CBT had no beneficial effect over supportive counseling for both groups (A14)\. More recent, Burns et al. and Pearson et al. investigated CBT in a pilot RCT and randomized 36 British women who received up to 12 sessions of individual CBT (A2,A21). At 15 weeks post-randomization (linked to a gestational age of approx. 29 weeks), there were more women in the intervention group who did not met ICD-10 criteria for depression any more than in the control group (68.7% vs. 38.5%) and Pearson et al. suggested that the attentional biases of women might improve after CBT. In a pilot RCT, O'Mahen et al. showed that CBT is also a feasible and acceptable treatment for low-income, racial minority women with MDD, however depression scores did not significant differ between the intervention and treatment as usual group (A19). Milgrom et al. showed promising results of an adapted version of a postnatal CBT program, containing 8 antepartum sessions and also reports infant outcomes at 9 months, however post-treatment the depression scores were not significant better for the intervention group (A29).

Interpersonal Psychotherapy (IPT)

Spinelli and colleagues were the first to compare a 16-week IPT intervention with parent education matched in time and intensity (A24)[47]. The majority of women were low-income Spanish speaking immigrants, and patients who received IPT had a significant >50%

improvement in their mood symptoms. This trial was replicated in 2013 and showed equal benefits of both interventions (A25). Grote et al. reduced the number of sessions from 16 to 8 (brief-IPT) and still a significant larger proportion (95%) of the women in the intervention group no longer met the criteria for MDD compared to the enhanced usual care (58%) at 3 months postpartum (A13). Field et al. studied IPT in a group of women with dysthymia or major depression and after 12 sessions there was no difference in mood symptoms between the intervention and the control peer-support group (A6).

Bright light therapy

Three trials have examined the use of bright light therapy for the treatment of antepartum depression. Oren et al. exposed 16 patients for 3 weeks to active bright light in an ABA-design and SIGH-SAD scores improved by 49% from baseline (A20). Withdrawal of bright light treatment was associated with an increase of depressive symptoms. Epperson and colleagues found no significant benefit of bright light over placebo during a 5-week RCT (A4). However, in the extended 10-week trial, active bright light with 20,000 lux had a significant treatment effect compared to 500-lux dim light (effect size 0.43). Wirz-Justice et al. reported a significant difference on HDRS and SIGH-ADS (MD= -5.00, 95%CI:-10.00 to 0.00) scores comparing active (7000 lux) to placebo (70 lux) light therapy after 5 weeks of treatment (A28).

Body-oriented interventions

Field et al. studied extensively alternative antepartum interventions for depression (A5-A11). Massage by a significant other, compared to standard care significantly decreased the number of women with depressive symptomatology on the Center for Epidemiological Studies Depression Scale (CES-D) immediately post-treatment in a small (n=47, MD=-4.9) (A11) and bigger sample (n=149, MD=-6.7, 95%CI:-9.8 to -3.6) (A9). Field et al. studied also group-IPT in pregnant women and added 6 sessions of massage therapy for the intervention group (A5). The group that received both interventions, showed a greater decrease in depression and anxiety scores. Recently these authors compared yoga or massage therapy twice weekly (A10), tai chi/yoga therapy (A8) and weekly yoga to standard antepartum care for 12 weeks (A7). These three trials showed a significant greater decrease of depression and anxiety scores in the intervention groups compared to the control groups. Uebelacker compared group yoga with a mom-bay wellness workshop and found no difference in depression scores (A27).

Acupuncture

Two trials examined the role of acupuncture, Manber and colleagues studied depression-specific acupuncture in comparison with non-specific acupuncture and massage therapy (A16-A17). In a small sample in 2004, there were no differences in pregnant women diagnosed with clinical depression after treatment nor at 10 weeks postpartum (A16). A new sample of

150 patients in 2010 showed that women who received acupuncture specific for depression experienced a greater reduction of HDRS-rates, compared with the combined controls or control acupuncture after 8 weeks of treatment (A17).

Food supplements

Three trials have explored the potential value of food supplements. For example, Freeman performed a randomized double blind placebo controlled trial to compare the use of omega-3 fatty acids to placebo, with supportive psychotherapy provided to all patients (A12) and studied therapy adherence [48]. Both groups experienced a significant improvement in self-reported and observer rated depression over 8 weeks, although there were no group differences. In contrast, Rees et al. published a negative but properly executed trial on the use of omega-3 fatty acids in a double blind, placebo-controlled trial (A23). Su et al. concluded the superiority of omega-3 fatty acids and showed that the intervention group had significantly lower mean HDRS scores (MD=-4.70, 95%CI:-7.82 to -1.58) after 8 weeks of treatment (A26). At the trial endpoint, patients in the omega-3 group also had lower depressive symptom ratings on the EPDS and BDI.

Integrative collaborative care (ICC)

Multidisciplinary care and personalized care have received a lot of attention. Melville et al. evaluated their ICC in a RCT at an obstetric outpatient clinic which included an engagement session, an assessment by a Depression Care manager and potentially supported by antidepressant medication or problem-solving therapy for primary care for 1 to 4 weeks (A18). After one year, the intervention group had significant greater decrease of depressive symptoms on the Hopkins Symptom Checklist-20 compared to the usual care group.

Anxiety disorders

Only one trial fulfilled the inclusion criteria for the treatment of anxiety disorders in pregnant women. This trial included patients that met criteria for anxiety disorder or blood- and injection phobia according to DSM-IV criteria. The sample size of the included trial was 76 patients and evaluated CBT in an open trial (A15). Patients received two sessions of group-CBT and were compared with 46 women diagnosed with blood- and injection phobia, but untreated. CBT-treated women scored significantly lower after each session and postpartum on anxiety and avoidance scores.

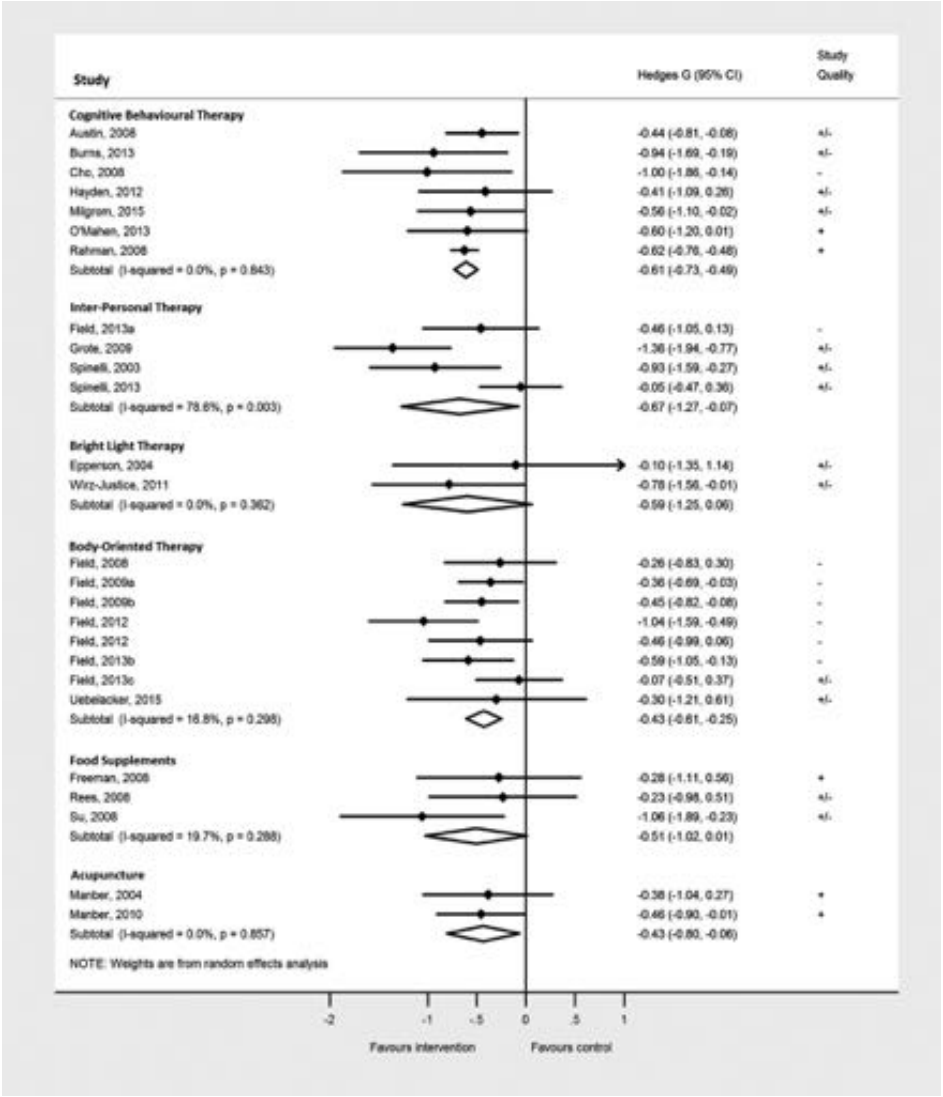
Methodological quality of trials and risk of bias

Data available for the meta-analysis was provided by 25 trials and methodological quality was reported in a risk of bias table in Appendices B. Twelve trials did not describe the procedure of concealment of allocation and randomization. Blinding of the participants was not always feasible, but in twelve trials participants or assessors were blinded. Attrition rates varied from

0 to 52%. Majority (72%) of the trials did not publish a protocol and/or was registered in a trial register. Inter-rater agreement with regards to the quality assessment was substantial (raw inter-rater agreement= 83%; κ=0.70).

A visual inspection of the funnel plot revealed that the plot was symmetric, so we had no indication of a publication bias (see Fig 3). Only three studies were identified outside the pseudo 95% confidence interval (A10,A12,A24). Also, the Egger's test did not suggest the presence of publication bias (β=0.08; 95%CI:-0.83 to 0.99; p=0.86).

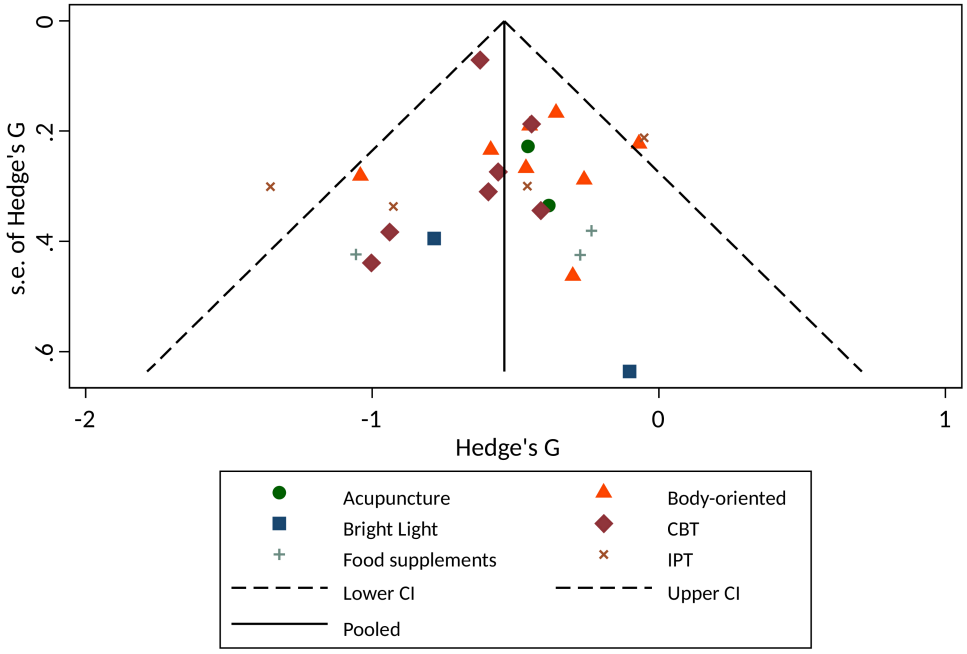
Figure 3 - Hedges *g* of interventions to reduce depressive symptoms in pregnant women.



Meta-analysis

For the patients with depression, we grouped the available interventions together in 1) CBT; 2) IPT; 3) bright light therapy; 4) body-oriented therapies; 5) acupuncture; and 6) food supplements (see Fig 2). No overall statistics were calculated for Integrating Collaborative Care (k=1) and a trial focussing on patients diagnosed with an anxiety disorder (k=1). For each intervention subgroup, we compared all available trials on improvement of psychiatric symptoms and study quality as reported in S1 Table. Analysed in a random effect model, the psycho-therapeutically interventions were both associated with reduction of depressive symptoms. In case of CBT, treatment size was medium with little inconsistency between trials (g=-0.61; 95%CI:-0.73 to -0.49), and overall effect was significant (Z-value=10.04; p<0.001). Among the 7 trials evaluating CBT, there was no evidence of heterogeneity (Tau^2<0.001; $Chi^2(6)$= 2.72; p=0.84; I^2<1%). In case of IPT the effect was also medium. However, the magnitude of the imprecision shows large inconsistencies between the trials (g=-0.67; 95%CI:-1.27 to -0.07). Inconsistency among the four IPT trials was supported by the test for heterogeneity (Tau^2=0.29; $Chi^2(3)$= 14.01; p<0.001; I^2=79%). Overall the treatment effect of IPT was significant (Z-value=2.20; p=0.03). Overall treatment effect of bright light interventions was not associated with a decrease of depressive symptoms (g=-0.59; 95%CI:-1.25 to 0.06; I^2=0%; Z-value=0.77; p=0.08). Heterogeneity was not tested significantly (Tau^2<0.001; $Chi^2(1)$= .83; p=0.36; I^2<1%). Body-oriented intervention was associated with a medium sized improvement, consistent over the trials (g=-0.43; 95%CI:-0.61 to -0.25), overall treatment effect was significant (Z-value=4.62; p<0.001). Heterogeneity was not tested significantly (Tau^2=0.02; $Chi^2(7)$= 8.41; p=0.30; I^2=17%). Treatment with food supplements was not associated with decrease of depressive symptoms (g=-0.51; 95%CI:-1.02 to -0.01; Z-value=1.92; p=0.06). Heterogeneity was not tested significantly (Tau^2=0.04; $Chi^2(2)$= 2.49; p=0.29; I^2=20%). Finally, the two trials evaluating acupuncture showed a significant medium overall treatment effect (g=-0.43; 95%CI:- 0.80 to 0.07; Z-value=2.30; p=0.02). Heterogeneity was not tested significantly (Tau^2<0.001; $Chi^2(1)$= 0.03; p=0.86; I^2<1%).

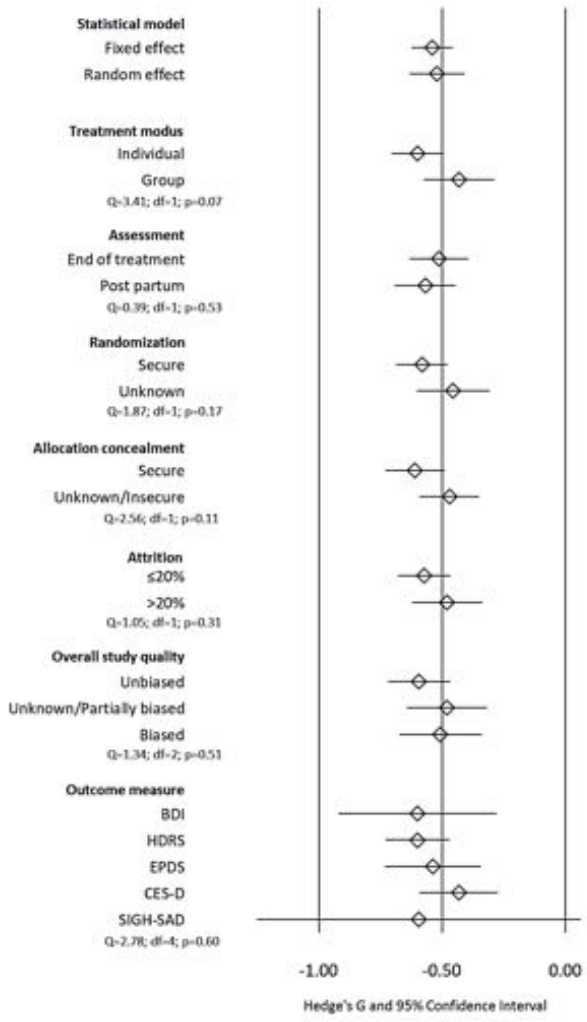
Figure 2 - Funnel plot including pseudo 95% confidence limits of the included trials (k=25) stratified by intervention.



Sensitivity analysis

Fig 4 depicts the results from the sensitivity analyses. As the figure shows, the overall treatment effect regarding symptoms of depression is robust to intervention and trial characteristics and statistical method. The mode of intervention, i.e. group vs. individual therapy, nor any of the trial design characteristics, i.e. outcome measure, moment of assessment, nor any of the trial quality characteristics showed a significant impact on the overall intervention effect. Regression analysis revealed no significant association between treatment effect and the age of the included patients (β =0.01; 95% CI:-0.03 to 0.06, p=0.69).

Figure 4 - Intervention effect in the full set of included trials (k=25) using fixed and random estimation, and for different subgroups of trials. Pooled effect sizes for subgroups of trials are estimated using random-effects estimation. Fixed-effect estimation was used to compare differences over subgroups.



Discussion

Summary of evidence

The aim of this systematic review was to provide an overview of trials that evaluated pharmacological and non-pharmacological interventions for AMD and in addition to provide an estimation of the overall effect size of categorized interventions per mental health outcome.

Given the importance of treating mental disorders during pregnancy for mother and child, this meta-analysis extends the literature [29, 33, 34, 49] by thoroughly examine all available treatments for AMD.

Until this date there are no controlled studies on the effect of psychotropic medication for AMD. We could only estimate effect sizes for treatment of patients diagnosed with Major Depressive Disorder (MDD) by a lack of studies on other mental disorders during pregnancy. A form of psychotherapy for MDD has robust effect sizes, e.g. Cognitive Behavioural Therapy (CBT, *g*=-0.61), and to a lesser extent Interpersonal Psychotherapy (IPT, *g*=-0.67). Both may hold potential benefit for pregnant women with MDD in this analysis. This is in line with current NICE guideline that advises clinicians to offer a form of psychotherapy to every pregnant woman with a history of mild to severe depression and emphasizes close consultation with patients [50].

Other potential beneficial non-pharmacological intervention categories to treat MDD were body-oriented interventions and acupuncture. Our data suggests that bright light therapy is not associated with a decrease of depressive symptoms, but this is based on two trials. Overall, we identified only a small number of studies for each intervention category with small sample sizes and potential risks of bias. We performed sensitivity analyses to evaluate the impact of these moderator variables on the overall treatment effect, but none showed to be significant. However, the ability to perform certain moderation analyses was limited by the size and quality of current English literature. In the majority of the trials only per protocol data was available and this has likely resulted in an overestimation of our effect sizes.

Our results showed that the overall effect sizes of all non-pharmacological intervention are in close range to each other and may be redeemable for one other, bearing in mind the high attrition rates of most trials. Furthermore, the effect sizes are similar or even higher than the effect of psychotropic medication in non-pregnant depressed patients [51-53]. In summary, the effect sizes of the different interventions to treat depressive symptoms are close to each other and therefore we suggest that the preference of the patient have to weigh heavily in the decision for a psychiatric treatment in a clinical setting.

Strengths and limitations

To our knowledge, a broad approach to examine various interventions for mental disorders during pregnancy is not performed before. We limited our study to a clinical group of patients with a diagnosed disorder, in order to extrapolate the evidence on treatment of AMDs for clinicians. The disadvantage of this approach is that we missed potentially effective interventions in a healthy population that could be beneficial also for a clinical sample. By pooling the interventions by six subgroups in our meta-analysis and conducting several sensitivity analyses, we believe that we have been able to show the effects of each intervention and gained insight in sources of variability between the included studies. Our estimates are lower than other meta-analysis

which report average effect for IPT, ranging between 1.14 (one-group studies) [33] to 1.26 [29]. We focused only on the treatment period during pregnancy, on a clinical diagnosis and controlled trials, therefore our results show a more robust estimate of the beneficial effect of IPT for pregnant women with MDD. Post-hoc analysis of Claridge et al. focusing on high quality clinical samples, found similar effect sizes (d=0.40) [33].

We considered also open trials in our qualitative systematic review, because it is known that this hard-to-reach population is difficult to enrol and randomize for trials, due to practical and ethical reasons. As indicated by the funnel plot and Egger test, there was likely no publication bias in this synthesis, and also our sensitivity analysis showed no potential biases. Altogether, the advantage of our broad and systematic approach resulted in a comprehensive overview and robust results.

Implications and conclusions

This meta-analysis contributes to the literature in several ways. Our review shows that the number of trials on treatment of AMD is low, although rising every year. No controlled studies were found to show evidence for the use of psychotropic medication during pregnancy. We highlight the continuing need for further research of antepartum treatment for the full spectrum of AMDs, e.g. anxiety disorders, psychotic disorders, eating disorders, psychosomatic disorder and comorbidity like personality disorders. The evidence provided is inconclusive, and is predominantly based on trials evaluating major depressive disorder during pregnancy in small sample sizes. It is recommended that future research include other mental disorders in larger numbers and study alternative non-pharmacological interventions in comparison with pharmacotherapy. Findings of alternative interventions offer the promise of efficacy without the complexity of weighing pros and cons regarding foetal exposure to psychotropic medication and maternal stress. For example body-oriented therapies (g=-0.43) and acupuncture (g=-0.43) are promising alternatives, but the evidence is based on two to four trials and the results should be replicated, preferably by researchers from different institutes. The results of omega-3 fatty acids intake are mixed and also a recent meta-analysis in non-pregnant depressed patients suggests a small, non-significant benefit. However, nearly all of the treatment efficacy might be attributable to publication bias [54]. Bright light therapy showed to be effective for the treatment of non-seasonal depression in non-pregnant population [55], but needs further research in pregnant women.

Our systematic review found also a high number of protocols, which are promising as well. For example protocols for tapering antidepressants during pregnancy [56], for a broader range of mood disorders [57-59] and a rise of mindfulness-based therapies is observed [60]. Due to the small number of participants or weaknesses in design of the studies, we could not include other alternative interventions that showed promising effect in case-series, e.g. Electroconvulsive Therapy [61] and Transcranial Magnetic Stimulation [62, 63], or in healthy

pregnant women, e.g. exercise [64], music therapy [65] or multicomponent psychotherapy [66]. For future research it would be interesting to examine the association between the severity of the disorder with the improvement of psychiatric symptoms to further personalize treatments. It should also be noted that the evidence was identified for short-term outcomes of AMD, and that further research is needed to evaluate longer-term mother and child outcomes. To conclude, in the field of perinatal psychiatry there is a lot of attention for depression and a couple of evidence-based therapies are available and redeemable. However, the broader range of mental disorder are not represented in current literature, while anxiety, bipolar and other psychotic disorders may adversely affect mother and foetus, we strongly recommend further research on both pharmacological and non-pharmacological treatment options for all mental disorders during pregnancy.

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Table 1 – Overview of included studies

MAJOR DEPRESSIVE DISORDER	Source	Study design	Participants (sample size)	Intervention, duration, (number of sessions)	Control condition	Outcome measurement of interest†† and analysis	Outcome of psychiatric symptoms
Cognitive Behavioural Therapy (CBT, k=8)	Austin, 2008	RCT	Pregnant women with an EPDS* of >10 and/or a score of >23 on the Antenatal Risk Questionnaire, or a reported prior history of depression were assessed with the depression and anxiety components of the MINI (n=191)	Group-CBT, weekly 2-hour session for 6 weeks (6)	Booklet control group	EPDS* Per protocol	Significant greater decrease of depression scores (time x treatment interaction term: F=5.81) in the intervention compared to the control group at end of treatment period and 2 months postpartum.
	Cho, 2008	RCT	Pregnant women with a score of >16 points on BDI** and MDD, verified with SCID (n=27)	Individual CBT, twice weekly 1-hour sessions (9)	Psycho-education	BDI** Per protocol	Significant greater decrease in depression scores (BDI: 9.3 vs. 18.1) in the intervention group compared to the control group at 1 month postpartum.
	Rahman, 2008	RCT	Pregnant women who met criteria for a DSM-IV MDD episode, verified with SCID (n=903)	Individual CBT-like intervention by trained primary health workers, weekly session in the last month of pregnancy and 3 sessions in the first month postpartum (7)	Untrained health workers, equal number of visits	HDRS*** ITT	Significant greater decrease in depression score (HDRS: 4.5 vs. 8.7) in the intervention group compared to the control group at 6 months postpartum.
	Hayden, 2012	RCT	Pregnant women with diabetes and with depression, determined using the DIS (n=34)	Individual CBT, weekly sessions for 10 weeks (10)	Supportive counselling (listening visits)	BDI Per protocol	No significant differences in depression scores (BDI: 17.3 vs. 22.1) between intervention and control group after treatment period
	Burns, 2013	RCT	Pregnant women who met ICD-10 criteria on the Clinical Interview Schedule-Revised (CIS-R) for depression (n=36)	Individual CBT, weekly sessions for 12 weeks (12)	Usual care	EPDS ITT	Significant difference in depression scores between the intervention group (EPDS: 7.9 vs. 13.8) and control group at 15 weeks post-randomisation (before childbirth)
	O'Mahen, 2013	RCT	Pregnant women who met the DSM-IV criteria for MDD (n=55)	Individual CBT, adapted for perinatal period, weekly 50-min sessions (12)	Usual care	BDI ITT	No significant differences in depression scores (BDI: 15.9 vs. 22.2) between intervention and control after treatment period
	Pearson, 2013†	RCT	Pregnant women who met ICD-10 criteria on the Clinical Interview Schedule-Revised (CIS-R) for depression (n=24)	Individual CBT, weekly sessions for 12 weeks (12)	Usual care	CIS-R****	Significant difference in change of depression score (CIS-R: 15.1 vs. 26.1) between intervention and control group

	Milgrom, 2015	RCT	Pregnant women with a >13 score on the EPDS and who met criteria for MDD, minor depression or adjustment disorder with mixed depression and anxiety, verified with SCID (n=54)	Individual-CBT, adapted for antenatal period, weekly 1-h sessions (8)	Individual treatment	BDI ITT	after treatment period Marginally not significant differences in depression scores (BDI: 12.8 vs. 18.4, p=0.06) between intervention and control group after treatment period
Interpersonal Psychotherapy (IPT, k=4)	Spinelli, 2003	RCT	Pregnant women with a >12 score on the HRSD and who met DSM-IV criteria for MDD (n=38)	Individual Interpersonal psychotherapy, weekly 45-min sessions (16)	Parenting education program	EPDS ITT	Significant greater decrease in depression scores (EPDS, t=2.99) in between intervention and control group after treatment period
	Grote, 2009	RCT	Pregnant women with a >12 score on the EPDS and current MDD was verified with SCID and other psychiatric disorders were assigned using the DIS (n=53)	Individual enhanced IPT-Brief, augmented with culturally relevant modifications (8)	Enhanced usual care	EPDS Per protocol	Significant greater decrease of depression diagnoses and depressive symptoms in the intervention group (EPDS: 13.6 vs. 5.7) compared to the control group after 3 months post-baseline (before childbirth)
	Field, 2013a	RCT	Pregnant women with dysthymia or major depression, verified with SCID (n=44)	Group-IPT, weekly 1 hour session for 12 weeks (12)	Peer-support group	CES-D**** Per procotol	No significant differences in depression scores (CES-D: 17.5 vs. 21.0) between intervention and control group after treatment period
	Spinelli, 2013	RCT	Pregnant women with a >12 score on the HRSD*** and diagnosis of major depressive episode, verified with SCID (n=142)	Individual IPT, weekly for 12 weeks (12)	Parenting education program	EPDS ITT	No significant differences for EPDS interaction term for treatment group between intervention and control group (F=0.61) after treatment period
Bright light therapy (k=3)	Oren, 2002	Open	Pregnant women with the diagnosis of MDD, verified with SCID (n=16)	Bright light (10000 lux), daily 1 hour sessions for 3 or 5 weeks (15-25)	ABA-design	SIGH-SAD* Per protocol	In the intervention group, SIGH-SAD depression ratings improved by 49% after 3 weeks. Subjects following 5 weeks of light treatments, mean scores on SIGH-SAD improved by 59% from baseline
	Epperson, 2004	RCT	Pregnant women with a score >20 on the SIGH-SAD and who met DSM-IV criteria for MDD (n=10)	Bright light (7000 lux), daily 1 hour session for 5 weeks (25)	500 lux dim light	SIGH-SAD Per protocol	No significant differences in observer rated depression scores between intervention (SIGH-SAD: 16.6 vs. 17.3) and control group after treatment period
	Wirz-Justice 2011	RCT	Pregnant women with a score of >10 EPDS* and met DSM-IV criteria of MDD in an	Bright light (7000 lux), daily 1 hour session for 5 weeks (25)	70 lux red dim red light	SIGH-Atypical Depression	Significant greater decrease of depression scores (SIGH-ADS, F=3.91) in the intervention

			interview with a staff psychologist (n=27)			Supplement Per protocol	group, compared to the control group after treatment period
Body-oriented therapies (k=7)	Field, 2008	RCT	Pregnant women with the diagnosis of major depression or dysthymia, verified with SCID (n=47)	Massage therapy from their partners, twice weekly for 16 weeks (32)	Control group, unspecified	CES-D Per protocol	Significant greater decrease in depression scores (CES-D: 16.5 vs. 21.4) in the intervention group compared to the control group after treatment period
	Field, 2009a	RCT	Pregnant women with the diagnosis of major depression, verified with SCID (n=149)	Massage therapy from their partners, twice weekly for 12 weeks 20 min sessions (24)	Standard treatment control group	CES-D Per protocol	Significant greater decrease in depression scores (CES-D: 14.8 vs. 21.5) in the intervention group compared to the control group after treatment period
	Field, 2009b	RCT	Pregnant women with the diagnosis of major depression or dysthymia, verified with SCID (n=112)	Group-IPT and massage therapy, weekly 1 hour session for 6 weeks (6)	IPT	CES-D Per protocol	Significant greater decrease in depression scores (CES-D: 16.6 vs. 18.0) in the intervention group compared to the control group after treatment period
	Field, 2012a 2012b	RCT	Pregnant women with the diagnosis of depression, verified with SCID (n=84)	Group yoga (2012a) or massage therapy (2012b), twice weekly 20 min sessions for 12 weeks (24)	Standard prenatal care	CES-D Per protocol	Significant greater decrease of depression scores in both intervention groups (CES-D massage: 21.3 vs. yoga: 20.1) compared to the control group (CES-D: 19.3) after treatment period
	Field, 2013b	RCT	Pregnant women who met criteria for major depression or dysthymia on the SCID (n=46)	Group tai chi/yoga therapy, weekly 20 min sessions for 12 weeks (12)	Control group (waitlist)	CES-D Per protocol	Significant greater decrease in depression scores (CES-D 23.5 vs. 23.9) in the intervention group compared to the control group after treatment period
	Field, 2013c	RCT	Pregnant women who met criteria for depression, verified with SCID (n=92)	Group yoga therapy, weekly 20 min sessions group sessions for 12 weeks (12)	Social support group	CES-D Per protocol	Significant greater decrease in depression scores (CES-D 23.8 vs. 25.2) in the intervention group compared to the control group after treatment period
	Uebelacker 2015	RCT	Pregnant women who met criteria for depression, verified with SCID (n=20)	Group yoga therapy, weekly 75 min sessions for 9 weeks (9)	Mom-baby wellness workshops	EPDS Per protocol	No significant differences in decrease of depression scores (EPDS 5.3 vs. 7.4) between intervention and control group
Acupuncture (k=2)	Manber, 2004	RCT	Pregnant women with a score of >14 on HDRS and who met the criteria for major depressive episode, verified with SCID (n=61)	Individual depression-specific acupuncture, 25-30 min sessions for 8 weeks (12)	Non-specific acupuncture Massage	HDRS ITT	No significant difference in decrease of depression scores (HDRS 9.6) between intervention and control groups (HDRS non-specific acupuncture: 12.6 and massage: 10.3) after treatment period

	Manber, 2010	RCT	Pregnant women with a score of >14 on HDRS and who met the criteria for MDD, verified with SCID (n=150)	Individual depression-specific acupuncture, 8 weeks (12)	Non-specific acupuncture Massage	HDRS ITT	Significant greater decrease of depression scores for the intervention group compared with non-specific acupuncture (Cohen's d=**0**.46) and for both control conditions (Cohen's d=0.39) after treatment period
Food supplements (k=3)	Freeman, 2008	RCT	Pregnant women with an EPDS* score >9 and a diagnosis of MDD, verified with SCID (n=21)	Omega-3-fatty acids (1,9 mg/daily) and 30 minute session of supportive psychotherapy, 8 weeks (6)	Placebo, 30 min sessions of supportive psychotherapy (6)	EPDS Modified-ITT	No significant difference in decrease of depression scores between the intervention (EPDS 7.8 vs. 11.2) and control group after treatment period during pregnancy
	Rees, 2008	RCT	Pregnant women with a score of >13 on the EPDS* and >14 on the HDRS who met DSM-IV criteria for MDD or dysthymia, verified with the CIDI and a clinical assessment by a psychiatrist (n=26)	Omega-3 fatty acids, 6g day, for 6 weeks	Placebo	EPDS ITT	No significant differences between intervention group and the control group on EPDS (8.5 vs. 9.0) after treatment period
	Su, 2008	RCT	Pregnant women who met DSM-IV criteria for MDD, verified with the MINI (n=36)	Omega-3-fatty acids, 3.4g day, for 8 weeks	Placebo	EPDS ITT	Significant lower depression score in the intervention group (EPDS 7.1 vs. 14.0) compared to the control group after treatment period
Integrative Collaborative Care (ICC, k=1)	Melville, 2014)	RCT	Pregnant women with a score of >10 on PHQ-9 and diagnosis of MDD and/or dysthymia, verified with MINI (n=205)	Integrative collaborative care: engagement session, assessment by Depression Care manager and supported by antidepressant medication or individual problem-solving therapy for primary care every 1-4 weeks	Usual care	SCL-20** ITT	No significant differences in decrease of depression score between intervention (SCL-20: 0.72 vs. 0.69) and control groups at 6 months follow-up
ANXIETY DISORDERS							
Cognitive Behavioural Therapy (CBT, k=1)	Lilliecrona str, 2010)	Open	Pregnant women who met DSM-IV criteria for blood and injection phobia (n=76) and 70 healthy controls	Group-CBT for blood- and injection phobia, two sessions (2)	Regular antenatal health care	IPSA*** ITT	Significantly greater decrease of IPSA scores for the intervention group (IPSA: 18.6 vs. 40.3) compared to the untreated group at 3 months postpartum, but higher scores than healthy controls (IPSA: 2.5)

Notes:
† Not included in the meta-analysis.
†† Most trials used multiple outcomes measures and our interest is to include the outcome measure that operationalized the clinical psychiatric symptoms best.
Questionnaires = * Edinburgh Postnatal Depression Scale (EPDS, range 0-30), ** Beck's Depression Inventory (BDI, range 0-63), *** Hamilton Depression Rating Scale (HDRS, range 0-54), **** Clinical Interview Schedule-Revised (CIS-R, range 0-57), ***** Center for Epidemiological Studies Depression scale (CES-D, range 0 - 60), # Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders (SIGH-SAD, range 0-23), ## Hopkins Symptom Checklist-20 (SCL-20, range 0-4) ### Injection Phobia Scale-Anxiety (IPSA, range 0-72)

Appendices A - Reference list of all included articles

References Qualitative synthesis: 1 - 29

References Quantitative synthesis: 1-14, 16, 17, 19, 22-29

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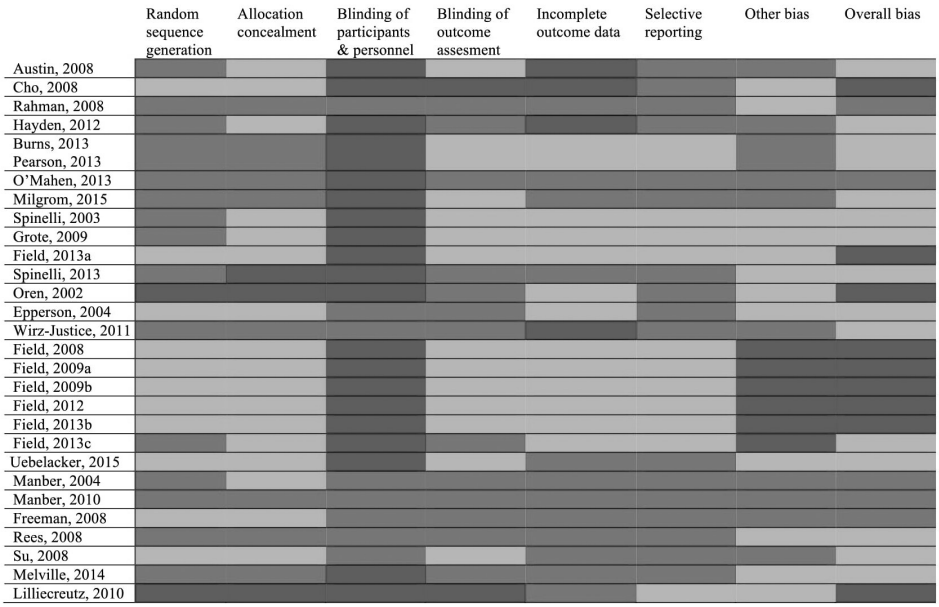
Appendices B - Risk of bias table



Chapter 3

Group-based multicomponent treatment to reduce depressive symptoms in women with co-morbid psychiatric and psychosocial problems during pregnancy: a randomized controlled trial

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Under review

Abstract

Background: Depressive symptoms in pregnant women, which are common and debilitating, are often co-morbid with other mental disorders (e.g. anxiety and personality disorders), and related to low socioeconomic status (SES). This situation may hamper treatment outcome, which has often been neglected in previous studies on the treatment of depression during pregnancy. We developed a new group-based multicomponent treatment (GMT) comprising cognitive behavioral therapy, psycho-education and body-oriented therapy and compared the effect on depressive symptoms with individual counseling (treatment as usual, TAU) in a heterogeneous group of pregnant women with co-morbid mental disorders and/or low SES.

Methods: An outpatient sample from a university hospital of 158 pregnant women who met DSM-IV criteria for mental disorders were included and 99 participants were randomized to GMT or TAU from January 2010 until January 2013. The Edinburgh Depression Scale (EDS) was used at baseline, every 5 weeks during pregnancy and as the primary outcome measure of depressive symptoms at 6 weeks postpartum. Secondary outcome measures included the clinician-reported Hamilton Depression Rating Scale (HDRS), obstetric outcomes and a 'Patient Satisfaction' questionnaire.

Results: 155 participants were included the intention-to-treat (ITT)-analysis. GMT was not superior above TAU according to estimated EDS (β=0.13, CI=-0.46 – 0.71, p=0.67) and HDRS scores (β=-0.39, CI=-0.82 – 0.05, p=0.08) at 6 weeks postpartum. There were no differences in secondary outcomes between the GMT and TAU, nor between the randomized condition and patient-preference condition. Limitations: The ability to detect an effect of GMT may have been limited by sample size, missing data and the ceiling effect of TAU.

Conclusions: GMT is an acceptable treatment for a heterogeneous group of pregnant women with depressive symptoms and co-morbid mental disorders and/or low SES, but not superior to TAU. Further research should focus on understanding and treating co-morbid disorders and psychosocial problems during pregnancy.

Introduction

Depression during pregnancy is common, with prevalence rates varying between 3.1% and 11.0% in the general population [1]. Fortunately, there is growing awareness of the risks of untreated prenatal depression for both mother and her unborn child [2, 3]. For example, untreated or incompletely managed depressive symptoms increase the risk of postpartum depression [4] and maternal suicide [5]. Also, indirect influences of prenatal depression (e.g. reduced self-care, more smoking and substance use) [6] [7] and direct influences of maternal stress in utero associated with depression may impair fetal development [8], leading to a lower birth weight [9], premature birth [10] and long term infants' neurodevelopment [11, 12]. The growing awareness of the negative impact of maternal depression on maternal and child outcomes has led to the development of various psychosocial and psychological therapies to treat depression during pregnancy [13, 14]. Because of unknown risks of psychotropic medication for the unborn child [15], clinicians and patients express a preference for non-pharmacological interventions [16]. There are several studies that investigated the effects of psychotherapy on depression during pregnancy [17-19]. For example, Cognitive Behavioral Therapy [20-23], Interpersonal Psychotherapy [24, 25] and mindfulness-based cognitive therapy [26] showed small to moderate effect sizes in pregnant women [18]. Various psychosocial and multimodal interventions have been carried out during pregnancy to reduce depressive symptomology, however the evidence is inconclusive [27-29]. The majority of these studies targeted women with sub-clinical symptomatology, or had the primary aim to prevent postpartum depression, for example in antenatal classes [30, 31].

However, next to depression, other psychiatric disorders may co-exist during pregnancy [32-34]; 5.0% to 24.0% of patients in a clinical setting have two or more diagnosed co-morbid psychiatric disorders [35-37], with a high incidence of anxiety-related disorders. To our knowledge, only one study focused on the prevalence of personality disorders during pregnancy, which turned out to be 6% based on a self-report measure [38]. Emerging evidence suggests that comorbidity and psychosocial problems, including low socioeconomic status (SES) are important risk factors in the pathway of depression leading to adverse obstetric outcomes [39]. Also, women with pre-existing psychiatric vulnerability might relapse during pregnancy [38], for example due to unplanned pregnancy or inadequate social support or unhealthy life style. Moreover, treatment of pregnant women with psychiatric disorders puts extra challenge in a limited period of time because of lower rates of engagement and compliance, comorbidity, stigma and other barriers to seek treatment [40-43]. Women in large urban areas might be more at risk due to clustering of a multi-ethnic population and large socioeconomically deprived neighbourhoods, which is associated with adverse birth outcomes [44, 45]. As a consequence, in clinical practice, psychiatrists are often faced with a heterogeneous group of pregnant women with psychiatric co-morbidity and low SES who are not eligible for routine treatments mainly focusing on depression.

Based on longstanding clinical experience and relying on evidence-based components from other treatments during pregnancy [19], we composed a Group-based Multicomponent Treatment (GMT) that aims to reduce stress, depressive and anxiety symptoms in women with co-morbid psychiatric and psychosocial problems with a special focus on emotional and practical preparation for motherhood. This weekly one-day treatment is provided in an open group, as positively viewed by women in a recent Cochrane review [46], to encourage peer-support and decrease social isolation and stigma. The treatment consisted of the following 5 consecutive components, based on our longstanding clinical experience and the existing evidence to treat mental disorders during pregnancy [19, 47]: 1) weekly evaluation of treatment goals by a social psychiatric nurse; 2) psycho-education by a perinatal psychiatrist; 3) cognitive behavioral therapy (CBT) by a clinical psychologist; 4) body-oriented therapy by an Infant Mental Health specialist, and 5) relaxation therapy by a creative arts therapist. Treatment as usual (TAU) comprised low frequent, individual counseling sessions provided by a social psychiatric nurse or a medical doctor. Both treatments were provided at the outpatient clinic and the number of sessions was based on an assessment of the patient's needs.
We hypothesized that Group-based Multicomponent Treatment (GMT) would be more effective than treatment as usual (TAU) in reducing depressive symptoms in women with co-morbid psychiatric and psychosocial problems. Because of known low recruitment and engagement rates in this hard-to-reach population [42], we introduced a patient-preference condition, for women not willing to randomize, to additionally investigate the effect of patients' preference for a group-based or individual therapy on treatment response [48]. This patient-preference randomized controlled trial enabled us to compare the effectiveness of our GMT vs. TAU and randomized vs. patient-preference conditions, in terms of reduction of depressive symptoms, obstetric outcomes, feasibility and patient's satisfaction on the treatment.

Methods

Study design and procedure

The study design was a single center patient-preference randomized controlled trial, comparing Group-based Multicomponent Treatment (GMT) versus individual counseling (treatment as usual, TAU). Eligible participants were randomized to GMT and TAU condition (1-to-1), stratified for gestational age less <24 weeks or more than ≥24 weeks). Participants who rejected randomization were invited to participate in parallel non-randomized patient-preference treatment conditions. Participants in the patient-preference treatment conditions underwent the same procedures as the randomized patients. This design provided four arms: a) randomized GMT; b) randomized TAU; c) patient-preference GMT and d) patient-preference TAU. We compared treatment effect of GMT versus TAU, and randomized versus patient-preference conditions.

Participants

Pregnant women were recruited between January 2010 and January 2013 after a diagnostic procedure at the tertiary outpatient clinic for perinatal psychiatry of the Department of Psychiatry, Erasmus University Medical Center (Erasmus MC), Rotterdam, the Netherlands. Rotterdam is the second largest city of the Netherlands and is characterized by a multi-ethnic population and large socioeconomically deprived neighborhoods. Patients were referred by general practitioners, midwives, gynecologists and psychiatrists from the bigger area of Rotterdam-Rijnmond. Inclusion criteria were: a) psychiatric and/or personality disorder verified with the Structured Clinical Interview for DSM-IV-TR Disorders (SCID) [49] by a trained medical doctor; b) gestational age between 12 and 33 weeks; and c) written informed consent. Exclusion criteria were: a) indication for hospital admission; b) inability to function in a group due to severe behavioral problems e.g. aggression, suicidal behavior, uncontrollable addictive behavior; c) insufficient command of the Dutch language; or d) inability to visit the outpatient clinic. Ethical approval was obtained from the hospital's Medical Ethics Committee of the Erasmus Medical Center. The trial was registered in the Dutch Trial Registry (www.trialregister.nl, number NTR3015).

Group-based multicomponent treatment

We composed a weekly, all-day (6 hours) therapy for an open group of maximum eight pregnant women, as described in the GMT treatment protocol [47]. The treatment focuses on reducing stress, depressive and anxiety symptoms and preparing for the emotional and practical impact of motherhood. At the start of the treatment each woman formulates individual treatment goals, which she shared with the other group members. The treatment consisted of the following consecutive components of one hour: 1) weekly evaluation of treatment goals and enhancing social support at home by a social psychiatric nurse; 2) psycho-education by a perinatal psychiatrist, with a focus on recognizing and interpreting psychiatric symptoms and stimulating healthy behavior; 3) cognitive behavioral therapy (CBT) by a clinical psychologist aiming at strengthening coping strategies, problem-solving techniques and avoiding potential stressful situations; 4) body-oriented therapy by an Infant Mental Health specialist, focusing on increasing maternal mentalization and stimulating bonding to the unborn child, and 5) expressive and relaxation therapy by a creative arts therapist, who provides women with several techniques and activities to find distraction and reduce stress when they are at home. The content changed every week. Content was adapted to the needs of the participants, but also covered recurring themes like 'preparing for motherhood and delivery'.

TAU comprised low frequent, individual counseling sessions for approximately 1 contact hour provided by a social psychiatric nurse or a medical doctor at the outpatient clinic for perinatal psychiatry at the Erasmus MC. This could be on a weekly to monthly basis, based on an assessment of the patient's needs. The primary goal of the counseling is providing psycho-

education, emotional and practical preparation for motherhood and enhancing social support at home.
In both conditions, if necessary, patients were seen by a psychiatrist to monitor psychiatric symptoms and, if applicable, evaluate the effect of psychiatric medication. Median number of sessions for both treatment conditions was 4 (range 1 – 23) during pregnancy.

Outcomes and data collection

The primary outcome was the change of the Edinburgh Depression Scale (EDS) score at 6 weeks postpartum. The EDS is a 10-item self-report questionnaire that is validated to measure depressive and anxiety symptoms during pregnancy (score range: 0-30). Secondary outcomes were a) the score of the Hamilton Depression Rating Scale (HDRS) at 6 weeks. The HDRS was added as a clinician-rated scale to assess depressive symptoms based on 17-items (score range: 0-52) [50]. Other secondary outcomes were b) obstetric outcomes e.g. perinatal (gestational diabetes, pre-eclampsia, pregnancy-induced hypertension or suspected fetal distress) and postnatal complications (neonatal or maternal hospitalization), mode of delivery, gestational age, birth weight and pain relief during delivery; and c) Patient satisfaction expressed as a weekly mark ranging from 1= not at all to 10= most satisfactory on the treatment. Weekly scores were averaged per patient.
Participant and clinician completed the EDS and HDRS at baseline, 5, 10 and 15 weeks after treatment onset. Assessments were conducted due to personal contact at the outpatient clinic, or by telephone or via postal questionnaire and the preferences of the participants were taken into account. Treatment satisfaction was assessed weekly for which participants received a text message as a reminder. Demographic characteristics, baseline EDS and HDRS were assessed before randomization. At 6 weeks postpartum, a researcher collected the EDS, HDRS, obstetric outcomes and treatment satisfaction during a home-visit interview. Demographic characteristics, psychiatric history, compliance, obstetric outcomes were collected from the electronic patient records.
We expected a small to moderate treatment effect (eta2 of 0.05 to 0.10 of time x treatment interaction) on affective symptoms (measured using the EDS) for women in the randomized condition [19]. To demonstrate this (with an alpha of 0.05 and beta of 0.80), we needed a sample size of 96 pregnant women per arm (192 in total). We aimed at inviting 275 pregnant women for participation in the RCT and preference group, adjusting for a 30% of participants not willing to consent for study participation. No a priori power calculation was performed with regards to the estimated treatment effect for women in the patient-preference conditions.

Statistical analyses

Baseline characteristics were compared between the randomized condition and patient-preference condition. Continuous variables (EDS and HDRS-scores on baseline, maternal and

gestational age) were tested using T-tests; categorical variables (parity, planned pregnancy, marital status, ethnicity, educational level, employment status, psychiatric diagnosis, personality disorder, previous episode of depression and/or anxiety, psychotropic medication use, smoking, alcohol and illicit drug use) were tested using Chi2-tests. As primary analysis we estimated the change of EDS and HDRS scores over time between the randomized and patient-preference condition as well as between the randomized GMT and TAU conditions using generalized linear mixed modelling analysis. In the random-intercept model we included time, treatment allocation (GMT vs. TAU or randomized vs. patient-preference), and the time x treatment allocation interaction, as well as the standardized baseline score of EDS or HDRS. Regression coefficients including 95% Confidence Interval (CI) and p-value are reported. Primary analyses were conducted according to the intention-to-treat (ITT)-principle and excluded only participants who lost their pregnancy during the study. By means of sensitivity analysis, we repeated our primary analysis using 1) dichotomized outcomes of the EDS baseline using cut-off score ≥13 2) on a subsample of the women having an EDS score ≥10 at baseline [52]; 3) on a subscale of the EDS focusing on anxiety (item 3, 4 and 5) [53]; 4) adjusted for age, education level, parity and ethnicity; and a per protocol analysis based on a compliance rate of ≥50% attendance [54, 55]. Compliance rate was defined as the proportion of attended treatment sessions related to the total number of offered treatment sessions during the treatment period. The treatment period is the number of weeks between date of informed consent and delivery date, or drop-out date because of withdrawal of informed consent or lost to follow-up. Participants were permitted to rebook a session. Differences on obstetric outcomes between the randomized and patient-preference condition as well as between the randomized GMT and TAU conditions were analyzed using linear (continuous outcomes, i.e. gestational age, birth weight) and logistic regression (categorical outcomes, i.e. (perinatal and postnatal complications, mode of delivery, prematurity, birth weight and pain relief during delivery) outcomes. By means of observational analysis, we repeated the analyses comparing GMT versus TAU within the patient-preference condition. Results are reported in Supplementary Tables 1 and 2.

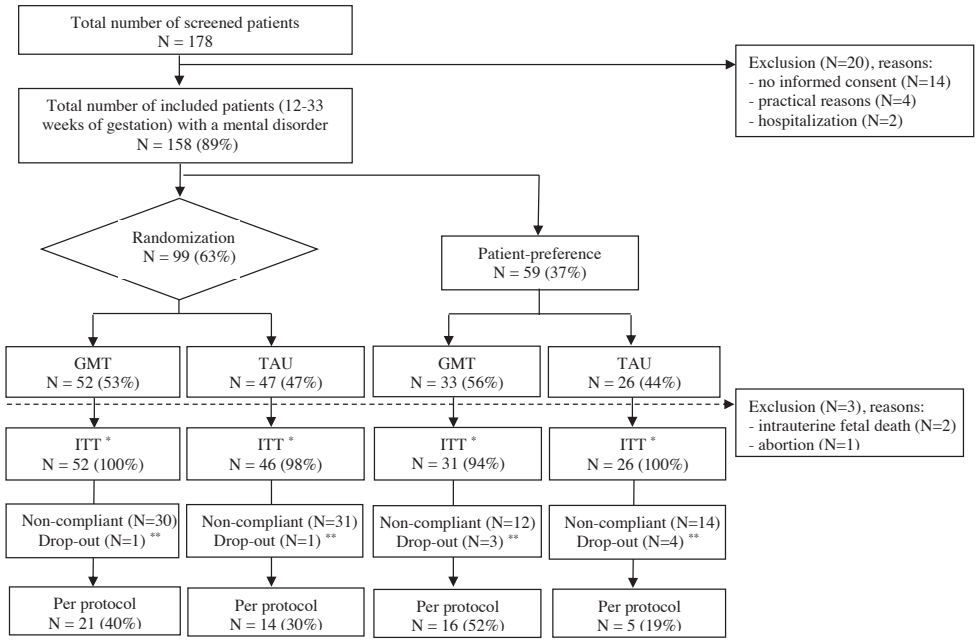
To explore whether subgroups of women benefitted more from the treatment, primary analyses were repeated in the sample stratified by 1) non-viable gestational age of <24 weeks or ≥24 weeks; 2) psychiatric disorders e.g. depressive and anxiety disorder; 3) the presence of a personality disorder; 4) use of psychotropic medication which may dilute the treatment effect; 5) ethnicity; and 6) overall treatment satisfaction.

Data was checked for non-normality and outliers. The majority of women were assessed three or more times during the study (N=116; 75%). In total, the dataset included 58% of EPD, and 52% of HDRS assessments. Patient-preference subsample, and 10 and 15 week follow-up assessments showed most missing assessments (54%, 56%, and 81% missing assessments, respectively). Missings were mainly due to con-compliance with treatment,

drop-out, and incomplete assessments. Non-compliance with treatment and assessment schedule increased over the course of pregnancy, as the physical burden of the pregnancy increased with the approach of the delivery date. With regards to secondary outcomes measures, 29% of data were missing. Missing data on secondary outcomes were handled using multiple imputations. Ten imputed datasets were created and all predictor and outcome variables were used for imputation modelling. We report pooled estimates [56]. Analyses were performed using SPSS 24.0.

Results

Figure 1 - Flow chart of the study



Note:
* Intention-to-treat analysis
** Non-compliance is defined as less than 50%, the percentage of treatment sessions within the potential treatment period in weeks between delivery date and date of informed consent. Drop-out is defined as withdrawal of informed consent or lost to follow-up.

Flowchart and demographic characteristics

Figure 1 displays the flow chart of the study. A total of 158 participants were included in the study, 99 (63%) participants consented to randomization; and 59 (37%) participants declined randomization but agreed to participate in the patient-preference condition. One participant terminated her pregnancy at a gestational age of 20 weeks and two pregnancies

resulted in fetal death. We included 155 participants in the intention-to-treat (ITT)-analysis, 98 participants from the randomized group and 57 participants from the non-randomized group. Non-compliance and drop-out did not differ between the randomized groups (GMT 40.3% vs. TAU 30.4%, p=0.29). Compliance was comparable between the randomized condition (35/98 participants, 35.7%) and patient-preference condition (21/57 participants, 36.8%). There were no baseline differences between participants who were non-compliant or dropped-out and those who were included in the per protocol analysis, only participants with a planned pregnancy were less likely to be compliant (p=0.03).

Table 1 shows the baseline characteristics for each of the four conditions. Presented characteristics showed no significant differences between the randomized and patient-preference condition, with the exception that the randomized condition composed more primiparae. Participants who planned their pregnancy were more likely to choose GMT, instead of TAU. A major depressive disorder was diagnosed in 46.2% of all participants and one third suffered from an anxiety disorder. Almost half (49.4%) of the participants met criteria for a personality disorder and most prevalent were Cluster B disorders, e.g. borderline personality disorder. Half (50.0%) of the participants reported a history of two or more episodes of an anxiety disorder or depression. More than one third (38.6%) of all participants used psychotropic medication during the treatment. There were no differences in baseline symptomatology score on EDS or HDRS between the randomized and patient-preference condition, and between GMT and TAU in the patient-preference condition.

Treatment effect after six weeks postpartum

Table 2 shows the regression coefficients for EDS scores for the primary outcome, various subgroups and sensitivity analysis. In the randomized condition, GMT was not superior above TAU according to estimated EDS (β=0.13, CI=-0.46 – 0.71, p=0.67) and HDRS scores (β=-0.39, CI=-0.82 – 0.05, p=0.08). There were no differences in observed mean EDS and HDRS scores in the randomized condition compared to the patient-preference condition. The sensitivity and subgroup analysis supported the findings of our primary analysis. None of the sensitivity or subgroup analysis (stratification, psychiatric disorder, personality disorder, psychotropic medication, ethnicity, substance use and treatment satisfaction) were significantly different between GMT and TAU, neither randomized vs. patient-preference condition. Observational analyses (reported in Supplementary Table 1) show no differences between GMT and TAU of the estimated means for EDS scores for the primary outcome, and with regards to sensitivity and subgroup analyses.

Table 1 – Demographic and clinical characteristics of 158 included participants in the study

	RANDOMIZED		PATIENT-PREFERENCE		PATIENT-PREFERENCE GMT VS. TAU	RANDOMIZED VS. PATIENT-PREFERENCE
GMT N = 52	TAU N = 47	GMT N = 33	TAU N = 26			
Demographic characteristics	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p-value	p-value
Maternal age (years)	29.4 (4.5)	30.8 (5.5)	30.8 (5.5)	30.4 (4.4)	0.76	0.52
Gestational age (weeks)	21.1 (6.1)	21.1 (6.7)	19.8 (5.5)	22.5 (6.4)	0.08	0.94
	N (%)	N (%)	N (%)	N (%)		
First child	33 (63.5)	25 (53.2)	17 (51.5)	7 (26.9)	0.06	0.03
Planned pregnancy	33 (63.5)	24 (51.1)	22 (66.7)	8 (30.8)	0.006	0.41
Marital status						
Married/co-habiting	43 (82.7)	36 (76.6)	26 (78.8)	21 (80.8)	0.99	0.98
Ethnicity						
Caucasian	46 (88.5)	36 (76.6)	26 (78.8)	18 (69.2)	0.55	0.21
Education level						
Low education level	40 (76.9)	31 (66.0)	21 (63.6)	19 (73.1)	0.58	0.60
Employment status						
Unemployed	43 (82.7)	28 (59.6)	27 (81.8)	17 (65.4)	0.15	0.70
Clinical characteristics	N (%)	N (%)	N (%)	N (%)		
Axis 1 Psychiatric disorder					0.55	0.64
Depressive disorder	26 (50.0)	23 (48.9)	12 (36.4)	12 (46.2)		
Anxiety disorder	14 (26.9)	15 (31.9)	11 (33.3)	10 (38.5)		
Psychotic disorder	2 (3.8)	1 (2.1)	1 (3.0)	0		
Other [a]	1 (1.9)	2 (4.3)	2 (6.1)	2 (7.7)		
No Axis 1 disorder	9 (17.3)	6 (12.8)	7 (21.2)	2 (7.7)		
Axis 2 Personality disorder					0.71	0.18
Cluster A	1 (1.9)	1 (2.1)	0	0		
Cluster B	19 (36.5)	13 (27.7)	13 (39.4)	8 (30.8)		
Cluster C	4 (7.7)	7 (14.9)	7 (21.2)	5 (19.2)		
No personality disorder	28 (53.8)	26 (55.3)	13 (39.4)	13 (50.0)		
Previous episode of anxiety/depression[b]					0.12	0.31
≥ 2 episodes	9 (17.3)	12 (25.5)	14 (42.4)	5 (19.2)		
None	31 (59.6)	21 (44.7)	14 (42.4)	13 (50.0)		
	12 (23.1)	14 (29.8)	5 (15.2)	8 (30.8)		
Psychotropic medication use						
SSRI/nSRI/TCA	14 (26.9)	16 (34.0)	15 (45.5)	8 (30.8)	0.50	0.34
Antipsychotics	1 (1.9)	0	1 (3.0)	1 (3.8)		
Lithium	0	3 (6.4)	0	0		
Benzodiazepines	1 (1.9)	1 (2.1)	0	0		
Other [c]	1 (1.9)	0	0	0		
None	35 (67.4)	27 (57.5)	17 (51.5)	17 (65.4)		
Smoking in pregnancy [d]	19 (36.5)	18 (38.3)	16 (48.5)	8 (30.8)	0.17	0.68
Alcohol in pregnancy [d]	13 (25.0)	13 (27.7)	8 (24.2)	5 (19.2)	0.65	0.55
Illicit drug use [d]	6 (11.8)	2 (4.3)	3 (9.1)	2 (7.7)	0.85	0.95
Symptomatology at baseline	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
EDS score	14.4 (7.5)	15.9 (7.5)	14.8 (7.0)	15.7 (8.1)	0.65	0.96
HDRS score	11.8 (5.8)	11.6 (5.7)	10.6 (6.4)	12.0 (5.0)	0.38	0.63

Note:

[a] Includes: eating disorder and ADHD

[b] An episode of anxiety or depression which needed treatment

[c] Includes: ADHD medication

[d] Any exposure during pregnancy

Table 2 – Estimated means of Edinburg Depression Scale (EDS) at six weeks postpartum between GMT vs. TAU, and randomized vs. patient-preferenc[e^]

	RANDOMIZED		PATIENT-PREFERENCE		GMT vs. TAU		RANDOMIZED VS. PATIENT-PREFERENCE	
	GMT N = 52	TAU N = 46	GMT N = 33	TAU N = 26	β [#] (95% CI)	p-value	β (95% CI)	p-value[##]
Primary outcome: EDS mean (SE)	10.1 (0.8)	9.9 (0.9)	10.4 (1.3)	10.0 (1.6)	0.13 (-0.46 – 0.71)	0.67	0.11 (-0.44 – 0.66)	0.69
Hamilton Depression Rating Scale estimated mean (SE)	5.6 (0.6)	7.7 (0.6)	7.1 (1.0)	5.1 (1.1)	-0.39 (-0.82 – 0.05)	0.08	0.07 (-0.33 – 0.47)	0.73
Sensitivity analysis								
Estimated mean EDS score (SE)	**GMT**	**TAU**	**GMT**	**TAU**	**β [#] (95% CI)**	**p-value**	**β (95% CI)**	**p-value[##]**
Dichotomised outcome (cut-off EDS<13) (estimated proportion below cut-off, SE)	0.81 (0.1)	0.72 (0.1)	0.79 (0.1)	0.84 (0.1)	0.60 (-0.26 – 0.38)	0.72	0.51 (-0.23 – 0.33)	0.71
Inclusion criterion of baseline cut-off score ≥10 on EDS	11.7 (0.9)	11.4 (0.9)	10.9 (1.4)	11.8 (1.7)	0.07 (-0.58 – 0.73)	0.82	0.17 (-0.45 – 0.79)	0.67
EDS anxiety subscale	4.4 (03)	3.8 (0.3)	4.5 (0.5)	4.8 (0.6)	-0.03 (-0.71 – 0.65)	0.92	-0.13 (-0.73 – 0.48)	0.69
Adjusted mean score *	10.2 (0.9)	9.8 (0.9)	10.2 (1.4)	9.6 (1.7)	0.15 (-0.44 – 0.74)	0.62	0.12 (-0.43 – 0.67)	0.67
Per Protocol mean score **	10.9 (1.0)	11.1 (1.4)	11.6 (2.0)	12.2 (3.2)	-0.05 (-0.96 – 0.86)	0.92	0.05 (-0.82 – 0.92)	0.92
Subgroup analysis								
Estimated mean EDS score (SE)	**GMT**	**TAU**	**GMT**	**TAU**	**β [#] (95% CI)**	**p-value**	**β (95% CI)**	**p-value[##]**
Stratification based on gestational age at inclusion: <24 weeks	9.5 (0.9)	9.5 (1.2)	9.0 (1.4)	5.1 (2.5)	0.18 (-0.58 – 0.94)	0.63	-0.16 (-0.84 – 0.52)	0.64
▪ ≥24 weeks	11.9 (1.3)	10.8 (1.1)	17.8 (3.3)	14.2 (2.0)	0.02 (-0.84 – 0.89)	0.96	0.79 (-0.06 – 1.64)	0.07
Categorized by psychiatric disorder:								
▪ depression	10.8 (1.2)	11.6 (1.3)	8.5 (2.4)	11.4 (2.2)	-0.01 (-0.93 – 0.90)	0.98	-0.18 (-1.09 – 0.73)	0.70
▪ anxiety	11.3 (1.3)	9.8 (1.3)	11.9 (1.8)	9.8 (2.5)	0.21 (-0.77 – 1.10)	0.67	0.14 (-0.72 – 1.00)	0.75
Presence of personality disorder:	11.9 (1.1)	9.1 (1.3)	8.3 (1.6)	11.9 (2.4)	0.60 (-0.27 – 1.46)	0.17	0.17 (-0.61 – 0.95)	0.66
▪ no personality disorder	8.6 (1.1)	10.6 (1.2)	12.4 (1.9)	8.7 (2.0)	-0.27 (-1.07 – 0.54)	0.51	0.12 (-0.64 – 0.88)	0.75
Psychotropic medication use:	8.3 (1.4)	8.6 (1.3)	8.9 (1.8)	8.5 (2.5)	-0.15 (-1.12 – 0.83)	0.77	-0.48 (-1.35 – 0.40)	0.28
▪ no use	11.4 (0.9)	11.0 (1.1)	12.5 (1.8)	10.8 (1.9)	0.20 (-0.51 – 0.91)	0.58	0.65 (-0.01 – 1.31)	0.05
Caucasian ethnicity:	9.4 (0.8)	10.1 (1.0)	9.7 (1.3)	10.3 (1.8)	-0.07 (-0.69 – 0.56)	0.83	0.22 (-0.37 – 0.80)	0.47
▪ non-Caucasian	14.2 (2.5)	10.0 (1.9)	12.4 (3.4)	10.9 (3.1)	0.85 (-0.81 – 2.51)	0.31	0.01 (-1.36 – 1.38)	0.98
Patients treatment satisfaction on a weekly mark: <6	11.7 (2.6)	10.5 (2.6)	-	-	0.10 (-2.02 – 2.21)	0.92	-1.05 (-3.53 – 1.42)	0.40
▪ ≥6	11.1 (0.9)	10.4 (1.1)	8.7 (1.2)	9.6 (2.3)	0.20 (-0.54 – 0.96)	0.58	0.22 (-0.41 – 0.86)	0.49

Note:

^ Generalized linear mixed model including time, treatment allocation and baseline score of EDS/HDRS, reported in regression coefficients with confidence intervals and p-values

[#] Difference between GMT vs. TAU in the randomized condition, TAU is reference condition.

[##] Difference between randomized vs. patient-preference conditions, randomized condition is reference.

* Adjusted for age, ethnicity, education level, and parity.

** Per protocol analysis is based on ≥50% compliance during treatment period.

Table 3 shows the obstetrical outcomes for the four conditions. There were no significant differences on this secondary outcome between GMT and TAU, nor for the randomized versus the patient-preference condition. Supplementary Table 2 shows the observational analysis in the patient-preference condition for the obstetrical outcomes. Participants who chose GMT were more likely to deliver a child with a lower birth weight. The higher number of primiparae in the patient-preference GMT condition might have confounded this result.
Weekly report of treatment satisfaction marks showed an overall moderate satisfaction with a mean mark ranging from 6.8-7.1 for the GMT. Satisfaction marks did not significantly differ between GMT (6.8±1.9) and TAU (7.2±1.1, p=0.28). Women in the patient-preference condition were not significantly more satisfied with the chosen treatment condition, compared to women in the randomized condition. The subgroup analysis for a low satisfaction mark (<6) did not show to be significantly different between GMT and TAU, nor between the randomized versus patient-preference condition.

Figure 2 depicts the profiles of estimated mean EDS scores during the first 15 weeks of treatment period and 6 weeks postpartum, for the randomized condition (figure 2A) and the patient-preference condition (figure 2B). EDS follows the same pattern in all four groups resulting in a steadily decrease during treatment period and a further decrease in the postpartum period to an estimated mean score below the cut-of value ≤13 at 6 weeks postpartum for all conditions.

Table 3 - Obstetrical outcomes, data and results from pooled data

	RANDOMIZED		GMT VS. TAU		PATIENT-PREFERENCE		RANDOMIZED VS. PATIENT-PREFERENCE	
	GMT N = 52	TAU N = 47	β # 95%CI	p-value	GMT N = 33	TAU N = 26	β # 95%CI	p-value
Perinatal complication*	N (%) #	N (%)			N (%)	N (%)		
Any complication	21 (42.3)	24 (51.1)	0.65 (0.29 - 1.47)	0.31	17 (51.5)	12 (46.2)	1.16 (0.59 - 2.26)	0.67
Fetal distress	11 (21.2)	12 (25.5)	0.76 (0.28 - 2.03)	0.58	8 (24.2)	6 (23.1)	0.99 (0.41 - 2.38)	0.99
Mode of delivery:								
Spontaneous vaginal delivery	36 (69.2)	27 (59.6)	1.70 (0.70 - 4.15)	0.24	24 (72.7)	14 (53.8)	1.08 (0.51 - 2.28)	0.85
Instrumental vaginal delivery	8 (15.4)	10 (21.3)	0.62 (0.21 - 1.88)	0.40	4 (12.1)	4 (15.4)	0.65 (0.25 - 1.69)	0.37
Caesarean section	8 (15.4)	10 (21.3)	0.69 (0.24 - 2.03)	0.51	5 (15.2)	8 (30.8)	1.26 (0.53 - 2.96)	0.60
Pain relief during delivery	37 (71.2)	30 (63.8)	1.34 (0.54 - 3.29)	0.53	21 (63.6)	17 (65.4)	0.88 (0.40 - 1.96)	0.76
Gestational age, mean (SD)	38.9 (2.1)	38.9 (1.9)	1.00 (0.42 - 2.37)	0.99	34.5 (2.3)	39.0 (1.6)	0.81 (0.34 - 1.83)	0.62
Premature birth (<37 weeks)	8 (15.4)	5 (10.6)	1.51 (0.39 - 5.82)	0.55	6 (18.2)	3 (11.5)	1.17 (0.39 - 3.52)	0.78
Birth weight in grams, mean (SD)**	3174 (582)	3219 (573)	0.96 (0.75 - 1.22)	0.72	3288 (470)	3559 (671)	1.17 (0.94 - 1.46)	0.17
SGA (p<10)	10 (19.2)	11 (23.4)	0.85 (0.31 - 2.31)	0.74	3 (0.9)	4 (15.4)	0.39 (0.09 - 1.64)	0.21
Postpartum complication:***								
Any complication	11 (21.2)	11 (23.4)	0.82 (0.30 - 2.23)	0.70	7 (21.2)	5 (19.2)	0.87 (0.34 - 2.24)	0.78

Note:

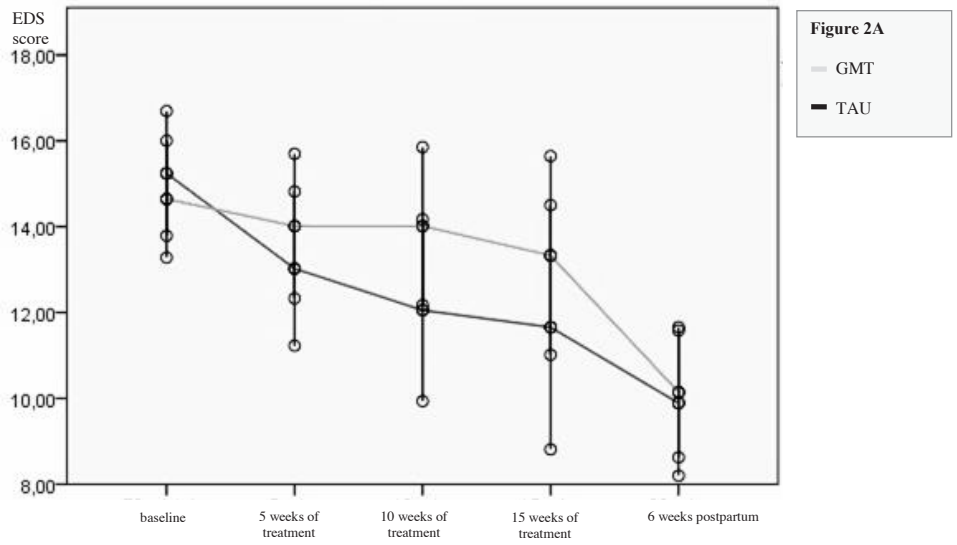
Difference between GMT vs. TAU in the randomized condition, TAU is reference condition. Difference between Randomized vs. Patient-preference condition, Patient-preference is reference condition.

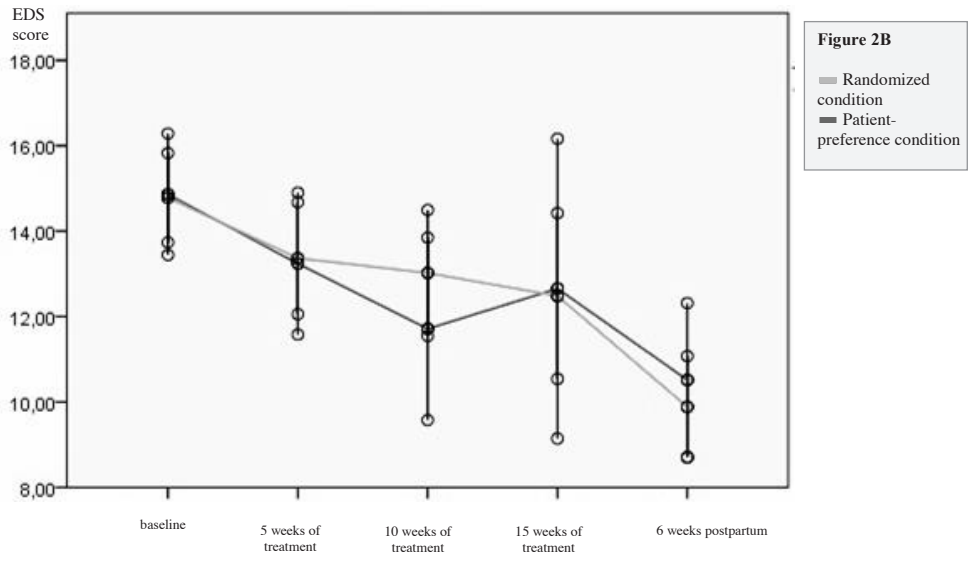
* Perinatal complications were grouped as: gestational diabetes, pre-eclampsia, pregnancy-induced hypertension, hospitalization >24 hour or suspected fetal distress (diagnosed on the basis of a pH < 7.2 on a fetal blood sample during delivery or Apgar score <7 after 5 minutes)

** Birth weight obtained from obstetric records (recorded in grams); small-for-gestational-age (SGA) determined using birth weight adjusted for gestational age, parity and fetal gender.

*** Postpartum complications included hospital admission, 6 weeks postpartum women were asked whether the patient or baby had been hospitalized in the first 6 weeks after delivery

Figure 2 - Profiles of estimated means of Edinburgh Depression Scale (EDS) scores including confidence intervals during treatment period, GMT vs. TAU (figure 2A) and randomized vs. patient-preference condition (figure 2B)





Discussion

This is the first randomized controlled trial among a clinical sample of pregnant women with co-morbid psychiatric and psychosocial problems, mainly reflected in low SES (i.e. low educational level and/or high unemployment), that compared a Group-based Multicomponent Treatment (GMT) to individual counseling for the reduction of depressive symptoms during pregnancy. Overall, there was no significant difference observed in decrease of depressive symptoms between GMT and treatment as usual (TAU).

A major strength of our study is that we were able to successfully recruit a hard-to-reach population; only 20 (11.2%) eligible women refused participation, almost two out of three women willing to participate consented to randomization and drop-out was low (9/155, 5.8%). Included women were next to major depressive disorder, also diagnosed with a high number of anxiety disorder (31.6%) and a comorbid personality disorders (49.4%). We believe that this heterogeneity reflects clinical practice and this enhances the generalizability of our results to other clinical populations. Strength of the study design is that it allowed us to additionally investigate the effect of patient's preference for group-based or individual therapy on treatment response [57]. Since there were no differences in baseline characteristics, compliance, drop-out and outcomes between the randomized and patient-preference condition, also in this respect the results of our study support generalizability to clinical practice [48].

In comparison with other studies focusing on reducing depressive symptoms during pregnancy, a few small RCT's have been carried out which confirmed that individual CBT is effective for prenatal depression [22, 58]. One group-based RCT (n=191) showed a significant beneficial effect for the CBT group in the completers group compared to a booklet group [20]. In line with three other medium-sized RCT's (n=34-55), we found no significant differences in overall decrease of depressive symptoms after the treatment between the intervention and control group [21, 59, 60]. One possible explanation is that our sample size was too small; unfortunately this is reality in this hard-to-reach population. Exclusion, drop-out and non-compliance was not associated with patient characteristics, presumably this has not lead to a selection bias, however the feasibility of an RCT within this population continues to be an issue [42, 43]. Also, we missed more than half of the 10 and 15 week follow-up assessments during pregnancy and this may have limited the study to detect a direct treatment effect. These missing data due to the low compliance are comparable with other studies for depression during pregnancy for a low-income population, as well for IPT [24, 61] as CBT [21, 60]. However, generalized mixed model analysis is robust for missing values. Sensitivity analyses supported the validity of our findings and showed no differences in the ITT and per protocol analysis. It is questionable whether a larger sample size had ensured an effect; we think it might also be related to the ceiling effect of our TAU. The treatment as usual was offered in a specialized tertiary center for perinatal mental illness with experienced clinicians and this tailored treatment could be

as effective as GMT. We limited our outcome measurement to depression scores based on the validated EDS and it is questionable whether the EDS thoroughly assess also comorbid anxiety symptoms [53]. Since we did not investigate other potential benefits of GMT above TAU, like improvement of lifestyle, social support or maternal mentalization or bonding to the unborn child, we cannot exclude that women improved on other domains, or the GMT missed to specifically address the mental health concerns of specific disorders.

Based on our study, we recommend that further research on antenatal therapies treating depression should also focus on co-morbid psychiatric and psychosocial problems, like personality disorders, low SES, social support and life style. For example, our previous study focusing on the role of psychiatric and psychosocial problems on birth outcomes showed that low SES and the accumulative effects of psychiatric and psychosocial risk factors have bigger impact on decreased birth weight and preterm birth above depressive symptoms [39].

In conclusion, our Group-based Multicomponent Treatment (GMT) showed to be a feasible treatment for a clinical sample of pregnant women with co-morbid psychiatric and psychosocial problems. We could not demonstrate that GMT is more effective than individual counseling. Both interventions could be ineffective or the effect of a natural course. A new (multicomponent) treatment should ideally be compared with a golden standard. However, evidence is inconclusive or not eligible for this heterogeneous group [18]. NICE guidelines recommend for women with a moderate or severe depression in pregnancy a high intensity psychological intervention (for example, CBT) [62]. Depending on local availability and costs, clinicians should consider and discuss different treatment options, taking into account personal circumstances and preferences of the patient.

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Supplementary Table 1 – Observational patient-preference analysis: Estimated means of Edinburg Depression Scale (EDS) at six weeks postpartum between GMT vs. TAU ^

	PATIENT- PREFERENCE		GMT vs. TAU	
	GMT N = 33	**TAU N = 26**	**β # (95% CI)**	**p-value**
Primary outcome: EDS mean (SE)	10.4 (1.3)	10.0 (1.6)	0.06 (-0.96 – 1.08)	0.91
Hamilton Depression Rating Scale mean (SE)	7.1 (1.0)	5.1 (1.1)	0.51 (-0.24 – 1.25)	0.18
Sensitivity analysis				
Estimated mean EDS score (SE)	**GMT**	**TAU**	**β # (95% CI)**	**p-value**
Dichotomised outcome (cut-off EDS<13) (estimated proportion below cut-off, SE)	0.79 (0.1)	0.84 (0.1)	0.08 (-0.39 – 0.54)	0.74
Inclusion criterion of baseline cut-off score ≥10 on EDS	10.9 (1.4)	11.8 (1.7)	-0.10 (-1.27 – 1.08)	0.87
EDS anxiety subscale	4.5 (0.5)	4.8 (0.6)	-0.10 (-0.47 – 0.27)	0.58
Adjusted mean score *	10.2 (1.4)	9.6 (1.7)	0.06 (-0.98 – 1.09)	0.92
Per Protocol mean score **	11.6 (2.0)	12.2 (3.2)	-0.05 (-2.06 – 1.97)	0.96
Subgroup analysis				
Estimated mean EDS score (SE)	**GMT**	**TAU**	**β # (95% CI)**	**p-value**
Stratification based on gestational age at inclusion: <24 weeks	9.0 (1.4)	5.1 (2.5)	0.47 (-0.84 – 1.81)	0.47
▪ ≥24 weeks	17.8 (3.3)	14.2 (2.0)	0.85 (-1.14 – 2.85)	0.39
Categorized by psychiatric disorder:				
▪ depression	8.5 (2.4)	11.4 (2.2)	-0.80 (-2.54 – 0.94)	0.36
▪ anxiety	11.9 (1.8)	9.8 (2.5)	0.26 (-1.33 – 1.85)	0.74
Presence of personality disorder:	8.3 (1.6)	11.9 (2.4)	-0.90 (-2.20 – 0.40)	0.17
▪ no personality disorder	12.4 (1.9)	8.7 (2.0)	0.30 (-1.09 – 1.68)	0.67
Psychotropic medication use:	8.9 (1.8)	8.5 (2.5)	-0.12 (-1.17 – 1.43)	0.87
▪ no use	12.5 (1.8)	10.8 (1.9)	0.38 (-0.87 – 1.62)	0.55
Caucasian ethnicity:	9.7 (1.3)	10.3 (1.8)	-0.31 (-1.41 – 0.80)	0.59
▪ non-Caucasian	12.4 (3.4)	10.9 (3.1)	0.55 (-1.99 – 3.08)	0.66
Patients treatment satisfaction on a weekly mark: ≥6	8.7 (1.2)	9.6 (2.3)	-0.25 (-1.47 – 0.97)	0.69

Note:
^ Generalized linear mixed model including time, treatment allocation and baseline score of EDS/HDRS, reported in regression coefficients with confidence intervals and p-values
# Difference between GMT vs. TAU in the patient-preference condition, TAU is reference condition.
* Adjusted for age, ethnicity, education level, and parity.
** Per protocol analysis is based on ≥50% compliance during treatment period.

Supplementary table 2 – Secondary outcome observational analysis

	PATIENT-PREFERENCE		GMT vs. TAU	
	GMT N = 33	**TAU N = 26**	**β # (95%CI)**	**p-value**
Perinatal complication*	N (%)	N (%)		
Any complication	17 (51.5)	12 (46.2)	1.39 (0.47 – 4.15)	0.56
Fetal distress	8 (24.2)	6 (23.1)	1.14 (0.26 – 5.04)	0.86
Mode of delivery:				
Spontaneous vaginal delivery	24 (72.7)	14 (53.8)	2.25 (0.59 – 8.51)	0.24
Instrumental vaginal delivery	4 (12.1)	4 (15.4)	0.82 (0.14 – 4.81)	0.82
Caesarean section	5 (15.2)	8 (30.8)	0.38 (0.07 – 1.92)	0.24
Pain relief during delivery	21 (63.6)	17 (65.4)	0.86 (0.25 – 3.04)	0.82
Gestational age, mean (SD)	34.5 (2.3)	39.0 (1.6)	0.59 (0.15 – 2.28)	0.62
Premature birth (<37 weeks)	6 (18.2)	3 (11.5)	2.28 (0.32 – 12.86)	0.46
Birth weight in grams, mean (SD)**	3288 (470)	3559 (671)	0.69 (0.48 – 0.99)	0.048
SGA (p<10)	3 (0.9)	4 (15.4)	-	0.99
Postpartum complication***				
Any complication	7 (21.2)	5 (19.2)	0.98 (0.24 – 4.00)	0.98

Note:

Difference between GMT vs. TAU in the patient-preference condition, TAU is reference condition.

* Perinatal complications were grouped as: gestational diabetes, pre-eclampsia, pregnancy-induced hypertension, hospitalization >24 hour or suspected fetal distress (diagnosed on the basis of a pH < 7.2 on a fetal blood sample during delivery or Apgar score <7 after 5 minutes)

** Birth weight obtained from obstetric records (recorded in grams); small-for-gestational-age (SGA) determined using birth weight adjusted for gestational age, parity and fetal gender. SGA could not be calculated.

*** Postpartum complications included hospital admission, 6 weeks postpartum women were asked whether the patient or baby had been hospitalized in the first 6 weeks after delivery.

Part 2

Impact of a mental disorder during pregnancy

Chapter 4

Perceived Sleep Quality Is Worse Than Objective Parameters of Sleep in Pregnant Women with a Mental Disorder

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Abstract

Objective: Disturbed sleep during pregnancy is associated with adverse obstetric outcomes and less mental well-being. In pregnant women with a mental disorder, who frequently suffer from sleep problems, it is unknown whether predominantly objective or subjective sleep quality is more affected. To clarify this, we compared objective and subjective parameters of sleep quality between patients and healthy controls during pregnancy.

Methods: This observational study was embedded in an ongoing study among pregnant women with a mental disorder at the department of Psychiatry of Erasmus University Medical Center Rotterdam, the Netherlands. We compared 21 pregnant women with a confirmed mental disorder with 33 healthy controls (gestational age, 23-29 weeks). To measure objective parameters of sleep quality, all participants continuously wore a wrist actigraph for 7 days and nights. Subjective sleep quality was retrospectively assessed using the Pittsburgh Sleep Quality Index (PSQI) and on a daily basis with the Subjective Sleep Quality-scale (SSQ). Differences in parameters of sleep between patients and controls were tested using a multivariate linear regression analysis adjusted for parity, gestational age, educational level, and employment status.

Results: Objective parameters of sleep quality and subjective sleep quality as assessed by the PSQI did not differ significantly between patients and controls. Daily sleep reports showed that, relative to controls, patients had a significantly worse average SSQ-score (5.2 vs. 7.6, adjusted β=0.12, 95%CI = 0.03-0.53, $p<0.01$).

Conclusions: Our exploratory study suggests that perceived sleep quality reported on a daily basis by pregnant women with a mental disorder is worse than the sleep quality as measured by wrist actigraphy.

Introduction

Approximately one-third of all pregnant women report sleeping problems [1]. Poor sleep quality and the persistence of disturbed sleep is associated with less mental well-being and adverse obstetric outcomes [2-4]. However, little is known about the causal pathways that explain the association between poor sleep quality and adverse obstetric outcomes. For example, disrupted sleep can be a (prodromal) symptom of a mental disorder or a consequence of the mental disorder [5]. From studies in non-pregnant psychiatric patients compared to healthy controls, it is known that a mental disorder is associated with prolonged sleep onset latency, increased wake after sleep onset, and reduced sleep efficiency [6-8]. Moreover, having a mental disorder itself is associated with adverse birth outcomes [9]. A first step that could help to clarify these underlying causal pathways is to investigate whether objective and subjective parameters of sleep quality during pregnancy differ between patients and healthy controls. Previous studies showed that pregnant women with a depressive disorder report more fragmented sleep, as reflected in longer sleep latencies and poorer sleep efficiency, than pregnant women without a depressive disorder [10, 11].

Non-pregnant patients with depression and sleep problems also showed discrepancy between subjective and objective sleep measurements [12] - e.g., objective sleep quality - as measured by actigraphy more closely approximated those of the golden standard (polysomnography) than subjective measurements in depressed insomniacs [13].

It is unclear whether sleep quality in pregnant women is objectively worse in a sense of reduced or fragmented sleep, or whether their perception of it is altered, possibly as a result of co-occurring psychiatric symptoms. The interpretation of perceived poor sleep quality in pregnant women with a mental disorder could help clinicians to determine whether they should primarily focus on the perception of sleep quality and treatment of the underlying mental disorder, or whether they should intervene on the objective parameters of sleep. To identify sleep quality in pregnant women with a mental disorder, we studied both objective (wrist actigraph) and subjective (questionnaires) indicators of sleep in patients and in healthy controls during the second trimester of their pregnancy.

Methods

The protocol of this cohort study was, as part of a larger randomized controlled trial (DAPPER, NTR3015 http://www.trialregister.nl), approved by the Medical Ethical Committee at Erasmus MC Rotterdam. In short, the aim of the DAPPER study is to evaluate the effectiveness of a group-based multicomponent psychotherapy intervention for pregnant women with a mental disorder, compared to individual counselling. Eligible participants were pregnant women

diagnosed with a mental disorder and/or personality disorder, confirmed by a Structured Clinical Interview for DSM-IV diagnosis by one trained medical doctor [14]. We chose to recruit participants at the end of their second trimester (23-29 weeks of gestation), when sleep quality seems to be less affected by the pregnancy itself or by the routine 20-week fetal ultrasound examination in Dutch antenatal care, which can be potentially stressful. Through contact with 4 community midwifery practices in Rotterdam, we recruited pregnant women (1) without current psychiatric symptoms on the Brief Symptom Inventory [15] (BSI, global severity index score: <0.71) and (2) without psychotropic medication use. Participants were excluded if they suffered from a tremor or medical conditions that could affect sleep (e.g., sleep apnea) or were unable to read or write in Dutch. Once written informed consent had been obtained, all participants provided demographic information. A low educational level was defined as: no education, only attending primary school or finished secondary school on the lowest level.

Objective parameters of sleep were measured using the Actiwatch Actigraphy model AW4 (Cambridge Neurotechnology Ltd, UK). Agreement of the Actiwatch Actigraphy model AW4 with the golden standard (polysomnography) has been demonstrated [16], though not in a population of pregnant women. When placed on the non-dominant wrist, the Actiwatch measures the number of movements above a certain threshold per 60-s epoch, and provides the following indices: total sleep time (TST); sleep latency (time until asleep); sleep efficiency (percentage of time spent asleep while in bed); and the fragmentation index (percentage immobility phases of one minute). Sleep data were analysed using the Actiwatch Sleep Analysis program (Version 1.16, Cambridge Neurotechnology Ltd, UK). Although all participants wore an Actiwatch for 7 consecutive days and nights, only the weekdays (≥3 days and nights) were used for analysis because of the increase in variability during the weekends and also in agreement with recent literature [17-19]. The precision of the 5-weekday assessment period was better than for 7 days and did not differ between the groups. Correlation of the 5-weekday assessment period was moderate for the actigraphically measured TST (ICC=0.60) and sleep latency (ICC=0.51), and good for sleep efficiency (ICC=0.76) and sleep fragmentation (ICC=0.68) for all participants. The correlation for the subjective parameters was weaker than the actigraphically measured parameters; the ICCs for TST, sleep latency, and SSQ were respectively 0.48, 0.46, and 0.46.

Subjective sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), a self-rating questionnaire that measures sleep quality and disturbances retrospectively over a 1-month period. The PSQI scoring method produces an overall score between 0 and 21, with higher scores indicating poorer sleep quality [20]. A PSQI-score ≥5 is considered the cutoff point, which discriminates a good sleeper (<5) from a poor one. Relative to a combination of clinical interviews and polysomnographic measures, the threshold of ≥5 yields a diagnostic sensitivity of 89.6% and a specificity of 86.5% [21]. The PSQI has good validity in depressed and pregnant populations [22]. By analogy with the actigraphically measured parameters, we included two specific PSQI-domains: sleep latency and sleep efficiency.

Participants kept a daily sleep diary for one week and received a text message to remind them to fill it in after breakfast. The diary included questions on total sleep time, sleep latency, and the Subjective Sleep Quality scale (SSQ), an 11-item true-or-false questionnaire that culminates in a sum score of between 0 and 11, with higher scores indicating good sleep quality [23].

By analogy with the actigraphically measured parameters, a minimum of 3 weekday dairies of each participant were averaged, based on a threshold setting of 20 activity counts within a 1-min epoch for the analysis of the Actiwatch data. The number and length of naps during the day were not included in the TST calculations of the diary or in the actigraphically measured TST.

Data Analysis

Differences on demographic characteristics (age, gestational age, parity, family status, ethnicity, educational level, employment and the percentage of available weekday data) between patients and controls were tested using T-tests (continuous variables) or $\chi 2$ tests (categorical variables). Actigraphically measured parameters and SSQ-scores were averaged over ≥ 3 weekday nights for each participant. All parameters of sleep were tested for normality using Q-Q plots and histograms; variables that violated the assumption of normality were logtransformed to resemble a normal distribution. Differences in sleep parameters between patients and controls were tested using univariate and multivariable linear regression analyses, adjusting for parity, gestational age, education level, and employment status. Beta values (95% CIs) are reported and a twosided p-value of <0.05 was taken as statistically significant. A total sample size of 52 participants allows for the detection of large effect sizes (≥0.8) with a significance level of 0.05 and a power of 0.80 [24]. Data were analysed using SPSS (version 20) for Windows.

Results

Patients were diagnosed with a current unipolar major depressive disorder (n=12), generalized anxiety disorder (n=6), personality disorder (n=2), or bipolar disorder (n=1). None of the participants used sleep medication; one patient with depression used an SSRI during pregnancy. Patients had a significantly lower educational level, and significantly more of them were unemployed than controls (Table 1). Other demographic characteristics did not differ. All participants completed the protocol. The percentage of analysed weekday nights out of the total nights collected did not differ between the groups, not for the Actiwatch data (patients 92% vs. controls 97%, p=0.15) nor for the sleep diaries (patients 92% vs. controls 97%, p=0.09). There were no significant differences between patients and controls in the actigraphically measured

parameters of sleep (Table 2). Patients reported longer sleep latency than controls and had a significantly poorer average score on the Subjective Sleep Quality Scale in the diaries. The SSQ-score remained significantly different between patients and controls after adjustment for parity, gestational age, educational level, and employment status. Sleep quality reported retrospectively over a 1-month period (PSQI-score) did not remain significantly different after adjustment, although in the crude analysis, a significantly larger proportion of patients scored above the non-adjusted threshold of a poor sleeper (patients 81% vs. controls 39%, p<0.01). The disagreement between the actigraphically measured and diary-reported TST was larger in patients (mean=1:25h; Bland-Altman 95% limits of agreement (LA) between 0:11 to 3:01) than in controls (mean=1:14h; LA between 0:12 to 2:20) [25]. A similar trend was observed regarding sleep latency and sleep efficiency.

Table 1 - Demographic characteristics of all participants at start of study.

		Patients (n = 21) Mean (SD)	**Controls (n = 33)** Mean (SD)	**Significance** p-value
Age		29.8 (5.2)	30.4 (3.5)	0.64
Gestational age in weeks		25.7 (1.7)	25.0 (1.4)	0.14
Parity	- Nullipara	15 (71%)	17 (52%)	0.15
Family status	- Married	19 (91%)	32 (97%)	0.31
Ethnicity	- Immigrant	5 (24%)	3 (9%)	0.14
Educational level	- Low	14 (67%)	7 (21%)	<0.01
Employment	- No	14 (67%)	3 (9%)	<0.01

Table 2 - Differences of actigraphically measured and subjective parameters of sleep between patients and controls.

Actigraphically-measured sleep parameters	**Patients (n = 21)**	**Controls (n = 33)**	B	**95% CI interval**	$\beta_{adjusted}$ #	**95% $CI_{adjusted}$ #**
Mean TST in hh:mm (SD)	6:44 (1:04)	6:32 (1:02)	1.22	0.69-2.16	0.81	0.40-1.63
Sleep latency in $hh:mm_{log}$	0:21 (0:13-0:45)	0:13 (0:10-0:23)	1.13	0.94-1.36	0.10	0.80-1.25
Sleep efficiency in $\%_{log}$	78.3 (76.3-84.0)	83.5 (76.2-86.5)	1.18	0.95-1.45	1.13	0.94-1.58
Fragmentation index in %	37.1 (13.5)	37.4 (14.7)	0.10	0.92-1.08	1.01	0.91-1.11
Subjective sleep parameters						
Mean TST diary in hh:mm (SD)	8:09 (1:15)	7:46 (0:49)	1.48	0.86-2.54	0.95	0.49-1.83
SSQ-score diary (range 0-11)	5.2 (2.2)	7.6 (2.2)	0.09	0.03-0.29***	0.12	0.03-0.53**
Sleep latency diary in hh:mm	0:35 (0:21)	0:19 (0:15)	1.31	1.12-1.53**	1.19	0.98-1.44
Total PSQI (range 0-21) $_{log}$	8.8 (5.5-11.5)	4.0 (3.0-7.0	1.31	1.14-1.50***	1.16	0.98-1.37
Sleep latency PSQI in $hh:mm_{log}$	0:30 (0:13-0:45)	0:10 (0:05-0:13)	1.35	1.06-1.71*	1.15	0.86-1.54
Sleep efficiency PSQI in $\%_{log}$	80.0 (57.3-89.9)	93.8 (76.4-95.8)	1.32	0.98-1.78	1.02	0.71-1.48

NOTE: Sleep parameters are reported in medians and interquartile range, unless stated otherwise. # Adjusted for education level, employment status, parity and gestational age in weeks. * p<0.05; ** p<0.01; *** p<0.001

Discussion

Our results indicate that subjective sleep quality as measured on a daily basis by the SSQ was significantly worse in pregnant women with a mental disorder than in those without a mental disorder. There was no significant difference regarding the objective parameters of sleep. In all participants, actigraphically measured TST was lower than the diary-reported TST. This is consistent with other studies reporting similar discrepancies between actigraphically measured TST and subjective perception of TST among non-pregnant insomnia sufferers and normal sleepers [26]. Recently, Herring and colleagues showed that the discrepancy between actigraphically measured and self reported TST in a majority of 80 healthy pregnant women was over one hour [27]. While our study confirms this finding, it also suggests that this discrepancy is greater in patients than in controls. Despite this discrepancy, it is worth noting that all participants' average actigraphically measured TST (6:40h) was shorter than that recorded in earlier studies in pregnant women (7.1-7.8h) [3, 28, 29]. The suboptimal sleep quality in pregnant women is also reflected by the overall less favourable scores on the PSQI.
This study has several limitations. First, our study is subject to limited power to detect small and medium effect sizes; as a consequence of that, we cannot exclude a type II error in our findings. However, our subjective measures did reach significance within the same sample size. Secondly, due to our small sample we had to group all mental disorders together and could therefore not make a statement for each mental disorder separately during pregnancy. We also acknowledge that the Actiwatch AW4 model is not validated against polysomnography in a population of pregnant women and that there are large differences in sleep variables between different brands of actigraphs and settings [30]. At last, we did not match for the daytime activities and level of education between patients and controls, although significantly more healthy controls were employed and highly educated. However, after adjusting for employment and level of education, as well as for the confounders parity and gestational age, the difference between subjective sleep quality as measured by the SSQ remained significant.
Despite these limitations, this study is one of the first in a clinical population to find that a mental disorder during pregnancy is more associated with poorer subjective sleep quality than with changes in parameters of objective sleep quality. Our results demonstrate the importance of focusing on the perception of sleep in pregnant women with a mental disorder who report sleep problems. Although this is an exploratory study, we speculate that these women might benefit from cognitive behavioural therapy, as demonstrated in studies with non-pregnant participants [31-33].
Future research should focus on whether the association between perceived poor sleep quality and adverse birth outcomes that has been found in previous studies is independent or could be explained by co-occurring psychiatric symptoms. Also, the consequences of perceived poor sleep quality during pregnancy for persistence or recurrence of mental disorders in the

postpartum period has to be investigated in women with a known mental disorder. For example, Park et al. recently showed that subjective perception of sleep quality of healthy pregnant women is a stronger predictor of depressive symptoms postpartum than actigraphy measures [34]. Although previous research has shown a clear association between postpartum reduced sleep and the occurrence or exacerbation of affective and psychotic disorders, little is known about whether these women are already at increased risk during pregnancy [10, 35].

Perinatal health-care professionals should be aware that overall sleep quality is reduced during pregnancy and should explain to their patients that this particularly concerns sleep perception. Cautious use of sleep medication (e.g., benzodiazepines) is recommended because of the potential risks for the fetus and the risk of addiction of the mother. Also, additional risks exist in women with sleep apnea. One exception to this involves pregnant women with a bipolar disorder or past or current psychosis, in whom sleep plays a crucial role in the prevention of postpartum psychosis [36].

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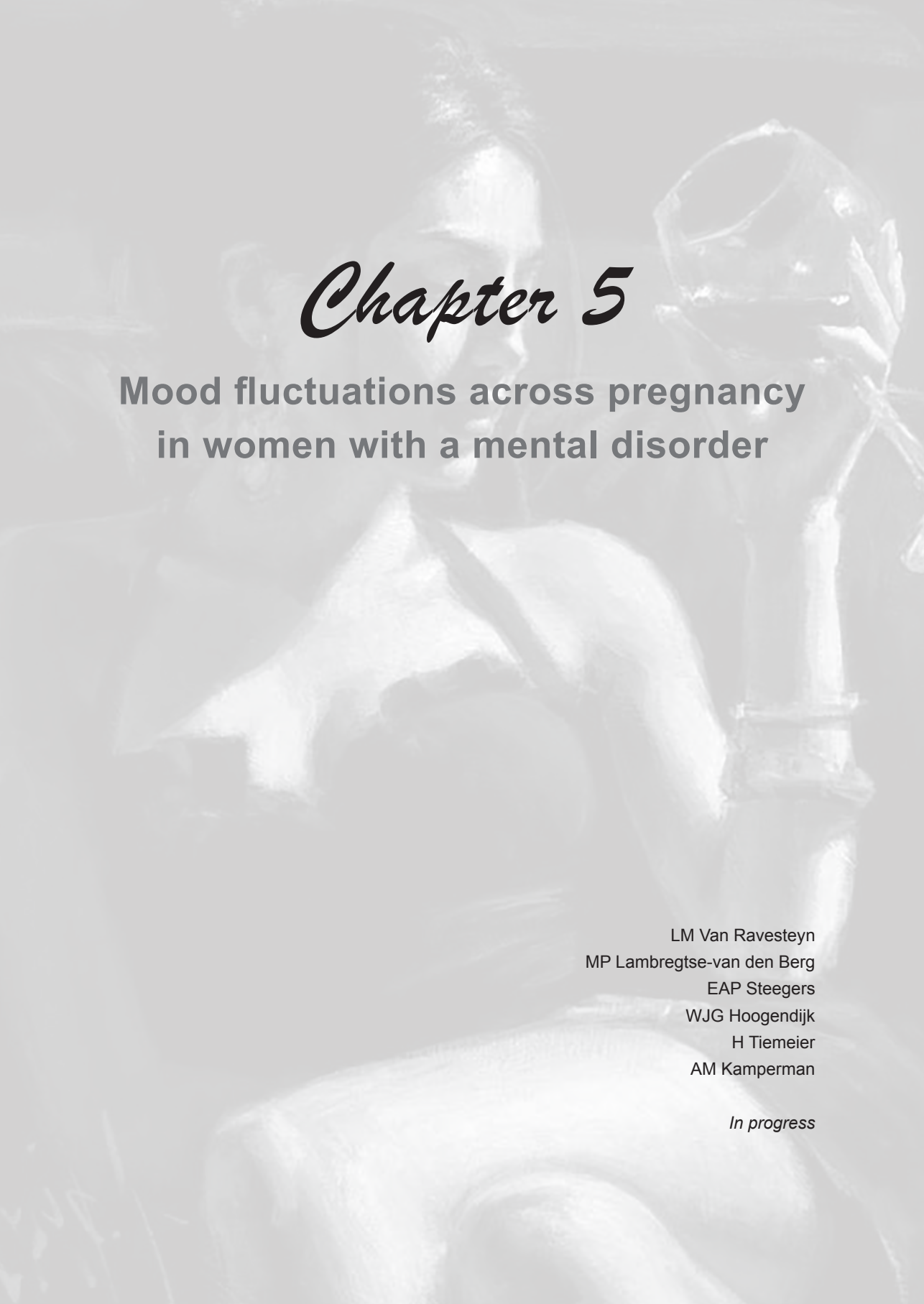

Chapter 5

Mood fluctuations across pregnancy in women with a mental disorder

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In progress

Abstract

Purpose: In pregnant women with a mental disorder, we observed mood fluctuations rather than chronic depressed mood. This pilot study aims to describe phenotypes of mood fluctuations across pregnancy, and to test if repeated measurement of mood contributes to a better understanding of the psychopathology. Furthermore, we explored if mood fluctuations are related to pregnancy outcomes and depressive symptomatology in the postpartum period.

Methods: We included a clinical convenience sample from a perinatal psychiatry outpatient clinic of a tertiary center in our study. Ninety-nine pregnant women met DSM-IV criteria of a mental disorder with clinical relevant symptoms based on the cut-off score of the Edinburg Depression Scale (EDS) and Hamilton Depression Rating Scale (HDRS) were included in this study. Women were asked to fill in a Profile of Mood State (POMS) in a weekly diary across pregnancy. The POMS assesses current feelings of depression, tension, anger, fatigue, vigour and together this represent the overall mood state (Total Mood Disturbances). We described three phenotypes of mood patterns over time: severe mood fluctuations, stable negative (more depressed/anxious) or stable positive mood (reference group). The demographic variables, pregnancy outcomes and postpartum depression rates are described of the different phenotypes.

Results: A lower birth weight was found in the phenotype with mood fluctuations, compare to the phenotypes with a stable negative or positive mood. We observed no significant differences on other demographic, clinical or pregnancy outcomes between the three phenotypes.

Discussion: In a clinical sample of pregnant women with a mental disorder, we identified a phenotype with severe mood fluctuations. This phenotype is also characterized by co-morbid psychiatric and psychosocial problems, and these women might be at risk for poor pregnancy outcomes. Future studies have to be carried out to further disentangle these findings, using repeated measurements of mood and investigate whether severe mood fluctuations result in a worse prognosis for mother and the (unborn) child.

Introduction

Mental disorders are a major cause of disability among women during the perinatal period and may have consequences for the offspring. Maternal psychopathology includes a broad spectrum of mental disorders during pregnancy, mainly depressive and anxiety related disorders [1]. It is also known that some pregnant women – with and without psychopathology – can show a characteristic pattern of mood fluctuations across pregnancy, likely due to hormone and other physical changes. In many pregnant women moodiness flares up around 6 to 10 weeks, eases in the second trimester, and then reappears as their due date approaches and more physical disabilities occur. Mood fluctuations are understood to be relatively benign and are described as feelings in the range of depression, tension, anger, fatigue, and lack of vigour.

In clinical practice mood fluctuations are observed in pregnant women with psychopathology, regardless of their underlying mental disorder. It is important to know how these mood fluctuations evolve and if this is associated with additional risks. This is of clinical importance because usually screening for psychopathology happens only once in antenatal care. As a snapshot of the current state, we might underestimate the severity of the psychopathology and the prognosis.

To our knowledge, there is no longitudinal study with repeated measurement of mood across pregnancy. First, we describe three fictional cases of pregnant women with a mental disorder and how their mood states evolve across pregnancy. The aim of this pilot study is primarily to describe phenotypes of mood fluctuations across pregnancy by intending a weekly assessment of mood states in women with a diagnosed mental disorder. Second, we explored if these phenotypes of mood fluctuations are related to pregnancy outcomes and depressive mood in the postpartum period.

Materials and Methods

This pilot study is a clinical convenience sample derived from a randomized controlled trial (RCT; DAPPER, NTR3015, www.trialregister.nl), approved by the medical ethical committee at Erasmus MC Rotterdam. In short, the DAPPER-trial aimed to evaluate a Group-based Multicomponent Treatment (GMT) for pregnant women with a mental disorder, using individual counselling as control treatment (TAU) [2]. This RCT showed that there was no difference in postpartum mood between the two conditions.

Procedure

We recruited pregnant women with a gestational age of >12 weeks at the outpatient clinic of the Perinatal Psychiatry Department of the Erasmus University Medical Center, a tertiary center in Rotterdam, the Netherlands. Once written informed consent had been obtained, all participants provided demographic information; a mental disorder and/or personality disorder were confirmed by a Structured Clinical Interview for DSM-IV diagnosis conducted by one trained medical doctor [3]. Demographic characteristics, psychiatric history and obstetric outcomes were additionally obtained from the electronic patient records. All participants received treatment on the outpatient clinic and depending on the severity of their symptoms, were also treated with psychotropic medication.

Assessment of mood and mood fluctuations across pregnancy

Our main interest were mood fluctuations across pregnancy. Every Tuesday, participants were asked to fill in a diary in the morning (after breakfast) and evening (before bedtime) after they received a text message reminder. The diary included questions about sleep quality, daily activity and mood state. Here we used only the morning measurements. The Profile of Mood State (POMS) was included in the diary to assess mood. The POMS is originally a 65-item self-report questionnaire for adults using self-descriptive adjectives that assess the state of mind at that time [4]. The Dutch POMS is a shortened version and consists of 32 items [5, 6], it has been shown to be a reliable tool to measure mood states [7]. Participants are asked to indicate on a 5-point Likert scale (0 = not at all and 4 = very good fit) to what extent different mood terms resemble their current mood state. The Dutch POMS has five subscales: depression, tension, anger, fatigue and vigour. We calculated subscale scores and Total Mood Disturbance (TMD)-score as a representation of participants' overall mood state. The TMD-score is computed by adding the negative scales (depression, tension, anger and fatigue) and subtracting the positive scale (vigour). Higher scores indicate more disturbed and affected mood.

Mood fluctuation phenotypes

The participants filled in 11 diaries on average. We included data of 959 consecutive morning TMD-assessments of 99 women (range: 3-23 assessments, median: 9 assessments). Women with less than 3 assessments were excluded from the analyses. For each woman, we calculated the mean and standard deviation of all available TMD morning scores. The subgroup of women in the highest variability in their TMD morning scores was determined using the standard deviation of their individual TMD scores. Women were categorized in three categories. Women in the highest tertile (with a standard deviation of 2.86 or higher) were labelled as suffering from 'severe mood fluctuations'. The remaining women were dichotomized into stable negative and stable positive mood subgroups using median split of their mean TMD

morning score (cut off score=1.70). The POMS scores were normally distributed for each phenotype. The number of diaries did not differ between the three phenotypes. Subscales of the POMS correlate highly (ranging from 0.75 to 0.90). The reliability of the categorization was checked by creating an alternative categorization, excluding the fatigue subscale to check the impact of common physical complaints. 93% of the women were categorized similarly (r=0.88).

Depressive symptomatology

The severity of the psychopathology was assessment by the self-rated Edinburg Depression Scale (EDS) and clinician-rated Hamilton Depression Rating Scale (HDRS) at baseline and at 6 weeks postpartum during a home-visit interview. The EDS is a 10-item self-report questionnaire that is validated to measure depressive and anxiety symptoms during pregnancy and in the postpartum period (score range: 0-30). A score of <13 represents no clinical relevant symptoms and a score above ≥13 justifies treatment [8]. The HDRS was added as a clinician-rated scale to assess depressive symptoms based on 17-items (score range: 0-52) [9].

Data analysis

Differences of the demographic and clinical characteristics and pregnancy outcomes across the mood phenotypes were tested with Chi Square test or Fisher Exact Test for categorical data, and ANOVA for normally distributed continuous data. We did not correct for multiple testing. Correlations between variables were calculated using Pearson (continuous variables) or Spearman's rank (categorical variables) correlation tests. Missing data analyses showed that 6% was missing, distributed over 14 cases. MAR and MNAR was explored. We found no indication that missing variables were not distributed at random. Normality of the data was checked visually using histograms, and Q-Q plots.

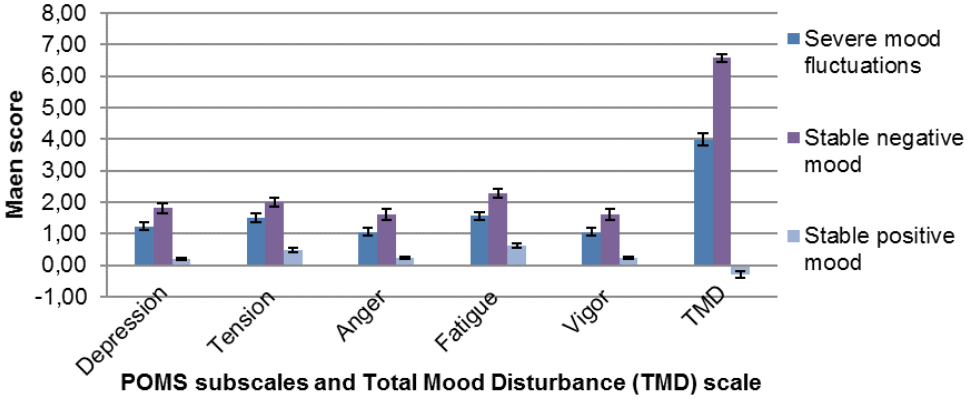
Results

From our clinical convenience sample of 99 pregnant women with a mental disorder, we identified three equally sized phenotypes based on their Total Mood Disturbance-score of the Profile of Mood States (POMS) across pregnancy:

I. Women that experienced severe mood fluctuations, eg. highly variable mood
II. Women with a stable negative mood
III. Women with a stable positive mood

Women with a fluctuating mood experienced feelings of depression, tension, anger, fatigue and a reduced vigour. The women with a stable negative mood experienced more severe feelings on all subscales. Stable positive women did not experience these feelings. All mean scores of the subscales and the Total Mood Disturbance (TMD) are depicted for the three phenotypes in Figure 1.

Figure 1 – Graphic presentation of three phenotypes of mood fluctuations across pregnancy (severe mood fluctuations variable, stable negative and stable positive mood) with mean POMS scores and error bars



The demographic and clinical characteristics are shown in Table 1. We found no differences between the three phenotypes. Mostly depressive and anxiety disorder were diagnosed in this sample, and more than half of the participants had a personality disorder. The phenotype with mood fluctuations included most cluster B personality disorders, but this was not statistically significant. At baseline, the mood scores across pregnancy according to the self-rated Edinburgh Depression Scale (EDS) and clinician-rated Hamilton Depression Rating Scale (HDRS) were significantly different between the three phenotypes, as expected from the POMS-scores. Women in the stable positive mood phenotype scored below the cut-off score of non-clinical relevant symptoms, and used a reference group.

Table 1 - Demographic and clinical characteristics of 99 participants

	Mood phenotypes			
	Mood fluctuations (n=33)	Stable negative (n=33)	Stable positive (n=33)	p-value
Demographic characteristics				
Maternal age in years (m;sd)	29.4 (5.0)	31.8 (4.6)	31.1 (4.9)	0.11*
Planned pregnancy	22 (67%)	16 (49%)	22 (67%)	0.22
Marital status (N;%)				0.63
Married/co-habiting	25 (76%)	28 (85%)	27 (82%)	
Ethnicity				0.14
Caucasian	25 (76%)	24 (73%)	30 (91%)	
Educational level				0.29
Low educational level	9 (27%)	11 (33%)	15 (46%)	
Employment status				0.32
Unemployed	24 (73%)	19 (58%)	24 (73%)	
Clinical characteristics				
Axis 1 Psychiatric disorder				0.07
Depressive disorder	15 (46%)	17 (52%)	11 (33%)	
Anxiety disorder	10 (30%)	12 (36%)	10 (30%)	
Psychotic disorders	-	-	4 (12%)	
Other	1 (3%)	3 (12%)	3 (9%)	
No Axis 1 disorder	7 (21%)	1 (3%)	5 (15%)	
Axis 2 Personality disorder				0.10
Cluster A	-	2 (6%)	-	
Cluster B	16 (49%)	8 (25%)	9 (27%)	
Cluster C	3 (9%)	7 (22%)	3 (9%)	
No Axis 2 disorder	14 (42%)	15 (47%)	21 (64%)	
Previous episode of anxiety/depression				0.08
1 episode	5 (15%)	15 (46%)	10 (30%)	
≥ 2 episodes	18 (55%)	14 (42%)	14 (42%)	
None	10 (30%)	4 (12%)	9 (27%)	
Psychotropic medication use				0.13
SSRI/nSSRI/TCA	13 (41%)	7 (21%)	10 (31%)	
Antipsychotics	-	1 (3%)	2 (6%)	
Lithium	1 (3%)	-	1 (3%)	
Benzodiazepines	1 (3%)	-	-	
Other	1 (3%)	1 (3%)	-	
None	16 (50%)	24 (73%)	19 (59%)	
Treatment in pregnancy				
Individual counseling	10 (30.3)	19 (57.6)	14 (42.4)	0.10
Multicomponent	23 (69.7)	14 (42.4)	19 (57.6)	
Any smoking in pregnancy	12 (36%)	10 (30%)	11 (33%)	0.96
Any alcohol in pregnancy	6 (18%)	11 (33%)	12 (36%)	0.22
Any illicit drug use in pregnancy	5 (16%)	1 (3%)	3 (9%)	0.06
Depressive symptomatology	Mean (SD)	Mean (SD)	Mean (SD)	
Edinburgh Depression Scale	15.3 (6.4)	17.6 (6.1)	8.7 (5.8)	<0.001*
Hamilton Depression Rating Scale	11.4 (5.0)	14.1 (4.8)	6.5 (4.2)	<0.001*

Note:

* All categorical variables were tested using Chi2-test, except for this variable Fisher Exact test is used.

Table 2 showed the obstetric outcomes for the three phenotypes. A lower birth weight was more common in the severe mood fluctuation phenotype than in the stable negative or positive mood phenotypes. The number of SGA children did not differ between the three phenotypes. Postpartum complications were more observed in the mood fluctuation phenotype.

Table 2 - Obstetric outcomes

	Mood phenotypes			p-value
	Mood fluctuations (n=33)	Stable negative (n=33)	Stable positive (n=33)	
Perinatal complications (N;%)*	18 (56.3)	15 (48.4)	11 (35.5)	0.25
Fetal distress (N;%)	5 (16.1)	8 (27.6)	7 (22.6)	0.56
Mode of delivery				0.95
Spontaneous	22 (68.7)	23 (74.2)	21 (67.7)	
Instrumental	5 (15.6)	5 (16.1)	5 (16.1)	
Caesarean section	5 (15.6)	3 (9.7)	5 (16.1)	
Gestational age (m;sd)	38.6 (1.9)	39.1 (2.2)	39.4 (1.8)	0.23#
Premature birth <37wks (N;%)	5 (15.6)	3 (9.7)	1 (3.2)	0.25
Birth weight in grams (m;sd)**	3112 (508)	3477 (516)	3448 (492)	0.01#
SGA <10 (N;%)	3 (9.4)	3 (9.4)	3 (9.4)	>0.99#
Postpartum complication (N;%)***	11 (34.4)	4 (14.8)	3 (10.3)	0.05
Pain relief (N;%)	24 (75.0)	21 (67.7)	20 (64.5)	0.65
Gestational diabetes	3 (9.4)	2 (6.7)	1 (3.2)	0.78#
Pre-eclampsia	1 (3.1)	0 (-)	1 (3.1)	0.99#
Hypertension	2 (6.2)	0 (-)	2 (6.5)	0.54#

Note:
In total 6% of outcome data was missing, distributed over 14 cases. Cases were distributed evenly over the clusters.
* Perinatal complications were grouped as: gestational diabetes, pre-eclampsia, pregnancy-induced hypertension, hospitalization >24 hour or suspected fetal distress (diagnosed on the basis of a pH < 7.2 on a fetal blood sample during delivery or Apgar score <7 after 5 minutes)
** Birth weight obtained from obstetric records (recorded in grams); small-for-gestational-age (SGA) determined using birth weight adjusted for gestational age, parity and fetal gender.
*** Postpartum complications included hospital admission, at 6 weeks postpartum women were asked whether the patient or baby had been hospitalized in the first 6 weeks after delivery
# All categorical variables were tested using Chi2-test, except for this variable Fisher Exact test is used.

Table 3 shows the depressive symptoms as measured by the EDS and HDRS at 6 weeks postpartum. Both the self-rated as the clinician-rated depression scores were lower postpartum for the three phenotypes, compare to baseline. As expected, the stable positive phenotype scored below the cut-off scores for clinically relevant symptoms in the postpartum period. The mood fluctuations phenotype was subclinical depressed according to the clinician-rated HDRS.

Table 3 - Depressive symptomatology 6 weeks postpartum

	Mood fluctuations (n=33)	Stable negative (n=33)	Stable positive (n=33)	p-value
Edinburgh Depression Scale (m;sd)	10.8 (6.7)	12.6 (5.5)	7.1 (4.8)	0.001
Hamilton Depression Rating Scale (m;sd)	6.4 (5.1)	8.6 (5.0)	3.6 (3.9)	0.001

Note: All variables were tested using ANOVA-test

Discussion

This pilot study describes in a sample of pregnant women with a mental disorder, a phenotype of severe mood fluctuations exists. This phenotype is also characterized by co-morbid psychiatric (e.g. more cluster B personality disorders) and psychosocial problems and we hypothesized that this might be related to poor pregnancy outcomes.

We identified three clinical relevant phenotypes based on their symptomatology, confirmed by depression rating questionnaires (EPDS/HDRS) at baseline and postpartum. We found that children of pregnant women with severe mood fluctuations - regardless of the underlying mental disorder - might have a lower birth weight within a normal range compared to those born to the women with a stable positive or negative mood. In line with this finding, the number of SGA babies was largest in the women with severe mood fluctuations, although this finding did not reach significance. Other obstetric outcome differences were not striking. Also more postpartum complications were observed in women with severe mood fluctuations. In this pilot study, the high variability of mood across pregnancy was associated with postpartum depressive symptomatology according to the Edinburgh (self-rated) depression scale (EDS) or clinician-rated Hamilton Depression Rating Scale (HDRS).

Up to date, we know that untreated or incompletely managed depression increases the risk of postpartum depression, but may also adversely impair obstetric and birth outcomes [10]. Some studies reported that maternal psychopathology is negatively related to birth weight [11-14], Other studies observed no (independent) relation between maternal psychopathology and low birth weight [15-18]. It has been hypothesized that exposure to elevated intrauterine cortisol levels makes the HPA-axis of the child already susceptible to programming during fetal life, which places children at risk intra-uterine and for developing other problems in later life [19-21]. However, the level of maternal psychopathology and mood fluctuations will be likely influenced by the mental disorder, psychiatric co-morbidity and several psychosocial factors, like financial problems, marital conflicts, lack of social support, and stressful life events. Maternal psychopathology could also lead indirectly to reduced self-care, less obstetric checks, reduced food intake or by a low intake of essential fatty acids or vitamins, such as folic acid or vitamin B6 and B12 [22]. Next to these co-morbid psychiatric and psychosocial

problems, there are also protecting factors and the promising effect of psychotropic treatment or/and non-pharmacological interventions for mother and the unborn child.

We hypothesized that one-time screening for maternal psychopathology in antenatal care could lead to an underestimation of the psychopathology due to mood fluctuations. The strength of this pilot study is that we collected a large number of repeatedly measurements of mood states in pregnant women with a mental disorder. We observed subclinical depression scores postpartum for the fluctuating mood phenotype, so severe mood fluctuations across pregnancy might not increase the risk of a postpartum depression.

This exploratory study suggests more studies with repeated measurements of mood states across pregnancy in order to investigate any additional risks for the mother and the unborn child due to severe mood fluctuations. Experienced sampling methods [23], for example by using an app on a smartphone would be non-invasive, relatively cheap and practical. Ideally one would like to examine mood and mood fluctuations across all trimesters because of embryogenesis and pregnancy outcomes, but it is difficult to engage women already in the first trimester. Also adjustment of pregnancy outcomes for clinical variables and correction for multiple testing would be recommended for future studies.

From this hypothesis forming study, we conclude that in a clinical sample of pregnant women with a mental disorder a phenotype of severe mood fluctuations exists and this may affect the prognosis for mother and the unborn child. Our hypothesis that a fluctuating mood across pregnancy has an adverse impact on pregnancy outcomes should be tested in larger studies using repeated measurement of mood states, in order to further optimize screening, treatment and prognosis of maternal psychopathology.

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Chapter 6

The prevalence and correlates of self-harm in pregnant women with psychotic disorder and bipolar disorder

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Abstract

Women with severe mental illness are at increased risk of suicide in the perinatal period, and these suicides are often preceded by self-harm, but little is known about self-harm and its correlates in this population. This study aimed to investigate the prevalence of suicidal ideation and self-harm, and its correlates, in women with psychotic disorders and bipolar disorder during pregnancy. Historical cohort study using de-identified secondary mental healthcare records linked with national maternity data. Women pregnant from 2007 to 2011, with ICD-10 diagnoses of schizophrenia and related disorders, bipolar disorder or other affective psychoses were identified. Data were extracted from structured fields, natural language processing applications and free text. Logistic regression was used to examine the correlates of self-harm in pregnancy. Of 420 women, 103 (24.5%) had a record of suicidal ideation during the first index pregnancy, with self-harm recorded in 33 (7.9%). Self-harm was independently associated with younger age (adjusted odds ratio (aOR) 0.91, 95% CI 0.85–0.98), self-harm in the previous 2 years (aOR 2.55; 1.05–6.50) and smoking (aOR 3.64; 1.30–10.19). A higher prevalence of self-harm was observed in women with non-affective psychosis, those who discontinued or switched medication and in women on no medication at the start of pregnancy, but these findings were not statistically significant in multivariable analyses. Suicidal thoughts and self-harm occur in a significant proportion of pregnant women with severe mental illness, particularly younger women and those with a history of self-harm; these women need particularly close monitoring for suicidality.

Background

The perinatal period is generally a time of both lower suicide risk [1, 2] and lower self-harm risk [3, 4], but for women with severe mental disorders (SMI), the risk of suicide is increased up to 70-fold in women admitted for postpartum psychiatric disorders [5]. The UK Confidential Enquiries into Maternal Deaths and other studies have highlighted mental illness as a significant contributor to maternal deaths and also highlight a history of self-harm in a significant proportion (25–50%) of maternal suicides [6]. Compared with the postnatal period, women who die by suicide during pregnancy are reported more likely to have a diagnosis of schizophrenia/related disorders or of bipolar disorder and less likely to have a diagnosis of depression [7].

Little is known about the prevalence and risk factors of self-harm in pregnant women with severe mental disorders even though self-harm in pregnancy is potentially harmful to the viability of the pregnancy in addition to being a potential risk factor for suicide. Risk factors for self-harm in the general population include a history of self-harm [8], younger age [9], substance misuse [10], domestic and sexual violence [11], genetic risk [12] and severity of illness [13]. In addition, in pregnancy, a recent study [14] showed younger age and depression diagnoses were risk factors for suicidal behaviour-related hospitalisations in pregnant women but did not look at other mental health diagnoses. Illness severity and relapse have been associated with discontinuation of medication in one small study in women with bipolar disorder [15], but associations with risk of self-harm remain under-investigated.

We therefore aimed to investigate the prevalence of suicidal ideation and self-harm in pregnant women with SMI (schizophrenia/related disorders, bipolar disorder and other affective psychoses). We hypothesised that self-harm would be associated with markers of illness severity (non-affective diagnosis, substance misuse, smoking, a recent history of self-harm, recent hospitalisation), younger age, discontinuation or switching of regular maintenance psychotropic medication and recent domestic violence.

Methods

Study design and data source

Historical cohort study uses de-identified electronic health records. Pregnant women with SMI were identified using the South London and Maudsley (SLaM) NIHR Biomedical Research Centre Clinical Record Interactive Search (CRIS) system [16]. This is a “new generation” of case register design, built on full electronic clinical records and allowing in-depth secondary analysis of both numerical, string and free-text data, while preserving anonymity through technical and procedural safeguards [17]. It is a rich source of prospective clinical data. SLaM

provides near-monopoly mental healthcare for a geographic catchment of around 1.2 million residents across four London boroughs, as well as specialist services. CRIS was approved as a source of the secondary data for research by Oxfordshire Research Ethics Committee C (08/H0606/71+5).

Fully electronic health records have been maintained since 2006, and at the time of data extraction, over 200,000 individuals had received care from SLaM. Several natural language processing applications have been developed for CRIS using General Architecture for Text Engineering (GATE) software in collaboration with Sheffield University [18]. Such applications derive structured data from free-text fields. As part of CRIS development, a data linkage service has been set up to link CRIS with other sources of secondary data, including Hospital Episode Statistics (HES) which provide national statistical data for all treatment in National Health Service hospitals in England, and includes maternity data.

Study population

This study is part of a larger programme of research on a cohort of pregnant women with SMI, described in detail previously [19]. The cohort includes all pregnant women with a diagnosis of schizophrenia and other non-affective psychoses, bipolar disorder, other affective psychoses including psychotic depression or previous puerperal psychosis (ICD-10 F20, F22, F23, F25, F28, F29, F30, F31, F32.3, F33.3 and F53.1), receiving SLaM care between 2007 and 2011. We excluded women with no SLaM clinical data during pregnancy. Structured fields and a GATE software application were used to extract the diagnosis nearest to the beginning of pregnancy.

Measures

We used a free-text search for records of suicidal ideation (SI) and self-harm during the first index pregnancy occurring in the study cohort. Self-harm was defined as a suicide attempt or self-injurious behaviour, including cutting, burning, hitting, hanging, overdosing, poisoning and electrocuting using terms validated in another CRIS study on self-harm and Emergency Department attendances [20]. Complete notes on the self-harm event were scanned for further information on the method of self-harm, triggers (reported hallucinations around 24h of the event, alcohol and substance use within 12h of the event) and location (whether event occurred on an inpatient ward or at home and whether the patient was under intensive Home Treatment).

Some socio-demographic variables were extracted from structured fields (age, ethnicity) and others from free text (partner status in index pregnancy). Free-text searches were also used for domestic violence before and/or during pregnancy and a history of child abuse. Smoking, alcohol and substance abuse during pregnancy were extracted using free-text searches and/or recent diagnosis of an alcohol or substance use disorder. Measures of illness

nature/severity were affective/non-affective SMI diagnosis at the beginning of pregnancy, self-harm and admissions to acute care in the previous 2 years. The highest total Health of the Nation Outcome Scale (HoNOS) score in the 2 years before pregnancy was extracted to approximate baseline level of functioning. HoNOS, a structured instrument, is a 12-item measure of health and social functioning of people with severe mental illness, routinely collected in UK mental health services; scores above 10 indicate poor functioning and are generally recorded in inpatients [21]. Information on acute admissions (including inpatient and intensive Home Treatment) was extracted from CRIS and HES [19]. Home Treatment Teams are a national network of teams providing intensive community-based support as an alternative to hospital admission for acutely unwell patients [22]. Regular psychotropic medication use (antidepressants, mood stabilisers or antipsychotics) and changes in the first trimester were also extracted: psychotropic drug names and changes in regular use of these medication groups during first trimester were extracted using GATE software to guide retrieval of clinical text [19]. Where no drugs were identified, a free-text search for "medication" was used, and where it was not possible to establish whether medication was being used or not in the first trimester, this was coded as "not known." Regular maintenance medication in the first trimester was categorised into "stopped or switched a medication," "continued a medication" and "no medication at the beginning of pregnancy." "Non-adherence" was coded if there was a comment in the notes regarding concern about adherence indicating the possibility of no exposure to a given medication in the first trimester. For self-harm and medication changes occurring in the first trimester, we checked the notes manually to ascertain which happened first: the self-harm or the medication change.

Data-analysis

We used Stata version 12 [23]. Independent-sample *T* tests and Mann-Witney tests (for continuous data) and Pearson's chi-square (for categorical data) were used to compare demographic and clinical characteristics between women with or without a record of self-harm during pregnancy. Cells containing $n < 5$ were not reported to maintain anonymity of the data. Cases with missing information on presence of a partner, reported abuse, substance misuse, current smoking and self-harm history were assumed to indicate that these were not present. Inter-rater agreement on self-harm data was assessed for the first 10 records and for a 10% random sample; two raters agreed on 89% of the data and consensus meetings resolved discrepancies; detailed guidance on how to code data was used for subsequent data coding. Multivariable logistic regression analysis using cases with known medication status was performed to examine the correlates of self-harm during pregnancy. We compared these women with those with missing medication status on age, ethnicity, baseline diagnosis and acute admissions (variables in the multivariable analysis that did not depend solely on clinical text). HoNOS was not entered into the multivariable model, as data were only available for

236 of 420 women. We conducted a sensitivity analysis excluding women who had a self-harm event before a medication change in the first trimester in order to address the potential issue of reverse causality. We also conducted sensitivity analyses using women who stopped medication only compared with continuers and excluding women reported as non-adherent to medication. Selection was based on our a priori variables and those with $p \leq 0.2$ in the bivariate analysis. All hypothesis testing was two-tailed with α set to 0.05.

Results

Our study population consisted of 420 women. Of these, 40 women had pregnancies which ended in the first trimester and 10 in the second. HoNOS scores were available for 236 women only, and 413 women had data on medication status in the first index pregnancy. There was no other missing data on covariates.

Prevalence of suicidal ideation and self-harm in the index pregnancy, n = 420 women

For 103 (24.5%) women, there was a report of suicidal ideation during the index pregnancy, while 178 (42.4%) women denied this; in the remaining 139 (33.1%) women, there was no mention of suicidal ideation or self-harm. For 70 (16.7%) women, there was a report of suicidal ideation but there was no event of self-harm reported during the pregnancy. Of the 420 women in the study, 33 (7.9%) had a self-harm event during their index pregnancy, and 9 of these had multiple events (range 1–7); 15 women had a self-harm event in the first trimester, 16 in the second trimester and 10 in the third.

Self-harm by event, n = 52 events

In total, 52 events of self-harm (but no suicides) were reported in 33 women out of 420 (1 event per 19 pregnancies). Of the 52 events, methods of self-harm were overdoses ($n = 20$, 38.5 %), hitting ($n = 12$, 23.1%), cutting ($n = 9$, 17.3%) or using a violent method ($n = 11$, 21.2%) such as jumping from height, burning or hanging. Of 52 self-harm events, 23 (43.1%) occurred while women experienced hallucinations. In 18 out of 52 (34.6%) events, drugs or alcohol were involved within 12h before the self-harm. The majority of self-harm events took place at home ($n = 38$, 73.1%) compared with an inpatient setting ($n = 14$, 26.9%). Of events that took place at home ($n = 43$), 13 (30.2) were carried out while the woman was under intensive Home Treatment care.

Factors associated with self-harm during the index pregnancy, n = 420 women

All women with self-harm in the first index pregnancy also reported suicidal ideation in pregnancy. Self-harm in pregnancy was associated with younger age, a history of child abuse or domestic violence, current (i.e. during pregnancy) domestic violence, a history of self-harm in the 2 years preceding pregnancy, substance misuse, smoking, non-affective disorder, acute admissions in the 2 years preceding pregnancy and stopping or switching rather than continuing a maintenance medication in the first trimester of pregnancy (Table 1)

For multivariable analyses, 7 women were excluded as their medication status in the first trimester of pregnancy was not known. Therefore, 413 women were included, 33 (8.0%) of whom had a self-harm event in their index pregnancy. Suicidal ideation was not included in the analyses due to perfect prediction. There were no differences in age ($t = -0.21$, $p = 0.833$), ethnicity (chi2 = 4.53, $p = 0.104$), diagnosis (chi2 = 1.59, $p = 0.208$) and admission rate (chi2 = 0.00, $p = 1.000$) between those who were included and not included in the multivariable analyses.

In the fully adjusted models (Table 2), there was evidence of associations between self-harm in pregnancy and younger age, smoking and a recent history of self-harm and the adjusted odds ratio for discontinuation or change in maintenance medication compared with continuing medication was attenuated by around 50% and no longer significant.

Fewer than five women had a medication change after the self-harm event. Sensitivity analysis excluding these women led to a further attenuation of the relationship between medication changes and self-harm (Table 2), and the association with history of self-harm was no longer significant. Non-affective diagnosis appeared to be associated with self-harm, but this did not quite reach statistical significance ($p = 0.055$). Other sensitivity analyses did not lead to substantial differences (see Table 2).

Table 1 - Baseline characteristics of 420 pregnant women with SMI, with or without a self-harm event during pregnancy – 33 with a self-harm event in pregnancy

	Whole sample, N=420	387 women without self-harm	33 women with a self-harm event	p-value
Age, mean (SD)[T]	31.9 (6.2)	32.3 (6.1)	27.6 (5.5)	<0.001*
Ethnicity, N (%)				
African Caribbean, other Black Background	209 (49.8)	193 (49.9)	16 (48.5)	0.283
White British, other White Background	136 (32.4)	128 (33.1)	8 (24.2)	
Mixed, Unknown and Other Background	75 (17.9)	66 (17.1)	9 (27.3)	
Has partner during pregnancy, N (%)	272 (64.8)	250 (64.6)	22 (66.7)	0.811
Deprivation score (N=404)[W] Median (range)	34.9 (6.8,61.5)	34.9 (6.8,61.5)	32.6 (13.0,56.6)	0.841
Child abuse or DV before pregnancy, N (%)	191 (45.5)	170 (43.9)	21 (63.6)	0.029*
DV in pregnancy, N (%)	82 (19.5)	70 (18.1)	12 (36.4)	0.011*
Self-harm 2 years before pregnancy, N (%)	62 (14.8)	47 (12.1)	15 (45.5)	<0.001*
Harmful use of alcohol or substances, N (%)	107 (25.5)	88 (22.7)	19 (57.6)	<0.001*
Smoking in pregnancy, N (%)	76 (18.1)	58 (15.0)	18 (54.6)	<0.001*
Baseline diagnosis, N (%)				
Non-affective	219 (52.1)	194 (50.1)	25 (75.8)	<0.005*
Affective	201 (47.9)	193 (49.9)	8 (24.2)	
Hospitalisation or home treatment within 2 years before pregnancy, N (%)	180 (42.9)	158 (40.8)	22 (66.7)	0.004*
HoNOS, median(range), N=236 [W]	12 (0,36)	12 (0,36)	14 (3,28)	0.090
Antipsychotic or mood stabiliser, 1st trimester, N (%), n=413	277 (67.1)	250 (65.8)	27 (81.8)	0.060
Antidepressant, 1st trimester, N (%), n=413	99 (24.0)	91 (24.0)	8 (24.2)	0.970
Medication change, 1st trimester, N (%) n=413				
Continuation of previous agent	168 (40.7)	162 (42.6)	6 (18.2)	Ref
Stopped/ switched agent	117 (28.3)	101 (26.6)	16 (48.5)	0.003*
No medication at start of pregnancy	128 (31.0)	117 (30.8)	11 (33.3)	0.074
Medication change, 1st trimester sensitivity analysis, N=409				
Continued	168 (41.1)	162 (42.6)	6 (20.7)	Ref
Stopped/ switched	115 (28.1)	101 (26.6)	14 (48.3)	0.009*
No medication at start of pregnancy	126 (31.0)	117 (30.8)	9 (31.0)	0.177

[E] Fisher exact; [T] independent-sample T-tests, [W] Mann-Whitney test

SMI= severe mental illness, self-harm= deliberate self-harm, DV= domestic violence

Table 2 - Associations between clinical variables and self-harm in pregnancy

	Whole Sample		Excluding medication changes after self-harm event		Excluding nonadherence to medication		Stopped only (excluding women who switched medication only)	
	Unadjusted N=413	**Fully adjusted N=413**	**Unadjusted N=409**	**Fully adjusted N=409**	**Unadjusted N=393**	**Fully adjusted N=393**	**Unadjusted N=388**	**Fully adjusted N=388**
Age	0.88 (0.83,0.94) *<0.001**	0.91 (0.85,0.98) *0.009**	0.88 (0.82,0.94) *<0.001**	0.91 (0.84,0.97) *0.008**	0.87 (0.82,0.93) *<0.001*	0.91 (0.84,0.97) *0.006*	0.90 (0.84,0.96) *0.001*	0.93 (0.86,1.00) *0.043*
Child abuse or DV before pregnancy	2.23 (1.07,4.67) *0.033**	1.31 (0.55,3.11) *0.536*	1.81 (0.84,3.89) *0.130*	1.12 (0.46,2.73) *0.801*	2.17 (1.03,4.45) *0.042*	1.37 (0.57,3.26) *0.482*	2.43 (1.06,5.55) *0.035*	1.46 (0.57,3.71) *0.427*
DSH in 2 years before pregnancy	5.90 (2.79,12.50) *<0.001**	2.55 (1.05,6.50) *0.039**	5.00 (2.25,11.13) *<0.001**	2.30 (0.90,5.86) *0.082*	5.46 (2.54,11.74) *<0.001*	2.30 (0.93,5.70) *0.071*	6.69 2.95,15.16) *<0.001*	3.02 (1.17,7.84) *0.023*
Harmful substance use	4.50 (2.17,9.35) *<0.001**	1.68 (0.61,4.59) *0.314*	4.08 (1.89,8.82) *<0.001**	1.67 (0.58,4.83) *0.342*	4.37 (2.09,9.17) *<0.001*	1.53 (0.54,4.29) *0.264*	4.00 (1.80,8.87) *0.001*	1.67 (0.58,4.82) *0.343*
Smoking in pregnancy	6.66 (3.18,13.96) *<0.001**	3.64 (1.30,10.19) *0.014**	5.95 (2.73,12.98) *<0.001**	3.36 (1.13,9.97) *0.029**	6.89 (3.24,14.65) *<0.001*	3.81 (1.32,10.99) *0.013*	5.99 (2.67,13.44) *<0.001*	3.48 (1.17,10.35) *0.025*
Baseline diagnosis (non-affective)	3.06 (1.35,6.96) *0.008**	2.29 (0.91,5.71) *0.077*	3.75 (1.49,9.43) *0.005**	2.66 (0.98,7.20) *0.055**	3.02 (1.32,6.89) *0.009*	2.18 (0.86,5.49) *0.099*	2.94 (1.21,7.12) *0.017*	2.15 (0.81,5.72) *0.125*
Admitted in 2 years before pregnancy	2.90 (1.37,6.16) *0.005**	1.87 (0.79,4.42) *0.153*	2.76 (1.25,6.09) *0.012**	1.87 (0.77,4.55) *0.168*	2.81 (1.32,6.01) *0.008*	1.65 (0.69,3.98) *0.264*	2.53 (1.13,5.69) *0.024*	1.63 (0.66,4.08) *0.292*
Medication change								
Continued	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
Stopped/ switched	4.28 (1.62,11.29) *0.003**	2.48 (0.84,7.31) *0.099*	3.74 (1.39,10.05) *0.009**	2.26 (0.75,6.77) *0.145*	4.23 (1.59,11.29) *0.004*	2.55 (0.85,7.65) *0.095*	3.29 (1.16,9.38) *0.026*	1.90 (0.58,6.17) *0.287*
No medication at start of pregnancy	2.54 (0.91,7.06) *0.074*	2.36 (0.76,7.32) *0.137*	2.08 (0.72,5.99) *0.177*	1.95 (0.60,6.26) *0.265*	2.43 (0.87,6.77) *0.088*	2.17 (0.70,6.71) *0.180*	2.54 (0.91,7.06) *0.074*	2.33 (0.75,7.23) *0.142*

Discussion

This is the first study, to our knowledge, to report on the prevalence of self-harm in pregnant women with severe mental illness, a group already recognised to be at increased risk of maternal suicide. We found that 25 of this cohort had recorded suicidal ideation in pregnancy, a similar rate to that reported in a clinical population of 360 pregnant women referred to a perinatal mental health programme with lifetime history of DSM Axis I mental disorder [24]. Of particular, clinical concern was our finding of self-harm in 8%, with violent methods used in a fifth, indicating potential severity of intent and illness which has been found in studies of suicide in general populations [25] and perinatal suicides [7]. We confirmed our hypotheses that self-harm was associated with illness severity - smoking, and previous self-harm and, though weaker evidence, non-affective diagnosis.

Medication discontinuation was not significantly associated with self-harm, though this may reflect a lack of statistical power. In pregnancy, clinicians as well as patients may be concerned to avoid medication due to concerns about teratogenicity, particularly in the first trimester, and we have described elsewhere that 78.6% of those who stopped medication in this cohort were indeed recorded as stopping “because of the pregnancy” [19]. Recent systematic reviews and well-designed cohort studies suggest that the small increased risk of congenital malformations in this population appears to be due to confounding factors, [26, 27] other than for some mood stabilisers, particularly valproate [28]. While this study cannot confirm whether or not medication changes in pregnancy could lead to self-harm, there are likely to be complex relationships between illness severity, medication change and self-harming behaviour that are not easy to disentangle in observational research. Screening and close monitoring is therefore essential for pregnant women with SMI, particularly those with markers of severity who discontinue medication, in order to prevent repetition of self-harm [9].

Finally, it was noteworthy that this population had high prevalence of substance misuse, smoking and reported domestic abuse - all risk factors for adverse foetal outcomes which need to be addressed by maternity and mental health professionals [29].

Strengths and limitations

Strengths of the study include the use of data from a large representative sample of pregnant women with SMI observed longitudinally within a comprehensive clinical database. The unique features of the data source enabled us to access data on a group who are a particularly hard-to-reach population to recruit into clinical studies [30]. Other studies looking at self-harm, suicide and suicidal ideation in pregnancy have often excluded patients with SMI; utilising these clinical records enabled us to capture a group of women who are potentially at particular risk and yet are under-represented in research, particularly women with schizophrenia. The use of Hospital Episode Statistics provided a robust method of identifying pregnancies regardless

of hospital of birth. It did not include home births, which account for about 2.4% of births for England in 2011 [31]; however, as women with SMI are high-risk pregnancies, it is unlikely that many deliver at home. Hospital Episode Statistics also enabled us to collect information on admission histories covering the whole of England for this potentially mobile population. An additional strength was the detailed information on psychotropic medication use, in addition to histories of abuse and other exposures usually not available in administrative datasets.
Limitations include the use of information recorded by clinical staff, which could underestimate suicidal ideation and self-harm prevalence - women may not disclose suicidal thoughts or acts as they may be worried about custody loss [32, 33]. There was no mention of suicidal ideation in the notes for 33% of women, which may have been due to suboptimal record-keeping. Finally, we cannot assume generalizability to all women with SMI and pregnancy, as we did not include women with SMI managed solely in primary care.

Conclusions

The comparatively high level of suicidal ideation reported, and the significant levels of self-harm recorded, indicates that women with SMI in pregnancy are a high-risk population who require close monitoring in pregnancy.

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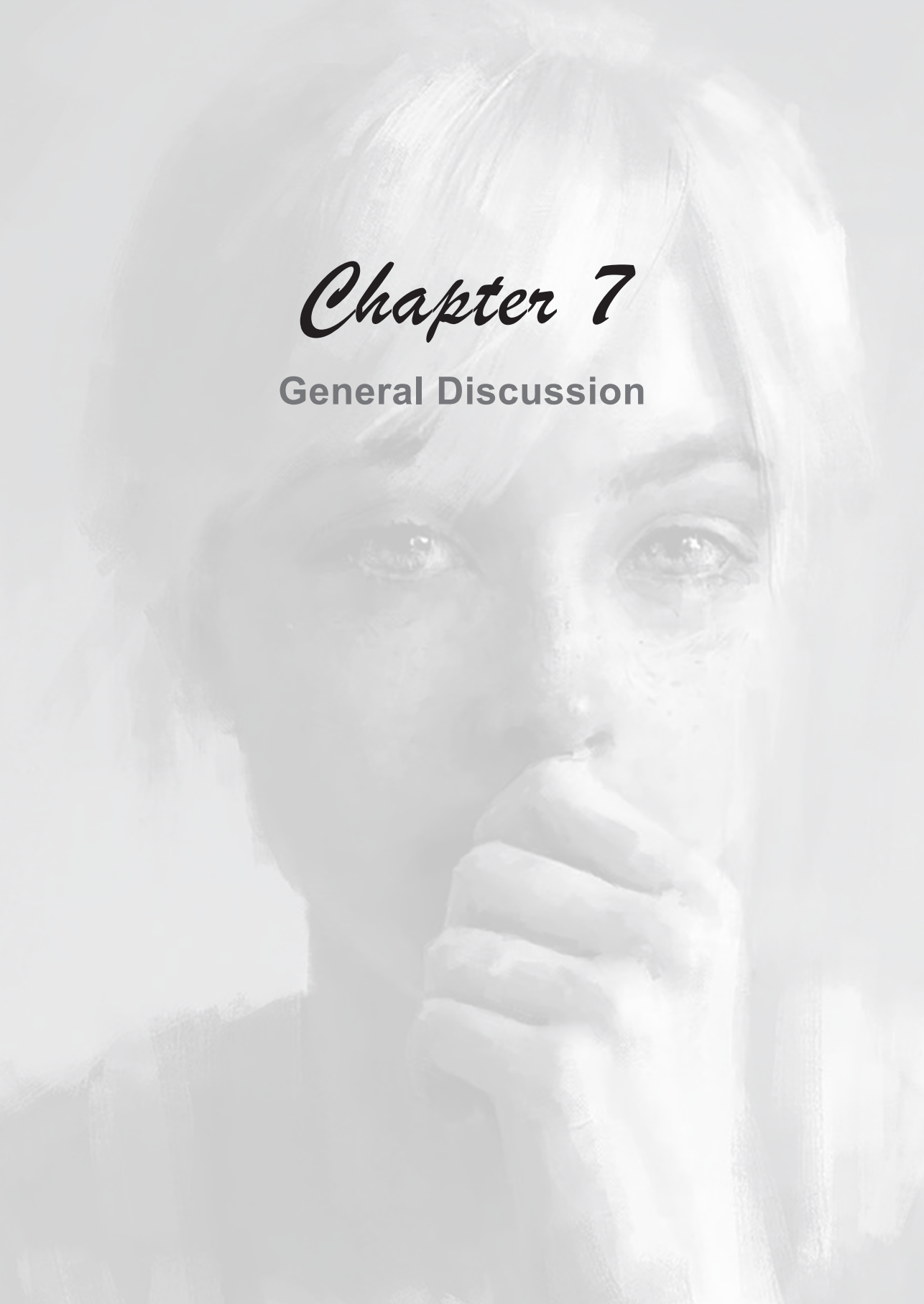

Chapter 7

General Discussion

General Discussion

The overall aim of this thesis was to extend the existing knowledge about the treatment and impact of mental disorders during pregnancy by evaluating a new group-based multicomponent therapy using a Randomized Controlled Trial (RCT). This therapy was based on clinical expertise and a systematic review of all interventions to treat mental disorders during pregnancy as described in Part I of this thesis. Part II explored the impact of having a mental disorder on sleep and mood fluctuations during pregnancy. In addition, the prevalence and correlates of suicidal ideation and self-harm were investigated in a cohort of pregnant women with psychotic disorders such as schizophrenia and bipolar disorders.
In the previous chapters, the main results, merits and shortcomings of the studies were discussed in detail. This chapter provides a general discussion of the main findings, methodological considerations, implications for further research and a final conclusion.

Main findings of studies presented in this thesis

Part I Treatment of mental disorders during pregnancy

After reviewing all controlled studies on interventions for the treatment of a broad spectrum of mental disorders during pregnancy, we found no controlled studies on the effect of psychotropic medication. With respect to non-pharmacological treatment of the broad spectrum of mental disorders, we only found controlled studies focusing on depression. Therefore we could only estimate effect sizes for treatment of patients diagnosed with Major Depressive Disorder (MDD). In our meta-analysis psychotherapy for MDD showed robust effect sizes, in particular Cognitive Behavioural Therapy (CBT, g=-0.61), and to a lesser extent Interpersonal Therapy (IPT, g=-0.67). This is in line with current NICE guidelines that advise clinicians to offer a form of psychotherapy to every pregnant woman with a current or history of mild to severe depression [1].
Based on the clinical experience of our perinatal mental health team and relying on evidence-based components from other treatments during pregnancy, a new Group-based Multicomponent Treatment (GMT) was composed for pregnant women with co-morbid psychiatric and psychosocial problems. GMT aimed at the reduction of stress, depressive and anxiety symptoms, and has a special focus on emotional and practical preparation for motherhood. An RCT – the DAPPER-trial – evaluated this weekly one-day GMT compared to individual counselling (Treatment As Usual) for the reduction of depressive symptoms during pregnancy. DAPPER is an acronym for Daycare Alternative Psychiatric Pregnant women Efficiency Research. Our study showed that GMT is a feasible and well-accepted treatment for a clinical sample of pregnant women with co-morbid and diverse psychiatric disorders

(e.g. anxiety disorders and personality disorders) and psychosocial problems. We observed a reduction of depressive symptoms during treatment, but we could not demonstrate that GMT is more effective than individual counselling. It might be that our control arm depicts the effect of individual counselling and/or the natural course of symptoms, leading to regression to the mean. We expected that depressive scores would be the same or lower in the postpartum period, based on cohort studies measuring depression across pregnancy and the postpartum period [2, 3]. Given the lack of evidence for superiority of any specific therapy, clinicians should consider and discuss different treatment options. I would recommend a form of CBT, but also taking into account personal circumstances and preferences of the patient. There were no differences on treatment outcomes or drop-out rates between women who were randomized or choose their treatment of preference (GMT or TAU). The literature shows that a tailored treatment advice enhances engagement and compliance of the patient, which is likely to increase the effect of the treatment.

Part II Impact of a mental disorder during pregnancy

Mental disorder and sleep during pregnancy

During pregnancy, symptoms of a mental disorder (e.g. MDD and anxiety disorders) affecting mood, sleep, appetite and energy are often difficult to distinguish from the normal experiences of pregnancy. We explored the impact of a broad spectrum of mental disorders on sleep quality and measured it subjectively by a daily sleep diary and objectively by an Actiwatch in a case-control study. A mental disorder during pregnancy is associated with poorer subjective sleep quality but not with worse objective sleep quality. This result demonstrates the importance of focusing on the perception of sleep in pregnant women with a mental disorder who report sleep problems. It is worth noting that most pregnant women – with and without mental disorder – had a suboptimal subjective and objective sleep quality. This was measured with the Pittsburg Sleep Quality Inventory (PSQI), which is a measure for sleep quality, and with actigraphy, which is an objective measure to determine sleep characteristics.

Mental disorder and mood fluctuations

Poor sleep quality influences mood, and vice versa. In another study we described three phenotypes of mood fluctuations in women with a mental disorder across pregnancy. Based on the weekly Profile of Mood State, we identified three phenotypes: severe mood fluctuations (highly variable), stable negative (more depressed/anxious) and stable positive mood. We observed no differences between the three phenotypes based on demographics, clinical or pregnancy outcomes, except for a lower birth weight in the fluctuating mood phenotype. In this clinical sample, there is a substantial group with severe mood fluctuations. This phenotype is also characterized by co-morbid psychiatric and psychosocial problems and we hypothesized that this fluctuating mood phenotype might be at risk for poor pregnancy outcomes. Although

these findings are interesting, they need to be replicated in a larger sample to further understand the underlying mechanisms and using repeated measurements of mood state.

Mental disorder and self-harm during pregnancy
In case of severe mood fluctuations, a clinical concern is suicidal ideation and self-harm. We studied the prevalence of self-harm in a group at increased risk of maternal suicide, i.e. a unique cohort of pregnant women with schizophrenia/related disorders and bipolar disorder from a 'new generation' case register (CRIS) in London. Out of the 420 women in the study, 25% recorded suicidal ideation and 8% had a self-harm event during their pregnancy, with violent methods used in a fifth. We confirmed our hypotheses that self-harm was associated with illness severity - smoking, and previous self-harm, and to a lesser extent with a non-affective psychiatric diagnosis.

Methodological considerations

All studies included in this thesis were embedded in the DAPPER-trial, except for one study. In this paragraph we will discuss the strengths and limitations of the DAPPER-sample, study design and measurements. Hereinafter we will discuss the limitations of the cohort of pregnant women with a severe mental disorder from London.

DAPPER cohort
A limitation of the DAPPER-trial was the relatively small number of participants (n=158) to test the efficacy of a Group-based Multicomponent Treatment. Compared to other studies in the field of perinatal psychiatry, this is still a substantial number since this is a hard-to-reach and difficult to engage population. Affected women are sometimes overwhelmed with both emotional adaptation to – often unexpected or unwanted – pregnancy and other time and energy consuming aspects (e.g. perinatal visits, practical preparation for the baby, and relational, family and work related issues). Due to our design and incentives, 20 (11.2%) eligible women refused participation and almost two out of three women who were willing to participate consented to randomization. The drop-out during the study was remarkably low (9/155, 5.8%). Drop-out and non-compliance was not associated with patient characteristics, such as parity and gestational age. We chose a clinical sample from an outpatient clinic and deliberately included other mental disorders next to major depressive disorder (MDD). Besides MDD (46.2%), our sample existed of anxiety disorder (31.6%) and comorbid personality disorders (49.4%). We did this, as this heterogeneity of mental disorders reflects clinical practice. Thus this practice enhanced the generalizability of our studies to other outpatient's clinics focusing on perinatal psychiatry. At the other hand, our GMT was not specially designed

for the treatment of a broader spectrum of mental disorders, including personality disorders or anxiety disorders. Our GMT was not supported by evidence-based literature, but is derived from effective treatments for MDD. The sensitivity analysis supported our main findings and most likely it was not the result of a certain subgroup.

The DAPPER-trial was designed as a patient-preference RCT and therefore suitable to compare the treatment effect of GMT versus Treatment As Usual (TAU). Strength of the study design was that it allowed us to additionally investigate the effect of patient's preference for group-based or individual therapy on treatment response [4]. Since there were no differences in baseline characteristics, compliance, drop-out or treatment outcomes between the randomized and patient-preference condition, also in this respect support our results the generalizability to clinical practice [5]. Depressive symptoms in both GMT and TAU group decreased until after delivery, our RCT did not show a significant difference in decrease of depressive symptoms between GMT and TAU. It could be a power issue due to our relatively small sample size. However, it is questionable whether a larger sample size had ensured an effect. We speculate it might be related to the effective control condition of TAU. The treatment as usual is offered in a specialized tertiary centre for perinatal mental disorders with experienced clinicians and this tailored treatment could be as effective as GMT.

A set of questionnaires was used in the DAPPER-trial. The Edinburgh Postnatal Depression Scale (EPDS) was used during pregnancy and as a primary outcome at 6 weeks postpartum according prepublished protocol. EPDS is a self-report questionnaire validated to measure depressive and anxiety symptoms during pregnancy and postpartum [6]. We missed more than half of the 10 and 15 week follow-up assessments during pregnancy and this most certainly limited the ability of study to detect a treatment effect. Generalized mixed model analysis is robust for missing values, but it cannot undo the effect of power loss due to the small sample size. Our findings showed no differences in the Intention To Treat-analysis and Per Protocol analysis. Possibly, the treatment effect during pregnancy was faded away after 6 weeks after giving birth and additional life-events.

Next to the EPDS, we also assessed depressive symptoms by the Hamilton Depression Rating Scale (HDRS) [7]. HDRS is a clinician-rated scale; unfortunately the assessor was not blinded for the treatment condition and there could possibly be information bias. It was also not possible to blind participants because of the overt treatment conditions.

Since we did not investigate other potential benefits of GMT above TAU, like improvement of lifestyle, social support or maternal mentalization capacity or bonding to the unborn child, we cannot exclude that women improved on other domains.

Although one third of the DAPPER-sample was diagnosed with an anxiety related disorder, we did not assess anxiety symptoms during pregnancy or used it as an outcome.

Cohort from London

From the literature we know that those women, who die by suicide during pregnancy, are more likely to have a diagnosis of schizophrenia related disorders or bipolar disorder and less likely to have a diagnosis of depression. Due to a very small number of these diagnoses in our DAPPER-sample, we decided to cooperate with the Section of Women's Mental Health of the Institute of Psychiatry of King's College London. As a result of this collaboration, we had access to data from a large representative sample of pregnant women with a severe mental disorder observed longitudinally within a comprehensive clinical database (CRIS). Other studies looking at self-harm, suicide and suicidal ideation in pregnancy have often excluded patients with a severe mental disorder. Utilizing these clinical records enabled us to study a group of women, who are potentially at particular risk, and yet are underrepresented in research, particularly women with schizophrenia.

A possible limitation by using information recorded by clinical staff on a sensitive topic, we might have underestimated suicidal ideation and self-harm prevalence. In other words, women may not disclose suicidal thoughts or acts, as they may be worried about custody loss. There was no mention of suicidal ideation in the records for 33% of women, which may have been due to suboptimal recordkeeping.

Implications of current findings and proposed future research

As mentioned in the Introduction and confirmed in our meta-analysis, we highlight the fact that the treatment of a broader spectrum of mental disorders during pregnancy is not represented in current research. While anxiety, bipolar and other psychotic disorders may adversely affect mother and unborn child too, next to depression, we strongly recommend further research on both pharmacological and non-pharmacological treatment options for each specific mental disorder during pregnancy.

Our well-designed RCT for a clinical sample did not show a significant difference in decrease of depressive symptoms between CBT-based GMT and treatment as usual (TAU = individual counselling). Also in our meta-analysis we found that the effect sizes of the different psychotherapies (CBT and IPT) are close to each other and possibly redeemable. It could be the case that it is not really important what kind of psychotherapy (CBT, IPT, GMT, or individual counselling) a patient is offered, as long as the patient is motivated for the treatment and being closely monitored by a specialised perinatal mental health care professional. It does not necessary mean, if more therapy components are offered that this will result in a more effective or beneficial treatment. An option would be to include a control condition in a trial, for example a 'waiting list'-condition. However, we are aware of the ethical concerns in this design, i.e. withholding treatment in women with an identified mental disorder. Another

challenge would be to formulate other treatment or composite outcomes, which measure other potential additional benefits of the enhanced treatment, e.g. improvement of several life domains like 1) health, e.g. visiting antenatal care; 2) daily functioning; 3) partner and family relationships or 4) preparation for motherhood, for example by using the Experience of Motherhood Questionnaire [8].

Fortunately, the last couple of years there have been a growing awareness of the special need and treatment for pregnant women with a mental disorder. This has resulted in the foundation of several perinatal psychiatric outpatient clinics, the POP (Psychiatry Obstetrics Paediatricians) clinics in the Netherlands. In general, these different clinics offer a personalized treatment advice composed by professionals of the aforementioned three medical specialties and (referral to) tailored psychiatric care. Often a form of counselling or psychotherapy is offered, but there are local differences in available options. For the future, it would be interesting to evaluate (the cost-effectiveness of) these POP-clinics. However, this is a challenge because there are different reasons for referral, different local triage and treatment regimes for each POP-clinic. It is difficult to define a homogenous sample, to standardise an evidence-based treatment and to use a sensitive measurement method to monitor treatment outcome for mother and/or child. Furthermore, a cost-effectiveness analysis is challenging due to a broad spectrum of – psychiatric-related – health care costs, e.g. psychiatric specialized care, obstetric care, hospitalisation and other psychiatric and psychosocial outpatient care.

Besides the evaluation of non-pharmacological interventions, there is a need for more controlled pharmacological trials because current evidence for the effectiveness and potential harm of psychotropic medication during pregnancy is based on naturalistic studies, case-series and case-reports. For other designs, e.g. for example a discontinuation trials, there are ethical and methodological issues. Despite the lack of evidence, about 2% of the women in the Netherlands use Selective Serotonin Reuptake Inhibitors (SSRIs) during their pregnancy [9]. However, SSRI use during pregnancy is controversial because of unknown risk for the unborn child. While on the other hand relapse of depression during pregnancy holds also risks for both mother and child. One of the first multicentre RCT on the effect of continuation or guided tapering of SSRIs on both mother and child is recently started at our Departments of Psychiatry and Obstetrics and Gynaecology in close collaboration with the University of Utrecht and Groningen (www.stoporgostudie.nl). This study is promising but prospective controlled trials on other psychotropic medication are also necessary, e.g. SNRI's, TCA's, mood stabilizers and antipsychotics. Of paramount importance is the follow-up of children exposed to intrauterine psychotropic medication and to study the obstetric outcomes and long-term child neurodevelopment.

Beyond the potential impact of the psychotropic medication, it would be very interesting to study the impact of intra-uterine stress related to maternal psychopathology on the fetus. A relatively new potential technique is to measure cortisol in hair as a biomarker of hypothalamic-pituitary-

adrenocortical (HPA)-activity and prolonged stress during the past months. One study found a positive relation between perceived maternal stress and hair cortisol concentration (HCC) in healthy pregnant women [10], in contrast to Wikenius et al. who did not find a correlation between depression during pregnancy and HCC [11]. These results are preliminary and heterogeneous. For future research, it would be interesting to simultaneously investigate whether self-reported stress reduction in an intervention trial could be also objectivised in a reduction of cortisol in both mother's and infant hair.

As suggested by Glover, prenatal anxiety or depression may contribute 10-15% of the attributable load for emotional and behavioural outcomes of the child [12]. These adverse outcomes have a wide range, including emotional problems, impaired cognitive development and developing a mental disorder later in life [13]. There is only a small number of studies investigating the effect of a non-pharmacological intervention during pregnancy on the long-term neurodevelopment of the child/adult. A small RCT in Australia showed that a brief CBT intervention reduced anxiety during pregnancy and improvements in depression in the postpartum period [14]. Nine-month infant outcomes showed several medium to large effects favouring the intervention in domains including problem solving, self-regulation and stress reactivity, which were independent of maternal postnatal mood. Other studies are still on-going, like the ACORN study in the UK that offers a brief intervention to reduce maternal anxiety and studies infant temperament and sleep [15]. The Dutch PROMISES-trial showed no difference on maternal depressive symptoms after a CBT invention compare to treatment as usual, but there is no data available yet on the infants' behavioural/emotional problems at 1.5 years [16].

Next to depressive symptoms, there is an increasing interest to screen and treat (co-morbid) anxiety disorders during pregnancy. The State Trait Anxiety Inventory has been used in research with pregnant women but there are some issues of validity for the use during pregnancy [17]. In the literature, there are a few anxiety inventories, which are validated for the use during pregnancy. A validated questionnaire on general and pregnancy-specific anxiety symptoms is necessary to accurately screen for anxiety symptoms and to evaluate interventions [18], e.g. the Perinatal Anxiety Screening Scale (PASS) seems promising [19]. Moreover, the Pregnancy-Related Anxiety Questionnaire (PRAQ) is a robust predictor of birth-related and childhood outcomes, independent of general anxiety measures [20]. Recently the question about previous deliveries is changed, so the revised version (PRAQ-R) can be used in both nulliparous and parous pregnant women [21]. A specific form of anxiety during pregnancy is fear of childbirth – tocophobia - and the Wijma Delivery Expectancy Questionnaire (WDEQ) is validated for the use during pregnancy and in the postpartum period [22]. This questionnaire could be useful to detect PTSD after childbirth and evaluate future treatments, e.g. Eye Movement Desensitization and Reprocessing (EMDR) [23].

In line with the above statements on the treatment of the full spectrum of mental disorders, future research should also focus on co-morbid psychiatric and psychosocial problems, like personality disorders, socio-economic status (SES), social support and life style. For example, our previous study focusing on the role of psychiatric and psychosocial problems on birth outcomes showed that low SES and the accumulative effects of psychiatric and psychosocial risk factors have a stronger impact on decreased birth weight and preterm birth above depressive symptoms [24]. For obstetric caregivers, it is important to systematically screen for psychosocial problems and substance use (for example through the validated Mind2Care instrument (7)) and to make sure that adequate and effective interventions will be offered and monitored. A Medical Social Worker can be of great added value to the perinatal treatment team of a psychiatrist, gynaecologist and paediatrician for case management. A local development is that a part of the treatment plan is executed in the neighbourhood, for example the program for vulnerable pregnant women in Rotterdam in close collaboration with Erasmus University Medical Centre called Mothers of Rotterdam (https://www.moedersvanrotterdam.nl/). In the Netherlands, a municipal initiative called 'VoorZorg' for the care of pregnant women until the age of 25 (https://cjgrijnmond.nl/prenataal-aanbod-voorzorg) is being implemented. A new initiative would be providing 'preparing for motherhood' group classes under professional supervision (e.g. Centering Pregnancy groups [25]), also to promote social cohesion among the vulnerable pregnant women and to save travel costs. This could be in close collaboration of the perinatal team with the general practitioner, midwife, outreaching psychosocial support institutions and Center for Youth and Families. This has also advantages for the postpartum period, to closely monitoring child development, support-parenting skills and to discuss contraception in an early phase.

Final conclusions

- In our comprehensive systematic review, we could not find any controlled study for the treatment of mental disorders during pregnancy with psychotropic medication (e.g. antidepressants, antipsychotics and/or mood-stabilizers). Non-pharmacological trials, other than within pregnant women with a major depressive disorder (MDD), are scarce. We found a robust moderate treatment effect of Cognitive Behaviour Therapy (CBT) for MDD during pregnancy, and to a lesser extent for Interpersonal Psychotherapy (IPT). In line with the NICE guidelines, we advise a form of psychotherapy and therapies might be redeemable, depending on local availability and personal preference.

- Our Group-based Multicomponent Treatment (GMT) is an acceptable treatment for a heterogeneous group of pregnant women with depressive symptoms and co-morbid mental disorders and/or low SES, but not superior to treatment as usual.
- Our exploratory study on the quality of sleep in pregnant women with a mental disorder suggests that perceived sleep quality reported on a daily basis is worse than the sleep quality as measured by wrist actigraphy.
- We found a high level of suicidal ideation and significant levels of self-harm records among pregnant women with psychotic disorders and bipolar disorder, indicating that women with a severe mental disorder in pregnancy from a high-risk population that require close monitoring in pregnancy.

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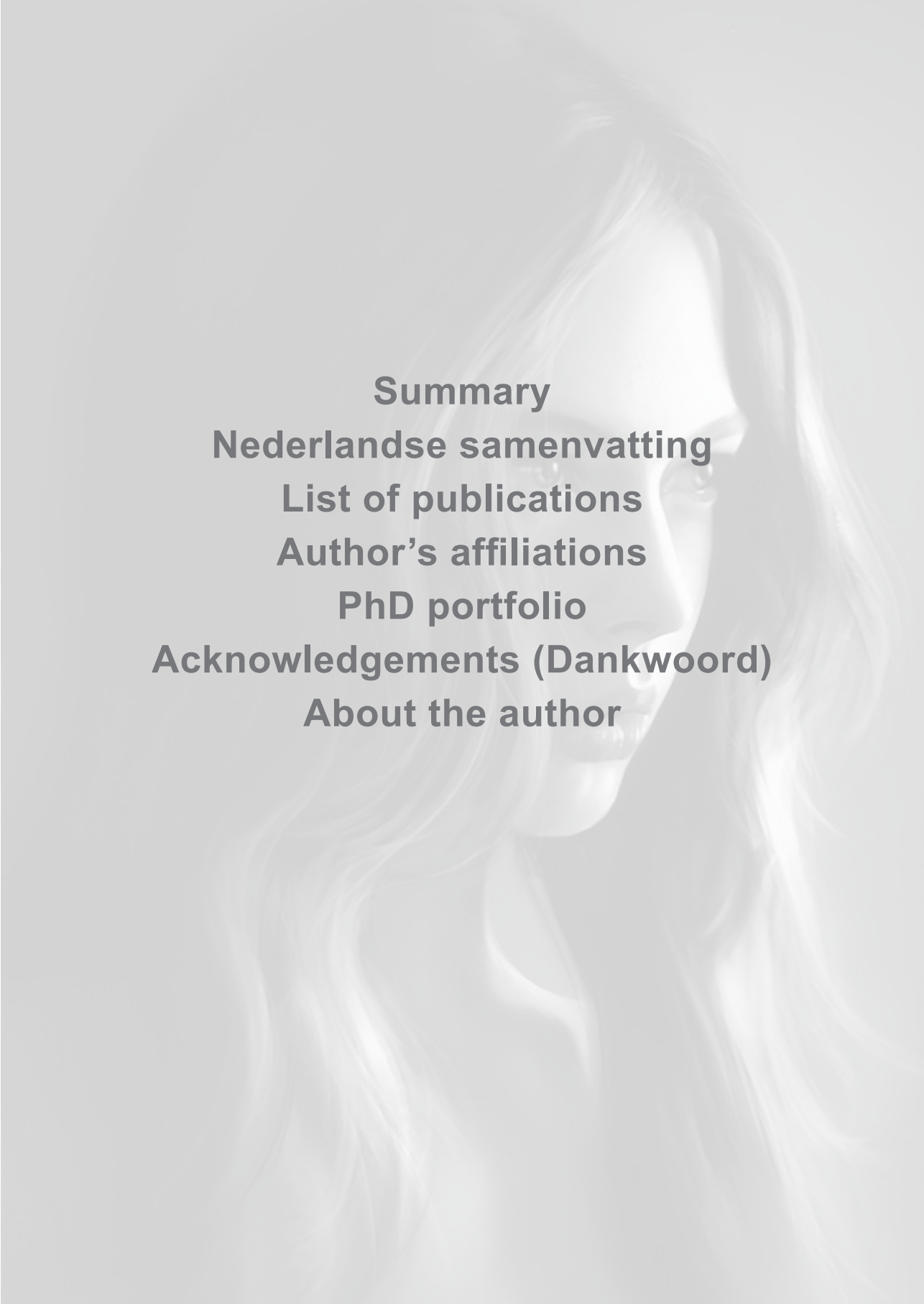
Part 3

Appendices



Summary

The aim of this thesis is to extend existing knowledge on the treatment and impact of a mental disorder during pregnancy, more specifically on sleep quality and patterns of mood fluctuations and evaluating a new group-based multicomponent treatment. **Chapter 1** provides a literature review of mental disorders during pregnancy and explains that a broader range of mental disorders and co-morbid mental disorders (e.g. anxiety disorders and personality disorders) is prevalent during pregnancy. This review applies to women who are previously diagnosed with a mental disorder, and those who experience psychiatric symptoms for the first time. According to prevalence rates varying from 3 to 11%, pregnancy seems to be neither protective nor exacerbating. The prevalence, symptoms and specific issues (e.g. course and concerns during pregnancy) related to pregnancy are not only discussed for Major Depressive Disorder (MDD), but also for bipolar disorder, anxiety related disorder, eating disorder and schizophrenia related disorders. Maternal psychopathology is related to increased intra-uterine cortisol levels, as a result of maternal stress. This mechanism is associated with impaired fetal development, leading to a lower birth weight and premature birth and affects long-term infants development. Besides the direct influences, there are also indirect negative effects, like worse self-care and more substance abuse. Also sleep and mood fluctuations are often reported during pregnancy, but little is known on specific patterns of mood and whether sleep quality is objectively worse or the perception is altered.

The challenge for the treatment of mental disorders during pregnancy is to balance between the deleterious effects of the disease and largely unknown effects - on the fetus - of pharmacotherapy. The NICE guidelines from the UK advise clinicians to do a risk-benefit analysis, to weigh the risk of relapse against the potential risk for the fetus and encourage the use of non-pharmacological interventions. Based on the findings from previous non-pharmacological intervention studies and our clinical experience, a new group-based multicomponent therapy (GMT) was developed from other evidence-based group-based treatments for mood disorder. GMT aims to reduce stress, depressive and anxiety symptoms in pregnant women with a special focus on emotional and practical preparation for motherhood. This weekly open group therapy includes Cognitive Behavioural Therapy (CBT), psycho-education, psychomotor therapy and relaxation therapy. An RCT, the DAPPER-trial evaluated GMT compared to individual counselling (treatment as usual, TAU) in reducing depressive symptoms in pregnant women with a mental disorder. After a structured diagnostic interview (SCID) and written informed consent, participants fulfilled 3 questionnaires on mood and sleep quality during pregnancy and the Edinburg Depression Scale at 6 weeks postpartum, which was used as primary outcome.

Chapter 2 gives a systematic review of the literature of all available treatments for the broad spectrum of mental disorders in pregnant women. Until today, there are no controlled studies

on the effect of psychotropic medication for mental disorders during pregnancy. In our meta-analysis we could only estimate treatment effect sizes for MDD due to a lack of studies on other disorders. Psychotherapy for MDD has robust effect sizes, e.g. CBT (*g*=-0.61), and less robust weighted-effect, Interpersonal Psychotherapy (IPT, *g*=-0.67). Both may hold potential benefit for pregnant women with MDD in this analysis. This is in line with current NICE guidelines that advise clinicians to offer a form of psychotherapy to every pregnant woman with a history of mild to severe depression and emphasizes close consultation with patients. Other potential effective non-pharmacological interventions to treat MDD were body-oriented interventions and acupuncture. Bright light therapy is not associated with a decrease of depressive symptoms, but this is based on two trials with low sample sizes. The overall effect sizes of all non-pharmacological intervention are in close range to each other and may be redeemable for one other, bearing in mind the high attrition rates of most trials. Therefore we suggest that the preference of the patient have to weigh heavily in the decision for a psychiatric treatment in a clinical setting.

Chapter 3 describes the DAPPER-trial, the first RCT among a clinical sample of pregnant women with co-morbid psychiatric and psychosocial problems, evaluating a new group-based multicomponent therapy to reduce depressive symptoms during pregnancy. Overall, there was no significant difference observed in decrease of depressive symptoms between GMT and treatment as usual (TAU) at 6 weeks postpartum. We were able to successfully recruit a hard-to-reach population (n=158); only 20 (11.2%) eligible women refused participation, almost two out of three women willing to participate consented to randomization and drop-out was low (9/155, 5.8%). We diagnosed next to major depressive disorder also a high number of anxiety disorders (31.6%) and a comorbid personality disorders (49.4%). The sample size was smaller than anticipated and we missed follow-up assessment during pregnancy, but our generalized mixed models and sensitivity analysis confirmed our findings that there is no difference in reduction of depressive symptoms between the two treatment conditions. This might be related to the effect of our specialized TAU or the natural course of symptoms, leading to regression to the mean. However, the new GMT showed to be feasible, well-accepted and a good option to reduce depressive symptoms during pregnancy. Depending on local availability and costs, clinicians should consider and discuss different treatment options, taking into account personal circumstances and preferences of the patient.

Chapter 4 focuses on the impact of a mental disorder on sleep quality by comparing subjective and objective sleep quality in a case-control study. To measure objective parameters of sleep quality, all participants (21 cases and 33 healthy controls) wore a wrist actigraph for 7 days and nights. Subjective sleep quality was retrospectively assessed using the Pittsburgh Sleep Quality Index (PSQI) and on a daily basis with the Subjective Sleep Quality-scale (SSQ). Objective parameters of sleep quality and subjective sleep quality as assessed by the PSQI did not differ significantly between cases and controls. Daily sleep reports showed that,

relative to controls, cases had a significantly worse average SSQ-score. Our exploratory study suggests that perceived sleep quality reported on a daily basis by pregnant women with a mental disorder is worse than the sleep quality as measured by wrist actigraphy.

Chapter 5 explores patterns of mood fluctuations in pregnant women with a mental disorder by the weekly Profile of Mood state and investigates associations with obstetric outcomes and postpartum depression. We identified three patterns: highly variable, stable negative (more depressed/anxious) and stable positive mood. Our exploratory study showed that severe mood fluctuations might affect pregnancy outcomes. These findings need to be replicated in larger studies with repeated measurements.

In **Chapter 6**, we describe the prevalence of suicidal ideation and self-harm events in pregnant women with schizophrenia related disorders and bipolar disorder, from a 'new generation' case register (CRIS) in London. Out of the 420 women in the study, 25% recorded suicidal ideation and 8% had a self-harm event during their pregnancy, with violent methods used in a fifth. Suicidal thoughts and self-harm occurred in a significant proportion of pregnant women with severe mental illness, particularly younger women and those with a history of self-harm; these women need particularly close monitoring for suicidality. We confirmed our hypotheses that self-harm was associated with illness severity, smoking, and previous self-harm, and though weaker evidence, non-affective diagnosis.

Main findings of this thesis, methodological considerations, implications of current findings and recommendations for further research were discussed in **Chapter 7.** A limitation of our DAPPER-trial was the relatively small number of participants, which is a known problem in this hard to reach population. Next to participants with MDD, we included also a high number of participants with anxiety disorders and comorbid personality disorders. This heterogeneity reflects clinical practice and enhances generalizability of our studies. A specific characteristic of our study design was the patient-preference RCT and therefore its suitability for comparing the treatment effect of GMT vs. TAU, and additionally randomized vs. patient-preference conditions. A limitation of the measurements was that we did not investigate the course of anxiety symptoms thoroughly or other potential benefits of GMT above TAU (e.g. preparation of motherhood and enhancing social support).

From our meta-analysis, as well from our RCT, we conclude that a form of psychotherapy (preferably CBT or IPT) needs to be offered to pregnant women with a mental disorder, but the different treatment options seem to be redeemable. However, we do need larger controlled trials to confirm this advice for non-pharmacological intervention for MDD, and also for the broader range of mental disorders.

Samenvatting

Het doel van dit proefschrift is om meer inzicht te krijgen in de behandeling en de impact van een psychiatrische stoornis tijdens de zwangerschap.

Hoofdstuk 1 geeft een overzicht van de psychiatrische stoornissen die tijdens de zwangerschap voorkomen en stelt dat er een breder scala aan psychiatrische stoornissen en co-morbide stoornissen (zoals angst- en persoonlijkheidsstoornissen) prevalent is tijdens de zwangerschap. Het gaat om zwangeren, die eerder gediagnosticeerd zijn met een psychiatrische stoornis, of die voor het eerst psychiatrische symptomen ervaren tijdens de zwangerschap. Volgens de prevalentiecijfers, variërend van 3 tot 11%, lijkt een zwangerschap niet beschermend te zijn noch de uitlokkende factor te zijn voor psychiatrische klachten. De prevalentie, symptomen en specifieke zaken (zoals beloop en aandachtspunten) rondom een zwangerschap worden besproken voor depressieve stoornis, maar ook voor een bipolaire stoornis, angst gerelateerde stoornissen, eetstoornissen en schizofrenie en psychotisch gerelateerde stoornissen. Een psychiatrische stoornis tijdens de zwangerschap beïnvloedt de maternale stress in utero direct en wordt geassocieerd met een vertraagde foetale ontwikkeling, wat leidt tot een lager geboortegewicht en vroeggeboorte en een ongunstig effect heeft op de latere ontwikkeling van het kind. Naast de directe invloed van maternale stress, zijn er ook indirecte negatieve effecten van een psychiatrische stoornis, zoals een verminderde zelfzorg en toename van drugsmisbruik. Ook slaap- en stemmingsstoornissen worden vaak gerapporteerd tijdens de zwangerschap, maar er is weinig bekend over de specifieke patronen van stemming, en/of de kwaliteit van de slaap objectief slechter wordt of alleen de perceptie daarvan.

De uitdaging in de behandeling van psychiatrische stoornissen tijdens de zwangerschap is het balanceren tussen de schadelijke effecten van de ziekte en de grotendeels onbekende effecten - op de foetus - van psychofarmaca. De NICE richtlijnen uit het Verenigd Koninkrijk adviseren om een risico-baten analyse te doen, om het risico op een terugval af te wegen ten opzichte van het potentiële risico voor de foetus, en het gebruik van niet-farmacologische interventies aan te moedigen. Een nieuwe groepsdagbehandeling (GDB) met meerdere bestaande therapieën werd samengesteld uit andere evidence-based groepsbehandelingen voor stemmingsstoornissen. GDB is gericht om stress, depressieve en angstsymptomen te verminderen bij zwangere vrouwen, daarnaast is er een speciale focus op de emotionele en praktische voorbereiding van het moederschap. Deze wekelijkse open groepstherapie omvat cognitieve gedragstherapie (CGT), psycho-educatie, psychomotorische therapie en ontspanningstherapie. Een gerandomiseerde studie (de DAPPER-studie) evalueerde de groepsdagbehandeling en vergeleek het met individuele ambulante begeleiding (gouden standaard in Nederland) in de afname van depressieve symptomen bij zwangere vrouwen met een psychiatrische stoornis. Na een gestructureerd diagnostisch interview (SCID)

en schriftelijke toestemming, vulden de deelnemers drie vragenlijsten in over stemming en slaapkwaliteit tijdens de zwangerschap, met als primaire uitkomstmaat de Edinburg Depression Scale op 6 weken postpartum.

Hoofdstuk 2 is een samenvatting van de huidige literatuur over alle beschikbare behandelingen voor psychiatrische stoornissen bij zwangere vrouwen. Tot de dag van vandaag, zijn er geen gecontroleerde studies naar het effect van psychofarmaca voor psychiatrische stoornissen tijdens de zwangerschap. In onze meta-analyse konden we alleen de effectgrootte voor de behandeling van een depressieve stoornis schatten, door een gebrek aan studies over andere stoornissen. Een vorm van psychotherapie voor een depressieve stoornis heeft een robuust behandelingseffect, bijv. CGT (g=-0,61), en in mindere robuste mate, Interpersoonlijke Psychotherapie (IPT, g=-0,67). In deze analyse behouden beide behandelingen hun potentiële nut voor zwangere vrouwen met een depressieve stoornis. Dit is in lijn met de huidige NICE-richtlijn die adviseert om een vorm van psychotherapie aan te bieden aan elke zwangere vrouw met een milde tot ernstige depressie en benadrukt dat dit in nauw overleg met de patiënte moet gaan. Andere potentiële niet-farmacologische interventies voor de behandeling van een depressieve stoornis waren lichaamsgerichte interventies en acupunctuur. Lichttherapie was niet geassocieerd met een afname van depressieve symptomen, maar dit is gebaseerd op twee studies. Het behandeleffect van alle niet-farmacologische interventies lag dicht bij elkaar en behandelingen zijn dus mogelijk inwisselbaar voor elkaar, zeker rekening houdend met de hoge uitval. Daarom vinden wij dat de voorkeur van de patiënte zwaar mee mag wegen in de beslissing voor een psychiatrische behandeling in een klinische setting.

Hoofdstuk 3 beschrijft de DAPPER-studie, de eerste RCT van een klinische sample met zwangere vrouwen met co-morbide psychiatrische en psychosociale problemen. De DAPPER-studie evalueert een nieuwe groepsdagbehandeling (GDB) en is gericht op een afname van depressieve symptomen tijdens de zwangerschap. Samenvattend, er was geen significant verschil in de afname van depressieve symptomen tussen GDB en individuele begeleiding op 6 weken postpartum. We zijn wel succesvol geweest in het rekruteren van een moeilijk bereikbare populatie (n = 158); slechts 20 (11,2%) van de geschikte vrouwen weigerde studiedeelname, bijna twee op de drie deelneemsters heeft ingestemd met randomisatie en de drop-out was laag (9/155, 5,8%). We hebben naast de diagnose depressieve stoornis, ook een groot aantal angst gerelateerde stoornissen (31,6%) en co-morbide persoonlijkheidsstoornissen (49,4%) vastgesteld. Het sample was klein en we misten een aantal follow-up metingen tijdens de zwangerschap, maar onze statistische analyses (mixed models) bevestigden onze bevindingen. Mogelijk vonden we geen verschil door het effect van onze gespecialiseerde individuele begeleiding en/of door het natuurlijk beloop. Echter, deze nieuwe groepsdagbehandeling is goed uitvoerbaar, geaccepteerd en zorgt voor een afname van depressieve symptomen tijdens de zwangerschap. Afhankelijk van de lokale beschikbaarheid en de kosten, zouden clinici de verschillende behandelingsmogelijkheden

moeten overwegen, rekening houdend met de persoonlijke omstandigheden en de voorkeuren van de patiënte.

Hoofdstuk 4 richt zich op de impact van een psychiatrische stoornis op de slaapkwaliteit door het vergelijken van subjectieve en objectieve slaapkwaliteit in een case-control studie. Van alle deelneemsters (21 patiënten en 33 gezonde controles) werden de objectieve slaapkwaliteit parameters gemeten door het dragen van een pols Actiwatch voor 7 dagen en nachten. Subjectieve slaapkwaliteit werd beoordeeld door de Pittsburgh Sleep Quality Index (PSQI) en op dagelijkse basis door een slaapdagboek met een Sleep Quality-schaal (SSQ). Objectieve slaapkwaliteit parameters en de uitslagen van de PSQI verschilden niet significant tussen de patiënten en gezonde controles. Uit de dagelijkse slaapdagboekjes bleek dat de patiënten, ten opzichte van de controles, een significant slechtere gemiddelde SSQ-score hadden. Onze verkennende studie suggereert dat de subjectieve slaapkwaliteit door zwangere vrouwen met een psychiatrische stoornis slechter is erger dan de objectieve slaapkwaliteit, gemeten door de Actiwatch.

In **hoofdstuk 5** werden specifieke patronen van stemmingsschommelingen bij zwangere vrouwen met een psychiatrische stoornis onderzocht, door wekelijks de 'Profile of Mood status' te meten. Daarnaast werd het verband van deze patronen met verloskundige uitkomsten en postpartum depressie onderzocht. We identificeerden drie patronen: zeer variabel, stabiel negatief (meer depressief/angstig) en stabiel positieve stemming. Onze verkennende studie toonde aan dat een zeer variabele stemming zou kunnen resulteren in een lager geboortegewicht. Deze bevindingen moeten worden gerepliceerd in grotere studies.

In **hoofdstuk 6** beschrijven we de prevalentie van suïcidale gedachten en automutilatie bij zwangere vrouwen met schizofrenie en psychotisch gerelateerde stoornissen of een bipolaire stoornis, door middel van een 'nieuwe generatie' case register (CRIS) in Londen. Van de 420 vrouwen in het onderzoek hadden 25% suïcidale gedachten en 8% had geautomutileerd tijdens de zwangerschap, met gewelddadige methoden in een vijfde van de gevallen. Suïcidale gedachten en automutilatie traden op in een aanzienlijk deel van de zwangere vrouwen met een ernstige psychiatrische stoornis, met name bij jongere vrouwen en patiënten met een voorgeschiedenis van automutilatie. Deze patiënten moeten in het bijzonder nauwkeurig in de gaten worden gehouden om suïcidaliteit te beoordelen. We bevestigden onze hypothese dat automutilatie is geassocieerd met de ernst van de ziekte - roken, en eerdere automutilatie en daarnaast in mindere mate, een niet-affectieve diagnose.

De belangrijkste bevindingen van dit proefschrift, de methodologische beschouwingen, implicaties van de huidige bevindingen en aanbevelingen voor verder onderzoek worden besproken in **hoofdstuk 7**. Een beperking van onze DAPPER-studie was het relatief klein aantal deelnemers, dit is een bekend probleem bij deze moeilijk te bereiken populatie. Naast de deelnemers met een depressieve stoornis, includeerden wij ook een groot aantal angst gerelateerde stoornissen en co-morbide persoonlijkheidsstoornissen. De heterogeniteit van

ons sample weerspiegelt de klinische praktijk en verbetert de generaliseerbaarheid van onze studies. Origineel was ook de studie-opzet, de patiënten-preferentie randomized controlled trial (RCT). Hiermee konden we het behandelingseffect van de groepsdagbehandeling vergelijken met de individuele begeleiding, en daarnaast konden we de vergelijking maken tussen de gerandomiseerde en de patiëntpreferentie conditie. Een beperking van de metingen was dat we niet grondig de algemene angstsymptomen hebben gemeten of andere potentiële voordelen van de groepsdagbehandeling, bijvoorbeeld een goede voorbereiding op het moederschap of een verbeterend steunsysteem.

Vanuit onze meta-analyse, maar ook vanuit de bevindingen van onze RCT, concluderen wij dat een vorm van psychotherapie aangeboden dient te worden aan zwangere vrouwen met een psychiatrische stoornis en de verschillende behandelopties lijken inwisselbaar. Echter, we hebben grotere gecontroleerde studies nodig om deze stelling te bevestigen voor niet-farmacologische interventies voor een depressieve stoornis, maar ook voor het bredere scala aan psychiatrische stoornissen.

List of publications

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Van Ravesteyn LM, Lambregtse-van den Berg MP, Hoogendijk WJG, Kamperman AM**.** Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment meta-analysis. *PLOS ONE 2017 12(3).*

Van Ravesteyn LM, Kamperman AM, Schneider AJ, Raats ME, Steegers EAP, Hoogendijk WJG, Tiemeier HW, Lambregtse-van den Berg MP**.** Group-based multicomponent intervention to reduce depressive symptoms in women with co-morbid psychiatric and psychosocial problems during pregnancy: a randomized controlled trial. *Under review.*

Van Ravesteyn LM, Lambregtse-van den Berg MP, Hoogendijk WJG, Kamperman AM. The role of mood fluctuations during pregnancy in adverse obstetric and birth outcomes. A study of mentally ill pregnant women and their newborns. *In progress.*

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Name PhD student: Leontien van Ravesteyn
Erasmus MC Department: Psychiatry & Obstetrics
Research School: NIHES

Promotor(s): Prof. Hoogendijk, Tiemeier & Steegers
Supervisor: Dr. M.P. Lambregtse - van den Berg

1. PhD training	**Year**	**Workload** (ECTS)
General courses		
- BROK (Basiscursus Regelgeving Klinisch Onderzoek)	18-3-2010	4.0
- Basic Statistics Molmed, Erasmus MC	10-6-2010	1.0
- Teach the Teacher-course, Desiderius School	13-2-2012	2.0
- Integrity in medical research, Erasmus MC	Apr 2012	4.0
- Biomedical English Writing and Communication, Erasmus MC	Dec 2012	4.0
- Systematic literature retrieval in PubMed & Embase, Endnote	Feb 2013	1.0
- Basic qualification in education (BKO), Desiderius School	Jun 2017	4.0
Specific courses (e.g. Research school, Medical Training)		
- NIHES master 'Clinical Epidemiology'	30-8-13	70.0
Summer program 2011 & 2012		
Core courses:		
Study Design	2012	
Classical methods for data-analysis	2012	
Clinical Epidemiology	2012	
Methodological topics in epidemiologic research	2012	
Modern statistical methods	2012	
Advanced short courses:		
Courses for the quantitative researcher	2011	
Repeated measurement in clinical studies	2013	
Psychiatric epidemiology	2013	
Child and maternal health	2013	
- SCID I and II training	2008	1.5
- Research internship, King's College London, supervisor prof. Howard	Sep'13-dec'13	22.0
Presentations		
- Various presentations at the Department of Psychiatry of Erasmus MC	2010 - 2014	3.0
- Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, "*Dapper-studie*", Amsterdam (oral presentation)	31-3-2011	1.5
- Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, "*Zwanger en slaapproblemen*", Maastricht (poster presentation)	3-4-2012	0.6
- LKPZ-symposium, "*Alternatieve therapieën voor tocofobie*", Utrecht (workshop)	20-9-2012	1.5
- ISPOG society, "O*bjective and subjective sleep quality*", Berlin, Germany (poster presentation)	23-5-2013	0.6
- EPA meeting, "Dapper-trial", Ulm, Germany (oral presentation)	23-4-2014	1.5
- Marce society, "Dapper-trial", Swansea, UK (oral presentation)	11-9-2014	1.5

(Inter)national conferences		
- Veilige Kribbe (Rotterdam)	'09,'11,'13,'15	1.2
- Voorjaarscongres NvvP (Maastricht)	'10 - '14	1.5
- LKPZ-symposia	'10, '12, '15	1.0
- Marce society (Pittsburg, USA)	28-10-2010	0.5
- Symposium "Neuro-imaging, genetics & endo, development & psychopathology" (Rotterdam)	02-09-2010	0.3
- Symposium UKIMS (London, UK)	19-9-2013	0.3
- Symposium "Dwang&drang in de zwangerschap"(Rotterdam)	28-1-2016	0.5
Seminars and workshops		
- PhD-day	Mar 2010	0.3
- CPO-symposium	Feb 2010	0.3
- BKO-workshop: "Individuele begeleiding"	Jun 2013	0.1
- NICE-guidelines "Perinatal psychiatry" seminar, London	Nov 2013	0.3
- Global mental health course, London School of Hygiene & Tropical Medicine	Nov 2013	0.5
- BKO-workshop: "Tentamenvragen maken"	Dec 2013	0.1
- BKO-workshop: "Omgaan met groepen"	Dec 2013	0.1
- Loopbaanorientation, Desiderius School	Mar 2014	1.5
- Medical Business Masterclasses	Apr 2014	1.5

2. Teaching	**Year**	**Workload** (ECTS)
Supervising practicals and excursions, tutoring		
- Vaardigheidsonderwijs 'De tuchtzaak'	2009 - 2012	1.5
- 2nd year 'keuzeonderwijs' medical students	2010 - 2014	4.0
- Vaardigheidsonderwijs 'Het kraambed'	2012	0.5
- Minor 'Womens health: from fetal life to ageing disease'	2011	0.5
- Begeleider Kennismaking Beroepspraktijk medical students	2012	1.0
Supervising Master thesis Erasmus MC		18.0
- Laura Schot	2010	
- Silvia Koeleman	2012	
- Esther Mooij	2012	
- Yvette Konijnendijk	2012	
- Monique Roggeveen	2012	
- Kim Schuurbiers	2013	
Other		
- Therapist group-based multicomponent therapy (psycho-education)	2010 - 2014	4.0
- Onderwijs & Onderzoek feestcommissie	2010 - 2013	0.5
- Initiator Research meeting Womens Mental Health	2012 - 2014	1.0
- Organisation of Veilige Kribbe-conference 2013	Jul - dec '13	2.0

Note: 1 ECTS (European Credit Transfer system) equals a workload of 28 hours

Dankwoord

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About the author

Leontien Marja van Ravesteyn was born in 1986 in Rotterdam, the Netherlands. After she graduated from secondary school at the Sint Laurenscollege in 2004, she started her study Medicine at the Erasmus University of Rotterdam. During her time as a bachelor student, she was an active member of IFMSA (International Federation of Medical students association) and worked at different surgical departments in the Erasmus MC. She did three extra-curricular exchanges, internship pediatrics in Ghana (2007), a public health internship in Tanzania (2008) and an elective obstetrics in Aruba (2011). Leontien came in contact with an enthusiastic perinatal psychiatry team at Erasmus MC and together they wrote a grant proposal to evaluate a new treatment program for pregnant women with a mental disorder. This grant proposal was awarded and in 2010 Leontien started her PhD-project presented in this thesis. She graduated from medical school in 2011 and combined her work as a PhD-student with a master degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES). After graduating in 2013, she worked as a research fellow for 3 months at the Institute of Psychiatry of King's College London under supervision of prof. Howard. In 2014 Leontien started her training to become a Medical Doctor in Global Health and Tropical Medicine. As part of her training, she was a surgical resident in the Zaans MC (supervisor dr. den Boer) and then in the Slingeland hospital in Doetinchem (supervisor dr. Staal). Subsequently as an Obstetrics and Gynaecology resident in Gelre hospital (supervisor dr. Paarlberg) and she finished her training program at the Royal Tropical Institute (KIT) in Amsterdam. Currently she works in St. Francis hospital in Zambia, together with her husband Joris Harlaar.