Stormy clouds in seventh heaven

Meijer, Judith Linda

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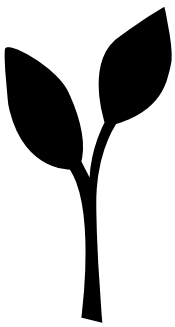
A study on anxiety and depression around childbirth



Judith Aris-Meijer

Stormy clouds in seventh heaven. A study on anxiety and depression around childbirth.

Thesis, University of Groningen, the Netherlands

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Stormy clouds in seventh heaven

A study on anxiety and depression around childbirth

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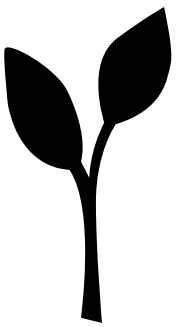

chapter 1

About anxiety and depression

Women are at increased risk for the experience of symptoms of anxiety or depression during their reproductive years[1]. Incidence rates are highest amongst women between 18 and 45 years of age[2-6]. During and outside pregnancy alike, approximately 10-15% of all women experience symptoms of anxiety or depression[7-10]. It has been estimated that in 2030, depression will be in the top 10 of most prevalent diseases[11].

In general, symptoms of anxiety and depression may include negative thoughts, loss of energy, sleep disturbances, loss of interest or pleasure, and in some cases suicidal ideations and plans [12]. Antenatal (i.e. during pregnancy) or postpartum (i.e. postpartum after delivery) anxiety and depression usually manifest with these same symptoms[12]. Box 1 contains the Postpartum Onset specifier for Depressive Disorders, according to the DSM-IV. Risk factors for antenatal symptoms are not necessarily related to pregnancy, though it is known that women who suffered previous pregnancy or infant loss often experience anxiety during the subsequent pregnancy[13,14].

Consequences of anxiety or depression during pregnancy or in the postpartum period

Symptoms of anxiety and depression during pregnancy have been associated with several adverse outcomes for mother and child. For example, women tend to seek less prenatal care, continue their use of alcohol and tobacco, and they are at increased risk for postpartum anxiety and depression[15-18]. Additionally, low birth weight, preterm delivery, insecure mother-child attachment and emotional and behavioral problems in the child have been found[19,20]. One of the hypotheses on the mechanism behind this latter observation is that cortisol levels are increased as a result of maternal stress, which influences the development of the fetal brain as cortisol passes the placenta.

BOX 1 SPECIFIER WITH POSTPARTUM ONSET – DSM-IV

"The specifier With Postpartum Onset can be applied to the current (or, if the full criteria are not currently met for a Major Depressive, Manic, or Mixed Episode, to the most recent) Major Depressive, Manic, or Mixed Episode of Major Depressive Disorder, Bipolar I Disorder, or Bipolar II Disorder or to Brief Psychotic Disorder (p.329) if onset is within 4 weeks after childbirth. The symptoms of the postpartum-onset Major Depressive, Manic, or Mixed Episode do not differ from the symptoms in nonpostpartum mood episodes. Symptoms that are common in postpartum-onset episodes, though not specific to postpartum onset, include fluctuations in mood, mood lability, and preoccupation with infant well-being, the intensity of which may range from overconcern to frank delusions. The presence of severe ruminations or delusional thoughts about the infant is associated with a significantly increased risk of harm to the infant.

Postpartum-onset mood episodes can present either with or without psychotic features. Infanticide is most often associated with postpartum psychotic episodes that are characterized by command hallucinations to kill the infant or delusions that the infant is possessed, but it can also occur in severe postpartum mood episodes without such specific delusions or hallucinations. Postpartum mood (Major Depressive, Manic, or Mixed) episodes with psychotic features appear to occur in from 1 in 500 to 1 in 1,000 deliveries and may be more common in primiparous women. The risk of postpartum episodes with psychotic features is particularly increased for women with prior postpartum mood episodes but is also elevated for those with a prior history of a Mood Disorder (especially Bipolar I Disorder). Once a woman has had a postpartum episode with psychotic features, the risk of recurrence with each subsequent delivery is between 30% and 50%. There is also some evidence of increased risk of postpartum psychotic mood episodes among women without a history of Mood Disorders with a family history of Bipolar Disorders. Postpartum episodes must be differentiated from delirium occurring in the postpartum period, which is distinguished by a decreased level of awareness or attention.

Women with postpartum Major Depressive Episodes often have severe anxiety and even Panic Attacks. Maternal attitudes toward the infant are highly variable but can include disinterest, fearfulness of being alone with the infant, or overintrusiveness that inhibits adequate infant rest. It is important to distinguish postpartum mood episodes from the "baby blues", which affect up to 70% of women during the 10 days postpartum, are transient, and do not impair functioning. Prospective studies have demonstrated that mood and anxiety symptoms during pregnancy, as well as the "baby blues", increase the risk for a postpartum Major Depressive Episode. A past personal history of nonpostpartum Mood Disorder and a family history of Mood Disorders also increase the risk for the development of a postpartum Mood Disorder. The risk factors, recurrence rates, and symptoms of postpartum-onset Mood Episodes are similar to those of nonpostpartum Mood Episodes. However, the postpartum period is unique with respect to the degree of neuroendocrine alterations and psychosocial adjustments, the potential impact of breast-feeding on treatment planning, and the long-term implications of a history of postpartum Mood Disorder on subsequent family planning."

Risk factors associated with anxiety or depression during pregnancy or in the postpartum period

Well known risk factors for the onset and persistence of anxiety and depression outside pregnancy are the experience of these symptoms earlier in life, a family history of mental health problems, the experience of traumatic events during childhood, recent major life events, low social support, and specific personality traits such as high neuroticism and low extraversion[21-26]. Additionally, personality traits and childhood trauma have been found to moderate the associations between life events and psychopathology[21,26,27].

These risk factors also hold for antenatal and postpartum anxiety and depression[18,28]. Additionally, a few large population-based cohort studies (n>5,000) found that experiencing obstetric events during pregnancy or events that were related to the condition of the newborn (i.e. low birth weight, preterm delivery, congenital malformations, admission to the hospital) increased the risk of symptoms of depression in the postpartum period[29,30]. In total however, the growing body of literature on the associations between events related to the pregnancy, delivery or newborn and postpartum symptoms of anxiety and depression is inconclusive[31-37].

Screening guidelines

International guidelines recommend screening for perinatal anxiety and depression during the first contact between the woman and the midwife or gynaecologist, and as early postpartum as possible[38,39]. The American College of Obstetricians and Gynecologists (ACOG) states that women should at least once during the perinatal period be screened, although definitive evidence of benefit is absent. Additionally, they advise to monitor women with current symptomatology or with risk factors for symptomatology closely. The National Institute for Health and Clinical Excellence (NICE) guidelines recommends the use of two questions based on the key symptoms of depression, i.e. low mood and anhedonia, and to ask for specific events in the past period. They recently added the recommendation to use a similar screening tool for anxiety, and a recommendation for further questionnaires or referral to the general practitioner or a psychiatrist in case the first two questions were answered positively. As antenatal anxiety or depression might develop into a clinical disorder when untreated[28,40], this seems a valuable addition.

Dutch guidelines for midwives (Koninklijke Nederlandse Organisatie van Verloskundigen, KNOV) include a specific supplement on depression, since 2008[41]. They do not recommend

specific screening for current symptomatology, but to ask questions about personal and family history of mental disorders during the first consult, and to be continuously alert on symptoms of depression.

Treatment options

The Dutch multidisciplinary guideline for mental healthcare[42] recommends to take hormonal changes into account when treating depression, and to educate women on the (continuation of) pharmacological treatment during pregnancy. The NICE has developed a specific multidisciplinary guideline for treatment of pregnant women with symptoms of depression[38], in which pharmacological treatment, non-pharmacological treatment or a combination of both is recommended. During pregnancy and the breastfeeding period, women generally prefer non-pharmacological treatment[43], as consequences of maternal antidepressant medication use for treating anxiety or depressive disorders are still unclear for the unborn child[44]. Several psychological therapies are used for treating anxiety and depression, such as interpersonal therapy, psychoanalysis, EMDR and cognitive behavioral therapy (CBT). The latter is known to be a widely used and the most studied effective therapy in treating anxiety and depression[45,46].

Overall aims of this thesis

The general objective of the current thesis was to unravel part of the etiology of developing symptoms of depression and anxiety in the antenatal period, and the transition of anxiety and depression from the antenatal into the postpartum period. This was accomplished by taking associations with specific life events into account, in order to better understand the development of these symptoms, and to provide evidence for future guidelines on screening.

This thesis focuses on risk factors and screening options in order to be able to prevent symptoms of anxiety or depression and disorders in the future. The prospective, population-based Pregnancy, Anxiety and Depression (PAD) cohort study has been designed to answer these questions amongst others. The final chapter before the general discussion presents the design of a trial including a psychological intervention in pregnant and postpartum women, the Pregnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES) study.

About the PAD and PROMISES study

The PAD study and the PROMISES study started in 2009. We cooperated with over 100 primary obstetric care centers and seven hospitals in the Netherlands to invite women in their first trimester to participate in the PAD study. In total 7,275 pregnant women were screened for symptoms of anxiety and depression. We sent follow-up questionnaires during the second and the third trimester and at six weeks, three months and six months postpartum. We gathered midwives reports for information about the pregnancy and delivery.

Women who scored above certain cut-off points for anxiety or depression at baseline in the PAD study were invited to participate in the PROMISES study. This is a randomized controlled trial, with which we wanted to gain insight in the mechanism behind the apparent associations found in women with elevated levels of anxiety or depression during pregnancy and a less favorable health of their children, e.g. through fetal programming, a concept introduced originally in studies on cardiovascular disease[47].

These women received follow-up questionnaires at the same measurement waves as in the PAD study, and additionally at 12 and 18 months postpartum. Their children are currently being tested at 18 months on development and behavior. In 2014, the target of including 300 women into the trial was reached.

Overall outline of the thesis

Chapter 2 discusses the associations between change in antenatal anxiety and depression levels with several categories of life events during pregnancy and personality traits. A distinction is made between general life events and pregnancy related events.

Chapter 3 studies change in anxiety and depression level from early pregnancy to half a year postpartum, by assessing the influence of life events during pregnancy. A distinction is made between general life events and pregnancy related events, similar to chapter 2. Additionally, the difference of these associations between women with and without prevalent antenatal symptoms is assessed, and exploratory analyses with events during delivery or related to the newborn are discussed.

Chapter 4 discusses whether a commonly used tool in identification and screening of antenatal and postpartum anxiety is accurate in predicting individual risk based on antenatal levels.

Chapter 5 demonstrates the predictive accuracy of a tool commonly used in the identification and screening of antenatal and postpartum depression, and explores whether this tool can be optimized by decreasing the number of questions or adding risk factors.

Chapter 6 presents the design of the ongoing randomized controlled trial.

Finally, the results of the analyses and the practical implications are integrated in the general discussion, **chapter 7**. Here, the Wilson and Jungner criteria for screening are applied in order to formulate a recommendation on screening and treatment of antenatal and postpartum anxiety and depression.

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Associations of life events during pregnancy with longitudinal change in symptoms of antenatal anxiety and depression.

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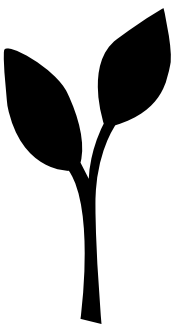

chapter 2

Abstract

Objective

To investigate the association of life events during pregnancy with change in antenatal anxiety and depression symptoms. We distinguished pregnancy related and non-pregnancy related events and assessed specificity of these associations for depressive or anxious symptoms. In addition, we investigated whether the associations were affected by personality or childhood adversities.

Measurements and findings

1,603 women during their first trimester of pregnancy were included between May 2010 and May 2012. We associated pregnancy related and non-pregnancy related life events, childhood adversities and the personality traits neuroticism and extraversion with the change in symptoms of anxiety (State Trait Anxiety Inventory) and depression (Edinburgh Postnatal Depression Scale) from week 12 to week 36.

Life events during pregnancy were associated with increasing antenatal symptoms of anxiety and depression. Effect sizes associated with the highest numbers of events observed ranged from 0.59 to 1.31. Pregnancy related events were specifically associated with increasing symptoms of anxiety, whereas non-pregnancy related events were merely associated with an increase in symptoms of depression. Neither personality traits nor childhood trauma influenced the associations under study.

Key conclusions

Compared to pregnancy related events, non-pregnancy related events show stronger associations with increases in symptoms of anxiety or depression. Pregnancy related life events during pregnancy increase levels of antenatal anxiety, whereas depression levels increase when women experience life events that are unrelated to pregnancy. There was no evidence of modification of these associations by neuroticism, extraversion or childhood trauma.

Implications for practice

Our findings may help midwifes to tailor psychosocial care to the specific risks of the pregnant woman which may eventually have a positive impact on the health of mother and child.

Background

During pregnancy, 10-15% of all women experience mild to moderate symptoms of anxiety or depression[1,2]. In addition to the burden to women themselves, these symptoms are associated with unfavorable obstetric outcomes, as well as with an adverse cognitive, motor and psychosocial development of the child[3,4].

The most consistent predictor of depression in both the general population[5,6]and pregnant women[7], is having experienced life events. However, studies among pregnant women mostly considered events that happened before pregnancy, ignoring life events experienced during pregnancy. Recency of a life event, however, has shown to be associated with particularly high levels of anxiety or depression[8]. Therefore, stressors that occur during pregnancy, e.g. physical problems[9], are likely to have a higher impact on antenatal symptoms of anxiety or depression than those occurring before pregnancy. Moreover, we hypothesize that in particular life events that are specifically related to pregnancy might trigger anxious or depressive feelings. As far as we know, neither life events during pregnancy as a separate category nor specific pregnancy related life events have been investigated in relation to change in levels of antenatal anxiety or depression to date.

Besides the experience of life events, personality traits are known to be closely linked to psychopathology[10,11]. High levels of neuroticism and low extraversion are not only directly associated with depression and anxiety. They have also shown to modify the promoting effects of life events on the onset and maintenance of psychopathology in such a way that being high neurotic or low extraverted makes people more vulnerable to become anxious or depressed when experiencing negative life events[6].

In addition to personality traits, a history of traumatic childhood events such as physical or sexual abuse or loss of a parent have been suggested as modifiers of the association of adult life events with psychopathology. Indeed, having experienced childhood trauma makes people more vulnerable to depression in adult life[5,12].

It is presently unknown whether the aforementioned relationships are any different during pregnancy. Animal studies have shown that female brains change during the transition to motherhood and that these changes might lead to a change in their behavior[13]. Women may therefore respond differently to an event during pregnancy than outside pregnancy, and personality traits as well as childhood events may play a disparate role herein.

The present study is the first to investigate the change in symptoms of antenatal anxiety or depression associated with life events during pregnancy making a distinction between pregnancy and non-pregnancy events. The specificity of these associations for depressive

symptoms and symptoms of anxiety is investigated as well as their potential modification by neuroticism, extraversion and childhood trauma.

Methods

Subjects

The present study was carried out within the ongoing Pregnancy, Anxiety and Depression (PAD) Study. This is a prospective cohort study that was set up to investigate symptoms of and risk factors for anxiety or depression during pregnancy and the first year postpartum. All pregnant women visiting primary and secondary obstetric care centers in the Netherlands during their first trimester are invited, and those who participate are followed up until 12 months postnatal. The study protocol was approved by the medical ethical committee of the University Medical Centre Groningen.

For the present study we included 3,358 women that were screened at a pregnancy duration of around 12 weeks from May 2010 to May 2012. By the end of that period, 101 primary and 7 secondary obstetric care centers were participating. Follow-up in the current study was collected at a pregnancy duration of approximately 36 weeks.

Response, follow-up and missing data

Out of 3,358 women responding to the baseline screening questionnaire, 1,603 (48%) also filled out the follow-up questionnaires and formed the study population for the present analysis. The majority of women who did not respond to the follow-up questionnaire had pregnancy durations of less than 36 weeks or gave birth before even reaching this duration and was therefore not eligible to be included in the present study. Women with pregnancy durations of 36 weeks or more who had not responded to the follow-up questionnaire, 453 in number (26%), showed no marked differences with those who did complete the follow-up assessment, with respect to mean baseline anxiety and depression, personality scores, number of life events, parity, age, educational level or income.

The percentage of missing data in the present study ranged from 3.5 to 37.1 for the variables of main interest; anxiety (3.7%), depression (4.2%), childhood trauma (3.5%), non-pregnancy related events during pregnancy (37.3%), pregnancy related events during pregnancy (35.1%), neuroticism (5.2%) and extraversion (4.4%). The percentage of missing data of the potential confounders ranged from 5.9 (maternal age) to 40.7 (total family income).

Complete case analysis can give biased results and exclusion of patients with missing data will decrease the statistical power of a study[14] . Missing values for all variables except for the outcome variables were imputed because it has been shown that when outcome measures are not imputed, the precision of a study is generally larger [14].

Missing data was imputed using multiple imputation by chained equations under the assumption that missing values were missing at random or missing completely at random. Multiple data sets (N=5) were generated to account for the uncertainty in imputed data. The regression coefficients and standard errors were pooled using Rubin's method for multiple imputation inference[15].

Imputation and all analyses were carried out using STATA MP 11.0.

Instruments

Anxiety, depression were measured at both baseline and follow-up. Personality traits, childhood trauma and measures on all potential confounders were assessed at baseline, and life events during pregnancy were assessed at follow-up.

The 6-item State Trait Anxiety Inventory (STAI) was used for the measurement of anxiety. This shortened version has demonstrated to be as valid as the original 20-item STAI[16]. Scores ≥42 indicate moderate to high levels of anxiety.

The Edinburgh Postnatal Depression Scale (EPDS) was used to measure state of depressive symptoms and has shown to be valid for both pregnant and postnatal women[17]. A cut-off score ≥12 indicates a moderate to high level of depression.

Data on life events during pregnancy was collected using a 50-item questionnaire developed in the Avon Longitudinal Study of Parents And Children (ALSPAC)[18]. This questionnaire measures life events regarding employment, marital problems, illness or death of loved ones, abuse of either the mother or one of her children and substance misuse in her family. In addition, it contains questions on life events that relate to pregnancy, i.e. testing for congenital anomalies, test results indicating that the baby might have abnormalities, being told that it is a twin pregnancy, finding out that the partner does not want to have the baby, bleeding and being afraid to miscarry, trying to get an abortion, and finding out that something that happened might be harmful to the baby. For the analyses, we used the number of life events during pregnancy categorized as general life events or life events related to pregnancy.

We defined childhood trauma as the occurrence of an event before the age of 16 that is generally considered relevant for developing emotional symptoms[12]. It was analyzed as the

number of positive responses to the following items from the Life Events Scale (CERQ)[19]: loss of a parent due to divorce or death, severe mental illness of a parent, substance misuse in family of origin, violence in family of origin, physical abuse and sexual abuse.

The Dutch version[20] of the NEO Five Factor Inventory (NEO-FFI) was used to assess personality traits. The NEO-FFI is a shortened version of the NEO-Personality Inventory-Revised (NEO-PI-R), has proved to be valid and has an internal consistency ranging from 0.68 to 0.86[21]. This instrument consists of 60 items covering the five major dimensions of personality; neuroticism, extraversion, openness, agreeableness and conscientiousness. A 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree) was used for the responses. In the present study, the dimensions neuroticism and extraversion were considered only because of their established relation with psychopathology[10,11].

Potential Confounders

Several a priori potential confounders were considered: marital status (married yes/no), maternal age at baseline, social support assessed by asking a rank for the satisfaction of the perceived support in specific situations on a scale from 1 to 6, primiparity (yes/no) and socio-economic position. Socio-economic position was calculated as the equally weighted average of the educational attainment level of the respondent, her partner, and their total income.

Statistical Analysis

To compare effect sizes between the associations studied, we started by creating Z-scores for personality traits, depression and anxiety. Numbers of life events were standardized to a continuous number between 0 and 1. This was done by dividing the number of events for each woman by the maximum number of events that had occurred within each category of life events, and then analyzed as continuous variables. Consequently, coefficients from subsequent regression analyses indicated the effect size (Cohen's d) of a difference between no life events and the maximum number of life events per category.

A paired t-test was performed to evaluate whether changes in levels of anxiety and depression between baseline and follow-up were statistically significant.

The associations of life events, childhood trauma and personality traits with the mean change of symptoms of anxiety and depression from baseline to follow-up were analyzed using linear regression models. Mean change of symptoms was analyzed as the follow-up level adjusted for its baseline value. First, the two distinct categories of life events, childhood trauma and both personality traits were entered separately as predictor variables.

As depression and anxiety are often comorbid, we additionally investigated specificity of the associations for either anxiety or depression by adjusting the analysis of anxiety for baseline and follow-up depressive symptoms, and vice versa. Second, we analyzed whether the associations of life events with symptom levels were modified by personality traits and childhood trauma. This was done by entering interaction terms for these variables and each of the life event variables, next to their main effects, and assessing their statistical significance.

In each regression analysis, potential confounders were added as independent variables and the amount of change in the coefficients of the variables of interest was assessed. The change was considered a measure of the extent of confounding. Confounders with substantial effects (>10%) were retained in all regression analyses.

Findings

At both baseline and follow-up, symptoms of antenatal anxiety were more prevalent than those of depression. Slightly more women experienced symptoms of anxiety at follow-up (N=219, 14%) compared to baseline (N=199, 12%). The prevalence of depression did not change during follow-up (N=98, 6%).

Table 1 shows that most women were medium to highly educated, and their total family income was generally modal. An ample half of all women experienced specific pregnancy related events during pregnancy (57%), whereas non-pregnancy related events were more common (78%). Childhood trauma was experienced by 26% of women. Mean levels of anxiety and depression slightly increased from baseline to follow-up in a statistically significant way ($p<0.001$). Subsequent regression analyses indicated that none of the confounders considered had a substantial influence on the associations. Therefore, they were not included in the final models.

Table 1 Characteristics of the study population (N=1,603)

Maternal age in years, mean (min-max)	30 (17-46)
Primiparae, N (%)	655 (41%)
Education, N (%)	
Elementary education	5 (0,3%)
Lower tracts of secondary education	71 (4%)
Higher tracts of secondary education	609 (38%)
Higher vocational education	640 (40%)
University education	278 (17%)
Total family income N (%)	
0 – 30.999 euros	294 (18%)
31.000 – 59.999 euros	823 (51%)
60.000 euros or more	486 (30%)
Pregnancy related life events [a]	
One or more, N (%)	914 (57%)
Median number (min-max)	1 (0-4)
Non-pregnancy related life events [a]	
One or more, N (%)	1250 (78%)
Median number (min-max)	2 (0-20)
Childhood adversities [b]	
One or more, N (%)	417 (26%)
Median number (min-max)	0 (0-6)
Anxiety (STAI) baseline level [c]**, mean (SD)**	32.35 (8,41)
Anxiety (STAI) follow-up level [d]**, mean (SD)**	32.96 (9,20)
Depression (EPDS) baseline level [c]**, mean (SD)**	4.32 (3,52)
Depression (EPDS) follow-up level [d]**, mean (SD)**	4.93 (3,68)

STAI – Spielberger State Trait Anxiety Inventory (min-max 20-80)

EPDS – Edinburgh Postnatal Depression Scale (min-max 0-30)

[a] experienced during pregnancy

[b] before age of 16

[c] pregnancy duration of 12 weeks

[d] pregnancy duration of 36 weeks

Table 2 shows the associations of the two categories of life events, childhood trauma, and both personality traits with the change in symptoms of anxiety and depression from baseline to follow-up.

Both types of life events, non-pregnancy related and pregnancy related, showed a statistically significant association with increasing levels of antenatal symptoms of anxiety and depression. These associations were monotonous and approximately linear. Effect sizes associated with the maximum number of events compared to no events were moderate to very large, i.e. ranged from 0.59 to 1.31. Compared to pregnancy related events, non-pregnancy related events showed stronger associations with increases in these symptoms. Life events that were related to pregnancy were still associated with the change in anxiety when correcting for depression, which indicates specificity of the association for anxious symptoms. Conversely, non-pregnancy related events merely had a statistically significant influence on change in depression when corrected for anxiety.

Childhood trauma was not associated with change in antenatal symptoms of anxiety or depression. Personality traits did show a statistically significant association; higher levels of neuroticism as well as lower levels of extraversion were associated with increasing levels of antenatal symptoms of anxiety and depression.

There was no statistically significant modification by the personality traits or childhood trauma of the associations between life events during pregnancy and change in anxious or depressive symptom levels (data not shown).

Table 2 Associations of life events during pregnancy, childhood adversities and personality with changes in antenatal symptoms of depression and anxiety

	Anxiety (STAI)		Depression (EPDS)	
	Mean change (95% CI)	Mean change (95% CI) [c]	Mean change (95% CI)	Mean change (95% CI) [d]
Non-pregnancy related life events [a]	1.166 (.598 ; 1.735)	.009 (-.008 ; .025)	1.312 (.807 ; 1.817)	.031 (.019 ; .043)
Pregnancy related life events [a]	.746 (.470 ; 1.022)	.085 (.024 ; .145)	.586 (.349 ; .823)	.025 (-.029 ; .078)
Childhood adversities [b]	.129 (-.369 ; .627)	-	-.222 (-.716 ; .273)	-
Neuroticism (NEO-FFI)	.260 (.207 ; .313)	-	.245 (.188 ; .302)	-
Extraversion (NEO-FFI)	-.172 (-.217 ; -.127)	-	-.096 (-.140 ; -.0521)	-

Mean changes are follow-up (week 36) values adjusted for baseline (week 12) values

Levels of depression, anxiety and personality traits were standardized by calculating Z-scores.

Number of life events and childhood adversities were standardized to values ranging from 0 to 1

STAI – Spielberger State Trait Anxiety Inventory (min-max 20-80)

EPDS – Edinburgh Postnatal Depression Scale (min-max 0-30)

a number per woman

b number per woman before the age of 16, standardized to values ranging from 0 to 1

c additionally corrected for depression level at baseline and follow-up

d additionally corrected for anxiety level at baseline and at follow-up

NEO-FFI NEO Five Factor Inventory

Discussion

In the present prospective cohort study, we investigated associations of pregnancy related and non-pregnancy related life events during pregnancy with longitudinal change in symptoms of antenatal anxiety or depression. We studied the specificity of the associations for anxiety or depression, and the potential modification of the associations by specific personality traits and childhood trauma.

We demonstrated that in general higher numbers of life events that had occurred during pregnancy were associated with increasing antenatal symptoms of anxiety or depression from 12 to 36 weeks of pregnancy. Non-pregnancy related events showed stronger associations than pregnancy related events. Pregnancy related events were specifically associated with increasing symptoms of anxiety, whereas non-pregnancy related events were merely associated with an increase in symptoms of depression. Further, we observed that higher levels of neuroticism and lower levels of extraversion were associated with increasing symptoms of both anxiety and depression, and that childhood trauma did not predict changes in symptoms of anxiety or depression. Neither neuroticism, nor extraversion, nor having experienced childhood trauma moderated the associations between life events and symptoms of anxiety or depression.

Contrary to our hypothesis pregnancy related events were less strongly associated with antenatal increases of anxiety or depression than non-pregnancy related events. Interestingly however, pregnancy related events were differentially associated with type of symptomatology, i.e. especially increases in anxiety were explained by these events. Conversely, non-pregnancy related events associated with development of depressive symptoms. This makes sense, as it is very likely that a woman's first response to an event such as hearing that prenatal screening results indicate that something might be wrong with the baby is worrying about the future of her child, whereas an event like the loss of a loved one is more likely to trigger feelings of depression. It is important to note that antenatal anxiety might have a larger impact on the child's neuromotor development than depression during pregnancy[22].

A limited number of studies have been conducted on psychological outcomes after experiencing specific pregnancy related events during pregnancy. Most studies addressed prenatal testing and diagnosis. Kowalcek (2003) found that women had higher anxiety levels both before and after prenatal testing, especially when they had a positive test result[23]. In addition, at the time of prenatal screening[24] or shortly after the diagnosis of an anomaly[25],

the majority of women in their respective samples had higher stress levels. In line with our finding is that a prenatal diagnosis of congenital heart disease was associated more with anxiety than with depression[26]. Nevertheless, results of the only randomized controlled trial on this topic conducted by Kleinveld et al. (2006) demonstrated that offering prenatal screening did not increase subsequent anxiety levels[27]. Our findings largely corroborate those obtained in a large cohort study showing that various pregnancy related and non-pregnancy related stressors went with increases in both antenatal anxiety and depression[28]. They did not demonstrate that specifically pregnancy related factors were associated with anxiety rather than depression. However, this study was cross-sectional with data collected at varying pregnancy durations. Another cross-sectional study showed that several pregnancy and non-pregnancy related events were associated with emotional and somatic distress but in the analyses no distinction between the two types of events was made[29].

As to the associations between personality traits and anxiety or depression, research has mostly been conducted in men and non-pregnant women[10,11]. We observed in our study that both high neuroticism and low extraversion are associated with increasing levels of both antenatal anxiety and depression, not contradicting our hypothesis that during pregnancy the associations of these traits with antenatal anxiety and depression are different[13].

We further hypothesized that the association between life events during pregnancy and the change in symptoms of antenatal anxiety or depression is modified by personality traits or childhood trauma. However, none of the pertaining interactions were substantial or significant. This is contrary to our expectation. Spinhoven et al. (2010) considered neuroticism as a modifier[30]; however, they studied this personality trait as a modifier in the association between childhood trauma and anxiety or depressive disorders, whereas we considered childhood trauma to be an effect modifier itself. In addition, our study did not consider disorders but subsyndromal symptoms.

Our findings did not identify childhood trauma as an effect modifier; which may indicate that having experienced childhood trauma does not make women more vulnerable to an adverse impact of life events during pregnancy. These findings are supported as well as contradicted by previous studies. For example, Comijs (2007) did not find evidence for moderation of the association between life events and depression or anxiety by childhood trauma[31]. However, this study consisted of an elderly population in which most reported childhood traumas were related to the Second World War. On the other hand, Brown and Harris (1978) found a moderating effect of a specific traumatic event[5], i.e. loss of the mother during childhood, on the association of recent stressful life events and ongoing difficulties.

Further, Bifulco et al. (2000) found that in particular the combination of childhood trauma and negative life events in adulthood predicted recurrent depressive episodes in women[32]. A possible explanation for the discrepancy of the findings in these studies with our observations is that they included people with anxiety or depressive disorders, not subsyndromal symptoms.

A few limitations of this study need to be considered. First, all assessments on life events were done using retrospective self-report checklists, which may be prone to recall bias. People with mental health problems tend to over-report the number and severity of stressors that they have experienced[33]. We used the number of life events and not the perceived severity to minimize this potential bias. Second, current affective state might influence the assessment of personality[10]. However, when we excluded women with moderate to high levels of anxiety or depression at baseline, results were similar. Third, the items measuring neuroticism in the NEO-FFI and the items of the EPDS are alike, which might have inflated the associations between depression and personality traits[10]. However, the time frames of both measurements differ; EPDS measures state ('how do you feel at this moment'), whereas NEO-FFI measures trait ('how do you usually feel'). Finally, although we observed increasing anxiety and depression associated with life events, mean scores remained below the cut-off value for subclinical and clinical disorders. Therefore our results are not necessarily applicable to pregnant women with anxiety or depressive disorders. Nevertheless, having subthreshold symptoms of depression is a risk factor for developing a clinical disorder as convincingly shown in a systematic literature review[34].

These limitations are potentially offset by strengths of this study. First, the sample size was considerable and as far as we know one of the largest in this field. Further, the present study is the first to investigate specific pregnancy related events compared to general types of events, and interactions between these categories and personality traits as well as childhood trauma. Finally, this study was the first to consider longitudinally assessed change in symptoms of antenatal anxiety or depression in relation to events during pregnancy. This approaches makes reverse causality, i.e. the events were induced by declining mental health unlikely. Furthermore, symptoms measured at a single time point in pregnancy may be the result of enduring depression or anxiety that started before pregnancy.

In conclusion, the present study shows that women do not essentially respond differently to a life event during pregnancy than outside pregnancy. Compared to pregnancy related events, non-pregnancy related events have more substantial associations with increases in symptoms of anxiety and depression. The study also shows that during pregnancy, events

that are related to pregnancy go with increases in anxiety, whereas levels of depression increase in association with non-pregnancy related events. We found no evidence of modification of these associations by neuroticism, extraversion or childhood trauma. Our findings may help midwifes to tailor psychosocial care to the specific risks of a woman and thereby to contribute to the health of mother and child.

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What if pregnancy is not seventh heaven? The influence of specific life events during pregnancy and delivery on the transition of antenatal into postpartum anxiety and depression.

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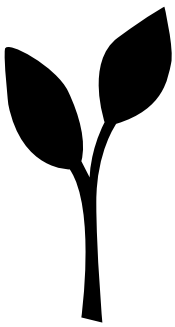

chapter 3

Abstract

Objective

Postpartum symptoms of anxiety and depression are known to have a negative impact on mother and child and major life events constitute a major risk factor for these symptoms. We aim to investigate to what extent specific life events during pregnancy, delivery complications and antenatal anxiety or depression independently contribute to the risk of these symptoms in the postpartum period and whether they interact.

Methods

Within a prospective population-based cohort study (n=3,842) in the Netherlands, antenatal symptoms of anxiety or depression were measured at the end of the first trimester and at five months postpartum. Antenatal life events were assessed during the third trimester, information on delivery complications was obtained from midwives and gynecologists. Linear regression analyses were performed to study change in symptoms over time associated with specific events. In addition, modification of these associations by antenatal anxiety and depression levels was tested.

Results

Women with elevated levels of anxiety or depression in their first trimester are at increased risk of these symptoms at five months postpartum. The experience of a life event that was related to health and sickness of self or loved ones, to the relation with the partner or conflicts with loved ones, or to work, finance or housing problems was significantly associated with higher postpartum levels of anxiety ($p<0.001$) and depression ($p<0.001$). None of the associations between postpartum levels of anxiety and depression and the experience of an eventwas modified by antenatal levels of anxiety or depression.

Conclusion

Elevated postpartum levels of anxiety and depression were strongly associated with increased antenatal levels of anxiety and depression. Experiencing life events during pregnancy that were related to the pregnancy, the mode of delivery or the newborn were found not to be associated with an increase in levels of anxiety and depression. This is not different for women with and without antenatal anxiety or depression.

Background

Reproductive age is a period in life in which women are vulnerable to the impact of symptoms of anxiety or depression. During and outside pregnancy alike, prevalence rates of these symptoms range from 8 to 15%[e.g. 1-12]. Antenatal symptoms of anxiety or depression are the most important risk factor for the occurrence of these symptoms postpartum[3,13-17], which in turn has been associated with insecure mother-child attachment[18,19]. In addition, these symptoms during pregnancy have been associated with several obstetric adverse outcomes in the child, such as preterm birth and low birth weight[20-22], as well as emotional, cognitive and behavioral problems[13,22-25].

Well-known risk factors for antenatal anxiety or depression are a history of anxiety or depression, low partner support, lower socioeconomic status, specific personality traits and major life events[e.g. 9,26]. Studies among pregnant women commonly classified recent major life events as general types of events during pregnancy[e.g. 14,27], while other studies focused on pregnant women who are facing stress due to specific conditions, i.e. obstetric complications[28,29]. A few population-based studies however, have shown that specific pregnancy related events are likely to increase symptoms of anxiety or depression during pregnancy[12,30,31].

Childbirth itself can also be considered a major life event, especially when the delivery was complicated, for example when the baby was delivered by an emergency caesarean section or the baby was admitted to the neonatal intensive care unit. During the past decade, there is a growing but inconclusive body of literature on the associations between delivery complications and postpartum symptoms of anxiety and depression[32-38].

A few large population-based cohort studies (n>5,000) found that experiencing obstetric events during pregnancy or events that were related to the condition of the newborn (i.e. low birth weight, preterm delivery, congenital malformations, admission to the hospital) increased the risk of symptoms of depression in the postpartum period[31,39]. However, both studies underline the consensual idea that a history of symptoms of depression is the main risk factor for symptoms of depression at a later moment in time. Nevertheless, there is no answer yet to the question to what extent the combination of antenatal symptoms of anxiety or depression and specific life events during pregnancy or delivery is associated with postpartum symptoms of anxiety or depression.

We investigated in a large population based cohort study to what extent specific life events during pregnancy, delivery complications and antenatal anxiety or depression independently contribute to the risk of these symptoms in the postpartum period and

whether they interact.

Methods

Sample

Data was drawn from the prospective population-based Pregnancy, Anxiety and Depression (PAD) Study[12], which has been designed to investigate symptoms of and risk factors for antenatal and postpartum symptoms of anxiety or depression. Midwives of the collaborating primary obstetric care centers (n=109) or hospitals (n=7) invited pregnant women at the first or second visit to participate. Due to logistic reasons it has been impossible to establish how many women were actually invited to the study. The number of included women was however considerably lower than we expected based on the number of participating centers. A survey among participating midwives indicated that time pressure caused the vast majority to not hand out the invitations to all visiting women, and that women who were under suspicion of having symptoms of either anxiety or depression were not specifically invited. Therefore, we have no reason to believe that, with respect to characteristics relevant to the study, responders and non-responders differed in any considerable way. After written informed consent was obtained, women were requested to fill out online baseline questionnaires at the end of the first trimester, and online follow-up assessments at the end of the second and third trimesters of pregnancy, as well as at five months postpartum. The medical ethical board of the University Medical Center Groningen approved the PAD-study.

Data used for the current study was collected between May 2010 and March 2015. Women who were at least four months postpartum were eligible to be included, as participants had the opportunity to fill out the follow-up questionnaire online between four and seven months postpartum. Women who indicated that they wanted to withdraw from the study (n=676) or who did not give consent for retrieving information from their midwives (n=1,669), were excluded. This resulted in a sample of 3,842 women (52.8%). Of these women, 2,729 filled out the follow-up anxiety and depression questionnaires at five months postpartum, yielding a response rate of 72.1%.

For postpartum measures of anxiety and depression, responders differed from non-responders on the following baseline characteristics; they generally completed a higher education ($p<0.02$) and they were more often multiparous ($p<0.04$). In addition, non-responders scored higher on antenatal measures of anxiety and depression compared to

women who did respond to the postpartum follow-up questionnaire, although mean scores on antenatal anxiety and depression measures were below the prevailing cut-offs for both responders and non-responders. Women who did not respond to the follow-up questionnaire, had experienced more general life events during pregnancy compared to women who did respond ($p<0.05$), although the means differed less than one event for all categories.

Measurements

Baseline symptom levels of anxiety and depression measured at 12 weeks of estimated gestational age (range 5-19) and at five months postpartum (range 4-7) were analyzed. Life events during pregnancy were assessed during the third trimester. Maternal age and educational level were assessed at baseline. Educational attainment level was defined as the highest completed education, and divided into four categories; elementary or lower tracts of secondary education, higher tracts of secondary education, higher vocational education and university education. Socio-economic position was calculated as the equally weighted average of the educational attainment level of the respondent, her partner, and their total income.

Antenatal and postpartum symptoms of anxiety were measured using the six-item state measuring version of the State and Trait Anxiety Inventory (STAI)[40]. Scores are on a scale from 20 to 80, with scores of ≥42 indicating an increased risk on anxiety[40].
To measure antenatal and postpartum symptoms of depression, we used the Dutch version of the ten-item Edinburgh Postnatal Depression Scale (EPDS)[41]. Scores range from 0-30. In line with Matthey[42], we considered antenatal scores of 13 or above and postpartum scores of 10 and above to indicate risk of minor or major depression.

Data on life events during pregnancy was collected with a 46-item questionnaire, developed in the Avon Longitudinal Study of Parents And Children (ALSPAC)[43]. We divided the events into four categories; A) work, finance or housing problems, B) partner relation and conflicts with loved ones, C) health, and sickness of self or loved ones and D) pregnancy related. The first three comprise a total of 26 items on employment, illness or death of loved ones and marital problems. The latter category includes seven items that are related to the current pregnancy, e.g. undergoing tests on potential congenital anomalies of the fetus, being told that it is a twin pregnancy, finding out that the partner does not want to have the baby, or finding out that something that happened that might be harmful for the fetus.

Information on mode of delivery and events that were related to the newborn was

retrieved from the midwives' or gynecologists' reports. We divided mode of delivery into A) unassisted vaginal delivery, B) instrumental vaginal delivery (i.e. forceps or vacuum extraction) and C) cesarean section, either elective of emergency. Events that relate to the newborn included preterm delivery (<37 weeks gestational age) and small for gestational age (i.e. >37 weeks gestational age but <2,500 grams).

Statistical analyses

Descriptive statistics for demographic variables, number of life events and levels of anxiety or depressive symptoms were calculated. To allow for valid comparison of effect sizes, we created Z-scores for the antenatal symptoms of anxiety and depression. Subsequently, we performed a series of multivariable linear regression analyses to quantify the associations under study. In a separate analysis, potential confounders were added (i.e. socioeconomic position and nulliparity). To investigate associations with anxiety or depression specifically, analyses were additionally adjusted for depressive symptoms in the analysis of anxiety, and vice versa.

Lastly, we assessed whether associations of specific life events and delivery complications with postpartum symptoms of anxiety or depression were modified by antenatal anxiety or depression.

Results

General descriptives

Mean levels for anxiety and depression were rather stable from the antenatal to the postpartum period (table 1), although symptoms of depression significantly increased between the antenatal and postpartum period (mean difference = 0.33, $p<0.001$).

Table 1 Characteristics of the study population (N=3,842)

Age at inclusion, mean (min-max)	31 (17-45)
Nulliparity, n (%)	972 (40,7%)
Educational level	
Elementary or lower tracts secondary, n (%)	243 (8,5%)
Higher tracts secondary, n (%)	860 (30,0%)
Higher vocational , n (%)	1142 (39,8%)
University , n (%)	626 (21,8%)
No events related to the pregnancy [a], n (%)	1551 (48,7%)
median (min-max)	1 (0-7)
No events related to health/sickness of self or loved ones [a], n (%)	1950 (62,4%)
median (min-max)	0 (0-8)
No events related to partner relation/conflicts with loved ones [a], n (%)	2445 (75,9%)
median (min-max)	0 (0-4)
No events related to work/finance/housing problems [a], n (%)	1441 (45,2%)
median (min-max)	1 (0-10)
Mode of delivery, n (%)	
spontaneous vaginal delivery	1768 (74,8%)
vacuum or forceps extraction	240 (10,2%)
sectio	356 (15,1%)
Newborn is preterm or has low birth weight, n(%)	148 (6,2%)
Baseline level anxiety (STAI) [b], mean (SD)	32 (9,06)
Postpartum level anxiety (STAI) [c], mean (SD)	32 (10,32)
Baseline level depression (EPDS) [b], mean (SD)	4 (3,70)
Postpartum level depression (EPDS) [c], mean (SD)	5 (4,06)

STAI – Spielberger State Trait Anxiety Inventory (min-max 20-80)

EPDS – Edinburgh Postnatal Depression Scale (min-max 0-30)

[a] experienced during pregnancy

[b] pregnancy duration of 12 weeks

[c] 5 months postpartum

Table 2 Associations of postpartum levels of anxiety and depression with antenatal symptoms, specific life events and delivery complications

	Postpartum anxiety (STAI)		Postpartum depression (EPDS)	
	Mean change (95% CI)	p-value	Mean change (95% CI)	p-value
Anxiety baseline	5.673 (5.305; 6.041)	<0.001	0.540 (0.327; -0.753)	<0.001
Depression baseline	2.750 (2.199; -3.300)	<0.001	2.444 (2.306; 2.582)	<0.001
Number of events related to the pregnancy [a]	0.240 (-0.248; 0.728)	0.335	-0.015 (-0.199; 0.170)	0.877
Number of events related to health/sickness of self or loved ones [a]	0.916 (0.492; 1.341)	<0.001	0.354 (0.197; 0.512)	<0.001
No events related to partner relation/conflicts with loved ones [a]	1.951 (1.352; 2.550)	<0.001	0.544 (0.313; 0.775)	<0.001
Events - work/finance/housing problems	0.834 (0.565; 1.104)	<0.001	0.199 (0.096; 0.302)	<0.001
No events related to work/finance/housing problems [a]				
spontaneous vaginal delivery vs. vacuum/forceps	-0.033 (-1.203; 1.137)	0.956	0.221 (-0.216; 0.657)	0.222
spontaneous vaginal delivery vs. sectio	-0.759 (-2.162; 0.643)	0.288	0.31 (-0.202; 0.869)	0.321
Newborn is preterm or has low birth weight	0.414 (-1.365; 1.193)	0.648	0.316 (-0.343; 0.976)	0.347

Multivariable linear regression analyses.

Antenatal levels of anxiety and depression were standardized by calculating Z-scores.

Analyses on postpartum anxiety were adjusted for baseline anxiety levels.

Analyses on postpartum depression were adjusted for baseline depression levels.

STAI – Spielberger State Trait Anxiety Inventory (min-max 20-80)

EPDS – Edinburgh Postnatal Depression Scale (min-max 0-30)

[a] experienced during pregnancy

Regression analyses of associations between experienced life events and postpartum levels of anxiety or depression

Antenatal symptoms of anxiety and depression were statistically significantly associated with postpartum level of anxiety and depression ($p<0.001$) (table 2).

All categories of number of life events that are not related to the pregnancy, delivery or newborn were significantly associated with higher levels of anxiety and depression in the postpartum period. Adding potential confounders did not notably change the associations. When adjusting for postpartum levels of anxiety, all associations between life events and postpartum depression lost their statistical significance. For anxiety, this was only true for life events that were related to sickness and health of self or loved ones and life events related to the partner relation or a conflict with a love one.

Moderation of the associations between experienced life events and postpartum levels of anxiety or depression by antenatal levels of anxiety and depression.

The associations between number of life events and postpartum symptoms of anxiety was only moderated by antenatal anxiety in case of events related to sickness and health of self or loved one. None of the associations between antenatal life events and postpartum levels of depression were moderated by antenatal levels of depression.

Discussion

The present study confirmed previous research showing that antenatal symptoms of anxiety or depression during pregnancy are strongly associated symptoms in the postpartum period. We showed that experiencing life events that were not related to the pregnancy, the mode of delivery or to the newborn were associated with elevated levels of anxiety and depression in the postpartum period. The association between postpartum levels of anxiety and events related to sickness and health of self or loved ones was found to be moderated by antenatal levels of anxiety.

Standardized effect sizes for levels of antenatal anxiety and depression were the highest of all predictor variables, indicating that antenatal symptomatology is the most important risk factor for having symptoms postpartum. This is in line with previous studies[3,13-15,17].

In our study, life events related to the partner relation or a conflict with a loved one, or to work, finance or housing problems increased the postpartum levels of anxiety and depression. In the general population, housing problems have been found to increase feelings of

stress[44]. Also, foreclosure induced a decline in mental health[45]. In addition, involuntary job loss and the past economic recession have been associated with higher suicidal rates[46,47]. However, this was not studied in specifically in pregnant women and especially found to be more prevalent in men.

Experiencing a major recent life event is widely considered to be an important risk factor for depression. We therefore hypothesized that when maternal and neonatal outcomes were complicated, childbirth could be considered a major life event. Surprisingly neither the events related to delivery nor to the condition of the newborn were associated with change in levels of anxiety and depression symptoms. For mode of delivery, this is in line with most studies[32,33,36,37]. One study found that mode of delivery increased depression scores in the postpartum period in nulliparous women[48]. Their sample of women who had a caesarean section was however rather small (n=48).

Strengths and limitations

Some limitations have to be borne in mind. First, symptoms of anxiety and depression were based on self-report questionnaires. Although both are commonly used in the identification of symptoms and have shown to have good validity[40,41], no clinical diagnostic tools have been used in the present study to establish the severity of symptoms. Second, life events were assessed using a retrospective self-report checklist, which may have been prone to recall bias through its potential link with symptoms at the time of the assessments[49], although the total sample was large, we had encountered a high percentage of missing data on events during delivery (38.5%) and events related to the newborn (38.1%). As the statistical power to demonstrate associations with a change in levels of anxiety and depression may thus be limited, these analyses should be considered exploratory.

However, a major strength of the present study is the large, prospective, population based cohort (n=3,842). Additionally, to our knowledge, this study was the first to investigate the role of specific life events that are either more general or related to the pregnancy, delivery or newborn, in relation to the specific symptoms of anxiety or depression in the postpartum period.

Concluding

Experiencing life events during pregnancy that were related to the pregnancy, the mode

of delivery or the newborn were found not to be associated with an increase in levels of anxiety and depression. This is not different for women with and without antenatal anxiety or depression.

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Predictive accuracy of Edinburgh Postnatal Depression Scale (EPDS) assessment during pregnancy for the risk of developing postpartum depressive symptoms: a prospective cohort study.

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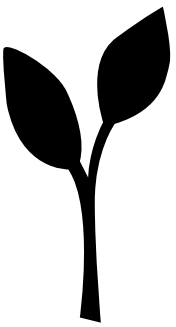


chapter 4

Abstract

Objective

To investigate whether the ten-item Edinburgh Postnatal Depression Scale (EPDS) administered antenatally in 1,620 women in the general population is accurate in predicting postpartum depressive symptoms (EPDS score ≥10), and whether a two-item EPDS has similar predictive accuracy.

Methods

Mean values, area under the receiver operating characteristics-curve (AUC), sensitivity, specificity and predictive values of antenatal EPDS for the likelihood of developing postpartum depressive symptoms were calculated. Analyses were repeated for each trimester, several cut-off values and a two-item EPDS (low mood and anhedonia).

Results

Mean EPDS scores were significantly higher during each trimester in women with postpartum depressive symptoms, compared to those without ($p<0.001$). Using the prevailing cut-off (≥10), the AUC was reasonable (0.74), sensitivity was 26.3%, positive predictive value 25.9%, specificity 93.0% and negative predictive value 93.1%. Using a lower cut-off value (≥5), sensitivity was 70.8% and specificity was 65.4%, but positive predictive value was low (15.9%). Negative predictive value was exceedingly high with 96.0%. Results were similar during the second and third trimester. The predictive accuracy of the two-item EPDS appeared inferior.

Conclusions

The EPDS was not sufficiently accurate in predicting risk of postpartum depressive symptoms. Nevertheless, when using the ≥5 cut-off value, it may be adequate for initial screening, followed by further assessments and possibly antenatal intervention when positive. Furthermore, when negative, women may be reassured that postpartum depressive symptoms are unlikely. A two-item version showed poor predictive accuracy.

Introduction

Depression affects 8-15% of women in the first year postpartum[1-4]. This poses a considerable burden to the women, their families and society[5,6]. Children born to women who experienced postpartum depression, are at risk of insecure attachment, which in turn is associated with cognitive, behavioral and emotional problems[7,8]. Moreover, postpartum depression is commonly preceded by antenatal depression[4,9,10], which has been associated with unfavourable obstetric outcomes and impaired child neurodevelopment[10-12], independent of effects due to postpartum depression[11]. Thus, timely detection of antenatal depressive symptoms is critical for mother and child. Correspondingly, the American College of Obstetricians and Gynecologists recommends antenatal screening[13].

The ten-item Edinburgh Postnatal Depression Scale (EPDS)[14,15] is commonly used for assessing depressive symptoms, and was validated as antenatal and postpartum screener for minor or major depression[16]. While depressive symptoms are known to be associated with the development of a depressive disorder[17], it is remarkable that predicting the absolute risk of postpartum depression, based on antenatal depressive symptoms as assessed by the EPDS, has been studied scarcely[10,18,19]. In a large cohort, the relative importance of several antenatal risk factors for postpartum depression was studied[18]. Yet, the predictive accuracy of the antenatal EPDS was quantified exclusively for a single cut-off value and not specified for trimester of pregnancy. In another large cohort, the pattern of depressive symptoms during pregnancy and in the postpartum period was studied, but not the predictive accuracy of the EPDS[10]. One study observed that when using a higher than commonly used cut-off in the second trimester, the EPDS was accurate in predicting depression at six weeks postpartum[19]. However, their study suffered from a high loss to follow-up rate.

Consequently, the predictive accuracy of the EPDS for identifying an increased risk of postpartum depression is still unknown. At the same time, a brief, reliable self-report antenatal screener to predict the likelihood of minor or major postpartum depression would facilitate midwives and gynaecologists in daily clinical practice[20], for example a screener that only includes the two key symptoms of depression, i.e. anhedonia and mood[21].

In the current prospective study, we examined to what degree the ten-item EPDS administered during the first, second and third trimester of pregnancy, using various cut-offs, is valid for the assessment of the absolute risk of postpartum depressive symptoms. Since a two-item version would be more convenient, we further investigated the predictive performance of a two-item EPDS including the key symptoms of depression only.

Methods

Sample

The present study was carried out within the ongoing population-based Pregnancy, Anxiety and Depression (PAD) Study[22]. This prospective cohort study has been set up to investigate symptoms of and risk factors for anxious or depressive symptoms during pregnancy and the first half year postpartum. All pregnant women in their first trimester of pregnancy, visiting a total of 109 collaborating primary obstetric care centers and seven hospitals in the Netherlands, are invited to participate. Written informed consent is obtained from each participant. After baseline assessments at the end of the first trimester, follow-up assessments using online questionnaires take place at the end of the second and third trimesters of pregnancy, as well as at six months postpartum.

Data used for the present study was collected from May 2010 to September 2012. By the end of that period, 4,157 women had completed the baseline assessments. The eligible population for the present analysis consisted of women who were six months postpartum by the time of the database closure (N=1,620, 39%). Out of these, 1,276 responded by filling out the questionnaires yielding a response rate of 78.8%. Non-responders did not significantly differ from responders on parity, educational level or antenatal depressive symptoms. However, non-responders were significantly younger (30 vs. 29 years, $p<0.02$).

Measurements

Demographic and pregnancy related variables included in the present study were age, parity and educational level, and were assessed at baseline. Educational level was defined as the highest completed education, and was divided into five categories; elementary education, lower and higher tracts of secondary education, higher vocational education and university education.

The Dutch version of the ten-item Edinburgh Postnatal Depression Scale (EPDS) was used to measure symptoms of depression[14]. This version of the EPDS has shown good internal validity with a Cronbach's alpha of 0.8214. The baseline EPDS was administered as part of the initial antenatal screening and each follow-up assessment wave. Total EPDS scores of ≥10 indicate depressive symptoms at a level corresponding to an increased risk of minor or major depression[14]. The outcome of this study, i.e. postpartum depressive symptoms at six months after giving birth, was defined accordingly.

Multiple imputation of missing data

Complete information on all variables was obtained on 1013 (62.5%) women. The percentage of missing data ranged from 1.5 (EPDS at baseline) to 21.1 (postpartum EPDS) for the variables of main interest. Under the assumption that missing values were missing at random (MAR) or missing completely at random, we imputed missing data using multiple imputation by chained equations. This was done to avoid the potential bias and decreased statistical power associated with complete case analysis[23,24]. We substantiated our assumption of the missing data mechanism being MAR by, for each variable separately, predicting missingness using logistic regression. Independent variables were all variables that were considered potential predictors of missingness[24] i.e. antenatal anxiety, age at baseline, parity and maternal educational level. The explained variance (Nagelkerke R2) from these analyses ranged from 7.1% to 63.2%, suggesting that at least in part data are MAR and imputation of missing values would likely improve the validity of our analyses. Multiple data sets (N=5) were generated to account for the uncertainty in imputed data.

Data analyses

Descriptive statistics for demographic variables were calculated according to the likelihood of the presence of postpartum depressive symptoms. We tested whether the mean value of each antenatal EPDS differed between women experiencing postpartum depressive symptoms and those who did not, using an independent samples t-test. Additionally, we calculated the prevalence of antenatal depressive symptoms (EPDS ≥10) at each assessment.

Subsequently, we evaluated the predictive accuracy of each antenatal EPDS in terms of sensitivity, specificity, predictive values and overall discriminatory power. We first constructed receiver operating characteristic (ROC) curves, by plotting the sensitivity against the 1-specifity for all possible cut-off values of antenatal EPDS. Informed by these curves, we constructed crosstabs using all possible cut-off values between 5 and 10, and calculated the measures of predictive accuracy. The overall discriminatory power of the EPDS independent of cut-off value was quantified as the area under the ROC-curve (AUC). The AUC can be interpreted as the extent to which the EPDS separates women with postpartum depressive symptoms from those without. Values of 0.70 to 0.80 indicate a reasonable AUC, 0.80 to 0.90 a good one and values of 0.90 or above are interpreted as excellent[25].

The above analyses were repeated for the EPDS scores recorded in the second and third trimester. In addition, we quantified the prevalence and predictive accuracy of exceeding the

≥10 cut-off at all three antenatal assessments.

Subsequently, we examined the predictive accuracy of the two EPDS items that refer to the key symptoms of depression. These are items 2 for anhedonia and 8 for depressed mood, according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)[21]. We summed the ratings of these items to a total score. This two-item version ranged from 0-6, the first cut-off value we tested was ≥3. Based on the results, the ROC-curve and the fact that, according to the DSM-IV, a diagnosis of depression needs at least one of these two items to be answered positively, we subsequently tested a cut-off value of ≥1.

Measures of predictive accuracy were supplied with 95% confidence intervals. Results were pooled using Rubin's method for multiple imputation inference[26]. Multiple imputation and statistical analyses were carried out using IBM SPSS Statistics 20.

Results

Descriptives

Mean gestational age of the study population (N=1,620) was 14, 23 and 34 weeks at the baseline, second and third trimester measurement waves, respectively. Women were five (range 4-7) months postpartum at the final measurement. At baseline, 139 women (8.6%) experienced depressive symptoms according to the cut-off value of ≥10. These figures were 154 (9.5%) and 164 (10.1%) at the second and third trimester measurements, respectively. One hundred and thirty-seven women (8.5%) experienced postpartum depressive symptoms, which is equal to their a priori risk.

Table 1 shows that demographic factors were equally distributed among women with and without postpartum depressive symptoms. At each instance of administration, scores on the EPDS were statistically significantly higher in the group with postpartum depressive symptoms than in the group without postpartum symptoms of depression ($p<0.001$).

Crosstabs

Table 2 shows parameters of predictive accuracy of the ten-item EPDS in the first trimester using cut-off values ≥10 and ≥5, as well as those for the two-item version using cut-off values ≥3 and ≥1. Although for the ten-item EPDS we tested all cut-off levels between those presented in table 2, we decided to show only the most clinically relevant results.

Table 1 Demographic characteristics of the study population (n=1,620) according to the presence of postpartum depressive symptoms

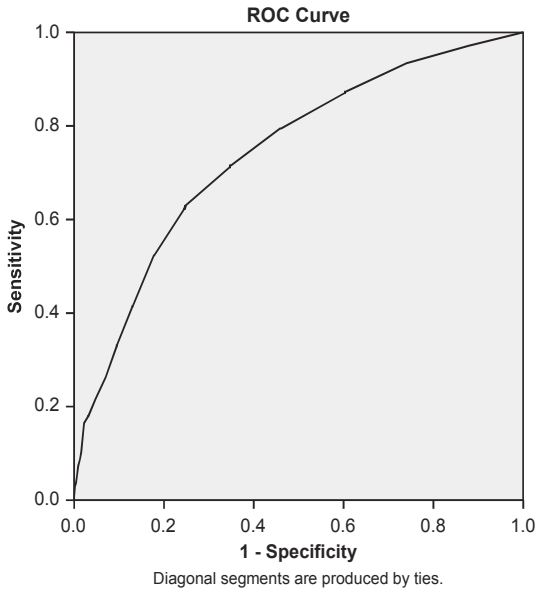
	No postpartum depressive symptoms [a] (n=1,483)	Postpartum depressive symptoms [a] (n=137)	Fraction of missing data
Age, mean (min-max)	30.0 (17-46)	29.7 (18-43)	4.1%
Primiparae, N (%)	625 (41%)	52 (38%)	29.8%
Educational level, N (%)			30.1%
Elementary education	7 (<1%)	1 (<1%)	-
Lower tracts of secondary education	139 (9%)	15 (11%)	-
Higher tracts of secondary education	508 (34%)	46 (34%)	-
Higher vocational education	596 (40%)	57 (42%)	-
University education	233 (16%)	18 (13%)	-
Depression level first trimester [b], mean (SD)	3.91 (3.32)	7.48 (4.86)	1.5%
Depression level second trimester [b], mean (SD)	4.62 (3.14)	8.79 (4.93)	18.2%
Depression level third trimester [b], mean (SD)	4.67 (3.17)	8.83 (4.58)	16.7%
Depression level postpartum [b], mean (SD)	3.81 (2.51)	13.36 (3.75)	21.2%

[a] According to Edinburgh Postnatal Depression Scale (EPDS), cut-off EPDS ≥10, min-max=0-30

[b] Based on EPDS at approximately 14 weeks pregnancy, min-max=0-30. Scores were statistically significantly higher in the group with postpartum depressive symptoms than in the group without postpartum symptoms of depression, with p ≤0.001

The ten-item EPDS using the ≥10 cut-off showed low sensitivity (26.3%) and high specificity (93.0%). However, the AUC of 0.74 was reasonable (figure 1). When we decreased the cut-off value to ≥5, the sensitivity increased to 70.8% and the specificity decreased to 65.4%. Positive predictive values were low at all considered cut-off values, whereas all negative predictive values were high. Although the positive predictive value for a score higher than 10 in the first trimester was only 25.9%, this risk is three times higher as the prior risk of postpartum depressive symptoms, which was 8.5%. Lowering the cut-off for the two-item version also showed higher sensitivity (59.1% vs. 12.4%) at the expense of the specificity and the positive predictive value (table 3). The AUC of the two-item version, i.e. 0.63, was considerably lower than that of the complete ten-item version.

Figure 1 Area Under the ROC Curve for baseline score Edinburgh Postnatal Depression Scale (EPDS)[a] in the prediction of minor or major postpartum depression[b]



AUC of 1.0 is perfect prediction

[a] Based on ten-item EPDS at approximately 14 weeks pregnancy, min-max=0-30, pooled for all imputed datasets.

[b] According to EPDS, cut-off ≥10, min-max=0-30

When test positive was defined as a score of ≥10 at all three measurements (N=50;3.1%), the positive predictive value increased to 40.0%, while the sensitivity decreased to 15.0%. The negative predictive value and the specificity remained high (92.5% and 97.9%, respectively).

All of the above analyses were repeated for the EPDS scores recorded in the second and third trimester. Results were essentially similar to those obtained using the first trimester scores. However, AUC's were slightly higher for the ten-item EPDS with 0.77 and 0.78 at the second and third trimester, respectively. For the two-item version the AUC was 0.68 at the second trimester and 0.71 at the third.

Table 2 **Test characteristics for predicting postpartum depressive symptoms from antenatal depressive symptoms**

	Cut-off ≥13 [a] (n=55, 3.4%) [b]	Cut-off ≥10 [a] (n=137, 8.5%) [b]	Cut-off ≥5 [a] (n=610, 37.7%) [b]	All antenatal scores ≥10 [a] (n=50, 3.1%) [c]
Sensitivity, % (95% CI)	16.8 (11.0-24.1)	26.3 (19.1-34.5)	70.8 (62.4-78.3)	14.6 (9.2-21.6)
Specificity, % (95% CI)	97.8 (97.0-98.5)	93.0 (91.6-94.2)	65.4 (62.9-67.8)	97.9 (97.0-98.6)
Positive Predictive Value, % (95% CI)	41.8 (28.7-55.9)	25.9 (18.8-34.0)	15.9 (13.1-19.0)	39.2 (25.8-53.9)
Negative Predictive Value, % (95% CI)	92.7 (91.3-94.0)	93.1 (91.7-94.3)	96.0 (94.6-97.2)	92.5 (91.1-93.8)
Area Under the Curve	0.74	-	-	-

[a] Based on ten-item Edinburgh Postnatal Depression Scale (EPDS) at approximately 14 weeks pregnancy, min-max=0-30

[b] Number and percentage of women scoring above the used cut-off at baseline EPDS

[c] Number and percentage of women scoring above the used cut-off at all antenatal measurements of the EPDS

Table 3 Test characteristics for predicting postpartum depressive symptoms from a two-item version for antenatal depressive symptoms

	Cut-off ≥3 [a] (n=65, 4%) [b]	Cut-off ≥1 [a] (n=586, 36.2%) [b]
Sensitivity, % (95% CI)	12.4 (7.4-19.1)	59.1 (50.4-67.4)
Specificity, % (95% CI)	96.8 (95.7-97.6)	65.9 (63.5-68.4)
Positive Predictive Value, % (95% CI)	26.2 (16.0-38.5)	13.8 (11.1-16.9)
Negative Predictive Value, % (95% CI)	92.3 (90.8-93.6)	94.6 (93.0-95.9)
Area Under the Curve	0.63	-

a Based on items 2 and 8 of the Edinburgh Postnatal Depression Scale (EPDS) at approximately 14 weeks pregnancy, min-max=0-6

b Number and percentage of women scoring above the used cut-off at baseline EPDS

Discussion

Main Findings

In this prospective cohort study, we found that women who developed postpartum depressive symptoms had statistically significantly higher antenatal EPDS scores. Irrespective of trimester, the ten-item EPDS had reasonable overall discriminatory power, but low sensitivity at the prevailing cut-off (≥10). When using a lower cut-off (≥5), both sensitivity and specificity were around 70%. However, for both cut-off values, positive predictive values were low, whereas negative predictive values were exceedingly high. A two-item version of the EPDS, consisting of merely the two key symptoms of depression, demonstrated a poor predictive performance. In addition, the EPDS was accurate in detecting current depressive symptoms. In the context of potential hazardous child effects of antenatal depressive symptoms, it is important that these symptoms are acknowledged by screening health care professionals.

Strengths and limitations

The present study is not without limitations. First, the EPDS is a self-report questionnaire and even though it is commonly used, based on the EPDS score we are merely able to identify women with a higher risk of depressive symptoms. However, almost 70% of women exceeding the threshold of 10 satisfy the criteria for a diagnosis of depression[31]. Second, anxiety and depression are known to be co-morbid and several studies have shown that

antenatal anxiety is a predictor of postpartum depression[32,33]. However, because the only aim was to test the predictive accuracy of the EPDS, anxiety is considered beyond the scope of the current paper, and should therefore be addressed in future research. Finally, although our antenatal prevalence rates (9-10%) are comparable with other studies[1,2], women experiencing depressive symptoms in their first trimester might have been more inclined to participate than women who are not familiar with depressive symptoms. In addition, we found a significant difference in age between the respondents and non-respondents. However, in absolute numbers the age difference is less than a year; therefore we do not think it affected our prevalence rates. Likewise, the prevalence of postpartum depressive symptoms in our study was relatively low (8%). Previous studies reported prevalence rates of 8-15%[1,2]. However, in these studies, the time at which postpartum depressive symptoms were assessed ranged from a few days after delivery to two years postpartum, which may have caused the inclusion of maternity blues, thereby falsely increasing the prevalence of postpartum depression.

Our study also has several strengths. The present study is the first to date to examine the EPDS as a tool for antenatal assessment of the risk of postpartum depressive symptoms, during each trimester of pregnancy, evaluating several cut-off values for the sum score, as well as the possibility of item reduction. In addition, the present sample is a large prospective cohort, including 1,620 pregnant women in their first trimester, with a response rate of 78.8%.

Interpretation

Despite reasonable overall discriminatory power, the EPDS appears to have limited predictive accuracy for absolute risk stratification, regardless of the cut-off value used or the trimester of administration, partly contradicting the findings of Lau et al.[19]. They concluded that when using a cut-off of ≥15, the EPDS during the second trimester of pregnancy appeared to be an accurate predictor of depression at six weeks postpartum, with parameters of predictive accuracy ranging from 63% to 85%, and an overall AUC of 0.76, the latter being in line with our findings. However, they suffered from a high loss to follow-up rate (72%), making the results susceptible to serious bias. From a more general point of view, Austin & Lumley concluded that no currently available antenatal screener is sufficient in predicting postpartum depression, due to the evidence that multiple risk factors are postpartum, which clearly cannot be included in antenatal screening[27]. Additionally, Milgrom et al. showed that adding prior history of depression and low partner support to antenatal EPDS yielded a

more accurate overall prediction, using a cut-off of >12, mainly administered during the third trimester[18]. They observed a low positive predictive value of 29%, which seems compatible with our findings; although the absolute risk of postpartum depressive symptoms for women scoring ≥5 was two times higher than the prior risk, it was still low (15.9%). In order to allocate interventions as much as possible to women who have a high risk of postpartum depressive symptoms, a two-stage screening may therefore be advocated, as previously suggested[20]. Women with an EPDS score of ≥5 during the first trimester can be screened more elaborately on well known risk factors, such as history of depression and low partner support, to decide whether an antenatal intervention is necessary.

In suggesting a two-stage screening, the exceedingly high negative predictive value of the ten-item EPDS seems important. Women who scored <5 at the antenatal screening had a very low risk of postpartum depressive symptoms (4.0%). As previously suggested[29], it could therefore be used to exclude women who are not at risk for depressive symptoms. However, due to the lowered cut-off, considerably more women were identified as having a high risk of postpartum depressive symptoms, comparable to the number of women identified with the two-item version. In that context, it could be argued that, as an initial screener, the two-item version would be more facilitating in daily clinical practice. The National Institute for Health and Clinical Excellence (NICE) recommends a two-item dichotomous screening tool based on the key symptoms of depression[30]. However, this tool was developed with the only purpose of detecting current depressive symptoms[20], in which it appears to be accurate[20,28,29]. In the present study, the two-item version also showed satisfactory predictive accuracy in the identification of current depressive symptoms, but the overall test parameters for predicting postpartum depressive symptoms are considerably lower. Therefore, in screening for high risk on postpartum depressive symptoms, we would suggest the use of the ten-item EPDS with a cut-off of ≥5.

Our study results do not suggest that timing of administering the EPDS during pregnancy affects its predictive accuracy. This is an important notion in view of the potential hazardous child effects of antenatal depressive symptoms, as this means that postponing screening for depressive symptoms cannot be justified by the argument that the predictive accuracy increases with duration of pregnancy.

Conclusion

In conclusion, we found that in no trimester of pregnancy the EPDS is a sufficiently accurate instrument to identify women with a high risk of symptoms of postpartum depression. However, when using a lower than commonly used cut-off value, the test characteristics were such that a stepwise approach using the EPDS as a first screening step could be recommended to clinicians, midwives and gynaecologists. Women with a high risk (i.e. EPDS score of ≥5 during the first trimester) can subsequently be screened more elaborately on well known risk factors, such as a history of depression and low partner support, to decide whether an antenatal intervention is necessary. Women scoring <5 on the antenatal ten-item EPDS can be reassured that it is very unlikely that they will develop a postpartum depressive symptoms. Although it would be convenient to use a brief screener in daily clinical practice, a two-item version showed poor predictive accuracy. Because the predictive accuracy of the ten-item EPDS was similar across the three antenatal administrations, there seems to be no reason to postpone screening and possible intervention until after the first trimester.

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Predictive accuracy of the six-item State and Trait Anxiety Inventory assessment during pregnancy for the risk of developing postpartum symptoms of anxiety: a prospective cohort study.

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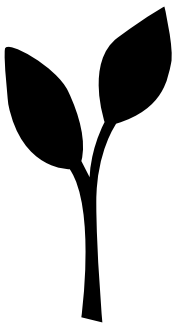

chapter 5

Abstract

Background

To investigate whether the six-item State and Trait Anxiety Inventory (STAI) assessed antenatally is accurate in predicting postpartum symptoms of anxiety, and whether antenatal Edinburgh Postnatal Depression Scale (EPDS) can improve the prediction.

Methods

A prospective, population-based cohort study in the obstetric care in the Netherlands, n=4,856. Mean values, odds ratios, area under the receiver operating characteristics curve (AUC), sensitivity, specificity and predictive values of antenatal STAI for the risk of postpartum symptoms of anxiety (STAI score ≥42) were calculated. Analyses were repeated for each trimester and several cut-off values. Odds ratios were also calculated including antenatal symptoms of depression.

Results

The AUC was only reasonable in the second and third trimester (0.73). Using the prevailing cut-off (≥42) in the first trimester, the odds ratio was 3.49 [95%CI 2.61, 4.67]. Adding symptoms of depression did not improve the prediction. Sensitivity and positive predictive value were approximately 30%, specificity and negative predictive value were around 90%. Using a lower cut-off value (≥36) in the second trimester, sensitivity and specificity were both approximately 67%, but positive predictive value was low (22.9%, [95%CI 21.0, 24.9]). Negative predictive value increased to 93.2% [95%CI 92.3, 94.1]).

Conclusions

The six-item STAI was not sufficiently accurate in predicting risk of postpartum symptoms of anxiety, irrespective of trimester and cut-off value. Women scoring below cut-off may be reassured that postpartum symptoms of anxiety are unlikely. Adding symptoms of depression did not improve the prediction.

Introduction

Due to a paucity of studies on specific symptoms of anxiety during pregnancy and in the postpartum period, it remains unclear how many women are affected by these symptoms[1,2], with estimates ranging from 7% to 33%[3-13]. Consequences that are associated with antenatal anxiety, however, have been studied relatively well. Multiple studies focus on unfavourable obstetric outcomes in terms of low birth weight and preterm birth[14,15]. In addition, associations between maternal anxiety/stress and multiple adverse outcomes in the child, such as cognitive, behavioral and emotional problems, were found in numerous studies[10,16-19]. Furthermore, antenatal anxiety often precedes postpartum symptoms of anxiety or depression[3,7,20], or both, as they are known to be highly comorbid[3,6].

A commonly used instrument in the identification of symptoms of anxiety is the State and Trait Anxiety Inventory (STAI)[21], which was validated both in samples of pregnant and postpartum women[21]. Although it is known that having symptoms of anxiety is a risk factor for developing an anxiety disorder[5], the STAI has not extensively been studied for its accuracy in predicting future symptoms of anxiety. As far as we know, only one study has been conducted on the predictive accuracy of the STAI in the postpartum period. This study showed that women with a high risk of anxiety symptoms in the first two months after delivery (n=522) can already be identified in the first days postpartum using the STAI[12]. Knowing that symptoms of anxiety that exist during pregnancy can have serious adverse outcomes for both mother and child, and that a psychological therapy such as cognitive behavioral therapy is a treatment with a high success rate for symptoms of anxiety, it is essential to identify these symptoms as early as possible.

In the current prospective study, we therefore examined to what extent the STAI applied during the first, second, and third trimester of pregnancy was accurate in predicting the absolute risk of postpartum symptoms of anxiety. In addition, we determined which cut-off value yielded the most accurate prediction. In view of the established co-morbidity of anxiety and depression, we also investigated whether assessing antenatal depressive symptoms would give a more accurate prediction of postpartum symptoms of anxiety.

Methods

Sample

The current study was conducted within the prospective Pregnancy, Anxiety and Depression (PAD) cohort study in the Netherlands (n=7,275), which included women in their

first trimester between May 2010 and September 2014, and aims to investigate antenatal and postpartum symptoms of and risk factors for anxiety or depression[13]. Midwives and gynaecologists of participating obstetric care centres (n=116) invited all visiting pregnant women to participate in the study. Due to logistic reasons, we are unable to determine how many women have actually been invited and, of these, how many agreed to participate. The number of participants was however considerably lower than we expected based on the number of participating centres. A survey among participating midwives showed that pressure of time meant that they could not hand out the forms to all visiting women and that they did not specifically invite women they suspected to have an increased risk of depressive symptoms. Therefore, we do not think that participants and non-participants differed in any considerable way with respect to characteristics relevant to the study due to selective inviting[22]. All participants gave written informed consent.

The study population of the current study was formed by 4,856 women who were five months postpartum (range four to seven months) at the time of database closure in December 2014. Of these women, 74.1% (n=3,600) responded by filling out the postpartum follow-up questionnaire on anxiety symptoms. Compared to these responders, non-responders were younger (difference less than a year, p=0.001), more often multiparous (p=0.001), had a lower educational attainment level (p=0.003) and higher scores on anxiety symptoms and depressive symptoms at all antenatal measurement waves (p <0.01).

The medical ethical review board of the University Medical Center Groningen approved this study.

Measures

Symptoms of antenatal anxiety and depression were measured at 12, 23 and 35 weeks of gestation. Postpartum symptoms of anxiety were assessed at five months postpartum.
Anxiety was measured using the Dutch six-item version of the STAI[21], which has acceptable concurrent validity when compared to the full 20-item form (r=0.92), and a good internal consistency (Cronbach's α=0.82)[21]. The questionnaire measures state anxiety ('how do you feel at the moment'), and was validated on a sample of pregnant women[21]. Scores are on the original scale from 20 to 80, with scores of ≥42 indicating an increased risk on anxiety[21], postpartum scores were dichotomized accordingly.

To measure antenatal depressive symptoms, we used the validated Dutch 10-item Edinburgh Postnatal Depression Scale (EPDS)[23], which has shown good internal consistency

(Cronbach's α=0.82)[23]. The scale ranges from 0 to 30. Total scores of 13 or higher indicate an increased risk of minor or major depression during pregnancy[24,25].

Multiple imputation of missing data

Complete information for all variables was present for 2,248 women, i.e. 46.3% of women who were at least four months postpartum. The percentage of missing data in the present study ranged from 7.8 (age at inclusion) to 26.1 (EPDS five months postpartum) for the variables of main interest. To avoid potential bias and decreased statistical power[26,27], we imputed all missing data on item level, using multiple imputation by chained equations under the assumption that missing values were missing at random (MAR) or missing completely at random (MCAR). For all variables of main interest, we assessed to what extent we could predict their values being missing, using logistic regression, in order to substantiate the assumption that the missing data mechanism was MAR. Independent variables were all variables that were considered potential predictors of missingness of a value[27,28], i.e. antenatal symptoms of anxiety and depression, age at baseline, parity and maternal educational attainment level. The explained variance (Nagelkerke R2) from these analyses ranged from 1.2% to 8.2%, which suggests that data are MAR to some extent, and imputation of missing values would likely improve the validity of our analyses. Therefore, all of these variables as well as the outcome variable, i.e. postpartum symptoms of anxiety, were included in the imputation model. All results were pooled using Rubin's method for multiple imputation inference[29]. However, the possibility that data were missing not at random has to be borne in mind[28]. We therefore performed a complete case analysis to compare the results with the results of the imputed dataset as a sensitivity analysis. Multiple data sets (n=5) were generated.

Statistical analysis

We first calculated the prevalence of symptoms of anxiety (STAI ≥42) and depression (EPDS ≥13) at all antenatal measurements, and the prevalence of postpartum symptoms of anxiety. Using a paired samples t-test, we tested whether antenatal levels of anxiety and depression significantly differed from postpartum levels. Subsequently, descriptive statistics were calculated for demographic variables and scores on the antenatal STAI and EPDS assessments. These calculations were done for the total sample and according to the presence of postpartum symptoms of anxiety. We tested whether mean values differed between women with and women without postpartum symptoms of anxiety, using an

independent samples t-test.

All following analyses were repeated for all three antenatal measurement waves.
We determined several performance parameters. First, we calculated the odds ratio for the association between increased antenatal and postpartum levels of anxiety or depression by conducting a logistic regression analysis. We added symptoms of antenatal depression to investigate whether this would give a more accurate prediction of postpartum symptoms of anxiety.

Subsequently, we constructed receiver operating characteristic (ROC) curves and calculated the area under the ROC-curve (AUC). Next, sensitivity, specificity and predictive values were calculated using several cut-off values for the antenatal STAI to define test positive. We started with the commonly used cut-off value of ≥42. Based on the results and the ROC-curve, we gradually lowered the cut-off value, and repeated all analyses. Measures of predictive accuracy were supplied with 95% confidence intervals.

Additionally, test positive was defined as a score exceeding the cut-off of ≥42 on the STAI at all three antenatal measurements, to test whether repeating the assessment of anxiety symptoms would give a more accurate prediction, compared to having a score above cut-off at one of the antenatal measurements. We repeated this analysis using a lower cut-off, i.e. ≥36 for all antenatal measurement waves.

Based on a previous study conducted by Dennis et al.[12], in which the time interval between measurements was four to eight weeks, we conducted a sensitivity analysis in which we repeated our analyses and calculated the predictive accuracy with the first trimester as predictor variable and the third trimester as outcome variable. Lastly, we performed a complete case analysis as a sensitivity analysis.

Multiple imputation and statistical analyses were carried out using IBM SPSS Statistics 20.

Results

Sample description

At baseline, 619 women (12.7%) experienced symptoms of anxiety (≥42), and 177 women (3.6%) experienced symptoms of depression (≥13). Prevalence rates of levels of anxiety and depression were highest in the second trimester (n=717, 14.8% and n=187, 3.9% respectively). Postpartum symptoms were experienced by 621 women (12.8%), i.e. the prior risk. A total of 164 women (3.4%) scored above the cut-off of ≥42 on the STAI at all antenatal measurement

Table 1 Demographic characteristics of the study population (n=3,612) according to the presence of postpartum anxiety symptoms [a]

	Total (n=3,612)	No postpartum anxiety symptoms (n=3,185, 88.2%)[a]	Postpartum anxiety symptoms (n=427, 11.8%)[a]	Fraction of missing data
Age, mean (min-max)	30.1 (17-45)	30.1	30.1	44.6%
Primiparity[b], n (%)	1489 (41%)	1337 (42%)	152 (36%)	34.3%
Educational level, n (%)[c]	-	-	-	32.5%
Elementary education	18 (<1%)	17 (<1%)	1 (<1%)	-
Lower tracts of secondary education	331 (9%)	282 (9%)	48 (11%)	-
Higher tracts of secondary education	1171 (32%)	1045 (33%)	126 (30%)	-
Higher vocational education	1422 (39%)	1251 (39%)	171 (40%)	-
University education	670 (19%)	590 (19%)	80 (19%)	-
Anxiety level first trimester[bd], mean (SD)	32.52 (8.19)	31.73 (7.50)	38.47(10.38)	19.9%
Anxiety level second trimester[bd], mean (SD)	33.08 (8.94)	31.98 (8.11)	41.22 (10.54)	12.8%
Anxiety level third trimester[bd], mean (SD)	33.17 (8.57)	32.12 (7.69)	41.04 (10.49)	14.5%
Anxiety level postpartum[bd], mean (SD)	32.11 (9.35)	29.55 (5.92)	51.19 (8.06)	19.0%
Depression level first trimester[be], mean (SD)	4.37 (3.39)	4.054 (3.09)	6.86 (4.40)	20.5%
Depression level second trimester[be], mean (SD)	5.02 (3.55)	4.60 (3.17)	8.17 (4.50)	12.9%
Depression level third trimester[be], mean (SD)	4.92 (3.51)	4.52 (3.17)	7.92 (4.39)	14.9%
Depression level postpartum[be], mean (SD)	4.66 (3.77)	3.78 (2.64)	11.18 (4.46)	19.5%

[a] According to six-item State and Trait Anxiety Inventory (STAI), cut-off ≥42, min-max=20-80

[b] Scores were statistically significantly higher in the group with postpartum anxiety symptoms than in the group without postpartum symptoms of anxiety, with p≤0.001

[c] Numbers may not add to the total due to rounding of imputed values

[d] Based on STAI at approximately 14 weeks pregnancy, min-max=20-80

[e] Based on EPDS at approximately 14 weeks pregnancy, min-max=0-30

Table 2 Test characteristics for predicting postpartum anxiety symptoms from antenatal anxiety symptoms **≥42**

	STAI score cut-off ≥42[a]			
	First trimester (n=619, 12.7%)[b]	**Second trimester (n=717, 17.8%)[b]**	**Third trimester (n=650, 13.4%)[b]**	**All antenatal scores above cut-off (n=164, 3.4%)**
Odds Ratio [95% CI]	3.49 [2.61, 4.67]	4.72 [3.78, 5.88]	5.15 [4.21, 6.28]	7.40 [5.24, 10.5]
Odds Ratio [95% CI] [c]	2.67 [2.00, 3.55]	3.73 [2.90, 4.79]	3.96 [3.13, 5.01]	5.64 [3.76. 8.47]
Sensitivity, % [95% CI]	28.7 [25.1, 32.4]	37.7 [33.9, 41.6]	36.4 [32.6, 40.3]	13.0 [10.5, 15.9]
Specificity, % [95% CI]	89.6 [88.6, 90.5]	88.6 [87.6, 89.6]	90.0 [89.0, 90.9]	98.0 [97.6, 98.4]
Positive Predictive Value, % [95% CI]	28.8 [25.2, 32.5]	32.6 [29.2, 36.2]	34.8 [31.1, 38.6]	49.5 [41.5, 57.3]
Negative Predictive Value, % [95% CI]	89.5 [88.6, 90.5]	90.7 [89.7, 91.5]	89.5 [88.5, 90.4]	88.5 [87.5, 89.4]

[a] Based on six-item State and Trait Anxiety Inventory (STAI), min-max=20-80

[b] Number and percentage of women scoring above the cut-off

[c] Including symptoms of depression as assessed by Edinburgh Postnatal Depression Scale (EPDS), min-max=0-30

Table 3 **Test characteristics for predicting postpartum anxiety symptoms from antenatal anxiety symptoms ≥36**

	STAI score cut-off ≥36[a]			
	First trimester (n=1,726, 35.5%)[b]	Second trimester (n=1,801, 37.1%)[b]	Third trimester (n=1,901, 39.1%)[b]	All antenatal scores above cut-off (n=702, 14.5%)
Odds Ratio [95% CI]	2.80 [2.19, 3.57]	4.10 [3.37, 4.99]	3.65 [2.99, 4.47]	4.54 [3.61, 5.72]
Odds Ratio [95% CI] [c]	2.01 [1.57, 2.58]	2.88 [2.30, 3.62]	2.62 [2.06, 3.34]	2.79 [2.21, 3.52]
Sensitivity, % [95% CI]	57.2 [53.2, 61.1]	66.5 [62.6, 70.2]	66.3[62.5, 70.1]	36.4 [32.6, 40.3]
Specificity, % [95% CI]	67.6 [66.2, 69.0]	67.3 [65.8, 68.7]	64.9 [63.4, 66.3]	88.8 [87.8, 89.7]
Positive Predictive Value, % [95% CI]	20.6 [18.7, 22.6]	22.9 [21.0, 24.9]	21.7 [19.9, 23.6]	32.2 [28.7, 35.8]
Negative Predictive Value, % [95% CI]	91.5 [90.5, 92.5]	93.2 [92.3, 94.1]	93.0 [92.0, 93.9]	90.5 [89.5, 91.4]

[a] Based on six-item State and Trait Anxiety Inventory (STAI), min-max=20-80

[b] Number and percentage of women scoring above the cut-off

[c] Including symptoms of depression as assessed by Edinburgh Postnatal Depression Scale (EPDS), min-max=0-30

instances. Seventy-six of these women did not experience postpartum symptoms of anxiety (47.8%). Of all women experiencing symptoms of either anxiety or depression at baseline (n=662, 13.6%), the vast majority experienced specific symptoms of anxiety (n=484, 73.1%), compared to a combination of both anxiety and depression (n=135, 20.4%) or specific symptoms of depression (n=43, 6.5%).

In the total sample, mean levels of anxiety and depression were rather stable (table 1), and did not significantly differ (p=0.168). In women experiencing symptoms of anxiety in the postpartum period, levels did increase significantly between the baseline and postpartum measurements (p<0.001). Parity and all scores of antenatal anxiety or depression differed significantly between women with and without postpartum symptoms of anxiety (p<0.0001, table 1).

Predictive accuracy of STAI

The performance parameters were calculated in all trimesters for several different cut-offs. Table 2 and 3 only show the results for the respective cut-offs ≥42 and ≥36, as the first is the prevailing cut-off, and the latter yielded the most accurate prediction in terms of predictive parameters. The odds ratios ranged from 2.86 [95% CI 2.23, 3.67] at the baseline measurement with cut-off ≥33 to 5.15 [95% CI 4.21, 6.28] at the third trimester measurement with cut-off ≥42. This same trend was observed after adding symptoms of depression to the model, with odds ratios ranging from 1.99 [95% CI 1.56, 2.56] at the baseline measurement with cut-off ≥33 to 3.96 [95% CI 3.13, 5.03] at the third trimester measurement with cut-off ≥42.

For STAI only, the AUC's were only reasonable in the second and third trimester (0.74 and 0.73 respectively)[30]. After adding symptoms of depression to the models, the AUC was below 0.64 in all trimesters.

Furthermore, for the STAI with a cut-off value of ≥42 in the first trimester, the sensitivity was low with 28.7% [95% CI 25.1, 32.4], as was the positive predictive value (28.8% [95% CI 25.2, 32.5]). Specificity and negative predictive values however, were high (89.6% [95% CI 88.6, 90.5] and 89.5% [95% CI 88.6, 90.5] respectively). When we lowered the cut-off to ≥36 in the first trimester, the sensitivity increased to 57.2% [95% CI 53.2, 61.1] and the negative predictive value to 91.5% [95% CI 90.5, 92.5], especially at the expense of specificity (67.6% [95% CI 66.2, 69.0]).

Including only women who scored above ≥42 at all three antenatal anxiety measurements yielded a sensitivity of 13.0% [95% CI 10.5, 15.9] and a positive predictive value of 49.5% [95% CI 41.5, 57.3]. Lowering the cut-off value to ≥36 increased the sensitivity to 36.4% [95% CI 32.6, 40.3], but decreased the positive predictive value to 32.2% [95% CI 28.7, 35.8].

Sensitivity analyses

In general, the results of the complete case analysis were comparable. Sensitivity and positive predictive values appeared to be higher in the complete case analyses, whereas specificity and negative predictive values were slightly lower in the complete case analyses. When using the levels of anxiety in the first trimester as predictor variable and the levels of anxiety in the second trimester as outcome variable, we found a sensitivity of 38.4, specificity of 91.7 and 44.4 and 89.6 for the positive and negative predictive values respectively.

Discussion

Main Findings

In this large prospective cohort study, we found that antenatal symptoms of anxiety are a strong predictor of symptoms of anxiety in the postpartum period. However, although we found reasonable overall discriminatory power in the second and third trimester (AUC 0.74 and 0.73 respectively), we found a low sensitivity for the prevailing cut-off (i.e. ≥42). Lowering the cut-off to ≥36 somewhat improved the predictive performance. For both cut-off values, we found exceedingly high negative predictive values; ≥89% for the cut-off value of ≥42 and ≥91% for the cut-off value of ≥36. This suggests that the prior risk for developing symptoms of anxiety in the postpartum period, i.e. 12.8%, could be nearly halved to 6.8% when using the cut-off of ≥36 in the second trimester. Although the odds ratios were reasonable after adding antenatal symptoms of depression as assessed by the Edinburgh Postnatal Depression Scale (EPDS), they were higher without symptoms of depression.

Interpretation

Our findings appear to be contradictive to the findings of Dennis et al.[12]. They used the STAI with a cut-off of >40, which is comparable to ≥42 due to the scale of the six-item version of the STAI, and concluded that it can very well be used to identify one-week postpartum women who are at risk for symptoms of anxiety seven weeks later (sensitivity 67.5%,

specificity 87.1%, positive predictive value 53.0%, negative predictive value 92.5%). This difference might be due to the time between measurements; Dennis et al. tested intervals of three and seven weeks, whereas the time between the second antenatal and the postpartum measurement in our study was approximately 40 weeks. We therefore performed a sensitivity analysis between antenatal measurements in the first and second trimester, which equalled a time interval of 11 weeks. We then found a more comparable predictive performance (sensitivity 38.4%, specificity 91.7%, positive predictive value 44.4%, negative predictive value 89.6%), although the sensitivity in our analysis was lower, and the specificity was slightly higher. In addition, Dennis et al. stated to accurately classify 84% of all women who either did or did not develop symptoms of anxiety. We found the same percentage in our sensitivity analyses (83.8%) and a similar percentage between the antenatal and postpartum measurements (81.8%). This suggests that the time interval might very well explain the contradiction in findings.

Literature on psychometric properties of the STAI and on postpartum symptoms of anxiety as distinct from depression is growing. The consensus is that having antenatal symptoms of anxiety or depression is a risk factor for developing postpartum symptoms of anxiety or depression. We found high odds ratios in the current study, which substantiate these findings. However, the STAI appeared to have limited predictive accuracy for absolute risk stratification. Although having antenatal symptoms of anxiety may be a risk factor for postpartum symptoms of anxiety as reflected by the high odds ratios, based on antenatal STAI measurements, we are not able to accurately identify individual women with a high risk of postpartum symptoms of anxiety.

In line with a previous study, adding symptoms of depression based on the EPDS did not increase the prediction of postpartum symptoms of anxiety[7]. The authors explain their finding by the low prevalence rate of depressive disorders (9%) compared to anxiety (33%). In the current study, we found that the prevalence of symptoms of depression (range 8.0%-10.4%) was considerably lower compared to rates of anxiety symptoms (range 11.8%-13.4%), which might indicate that depression is not as comorbid in women with anxiety as anxiety is in women with depression[7,31].

In a previous study[22], we found comparable predictive parameters for postpartum symptoms of depression as assessed with the EPDS. Based on our findings and the extensive literature on risk factors of postpartum symptoms depression, we were then able to suggest a strategy on screening options. Unfortunately, this is impossible for postpartum symptoms

of anxiety, as studies on risk factors for such symptoms are scarce. Knowing the potential negative consequences for mother and child, the risk of anxiety in either pregnancy or the postpartum period, as distinct from depression, should be subject to future research.

Strengths and limitations

A few limitations have to be considered in the current study. First, both the STAI and EPDS are self-report questionnaires, and even though both tools are commonly used in the identification of current symptoms of anxiety or depression, it is not possible to diagnose a disorder based on these questionnaires. Second, selection bias may be introduced, as women who are familiar with symptoms of anxiety or depression may be more inclined to participate. This would, however, have led to an underestimation of the found effect. In addition, prevalence rates for mental health problems are higher in a population with lower educational attainment levels[20]. In our sample, there is a significant difference between respondents and non-respondents on this specific characteristic. However, the percentage of women who have completed elementary school or lower tracts of secondary school does not considerably differ between respondents and non-respondents. Also, we found significant differences between respondents and non-respondents on age and antenatal symptoms of anxiety and depression. However, the difference in age was less than a year in absolute numbers and the mean scores on antenatal STAI and EPDS were below cut-off at all measurement waves for both groups. Therefore, we do not think that these differences affected our prevalence rates.

Several strengths have to be taken into account as well. The current study is a large prospective cohort (n=4,856) with a high percentage of women filling out the outcome measurement (74.1%). Moreover, by our knowledge, this study is the first to test the accuracy of the STAI over a considerably long period of time around childbirth, and to include the added value of depressive symptoms based on the STAI in predicting postpartum symptoms of anxiety.

Conclusion

Regardless of the cut-off value used or the trimester of administration, the overall predictive accuracy of the STAI appears to be limited, although we found a reasonable discriminatory power and an exceedingly high negative predictive value. In addition, although lowering the cut-off yielded a reasonable sensitivity and specificity, the positive predictive value was very low (24.3%). We think the STAI is therefore not suitable for absolute

risk stratification in individual women. However, pregnant women scoring below cut-off can be reassured that it is very unlikely that they will develop symptoms of anxiety in the postpartum period. While the potential adverse outcomes in physical and psychological health of both mother and child are relatively well known, future research should focus on the improvement of identifying the risk of antenatal and postpartum symptoms of anxiety as distinct from depression.

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Pregnancy Outcomes after a Maternity Intervention for Stressful EmotionS: the PROMISES study.

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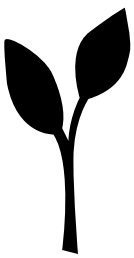


chapter 6

Abstract

Background

There is ample evidence from observational prospective studies that maternal depression or anxiety during pregnancy is a risk factor for adverse psychosocial outcomes in the offspring. However, to date no previous study has demonstrated that treatment of depressive or anxious symptoms in pregnancy actually could prevent psychosocial problems in children. Preventing psychosocial problems in children will eventually bring down the huge public health burden of mental disease. The main objective of this study is to assess the effects of cognitive behavioural therapy in pregnant women with symptoms of anxiety or depression on the child's development as well as behavioural and emotional problems. In addition, we aim to study its effects on the child's development, maternal mental health, and neonatal outcomes, as well as the cost-effectiveness of cognitive behavioural therapy relative to usual care.

Design

We will include 300 women with at least moderate levels of anxiety or depression at the end of the first trimester of pregnancy. By including 300 women we will be able to demonstrate effect sizes of 0.35 or over on the total problems scale of the child behavioural checklist 1.5-5 with alpha 5% and power (1-beta) 80%.

Women in the intervention arm are offered 10-14 individual cognitive behavioural therapy sessions, 6-10 sessions during pregnancy and 4-8 sessions after delivery (once a week). Women in the control group receive care as usual.

Primary outcome is behavioural/emotional problems at 1.5 years of age as assessed by the total problems scale of the child behaviour checklist 1.5 – 5 years. Secondary outcomes are mental, psychomotor and behavioural development of the child at age 18 months according to the Bayley scales, maternal anxiety and depression during pregnancy and postpartum, and neonatal outcomes such as birth weight, gestational age and Apgar score, health care consumption and general health status (economic evaluation).

Trial Registration: NTR2242

Background

The burden of mental disorders is huge and at least comparable to the burden caused by many severe physical diseases. In the WHO Global Burden of Disease project it was estimated that 50% of all daily adjusted life years (DALY's) in the 15-44 years old are due to nine psychiatry-related conditions[1]. Depressive disorders are projected to rank second on a list of 15 major diseases in terms of burden of disease in 2030[2]. In addition, a substantial part of the costs are caused by new cases, which accounts for 39.2% of the costs at population level[3]. Therefore, prevention of mental disorders is essential.

Maternal anxiety or depression during pregnancy is an important and potentially modifiable risk factor for cognitive, behavioural and emotional problems among the offspring children[4-9]. Around 10-20% of all women are suffering from depression or anxiety during pregnancy[10-13]. The magnitude of the effects of maternal anxiety or depression on the child's psychosocial problems is considerable: it is estimated that up to 22% of the variance in behavioural problems is linked with prenatal anxiety, stress or depression[6]. The adverse effects seem to be lasting. For example, antenatal anxiety of the mother was related to behavioural or emotional problems of 4 year old children, independent of the mother's postnatal depression or anxiety[4], and higher anxiety levels of the mothers early in pregnancy were related to an increase in ADHD and other externalizing problems in their 8-9 year old children[14].

There are several mechanisms through which depression or anxiety during pregnancy could have an adverse effect on the offspring. These mechanisms can be divided into direct and indirect. A direct mechanism that has been researched for decades is one in which depression or anxiety activates the maternal stress system leading to elevated glucocorticoid levels, which subsequently influence the development and long-term physiology of the foetus' brain by passing the placenta. This direct mechanism falls under the rubric of "early life programming" and has been a popular hypothesis for the explanation of not only brain disorders but has been suggested to play a role in cardiovascular disease as well[15]. Further, epigenetic variation has been proposed as a mediating mechanism in linking early life exposures to long-term psychological and behavioural outcomes[16].

The effect of maternal stress on the developing foetus might also be indirect. Women who suffer from antenatal depression have the tendency to take less good care of themselves (e.g. neglecting personal hygiene, the occurrence of sleeping problems, disturbed drinking and smoking habits, denying prenatal care). These consequences might all influence the

development of the foetus[17-20]. Another indirect way in which depression might influence the mental development of the offspring is when the antenatal depression remains after delivery and turns into a postnatal depression. In this way, mother-child attachment might be endangered, because the mother has a reduced ability to respond to the child. Children from depressed mothers have a higher risk of insecure attachment, which in turn is associated with cognitive, behavioural and emotional problems[1,21-23]. In addition, the association between antenatal depression and adverse outcomes in the offspring might be indirect because it could be explained by a shared genetic predisposition between mother and child.
Whatever the actual mechanisms involved are, there is presently convincing evidence that children whose mothers suffered from anxiety or depression during pregnancy constitute a high risk group for behavioural and emotional problems. On population level, substantial total mental health gains may be accomplished when depressed or anxious women are adequately treated during their pregnancy, even if the effect size of the treatment is relatively small.

The effectiveness of psychological therapy in the treatment of both depression and anxiety has been shown during the past 50 years, especially for cognitive behavioural therapy (CBT)[24-28]. Although guidelines state that medication is an alternative effective treatment, the safety of antidepressants during pregnancy remains insecure[29]. Still, it is too early to implement CBT for depressed or anxious women to prevent psychosocial problems in the offspring. This is because in the development of such a preventive strategy, demonstration of the causality and size of the effect of the reduction of symptoms of depression and anxiety on child outcomes is a crucial step, a step that has not been taken to date. This knowledge gap will be filled by the results of the present experimental study.

We are currently performing a randomized controlled trial (RCT) among pregnant women with symptoms of depression or anxiety to study the effect of CBT as compared to care as usual (CAU) on the offspring's behavioural and emotional problems. In the CBT arm, we expect more beneficial neonatal outcomes, in particular higher birth weight and less prematurity, which are risk factors for adverse cognitive and behavioural outcomes themselves[8]. We also anticipate reduced smoking and less drinking, with many physical and mental health benefits for the child as a result[20]. Since prenatal depression has shown to be related to postnatal depression, we hypothesize that our intervention will also counter postnatal depression, which in turn will benefit the mother – child attachment[30].

Finally, but not unimportantly, the reduction of symptoms of anxiety or depression during pregnancy and the early postnatal period is valuable in itself. CBT may further provide

for a safer approach to reducing symptoms in pregnancy than antidepressant medication[29]. To date, no such study has been performed as far as we are aware of.

Design

Objective

The aim of the present study is to examine the effect of CBT in women with at least moderate symptoms of anxiety and/or depression at the end of the first trimester of pregnancy, on the extent of total behavioural and emotional problems in their children at 1.5 years of age, as compared with CAU.

Setting

The source population consists of all pregnant women in the Netherlands in the first trimester of their pregnancy. Women are recruited in primary, secondary and tertiary obstetric care. Women are screened for anxiety and depression symptoms at the end of the first trimester of pregnancy. Women with at least moderate symptoms of anxiety and/or depression are either randomized to the intervention group in which they receive 10-14 sessions of CBT, or to the control group in which they receive care as usual. Figure 1 shows the detailed design of the study.

Study outcome measures

The primary outcome in this project is the total emotional and behavioural problems score of the child according to the Child Behaviour Check List 1.5 – 5 (CBCL 1.5-5) at 18 months of age. Secondary outcomes are the child's mental and psychomotor development at 18 months of age, the change in depressive and anxious symptoms in the mother, obstetric variables such as birth weight, gestational age and Apgar score, the socio-demographic and lifestyle factors, such as alcohol use, smoking and education, and cost-effectiveness of the therapy.

Sample size

Studies on the prevention of mental disorders tend to suffer from problems of insufficient statistical power[31]. In the current study we aimed to get around this problem by using a continuous primary outcome measure and by including a high risk group, i.e. selective

prevention.

We decided that effect sizes of 0.35 (midpoint of small – medium effect size) or over on the total problems scale of CBCL 1.5-5 are to be detected. With alpha 5% and power (1-beta) 80%, we have to include 260 participants in our analyses. To account for some drop out we aim at 300 women entering the trial. If 50% eventually meets all criteria and gives informed consent, 600 screen-positives must be identified. The 50% rate is based on studies with psychological interventions during pregnancy aimed at reducing the occurrence of postnatal depression[30]. Given the figures in the literature[12,32] we can expect amply 10% screen-positives on either the anxiety or depression screener. With an estimated 50% comorbidity between anxiety and depression this means that approximately 15% are eligible for the randomisation. Therefore, 4,000 women needed to be screened. Assuming a response rate of 75%[33] this implicates that 5,333 women must be offered screening. To be on the safe side, we aimed at screening 6,000 women. During the trial it appeared that only 25% rather than 50% of all screen-positive women meets all criteria and gives informed consent. Therefore, we adjusted the number needed to screen for including 300 women to approximately 12,000.

Inclusion

Women in obstetric care in the Netherlands with a significant level of anxiety (6 item STAI ≥42) or at least moderate depressive symptoms (EPDS ≥12) in their first trimester were invited to participate in the trial.

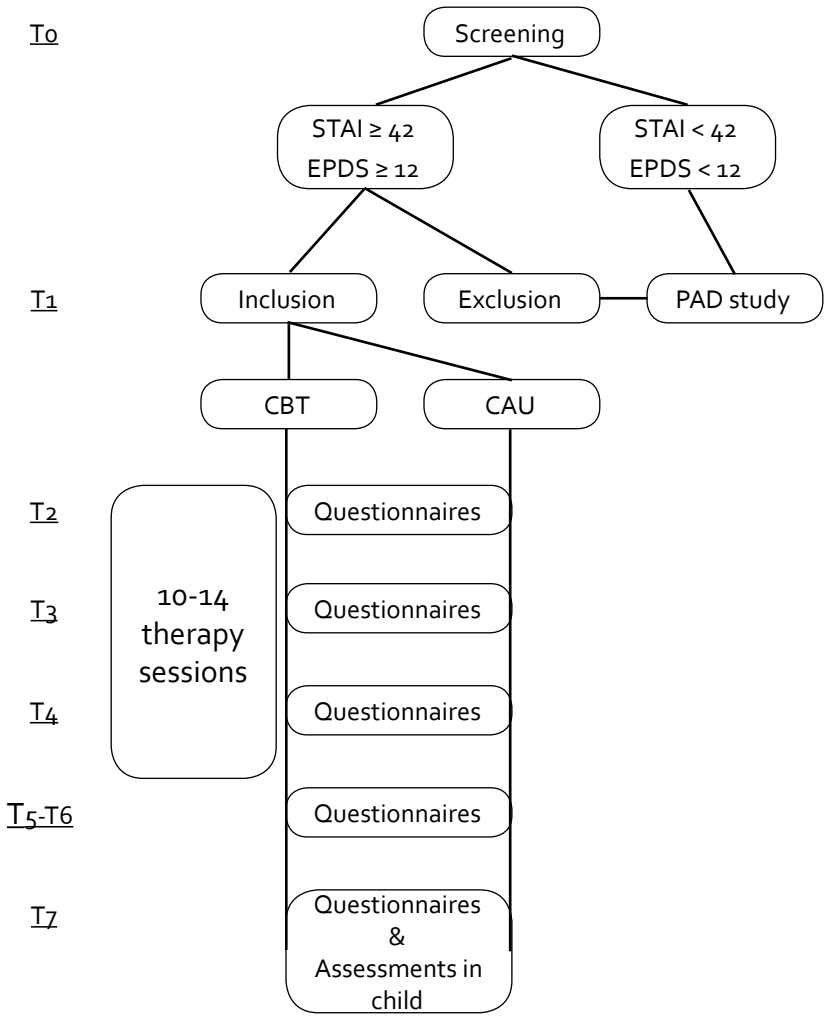
Exclusion

Women fulfilling one or more of the following criteria are excluded from participation:

1. Multiple pregnancy. We decided to exclude women with multiple pregnancy as they have a markedly increased obstetric risk; their inclusion would threaten the homogeneity of the study population and thereby decrease the sensitivity to detect effects.
2. High suicidal risk according to the suicidality subscale score on the MINI International Neuropsychiatric Interview (MINI, defined as a positive response on the question on concrete suicide plans)
3. Presently receiving psychotherapy
4. Substantial physical disease or illegal substance abuse
5. No mastery of the Dutch language
6. Having a psychiatric history on bipolar disorder, psychoses and manic disorder
7. History of in vitro fertilization

Due to a lower than expected response rate after commencement of the trial we decided to also include participants in hospitals to increase the eligible study population, as opposed to only including participants in primary care. This implied that we decided to no longer exclude multiple pregnancies and women with a history of in vitro fertilization.

Figure 1 Flow diagram



Assessments

Participating women are asked to fill out questionnaires until their child is 1.5 years. This is done at eight time points: the screener at baseline (T0), the additional baseline information (T1), and follow-up questionnaires at 24 and 36 weeks of gestation (T3 and T4), at 6 weeks postpartum (T5), 6 months postpartum (T6), 12 months postpartum (T7) and 18 months postpartum (T8).

At each time point, the levels of anxiety and depression are monitored by the STAI and the EPDS. As depicted in table 1, all other questionnaires are filled out once or at several time points. For anxiety, we use the Dutch version of the 6-item State Trait Anxiety Inventory (STAI). This self-report questionnaire is as valid as the full 20-item version and has frequently been used to measure antenatal anxiety[32]. For the screening on depression we use the Edinburgh Postnatal Depression Scale (EPDS), which has 10 items[34]. This is the most frequently used self report depression screener in the postnatal period as well as during pregnancy and has been found particularly valid during pregnancy because this scale omits somatic symptoms[33].

The following information is obtained from participants. The exact time of administration of the corresponding instrument can be found in figure 2.

- Life events before pregnancy are assessed at baseline, using the Negative Life Events Questionnaire (NLEQ)[35].
- Perceived social support is measured according to the 9-item Social Support Questionnaire (SSQ)-short form[36].
- General health, socioeconomic position, ethnicity, smoking behavior, alcohol use, psychiatric history (whether the participant has had depression and/or anxiety symptoms before, whether she was treated for this and whether she is presently in treatment for these symptoms is assessed. Socioeconomic position is measured using five indicators: family income, educational level (father and mother), and occupational level (father and mother). This questionnaire is based on a questionnaire used in the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project, www.lrgp.nl). General health status will also be taken into account according to the EQ-5D[37].
- Personality is assessed using the NEO Five Factor Inventory (NEO-FFI). The NEO-FFI is a shortened version of the NEO-PR-I[38] and covers the Big Five of personality (neuroticism, extraversion, openness, altruism and conscientiousness). These aspects each contain 6 subscales. The NEO-FFI contains 60 questions, 2 on each subscale. The present study will add 4 full subscales to the short version; two subscales of neuroticism, one

of extraversion and one of conscientiousness. This is because we expect them to have the strongest association with persistence of depression and/or anxiety. The NEO-FFI is translated and validated in Dutch[39].

- Information on previous pregnancies, family size and composition, pregnancy related life events and on reactions on becoming a parent is gathered using questionnaires from the ALSPACstudy (www.bristol.ac.uk/alspac).
- Suicide risk is measured using six screening questions from the MINI International Neuropsychiatric Interview[40].
- Maternal attachment style is measured according to the ECR[41], which has been translated and validated for the Netherlands by Conradi et al.[42].
- Health care consumption is assessed based on the TIC-P[43]. This instrument allows reliable recall over the past 6 months[44].
- Coping style is assessed using the Utrechtse Coping Lijst, the UCL[45].
- A Dutch version of the Dysfunctional Attitude Scale (DAS) is used to measure cognitions and attitudes[46].
- Obstetric variables such as gestational age, birth weight, Apgar score, complications such as (pre)eclampsia or HELLP, which is obtained from midwifes. Women are asked to give consent for this.
- Finally, we use the SCID-II to screen for a possible clinical depressive or anxiety disorder[47]. The SCID-II is the only questionnaire used that has to be taken in a personal interview.

Besides questionnaires for the mother during her pregnancy and the first 1.5 years postpartum, there are assessments of the child at 1.5 years of age. One of the assessments concerns the Bayley Scale of Infant Development (BSID-II)[48]. This is a formal neuropsychological tool to assess the developmental level of a child between 1 and 42 months. It is individually administered by one of the researchers and consists of 3 subscales: cognitive development (mental development index), gross and fine motor development and the behavioural rating scale. This tool is widely used in both research and clinical settings and is considered the best and most applied method for the assessment of the child's development to date[49]. Importantly, the instrument has shown to be sensitive. In the context of our proposal, maternal anxiety in pregnancy explained as much as 11% of the variance in the Bayley scores in a study among two year old toddlers by LaPlante et al.[50].

The second assessment is the Child Behaviour Check List 1.5 – 5 (CBCL 1.5-5) including the Caregiver-Teacher Report form (C-TRF) and the Language Development Survey (LDS)[51].This

well established, reliable and valid scale designed for parents and caregivers comprises seven syndrome scales: emotionally reactive, anxious depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive problems. In addition, it contains scales for internalizing, externalizing and total problems. Symptom scores may further be related to formal DSM-diagnostic criteria. The LDS provides a screen for delays in vocabulary and word combinations.

For the assessment of psychopathology in preschool children it is essential to obtain information from different sources[52]. Therefore we decided to include the C-TRF for the caregivers of the children other than their parents. Parents are asked to hand these lists to the actual caregivers of their children, e.g. grandparents, baby-sitters, kindergarten-coaches, et cetera. Relevant in this respect, a review by Skovgaard[49] underlined the significance of both the developmental aspects (e.g. as measured with the BSID II) and the infant caregiver relation in the assessment of children 0-3 years of age.

The CBCL has been used successfully in several studies, amongst others on externalizing problems[50]. It has been translated and standardized for use in around 60 countries, including the Netherlands. The CBCL 1.5-5 is considered a sensitive instrument also deployed in current intervention studies[54,55].

Also, mother-child interaction are measured by taping them for 15 minutes on video and scoring them afterwards on interaction points.

Additional baseline data

Women agreeing to participate are asked to provide additional baseline data at T1, as to find in table 1. About half of these questionnaires are sent to the participants in print, the other half can be answered online. All follow-up questionnaires are available online. After providing baseline data both in print and online, women are telephoned for the Structured Clinical Interview for DSM-II Disorders (SCID-II). The SCID-II will allow us to study treatment effects additionally according to diagnostic categories rather than symptom levels.

Table 1 Assessments per measurement

	T0	T1	T2	T3	T4	T5	T6	T7
Depression (EPDS)	X	X	X	X	X	X	X	X
Anxiety (STAI)	X	X	X	X	X	X	X	X
Personality NEO-FFI		X		X		X		
Life events before pregnancy (NLEQ)		X						
Life events during pregnancy		X		X		X		
Perceived social support (SSQ)		X						
Coping styles (UCL)		X	X	X	X			
Attitudes (DAS)		X	X	X	X			
Maternal attachment (ECR)		X					X	
Quality of life (EQ-5D)		X	X	X	X	X	X	
Sociodemographic & -economic factors		X						
Lifestyle		X		X		X		
Breastfeeding						X		
General health		X						
Health care consumption		X			X	X	X	
Previous pregnancies		X						
Suicidality (MINI)		X						
Clinical Diagnostic Interview (SCID-II)		X						
Child Behaviour (CBCL)								X
Child development (BSID-II)								X

Randomisation

Right after the SCID-II interview, women are randomised 1:1 to either CBT or CAU. We will create randomisation lists, stratified for parity and socio-economic position, with randomly permuted blocks of random size. Women randomized to the CAU arm are informed about being at risk of depression or anxiety disorder by the researchers and are advised to contact their GP. A close record is kept of all care provided in the CAU arm.

CBT Intervention

The intervention consists of 10-14 individual sessions: 6-10 sessions during pregnancy and 4-8 sessions after delivery (once a week). The CBT is conducted by registered psychologists, specialized in conducting CBT.

CBT posits that an individual's biased information processing leads to maladaptive feelings and behaviours which can culminate in psychological distress and eventually in psychiatric disorders. The main focus of the proposed intervention is targeted on identifying and changing dysfunctional cognitions and schemata (attitudes) specifically for pregnant depressed and anxious patients. In CBT, the Socratic dialog is used aiming to change these dysfunctional cognitions and attitudes permanently. CBT may therefore result in long term protection against psychosocial problems. It is therefore not surprising that cognitive therapy during the acute phase of depression also appears to be effective in reducing subsequent recurrence rates[28].

The first session will focus on the rationale CBT, i.e. the influence of (irrational or dysfunctional) cognitions and attitudes on feelings and behaviours. Additionally, goal setting is initiated. These therapy goals are unique for each patient. The subsequent sessions are targeted at identifying and amending irrational cognitions and attitudes related to pregnancy, delivery, concerns about the (unborn) child and the future family situation. Each session will address specific pregnancy-related cognitions. Additionally, patients are taught how dysfunctional cognitions and attitudes affect adversely feelings and behaviours.

These dysfunctional cognitions and attitudes are challenged and replaced by functional cognitions and attitudes. After each session, patients are given home work. For example, patients are asked to register negative experiences, and accompanying cognitions, feelings and behaviours. Finally, in the last two to four sessions, the newly learned cognitions and attitudes are consolidated.

Data analysis

If necessary, skewed continuous variables will be transformed to normality prior to the analyses. The primary outcome, i.e. the CBCL scores at month 18, will be compared between the treatment arms using the unpaired t-test. This test will also be used for detecting differences in the Bayley scores by month 18 and the obstetric variables measured at birth. The latter group of variables will be tested using the Chi^2 test if categorical. Differences in attachment style at month 12 will be analyzed using analysis of covariance with the baseline variable as a covariate. Continuous outcomes that were measured more than twice (e.g. EPDS and STAI) will be analyzed as dependent variables using linear mixed models for fixed and random effects. These models are superior for the analysis of longitudinally correlated data and can optimally deal with missing values[56]. A mixed model ascribes a unique intercept and slope estimate to each individual, while making use of information across individuals for predicting these quantities. In these analyses, a treatment*time variable indicating the effect of the intervention will be included as an independent variable. If despite randomisation important baseline differences exist in prognostically important variables such as the extent of social support or history of life events, they will be adjusted for. Additional analyses will be conducted to demonstrate mediation of the effect of CBT on the child's outcomes by maternal symptom level, alcohol or nicotine consumption in pregnancy, medication use or neonatal outcomes.

The analyses will primarily be carried out according to the intention-to-treat (ITT) principle, i.e. the participants will be analyzed according to their randomized allocation, regardless of the actual CBT undergone, or time in study after baseline. Aside from the optimal validity of ITT analyses, they quantify the effects on the outcome measures that would be obtained in practice. The magnitude of the effect measured in an ITT analysis incorporates the effects caused by non-adherence to CBT, behavioural changes, et cetera. Secondary analyses will be of the 'per protocol' type meaning that they will be restricted to those women that had all of the CBT sessions.

Considering specific target populations, there is evidence that the socio-economically deprived may have more benefit from treatment of depression during pregnancy[18]. Therefore, subgroup analyses will be undertaken according to socio-economic position. Subgroup analyses will also be undertaken according to parity.

Differences in effect of CBT between subgroups will be statistically evaluated by testing treatment by subgroup interaction terms. Effect parameters will be supplied with a 95%

confidence interval.

Economic evaluation

An economic evaluation will be conducted alongside the trial to assess the cost-effectiveness of CBT compared to care as usual in the current study population. Information on costs and health outcomes will be prospectively collected during 24 months (starting at baseline until 18 months after birth) for both mother and child. Two complementary economic analyses will be conducted. The primary outcome measure of the planned cost-effectiveness analysis is the total emotional and behavioural problems score of the child according to the CBCL at 18 months of age.

In the additionally planned cost-utility analysis, QALYs (Quality Adjusted Life Years) will be used as the primary outcome measure. The study will be performed from a societal perspective. Medical costs that will be assessed include costs related to CBT, contacts with healthcare professionals, and medication use. Outside the healthcare sector, costs of informal care and productivity losses will be taken into account. Unit prices will largely be based on Dutch standard prices in order to facilitate comparisons with other economic evaluations. Cost-effectiveness acceptability curves will be used to inform decision-makers on the probability that the studied intervention is cost-effective.

This study protocol was approved by the medical ethical committee of the University Medical Center Groningen.

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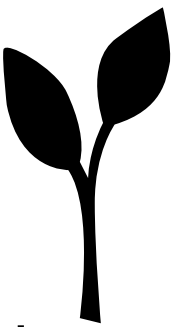
general discussion



chapter 7

Introduction

Symptoms of anxiety and depression during pregnancy and postpartum pose a major public health problem, as these symptoms are prevalent and can have serious consequences for the mother, her family and the (unborn) baby. Although literature on antenatal and postpartum anxiety and depression is extensive, there is a gap in knowledge on the influence of specific life events on the development and course of symptoms of anxiety and depression in the antenatal and postpartum period, and on accurate antenatal screening methods for postpartum symptomatology. As there is no evidence yet that personalized psychosocial screening methods and treatment interventions are effective, current screening methods do not allow for specific risk factors per woman. This thesis tried add to the existing literature in order to bridge this gap in the future.

We designed a cohort study (n=7,275) and within this cohort we set up a randomized trial (n=300). In the cohort, we included pregnant women in the Netherlands in the first trimester and followed them until approximately six months postpartum. Women with symptoms of anxiety or depression in the first trimester of pregnancy were invited to participate in the trial, in which they were randomized into a care as usual or a treatment group that received CBT, and were, or will be, visited by a research assistant to have their 1.5 year old child tested on its development.

Main findings

We found that prevalence rates of anxiety and depression are comparable in the antenatal and postpartum periods (chapters 2 – 5), which is in line with existing literature. We found that women with high levels of anxiety or depression in early pregnancy have an increased risk on high levels of anxiety or depression in late pregnancy and in the postpartum period (chapters 2 and 3), whereas women with low levels of anxiety or depression in early pregnancy are unlikely to experience these symptoms in the postpartum period (chapters 4 and 5). Additionally, women with symptoms of depression in early pregnancy are more likely to experience more symptoms of depression in the postpartum period when they are confronted with a life event in the meantime (chapter 3). During pregnancy, specificity of life events plays a major role (chapter 2); symptoms of anxiety increase after an event that is specifically related to the pregnancy or the unborn child, whereas symptoms of depression increase after events that are more general in nature. Based solely on the antenatal levels, it is unfortunately not yet possible to accurately predict the individual risk on having postpartum

symptoms of anxiety and depression (chapters 4 and 5), though women with no to very mild symptoms can be reassured that it is very unlikely that they will develop postpartum symptomatology. Therefore, screening in the first trimester may be the first step of a two-stage screening, subsequently followed by questions on other well-known risk factors for postpartum symptomatology (chapter 4).

Although a considerable number of women experience symptoms of anxiety or depression around childbirth, and a brief, reliable, self-report antenatal screening instrument to predict the likelihood of minor or major postpartum anxiety or depression would facilitate midwives and gynaecologists in daily clinical practice[1], the results of this thesis and the state of the art in literature raise questions on whether early screening for an increased risk of postpartum anxiety or depression should already be recommended This is not a new topic in the field. Several systematic reviews are available on the subject, but differ in their findings, and RCTs on the efficacy of a screening tool are inconclusive. At the same time, guidelines on antenatal maternal care often recommend screening, though they acknowledge that this recommendation is not based on a firm body of evidence[2,3].

The general discussion of this thesis therefore applies the criteria as set by Wilson and Jungner[4] and the WHO[5] to formulate a recommendation on antenatal screening for postpartum anxiety and depression. The criteria can be found in box 1. Some will be discussed separately, others are combined.

Box 1 Criteria Wilson & Jungner, and WHO

Condition and test

1. The condition sought should be an important health problem.
2. The screening programme should respond to a recognized need. (rev)
3. There should be a recognizable latent or early symptomatic stage.
4. The natural history of the condition, including development from latent to declared disease, should be adequately understood
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.

Treatment

7. There should be an accepted treatment for patients with recognized disease.
8. There should be an agreed policy on whom to treat as patients.

The programme

9. Case-finding should be a continuing process and not a "once and for all" project.
10. There should be a defined target population. (rev)
11. The programme should promote equity and access to screening for the entire target population. (rev)
12. The objectives of screening should be defined at the outset. (rev)
13. Programme evaluation should be planned from the outset. (rev)
14. The programme should integrate education, testing, clinical services and programme management. (rev)
15. The programme should ensure informed choice, confidentiality and respect for autonomy. (rev)
16. Facilities for diagnosis and treatment should be available.
17. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
18. There should be scientific evidence of screening programme effectiveness. (rev)
19. There should be quality assurance, with mechanisms to minimize potential risks of screening. (rev)
20. The overall benefits of screening should outweigh the harm. (rev)

Condition

For the purpose of this discussion, the following two criteria are combined; the condition sought should be an important health problem (1) and the screening programme should respond to a recognized need (2)

Mental health problems are known to have a high burden of disease. In fact, unipolar depressive disorder was ranking fourth in the list of leading causes of burden of disease in 2002, and it has been estimated to be ranking second in 2030, next to HIV/AIDS (rank 1) and ischemic heart disease (rank 3)[6]. Prevalence rates for depression are ranging from 5% to 10% and up to 20% for anxiety[7,8]. Women of reproductive age are known to be highly vulnerable for the development of anxiety and depression, as incidence rates are highest amongst women 18 to 45 years of age[9-14]. Thus it is no surprise that anxiety and depression occur frequently in pregnant or recently pregnant women, and that prevalence rates are comparable[15-18]. The context however accounts for a substantial difference.

Numerous studies showed that anxiety and depression in the antenatal and postpartum periods can have serious consequences for mother and child. Women with mental health problems are generally less inclined to take care of themselves and to get prenatal care which in turn might influence the development of the fetus[19-21]. Several studies have shown that antenatal anxiety and depression are associated with preterm delivery and low birth weight[23-25], as well as adverse cognitive, behavioral, and motor development in the child[25,26-30]. Anxiety or depression in the postpartum period can result in insecure mother-child attachment, which in turn can result in emotional and behavioral problems in the child and subsequently in psychopathology in adults[10,31,32]. Additionally, mental illnesses are costly to the society. It has been estimated that in 2003, major depression has cost the Netherlands €1.8 billion[33]. This includes costs for diagnosis and treatment, but also productivity loss.

This all has been the starting point for the PROMISES trial in 2009: the above-mentioned observational studies had shown the association between subsyndromal antenatal symptoms of anxiety and depression, and adverse somatic and psychological outcomes in the child, but the causal mechanism behind this had at that time not been found yet. From a public health perspective, it is important to unravel this mechanism in order to prevent future incident adult cases of psychopathology by decreasing the antenatal anxiety and depression levels in women. Although this may not have a high impact on the individual level, it may result in a reduced burden of psychiatric disease on the population level.

Given the high number of women who will experience symptoms of anxiety or depression in the antenatal or postpartum period, the burden it holds and the consequences it can have for herself, her baby, her family and society, anxiety and depression around childbirth should be considered important health problems.

Two criteria are combined; there should be a recognizable latent or early symptomatic stage (3), and the natural history of the condition, including development from latent to declared disease, should be adequately understood (4)

One way to consider depression is as a continuum, with no symptoms on one end and a major depression on the other end[34,35]. A subclinical depression, i.e. having depressive feelings but meeting less than five of the nine criteria or not meeting either one of the two core symptoms, can be found somewhere in between. It could develop into a depressive disorder, and although a subclinical stage almost always precedes a major depression, it is not necessarily an early symptomatic stage[36]. However, symptoms of depression are not exclusive for a depression; loss of interest, sleeping problems, change in dietary patterns or loss of libido can occur without being a symptom of depression. In the antenatal and postpartum period it may be more complex, as these symptoms can also relate to early pregnancy or the postpartum period.

We found that using the prevailing cut-offs for both anxiety and depression levels, sensitivity was low. The number of false positives was thus considerable, indicating that a substantial number of women with antenatal symptoms above a certain threshold did not experience symptoms above cut-off in the postpartum period. The percentage of false positives on the EPDS ranged up to 74%, and up to 70% on the STAI. Another finding of the thesis is that specific categories of life events during pregnancy are associated with increased levels of anxiety and depression in late pregnancy and the postpartum period. Although this may not be a sufficient cause, experiencing life events do add to the occurrence or persistence of anxiety and depression. A two-stage screening integrating both findings may be helpful. The first stage would be current antenatal symptomatology, followed by a more elaborate assessment of established risk factors. These include specific types of life events, social support or childhood trauma. Previous symptomatology and mental disorders may be the strongest predictor; a question on previous mental illness should thus certainly be included in the second step. Such a stepwise approach has been suggested previously for depression[37,38].

Concluding, it can be difficult to recognize an early stage of depression, especially in the antenatal and postpartum period. And though an accurate tool for a reliable prediction on who will develop postpartum anxiety or depression symptoms is not yet developed, there may be possibilities in a two-stage screening, including a 10-item self-report screening in the first step, followed by assessing other risk factors.

Two criteria are combined; there should be a suitable test or examination (5), and the test should be acceptable to the population (6)

Current symptoms of anxiety or depression in the antenatal or postpartum period can be identified using the 6-item State and Trait Anxiety Inventory (STAI)[39] and the 10-item Edinburgh Postnatal Depression Scale (EPDS)[40], respectively. Both questionnaires are self-report, are widely used to identify current symptomatology, and have shown to have good validity in samples of pregnant and postpartum women[39] (i.e. the ability to separate women with anxiety or depression from those without). However, for both the STAI and the EPDS, the number of true positives is low, indicating that the tests do not allow for risk estimation for future symptoms based on current symptomatology.

Due to the limited questions of the STAI and EPDS, and therefore the limited investment of time, both tests are acceptable to the women answering the questions, but are not sufficiently accurate and therefore not suitable in the antenatal detection of a high risk of postpartum symptoms of anxiety or depression.

Treatment

There should be an accepted treatment for patients with recognized disease (7)

Moderate to severe depression is commonly treated with either antidepressants, psychological therapy or a combination of both[2]. In pregnancy, women generally prefer psychological treatment[41], mostly because of the uncertainties about the safety of pharmacological therapies for the health of the unborn baby. The U.S. Food and Drug Administration system has classified most antidepressants into risk category C, indicating adverse fetal effects in animals. Literature on fetal effects of antidepressants in humans is inconclusive[42,43].

Several types of psychological therapy exist, e.g. interpersonal therapy, psychoanalysis,

Eye Movement Desensitization and Reprocessing (EMDR) and cognitive behavioral therapy (CBT), of which most have been extensively studied on its effectiveness in preventing and treating anxiety and depression. The efficacy of CBT for preventing and treating anxiety and depression is well-established[44-46]. However, studies on the effectiveness of CBT in depressed pregnant women are scarce. A recent systematic review found that CBT is effective in prevention and treatment of depression in the antenatal and postpartum period, although interventions were most effective when initiated postpartum[47]. Although this review included 40 randomized and quasi-randomized trials, only two trials included pregnant women who were offered individual CBT in the antenatal and postpartum period. These studies, however, were inconclusive in their results[48,49]. In other words, studies that can prove whether or not the general pregnant population with either subsyndromal or clinical levels of anxiety, depression or posttraumatic stress can benefit from CBT have yet to be performed. Currently, all women in the PROMISES-trial have delivered their babies. The first results on the effect of CBT on pregnant women can therefore be expected later this year.

Whether CBT is an accepted treatment for all pregnant and postpartum women without an urge to seek help, needs to be studied further, as 44% of the sample did not have a mental disorder, but subsyndromal symptoms.

Of all eligible women experiencing either symptoms of anxiety or depression or anxiety disorders and/or a depressive disorder and/or posttraumatic stress disorder at baseline (n=896, 12% of all screened women), 269 (30%) decided to participate. Reasons women gave for not participating were mostly practical in nature, e.g. care for other children or difficulties combining therapy and work. Another frequently heard reason was about the nature of the symptoms. Some women attributed their fatigue and loss of interest to pregnancy. Other women acknowledged that they were experiencing these symptoms, many of them had been in therapy before, but they did not want to do something about it during pregnancy, as they were afraid they would then not be able to enjoy the pregnancy.

Concluding, although anxiety disorders, depressive disorder and posttraumatic stress disorder in general can effectively be treated with psychotherapy such as cognitive behavioral therapy, there is mixed evidence for the effect in treating pregnant women. Additionally, a considerable number of women who were screened indicate that they do not want to be confronted with the issues behind their symptoms in the antenatal period, thus it cannot be stated that the treatment that is available is also an accepted treatment by the patient population. This should be taken into account when studying the effectiveness of the

treatment during pregnancy.

There should be an agreed policy on whom to treat as patients (8)

Relatively clear-cut criteria are available for the diagnosis of an anxiety or depressive disorder, as well as guidelines on treatment for these patients. Also, efficacy of preventive treatment for an anxiety or depressive disorder has been well-established[44-46], especially in high risk groups in the general population, such as individuals with subclinical symptoms. Subclinical symptoms in the antenatal and postpartum period may be difficult to recognize due to the similarity to symptoms related to the pregnancy as mentioned before (criteria 3 and 4). Also, there is no valid tool available yet that accurately identifies pregnant women at risk for developing a postpartum anxiety or depressive disorder. Altogether, this could make it more difficult to start the treatment while symptoms are (still) mild.

Additionally, the focus in health care is shifting towards precision or personalized medicine. As a depressive disorder can be diagnosed with 227 possible combinations of symptoms[50], it might provide a good basis for precision treatment. Although this is promising, current empirical evidence is lacking on whether personalized treatment based on individual symptom profiles is more effective than the current standard evidence based treatment.

The program

Case-finding should be a continuing process and not a "once and for all" project (9)

As pregnant women in the Netherlands who do not attend a midwife or gynecologist are exceptional, it is possible to screen pregnant women on their risk for postpartum anxiety or depression in the prenatal health care system. A screening program can therefore quite easily be implemented as a continuing process. However, even though midwives acknowledge the potential risks of antenatal anxiety or depression for mother and child, the slow inclusion rates in the PAD-study showed that midwives found it difficult to screen all pregnant women at the first consult. Based on the number of new clients per month per participating midwifery center, we had estimated to be able to screen 6,000 women in 36 midwifery centers in one year. After one year however, we had screened 1,400 women, and the 6,000th women was screened almost 3 years after the start, when we had expanded the number of collaborating

midwifery centers to 100. We conducted a survey amongst midwives to learn about their motivation for collaborating in the PAD- study. We found that they thought the study subject was very important, but that their time schedules were so tight that they forgot about the screening. This may be a problem when screening for anxiety and depression will become part of the protocol.

Two criteria are combined; there should be a defined target population (10), and the programme should promote equity and access to screening for the entire target population (11)

An obvious target population to screen in order to prevent postpartum anxiety and depression would be pregnant women attending a midwife or gynecologist. However, as incidence of anxiety and depression is highest in all women 18-45 years of age, there is reason to advocate that pregnancy and childbirth may be a necessary but not a sufficient cause. Considering also the potential consequences of antenatal anxiety and depression for mother and child, it would therefore be desirable to identify and treat women with an increased risk of developing anxiety or depression that could persist into the antenatal and postpartum period before pregnancy. Women with a desire for pregnancy are however not as easy to find as pregnant women, as they are not as regularly attending health care. Also, although they have a desire to become pregnant, they may not actually get pregnant.

Concluding, considering the potential consequences of antenatal and depression for mother and child, it is desirable to screen and treat in women with a desire to become pregnant. As this would result in other problems such as treating women for a disorder they could never experience, a perfectly eligible target population remains undefined.

Although one of the main objectives of the PAD-study was to screen women in the first trimester of pregnancy on symptoms of anxiety and depression, it was not designed as a screening program for future symptoms that would be implemented in usual care, but as a research program. The criteria were thus implicitly taken into account, and discussed together.

The objectives of screening should be defined at the outset (12), programme evaluation should be planned from the outset (13), the programme should integrate education, testing, clinical services and programme management (14), and the programme should ensure informed choice, confidentiality and

respect for autonomy (15)

When implementing an antenatal screening program for postpartum anxiety and depression in usual care, this will also automatically be taken care of, as health care professionals highly value confidentiality and informed choice. The specifics of the provided information however should be considered carefully, as informing pregnant women that elevated antenatal stress levels is associated with adverse outcomes in the unborn child, may actually induce stress.

Additionally, as screening can be considered an intervention, it is important to evaluate the effectiveness of the program, as well as the feasibility for health care professionals that have to work with it and women who are screened and maybe treated. In the PAD- and PROMISES-studies, we did not plan on evaluating the screening.

Regarding the informed choice criterion, The PROMISES-study showed that approximately 70% of all women with elevated anxiety or depression levels did not want to participate in the trial as they felt it was not the right time. Additionally, approximately 10% of women randomized into the treatment arm dropped out right after randomization, mainly because they thought the treatment would be too burdensome.

Concluding, it is only ethical to fully inform women of the reasons for screening and the follow-up protocol, but most women will presumably not start therapy after being identified to present with elevated scores of anxiety or depression. This may be tackled by adding one simple question to the screening tool; 'would you be willing to seek professional help for your problems?'.

Two criteria combined; facilities for diagnosis and treatment should be available (16), and the cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole (17)

Obstetric health care centers and psychologists are usually available nearby every town in the Netherlands. Midwives and gynecologists can be trained in the screening program, though the actual implementation of the program in their daily routine will be more complicated. When scores of antenatal anxiety or depression are elevated, psychologists can start treatment. This may be the largest obstacle, as women are not actively seeking for help, but are indicated to start therapy. Moreover, in the current Dutch health care system, they have to pay at least part of the psychological therapy themselves.

Regarding the financial aspects, many women will be treated who would not have developed the disease, as we are currently not able to accurately predict an individual risk on postpartum anxiety or depression based on their antenatal levels. In fact, based on the STAI ≥36 and EPDS ≥5, approximately 80% of all women solely experienced symptoms in the antenatal period.

Concluding, although facilities are physically available, it will be difficult to implement and very costly as most antenatal anxiety and depression symptoms did not persist into the postpartum period.

There should be scientific evidence of screening programme effectiveness (18)

Guidelines on antenatal maternal care often recommend screening but acknowledge this recommendation is not based on a firm body of evidence[2,3]. A recent systematic review showed that literature on the effectiveness of a screening program for antenatal and postpartum depression is inconclusive[51]. Most studies investigated efficacy of the treatment, rather than the screening per se. According to the review conducted by Thombs, only one study randomized women before screening[52], which found that postpartum screening was effective in preventing postpartum depression.

Concluding, scientific evidence showing effectiveness of an antenatal screening program for the risk of postpartum symptomatology is currently lacking.

Two criteria combined; there should be quality assurance, with mechanisms to minimize potential risks of screening (19), and the overall benefits of screening should outweigh the harm (20)

As approximately 80% of women who experience antenatal symptoms will not experience postpartum symptoms, there is a considerable risk in treating women who would not have developed the disorder at all. Moreover, if antenatal stress results in adverse outcomes in the child, identifying women with antenatal stress by screening in the first trimester may already be too late. The main benefit of screening for current symptomatology by using the STAI and EPDS lies in the reassurance of women with no symptoms in the antenatal period, as it is highly unlikely that they will experience symptoms of anxiety or depression in the postpartum period.

Conclusion & Future Directions

Anxiety and depression affect approximately 15% of all women of reproductive age, including women in the antenatal and postpartum periods. Mental health problems are known to be burdensome for the patients and their families. Having such symptoms in this unique period in life may have a larger impact. Several studies suggest that antenatal symptomatology can have serious consequences for mother and child. Dutch guidelines for midwives therefore recommend to assess personal or family history and to be continuously alert on symptoms of depression. International guidelines on antenatal maternal care often recommend psychological screening, but they acknowledge that they do not base this recommendation on a firm body of evidence. Accordingly, scientific evidence showing effectiveness of an antenatal screening program for the risk of postpartum symptomatology is currently lacking. Scientific evidence on treatment following identification of a high risk in this particular target population is not conclusive either.

The current thesis adds that treating all women with an increased risk of postpartum symptomatology based solely on antenatal levels would result in treating women of whom a majority would not have developed symptoms. Moreover, although the Dutch antenatal health care system is organized in such a way that implementing a screening program would not be very complicated, midwives and gynecologists have very tight schedules, and pregnant women are generally unwilling to be confronted with their symptoms.

On the other hand, there is consensus in literature on risk factors for onset and persistence of anxiety and depression, e.g. previous symptomatology and mental disorders, the experience of a major life event, certain personality traits and low social support. Also, several tools are accurate in identifying the likelihood of current anxiety or depressive disorders. The thesis at hand found that these tools are not fully suitable for risk stratification for postpartum symptomatology. Though women with none to very low levels of anxiety or depression can be reassured that it is very unlikely that they will develop symptoms in the postpartum period, it is uncertain what course can be expected for a woman with at least mild symptoms. Screening on antenatal symptomatology may however still be a good first step in a two-stage screening program. The first stage would be current antenatal symptomatology and mental disorders and the simple question 'would you be willing to seek professional help for your problems?', followed by a more elaborate assessment of the established risk factors when scoring above a certain threshold, including at least an assessment of previous symptomatology or mental disorders.

According to the criteria as set by Wilson and Jungner and the WHO (box 1), there are too many uncertainties for a heartfelt 'yes' on whether an antenatal screening program for postpartum

symptomatology would be beneficial. There are however several leads for future studies, starting with the results of the PROMISES-trial on the effect of the CBT on the children.

Condition and test		
1.	The condition sought should be an important health problem.	Yes
2.	The screening programme should respond to a recognized need. (rev)	Maybe
3.	There should be a recognizable latent or early symptomatic stage.	Maybe
4.	The natural history of the condition, including development from latent to declared disease, should be adequately understood	Maybe
5.	There should be a suitable test or examination.	Not yet
6.	The test should be acceptable to the population.	Yes
Treatment		
7.	There should be an accepted treatment for patients with recognized disease.	No
8.	There should be an agreed policy on whom to treat as patients.	No
The programme		
9.	Case-finding should be a continuing process and not a "once and for all" project.	Yes
10.	There should be a defined target population. (rev)	No
11.	The programme should promote equity and access to screening for the entire target population. (rev)	Yes
12.	The objectives of screening should be defined at the outset. (rev)	No
13.	Programme evaluation should be planned from the outset. (rev)	No
14.	The programme should integrate education, testing, clinical services and programme management. (rev)	Yes
15.	The programme should ensure informed choice, confidentiality and respect for autonomy. (rev)	Yes
16.	Facilities for diagnosis and treatment should be available.	Yes
17.	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.	No
18.	There should be scientific evidence of screening programme effectiveness. (rev)	No
19.	There should be quality assurance, with mechanisms to minimize potential risks of screening. (rev)	No
20.	The overall benefits of screening should outweigh the harm. (rev)	No

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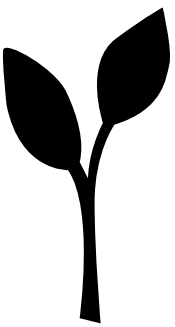


summary

Approximately 10-15% of all women experience symptoms of anxiety or depression during the antenatal or postpartum period. It has been known that having elevated stress levels in the antenatal period is associated with adverse outcomes in the child, but the mechanism behind this observation has not been found yet. Amongst the main risk factors for anxiety or depression in the antenatal or postpartum period are having a history of previous symptoms, traumatic events during childhood, recent major life events and specific personality traits. Literature is still inconclusive on the associations with traumatic events specifically during pregnancy, delivery or in the immediate postpartum period. Chapters 2 and 3 of this thesis focus on the influence of such events on the course of anxiety and depression in the antenatal and postpartum period.

Screening for anxiety and depression during pregnancy is generally recommended by guidelines on antenatal and postpartum anxiety or depression, although antenatal screening tools that accurately predict an individual risk on symptoms in the postpartum period are not available yet. Chapters 4 and 5 of this thesis investigate whether two commonly used tools in screening for current symptomatology can be used in predicting later symptomatology.

Treatment options for symptoms of anxiety or depression can be divided into pharmacological and non-pharmacological treatment. During the antenatal and breastfeeding period, women generally prefer non-pharmacological treatment, such as cognitive behavioral therapy. Outside pregnancy, this therapy has been proven to be successful in treating anxiety and depression. Chapter 6 focuses on a randomized controlled trial investigating the effect of cognitive behavioral therapy on pregnant women and their babies.

Chapter 2 investigates the association between specific types of life events during pregnancy and change in symptoms of antenatal anxiety and depression between the first and the third trimester (n=1,603). Life events were divided into pregnancy related and non-pregnancy related events. We hypothesized that experiencing an event that was related to the pregnancy, such as hearing that there might be something wrong with the baby or that the partner does not want the child, would have a larger effect on maternal symptomatology than non-pregnancy related events. Both types of events were statistically significantly associated with an increase in symptoms ofanxiety and depression. In contrast to our hypothesis however, effect sizes for non-pregnancy related events were larger than for pregnancy related events: 1.17 versus 0.75 for anxiety, and 1.31 versus 0.59 for depression. We subsequently tested whether the type of event would be associated with specific anxiety by adjusting for depression levels at the third trimester of pregnancy and vice versa, and found that non-pregnancy related events were specifically associated with an increase in symptoms

of depression (B0.62, 95%CI 0.37-0.86), whereas pregnancy related events were merely associated with increasing symptoms of anxiety (B0.4, 95%CI 0.10-0.58).

We further investigated associations with and potential moderation by levels of neuroticism or extraversion, or the experience of a childhood trauma. Personality traits were associated with increasing symptoms of both anxiety and depression, but no moderating effects were found. Childhood trauma did neither predict changes in anxiety and depression levels, nor did it moderate the associations between life events and symptomatology.

In chapter 3, the transition of symptoms from the antenatal into the postpartum period is studied (n=3,842). More specifically, to what extent specific life events during pregnancy or delivery contributed to the risk of having symptoms of anxiety or depression at six months postpartum when they already experienced symptoms in their first trimester of pregnancy. We found that experiencing life events during pregnancy that were related to the pregnancy, the mode of delivery or the newborn were found not to be associated with an increase in levels of anxiety and depression. This is not different for women with and without antenatal anxiety or depression.

Chapter 4 investigated the predictive accuracy of the ten-item Edinburgh Postnatal Depression Scale (EPDS) (n=1,620). This tool is commonly used in identifying symptoms of depression in the antenatal and postpartum period. The main objective was to investigate whether antenatal scores above cut-off accurately predict postpartum scores above cut-off. Although the overall discriminatory power was reasonable in all trimesters (AUC ≥0.74), the EPDS was not sufficiently accurate in predicting an individual risk of symptoms of depression in the postpartum period. We first tested the prevailing cut-offs, i.e. ≥13 for antenatal scores, and ≥10 for postpartum scores and subsequently lowered the cut-off gradually. Lowering the antenatal cut-off to ≥5 somewhat improved the prediction, though not sufficiently. Women scoring <5 can however be reassured that it is very unlikely that they will experience symptoms of depression in the postpartum period, as the negative predictive value was exceedingly high (96%). Lastly, we found that the predictive accuracy of a two-item screening including only items that are key symptoms in depression was not sufficiently accurate.

Although using only the antenatal scores of the ten-item EPDS may not be accurate in predicting an individual risk, they may be adequate in a two-stage screening of which the first step would be the EPDS screening in the first trimester. Women with a score ≥5 can subsequently be screened more elaborately on other risk factors, such as a history of depressive episodes, recent life events and social support. Future studies should focus on

developing and testing such a screening model.

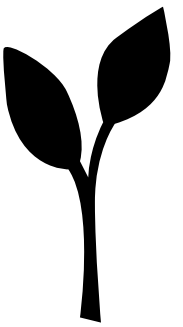
In chapter 5, the six-item State and Trait Anxiety Inventory (STAI) was investigated on its predictive accuracy (n=4,856). This tool is also commonly used, and validated in samples of pregnant and postpartum women. Using the prevailing cut-off (≥42), the odds ratio was >3.49 in all three trimesters. Adding the antenatal EPDS-scores decreased the odds ratios.

The overall discriminatory power was reasonable (AUC 0.73) in the second and third trimesters only. Irrespective of cut-off, the predictive performance was poor; with cut-off ≥42 in the first trimester, sensitivity and positive predictive value were approximately 30%, specificity and negative predictive value were around 90%. Using cut-off ≥36 in the second trimester, sensitivity and specificity were both approximately 67%, the positive predictive value was 23%, while the negative predictive value increased to 93%.

As negative predictive values were high at all times, women with low anxiety levels can be reassured that it is very unlikely that they will experience symptoms of anxiety in the postpartum period. A two-stage screening as proposed in chapter 4 cannot be recommended here, as there are still many uncertainties about specific risk factors for antenatal postpartum anxiety. Future studies should therefore focus on specific anxiety in the antenatal and postpartum period, rather than considering anxiety to be a comorbidity of depression.

Chapter 6 presents the design of a randomized controlled trial (RCT). We included 7,275 women in the cohort in order to include 300 women with mild to moderate levels of anxiety or depression in the trial. Women who are randomized into the intervention arm are offered 10-14 individual cognitive behavioral therapy (CBT) sessions, of which 6-10 will be received during pregnancy. Women in the control group receive care as usual (CAU). After baseline screening in the first trimester, there are 7 follow-up measurements. The final measurement at 18 months postpartum includes maternal anxiety and depression and testing the child on cognitive, psychomotor and behavioral development. Besides anxiety and depression, the follow-up questionnaires include the experience of life events, personality traits, lifestyle, attitudes, coping style, health care consumption and quality of life.

The thesis concludes with a general discussion in chapter 7 on whether or not to screen on antenatal symptomatology in order to prevent postpartum symptoms. The criteria listed by Wilson and Jungner and the WHO are applied. Although it is a recognized health problem with a high burden, there are too many uncertainties for a heartfelt 'yes' on whether an antenatal screening program for postpartum symptomatology would be beneficial.



samenvatting

Ongeveer 10-15% van alle vrouwen heeft angst- en/of depressieklachten tijdens de zwangerschap of na de bevalling. Verhoogde stress tijdens de zwangerschap hangt vaak samen met negatieve uitkomsten van het kind, zoals gedragsproblemen, maar hoe dit precies werkt is niet duidelijk. Belangrijke risicofactoren voor angst- en/of depressieklachten in deze periode zijn het hebben van een voorgeschiedenis van dergelijke klachten, traumatische gebeurtenissen in de kindertijd, recente stressvolle levensgebeurtenissen en bepaalde persoonlijkheidskenmerken. Uit de literatuur is niet duidelijk of het verloop van angst- en depressieklachten tijdens de zwangerschap en na de bevalling ook beïnvloed wordt door traumatische gebeurtenissen die tijdens de zwangerschap, de bevalling of directe na de bevalling hebben plaatsgevonden. De hoofdstukken 2 en 3 van dit proefschrift geven de resultaten van onderzoek naar de invloed van dergelijke gebeurtenissen op angst- en depressieklachten in de zwangerschap en na de bevalling.

Screening op angst- en depressieklachten tijdens de zwangerschap om klachten na de bevalling te voorkomen wordt door verschillende internationale richtlijnen aanbevolen. Goede vragenlijsten om nauwkeurig vast te stellen welke vrouw een hoog of juist een laag risico heeft, zijn echter nog niet beschikbaar. In hoofdstukken 4 en 5 worden de bevindingen gepresenteerd van onderzoek naar de voorspellende waarde van twee veelgebruikte vragenlijsten. We hebben onderzocht of aanwezige klachten gebruikt kunnen worden voor het voorspellen van om toekomstige klachten.

Behandelopties voor angst- en depressieklachten kunnen grofweg verdeeld worden in behandeling met medicijnen of middels een psychologische therapie. Tijdens de zwangerschap en de borstvoedingsperiode geven de meeste vrouwen de voorkeur aan een psychologische therapie, zoals een cognitieve gedragstherapie. Buiten de zwangerschap is deze behandeling bewezen effectief gebleken. Daarom bespreken we in hoofdstuk 6 de opzet van een onderzoek waarin het effect van een dergelijke psychologische therapie op moeder en kind onderzocht zal worden.

In hoofdstuk 2 wordt een onderzoek beschreven bij 1.603 zwangere vrouwen naar veranderingen in angst- en/of depressieklachten tijdens de zwangerschap en of deze veranderingen samenhangen met het meemaken van stressvolle levensgebeurtenissen. Deze gebeurtenissen werden onderverdeeld in zwangerschapsgerelateerde gebeurtenissen, zoals horen dat er misschien iets niet goed is met het kindje, of ontdekken dat de partner het kindje niet wil, en niet- zwangerschapsgerelateerde gebeurtenissen, zoals het overlijden van een dierbare, of aan een nieuwe baan beginnen. We verwachtten dat het meemaken van een gebeurtenis die wel gerelateerd was aan de zwangerschap een grotere impact op de klachten

van de moeder zou hebben dan het meemaken van een niet-zwangerschapsgerelateerde gebeurtenis. Beide types gebeurtenissen bleken echter samen te hangen met een toename in angst- en depressieklachten. Opvallend was dat niet-zwangerschapsgerelateerde gebeurtenissen een groter effect op deze toename hadden dan gebeurtenissen die wel aan de zwangerschap gerelateerd waren. We hebben vervolgens onderzocht of er tussen vrouwen met alleen angstklachten en vrouwen met alleen depressieklachten verschil was in het type gebeurtenissen dat ze hadden meegemaakt. We vonden dat niet-zwangerschapsgerelateerde gebeurtenissen alleen samenhingen met een toename in depressieklachten, en dat zwangerschapsgerelateerde klachten alleen samenhingen met een toename in angstklachten. We onderzochten tot slot of het meemaken van een traumatische gebeurtenis in de kindertijd of het hebben van bepaalde persoonlijkheidskenmerken, zoals hoog-neurotisch of laag-extravert, ook een rol speelde in de verandering van angst- of depressieklachten gedurende de zwangerschap. Kindertijdtrauma speelde geen rol. Het hebben van specifieke persoonlijkheidskenmerken bleek wel samen te hangen met een toename in angst- of depressieklachten. Het was echter niet zo dat vrouwen met deze kenmerken die tijdens de zwangerschap bepaalde levensgebeurtenissen meemaakten een grotere toename van angst-of depressieklachten hadden dan vrouwen die geen of minder levensgebeurtenissen mee hadden gemaakt.

In hoofdstuk 3 wordt bij 3.842 zwangere vrouwen gekeken of bepaalde stressvolle levensgebeurtenissen tijdens de zwangerschap of tijdens de bevalling bijdragen aan de verandering van angst- en depressieklachten tussen het eerste trimester van de zwangerschap en een half jaar na de bevalling. We vonden dat het meemaken van gebeurtenissen die aan de zwangerschap gerelateerd waren, de wijze van bevalling, het te vroeg bevallen van de baby of het bevallen van een baby met een laag geboortegewicht geen rol speelden in het hebben van klachten een half jaar na de bevalling. Bepaalde gebeurtenissen die plaatsvonden tijdens de zwangerschap, zoals ziekte of overlijden van een naaste, hingen wel samen met angst- of depressieklachten na de bevalling. Ook onderzochten we of vrouwen die al angst- of depressieklachten hadden tijdens het eerste trimester van de zwangerschap extra kwetsbaar waren om ook na de bevalling klachten te hebben wanneer ze dergelijke gebeurtenissen meemaakten. Dit bleek niet het geval te zijn.

In hoofdstuk 4 onderzochten we bij 1.620 zwangere vrouwen of we met een vragenlijst, de Edinburgh Postnatal Depression Scale (EPDS), kunnen voorspellen welke vrouwen na de bevalling depressieklachten zullen hebben. Deze vragenlijst bestaat uit 10 vragen en wordt veel gebruikt om aanwezige depressieklachten te identificeren, zowel tijdens de

zwangerschap als na de bevalling. Een score die hoger is dan een bepaalde waarde betekent dat deze vrouw meer depressieklachten heeft dan de gemiddelde zwangere vrouw. We noemen een dergelijke waarde een afkapwaarde. In dit hoofdstuk wilden we onderzoeken of een verhoogde score in de zwangerschap ook een verhoogde score na de bevalling voorspelt. Aanwezige klachten zoals gemeten met de EPDS bleken niet voldoende precies om het risico op klachten na de bevalling voor een individuele vrouw te kunnen voorspellen.

We testten eerst de meest gebruikte afkapwaardes, te weten ≥13 voor scores tijdens de zwangerschap en ≥10 voor scores na de bevalling. De afkapwaarde voor de score tijdens de zwangerschap lieten we vervolgens geleidelijk dalen. Wanneer we een afkapwaarde van ≥5 namen werd het voorspellen wel iets preciezer, maar het bleef niet voldoende. Dat betekent dat we een vrouw met een score ≥5 niet met zekerheid kunnen zeggen of ze al dan niet klachten zal ervaren na de bevalling. Vrouwen met een score van <5 kunnen echter wel gerustgesteld worden dat de kans dat zij een half jaar na de bevalling klachten zullen ervaren erg laag is, namelijk 4%. Tot slot onderzochten we of het ook mogelijk zou zijn om de kans op klachten na de bevalling te voorspellen op basis van slechts twee vragen. Dit zijn de vragen die belangrijk zijn in het stellen van de diagnose depressie, namelijk somberheid en verlies van plezier. Dit was niet het geval.

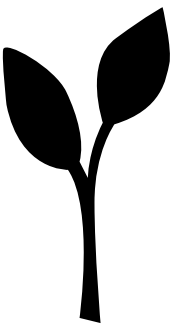
Ook al is het niet voldoende om alleen de scores in de zwangerschap te gebruiken om een individueel risico na de bevalling te voorspellen, het zou wel een eerste stap in een uitgebreidere screening kunnen zijn. Vrouwen met een score ≥5 zouden bijvoorbeeld gescreend kunnen worden op andere bekende risicofactoren voor postpartum depressie, zoals een voorgaande depressie, recente stressvolle levensgebeurtenissen of een klein sociaal netwerk. Dit is iets om in toekomstige studies te onderzoeken.

In hoofdstuk 5 hebben we een soortgelijk onderzoek uitgevoerd, maar dan naar angstklachten. We hebben dit bij 4.856 zwangere vrouwen gedaan, met de vragenlijst State and Trait Anxiety Inventory, de STAI. Deze 6-item vragenlijst wordt veel gebruikt om aanwezige angstklachten in de zwangerschap of na de bevalling te identificeren. We vonden op groepsniveau een erg sterke samenhang tussen scores boven de standaard afkapwaarde ≥42 tijdens de zwangerschap en na de bevalling. Deze samenhang werd minder sterk wanneer we rekening hielden met depressieklachten tijdens de zwangerschap. Dat betekent dat angstklachten na de bevalling vooral samenhangen met angstklachten in de zwangerschap. We testten zowel de standaard afkapwaarde als een aantal lagere afkapwaardes. Aanwezige klachten zoals gemeten met de STAI bleken niet voldoende precies wanneer we voor individuele vrouwen een risico op klachten na de bevalling wilden voorspellen, bij geen enkele

afkapwaarde. Wanneer we deze vragenlijst wel zouden gebruiken om iets te zeggen over angstklachten na de bevalling, zou een groot deel van de vrouwen te horen krijgen dat ze een hoge kans heeft op deze klachten terwijl ze uiteindelijk geen klachten ervaarde. Dat zou kunnen betekenen dat je deze vrouwen behandelt, terwijl haar klachten sowieso afgenomen zouden hebben. Net als in het voorgaande hoofdstuk kunnen we ook hier vrouwen met een lage score wel geruststellen dat de kans dat ze toch klachten ervaart na de zwangerschap erg klein is. Maar omdat er nog veel onduidelijk is over welke risicofactoren een rol spelen bij het ontwikkelen en blijven bestaan van angstklachten tijdens de zwangerschap en na de bevalling, kunnen we hier niet een tweetraps screening aanbevelen zoals bij depressieklachten. Toekomstige studies zouden zich daarom eerst moeten focussen op dergelijke risicofactoren.

Hoofdstuk 6 presenteert de opzet van een onderzoek waarbij zwangere vrouwen met bovengemiddelde klachten in het eerste trimester willekeurig worden ingedeeld in een groep waarin ze psychologische therapie krijgen, of een groep waarin ze deze therapie niet krijgen. We wilden 300 vrouwen laten deelnemen. De deelneemsters werden willekeurig verdeeld in twee groepen; de helft ontving 10-14 individuele sessies cognitieve gedragstherapie, de andere helft standaardzorg. Na de eerste screening kregen deze vrouwen nog zeven keer het verzoek een aantal vragenlijsten in te vullen. Hierin worden vragen gesteld over het meemaken van stressvolle levensgebeurtenissen, persoonlijkheidskenmerken, leefstijl, hoe ze met tegenslagen omgaan, van welke zorg ze gebruik maken en hoe de kwaliteit van leven ervaren wordt. Het laatste verzoek ontvangen ze anderhalf jaar na de bevalling, waarbij naast de angst- en depressievragen ook het kindje thuis getest wordt op zijn of haar ontwikkeling, zoals motorische en mentale ontwikkeling.

Het proefschrift sluit af met een algemene discussie in hoofdstuk 7. Hierin wordt besproken of het zin heeft om tijdens de zwangerschap te screenen op angst- en depressieklachten om dergelijke klachten na de bevalling te voorkomen. Criteria die door Wilson, Jungner en de Wereldgezondheidsorganisatie zijn opgesteld worden hiervoor als richtlijn gebruikt.
Angst- en depressieklachten in de zwangerschap en na de bevalling zijn een erkend gezondheidsprobleem, en de vrouw en haar omgeving ervaren hierdoor een grote last. Er zijn echter te veel onzekerheden over de werkelijke voordelen van screening en behandeling van deze groep vrouwen, om hartgrondig 'ja' te kunnen antwoorden op de vraag of alle vrouwen vroeg tijdens de zwangerschap gescreend moeten worden om problematiek na de bevalling te voorkomen.



acknowledgements

Zo ongeveer een jaar geleden zat ik rond middernacht in een dichte mist op de fiets naar huis. Ik had een kwartier ervoor het laatste artikel naar de co-auteurs gestuurd en was euforisch (en naar later bleek wat naïef): nu kon het eind toch niet ver meer zijn! En ineens overviel het me: het einde kwam in zicht. De euforie sloeg om in dikke tranen, van opluchting en ontlading. De afgelopen jaren zijn heel leerzaam en waardevol, maar soms ook best zwaar geweest. En nu is het klaar.

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We hebben in dit onderzoek ook veel te danken aan de verloskundigen van ruim 100 eerstelijnspraktijken, de research nurses van 7 ziekenhuizen, en ruim 30 psychotherapeuten. In hun drukke werkzaamheden vonden ze tijd om vrouwen te informeren over het onderzoek, om ze te screenen, of om ze op locatie te behandelen. Zonder hun inzet was dit onderzoek niet van de grond gekomen!

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onderdeel van het onderzoek!

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Met name de laatste tijd ging alle vrije tijd op aan werk en gezin. Gelukkig heb ik de liefste vriendinnen van de wereld die begrijpen hoe die dingen soms gaan. Jelly en Jacobine, dat het nooit een probleem was wanneer ik een afspraak afzegde om te schrijven, heeft me enorm gesteund. Ik ben ontzettend blij met onze vriendschappen, met hoe het altijd goed is als we elkaar weer zien, hoe we altijd tijd tekort komen en hoe we elkaar met een half woord kunnen begrijpen.

Ooms, tantes, neven en nichten van de Geertsma's en de Meijers, vanaf het begin af aan waren jullie geïnteresseerd in mijn onderzoek. Ik vind het heel bijzonder dat jullie er altijd voor me zijn, en dat we het de 23e samen kunnen vieren.

Lieve Jos en Nella, Nanda en Antoon, Jules en Merijn, Rosa en Jan, Vera en Bas, en Paul. Jullie hebben altijd veel interesse gehad in dit onderzoek, meegedacht over hoe het in elkaar zou kunnen zitten, maar ook over alles eromheen. Het is zo ontzettend mooi om te zien hoe Tamar bij jullie altijd zoveel meer dan welkom is; we zullen het niet gauw nog eens wagen langs te komen/weg te gaan zonder haar...!

Lieve Marij, het was voor mij altijd al duidelijk dat jij mijn paranimf zou zijn: belangrijke dingen kunnen niet zonder jou. We hebben de afgelopen jaren zo vaak gepraat over deze promotie, en je hebt me altijd gesteund bij de keus om toch door te zetten. Ik kan alleen maar hopen dat ik hetzelfde voor jou kan doen wanneer dat nodig is.

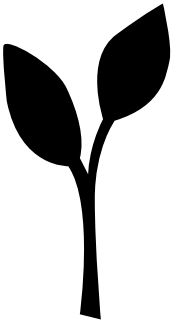
Sjoerd, jij had zoveel beter dan ik in de gaten hoe een promotie zou gaan zijn. Je hebt het slim bekeken. Ik hoop enorm dat je er de 23e weer bent!

Lieve pap en mam, jullie hebben een onbeschrijfelijk groot aandeel in mijn promotie. Naast hard werken was het ook een persoonlijke overwinning, één die jullie altijd gesteund hebben. Het meest zichtbare aandeel is natuurlijk jullie bereidheid om op Tamar te passen zodat ik door kon werken, dit was ons zowel verbaal ('is het dan niet handiger dat ze al een dag eerder komt?') als non-verbaal altijd heel duidelijk. De glinstering in jullie ogen als jullie haar zien is onbetaalbaar.

En natuurlijk onze eigen, groeiende familie.

Liefste kleine Tamar. Jouw oneindige vrolijkheid maakt het leven zoveel leuker! Je was tegelijkertijd de grootste motor achter het afmaken van het boek, als de grootste afleiding die er bestaat. Zo aan het eind was jij er ook wel klaar mee en sommeerde je me om na het werken snel weer naar huis te komen. Daar wachtte me gelukkig altijd een dikke knuffel, fijner thuiskomen is niet denkbaar. Vanaf nu zijn alle vrije uren voor jou!

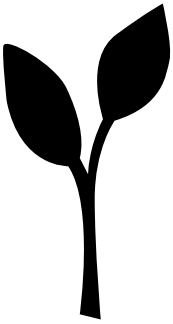
Liefste Gui, ik weet niet waar ik moet beginnen met je bedanken. Het is vast niet altijd even makkelijk geweest, dat ik avonden doorwerkte of energieloos thuiskwam. Er zit ook zoveel van jouw tijd in dit boek, maar je hebt er alles aan gedaan om te zorgen dat het afkwam, zelfs de meest rare vragen beantwoorden ('verplaats je eens in een vrouw zonder kinderwens'). Jouw liefde, aanstekelijke optimisme en hitlijsten maken altijd alles goed. Ik heb enorm veel zin in de toekomst samen!



curriculum vitae

Judith werd geboren op 4 februari 1984 in Ter Apel, waar ze ook haar lagere en middelbare schooltijd doorliep. Vanaf 2001 studeerde ze in Groningen een jaar pedagogiek aan de Rijksuniversiteit Groningen, en vervolgens verpleegkunde aan de Hanzehogeschool Groningen met de specialisatie GGZ, waar ze in 2006 haar bachelor diploma voor ontving. Aansluitend vertrok ze naar Amsterdam voor de studie gezondheidswetenschappen aan de Vrije Universiteit, master preventie en volksgezondheid, waar ze in 2008 haar diploma voor ontving.
Na een half jaar als junior onderzoeker bij huisartsgeneeskunde in het Universitair Medisch Centrum Groningen (UMCG) te hebben gewerkt, kon ze in april 2009 beginnen als promovendus bij epidemiologie in het UMCG. Zowel het PAD-cohort als de PROMISES-trial moesten nog volledig opgezet worden, waar ze ruim twee jaar van haar promotietijd aan besteed heeft. Sinds het aflopen van het contract in januari 2014 werkt ze bij de LifeLines Research Office. Eerst in het begeleiden van onderzoekers in het aanvragenproces, vervolgens een jaar als stafmedewerker wetenschapscommunicatie, en sinds kort als projectleider bij de Research Office, en als postdoc op een onderzoek naar de beleving van Big Data in de gezondheidszorg (epidemiologie, UMCG).

Judith was born on February 4th, 1984 in Ter Apel, the Netherlands. In 2001, she started a study in pedagogical sciences at the University Groningen, but switched to nursing (mental healthcare) at the Hanze University after a year, and received her bachelor's degree in 2006. She went to study Health Sciences at the VU Univeristy, and obtained her master's degree for Prevention and Public Health in 2008.
After working as a junior researcher at the department of general practice at the University Medical Center Groningen (UMCG), she started her PhD project in April 2009 at the department of epidemiology, UMCG. More than two years of her PhD project were dedicated to setting up the PAD-cohort and the PROMISES-trial. Since the end of her contract in January 2014, she has worked for the LifeLines Research Office. First, she guided researchers in their process of applying for data access, then worked as research communication officer for a year, and recently started as project manager at the Research Office and as postdoc on a study on perception of Big Data in healthcare (epidemiology, UMCG).



list of publications

Published

Burger H, Bockting CL, Beijers C, Verbeek T, Stant AD, Ormel J, Stolk RP, de Jonge P, van Pampus MG, **Meijer J**.
Pregnancy Outcomes After a Maternity Intervention for Stressful Emotions (PROMISES): A Randomised Controlled Trial.
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Beijers C, Ormel J, Verbeek T, van Pampus MG, **Meijer JL**, Burger H, Bockting CLH.

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Verbeek T, Bockting CLH, **Meijer JL**, Beijers C, Van Pampus MG, Burger H.

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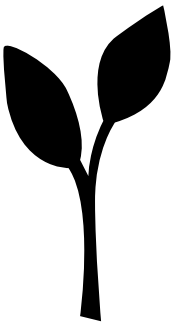
Verbeek T, Bockting CLH, Beijers C, **Meijer JL**, van Pampus MG, Burger H.



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