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### Stormy clouds in seventh heaven

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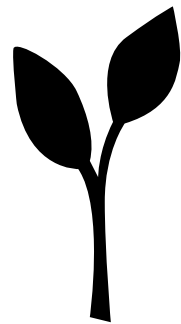
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*general discussion*



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<sup>3</sup>, 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<sup>2,3</sup>.

The general discussion of this thesis therefore applies the criteria as set by Wilson and Jungner<sup>4</sup> and the WHO<sup>5</sup> 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.

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**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)<sup>6</sup>. Prevalence rates for depression are ranging from 5% to 10% and up to 20% for anxiety<sup>7,8</sup>. 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<sup>9-14</sup>. Thus it is no surprise that anxiety and depression occur frequently in pregnant or recently pregnant women, and that prevalence rates are comparable<sup>15-18</sup>. 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<sup>19-21</sup>. Several studies have shown that antenatal anxiety and depression are associated with preterm delivery and low birth weight<sup>23-25</sup>, as well as adverse cognitive, behavioral, and motor development in the child<sup>25,26-30</sup>. 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<sup>10,31,32</sup>. Additionally, mental illnesses are costly to the society. It has been estimated that in 2003, major depression has cost the Netherlands €1.8 billion<sup>33</sup>. 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<sup>34,35</sup>. 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<sup>36</sup>. 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<sup>37,38</sup>.

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)<sup>39</sup> and the 10-item Edinburgh Postnatal Depression Scale (EPDS)<sup>40</sup>, 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<sup>39</sup> (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<sup>2</sup>. In pregnancy, women generally prefer psychological treatment<sup>41</sup>, 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<sup>42,43</sup>.

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<sup>44-46</sup>. 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<sup>47</sup>. 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<sup>48,49</sup>. 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<sup>44-46</sup>, 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<sup>50</sup>, 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 woman 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  $\geq 36$  and EPDS  $\geq 5$ , 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<sup>23</sup>. A recent systematic review showed that literature on the effectiveness of a screening program for antenatal and postpartum depression is inconclusive<sup>51</sup>. 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<sup>52</sup>, 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.

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**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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