Psychopathology, Psychosocial Problems and Substance Use During Pregnancy

- Screening and Referral Towards Care -

Chantal Quispel

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PhD thesis, Erasmus University Rotterdam, The Netherlands

Acknowledgements
All midwives, obstetricians, psychiatrists, social workers and supporting staff who provided the opportunity for the studies in this dissertation are gratefully acknowledged.

The research presented in this thesis was performed at the departments of Psychiatry and Obstetrics and Gynaecology, division of Obstetrics and Prenatal Medicine, Erasmus University Medical Centre, Rotterdam, The Netherlands.

Financial support for the studies in this thesis was obtained from Stichting Achmea Gezondheid (SAG grant no. z-282) for which we are very grateful.

Additional financial support for this dissertation was kindly provided by:

-BMA BV (Mosos)

-Goodlife Pharma

-Stichting Achmea Gezondheidszorg (SAG)

-The Rotterdam municipal authorities

ISBN: 978-94-6169-542-0
Printed and layout: Optima Grafische Communicatie, Rotterdam, The Netherlands
Cover design: Optima Grafische Communicatie, Rotterdam, The Netherlands

mind2care@erasmusmc.nl, www.mind2care.nl

Psychopathology, Psychosocial Problems and Substance Use During Pregnancy

- screening and referral towards care -

Psychopathologie, psychosociale problematiek en middelengebruik tijdens de zwangerschap

- screening en zorgtoeleiding -

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof.dr. H.A.P. Pols

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

dinsdag 9 september 2014 om 13.30 uur

door

Chantal Quispel
geboren te Gouda

PROMOTIECOMMISSIE

Promotoren	Prof.dr. G.J. Bonsel
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CONTENTS

CHAPTER 1

Introduction

Despite the high prevalence and the related adverse outcomes for both mother and child, systematic detection and subsequent referral towards care of women with psychopathology, psychosocial problems and substance use (together 'PPS') is often not part of routine obstetric care. As the provided treatment is fragmented, and many women perceive barriers to treatment, PPS problems need a targeted strategy during pregnancy to improve maternal and child well-being.

Psychopathology, psychosocial problems and substance use during pregnancy

Pregnancy and delivery are sensitive periods in which mental disorders can occur or relapse.[1] Triggers for mental disorders during pregnancy include pregnancy induced hormonal or physical changes, genetic vulnerability, stress, life events and environmental factors such as deprivation and living in an urban area.[2-5]

The prevalence of mental disorders during pregnancy varies from about 10% major depressive disorders to 6% personality disorders, 4% eating disorders, 4% post traumatic stress disorders, 2% panic disorders, 1% obsessive-compulsive disorders, and 1% bipolar disorders.[1,6-9]

One of the clinical complexities is the co-existence of psychopathology, psychosocial problems and substance use, especially in heterogeneous urban areas. Psychosocial problems include insufficient social support, relational problems, financial problems, housing problems, and sexual, physical or emotional abuse. Substance use exists of smoking, alcohol consumption and illicit drug use during pregnancy. The co-existence of PPS conditions complicates the clinical detection and decreases the success rate of psychiatric treatment.

PPS has serious short and long term consequences for both the expecting mother and her unborn child, in particular in case of accumulation of risks. Maternal consequences include an unhealthy life style, withdrawal from care, and the persistence of psychiatric symptoms throughout pregnancy and beyond. In more severe cases suicidal ideation and infanticide can occur.[1,10] Foetal consequences include adverse pregnancy outcomes such as preterm delivery and small for gestational age, leading to an increased risk for cardiovascular diseases and diabetes in later life; maternal bonding problems, insecure child attachment, and developmental disorders such as ADHD and autism spectre disorders.[11-14]

Interventions targeted at the improvement of these adverse outcomes have become important, as in The Netherlands rates of adverse pregnancy outcomes exceed European averages,[15] particularly in large urban areas.[16]

Lack of detection and lack of treatment

The negative effects of PPS on perinatal health could be decreased by a systematic and integral approach for treating psychopathology, psychosocial problems and substance use. In current practice, however, screening for PPS is not part of routine obstetric care; resulting in a lack of detection.[17,18] Proposed reasons from the professional's viewpoint include the overlap between psychiatric symptoms and pregnancy related complaints, the focus of obstetric

caregivers to detect and reduce medical-obstetrical risk factors, the confined time of obstetric caregivers to screen women on risk factors, and the lack of professional expertise of obstetric caregivers in the psychiatric and psychosocial domain and lack of knowledge about possible options for referral.[1,19,20] Unless asked for, women are often not inclined to disclose current or past psychiatric problems, psychosocial problems and substance use. From the pregnant women's viewpoint, this phenomenon is partly based on shame and partly on fear for stigmatisation.[17]

Last years show a changing attitude towards the detection of PPS. International guidelines now recommend routine screening of PPS in obstetric care.[21,22] As a response, a growing number of screen instruments has been developed and validated for use in pregnancy, e.g. the Edinburgh Depression Scale (EDS),[23] the Wijma Delivery Expectancy Questionnaire (W-DEQ),[24] the Prenatal Psychosocial Profile,[25] and the CAGE and T-ACE.[26] These screen instruments, however, are targeted to one specific topic only, and are often not implemented in routine obstetric care.

Besides screening, the reduction of PPS also implies referral towards care and the actual treatment of PPS. Once detected, referral and treatment are often lacking in current practice.[17,27,28] Several explanations have been proposed. From the professional's point of view, co-existence of multiple PPS conditions are difficult to manage, e.g. with regard to professional responsibility (case management) and financial invoices. The fragmented psychiatric and social care[29] and the absence of standardised integral protocols for referral and treatment of women with PPS are also likely contributors to the lack of referral and lack of treatment. From the women's viewpoint, referral and treatment may not seem necessary as screen results may reflect transient psychiatric symptoms caused by stress inducing circumstances, such as the first ultrasound examination.

In addition, the adherence to preventive and multidisciplinary care can be difficult to manage, particularly for deprived vulnerable women with PPS and a lack of personal economic or educational resources. First, the direct access to care is likely to be poor for vulnerable women, e.g. if medical insurance is absent or copayment is required. Second, the knowledge of unhealthy behaviours is likely to be low.[30]

To improve perinatal mental and psychosocial health for both mother and child, a systematic multidisciplinary approach is urgently needed. A systematic approach essentially encompasses risk management, contextual measures, active engagement of key professionals and patients, and should fulfill criteria of sustainability. Risk management implies a systematic detection, referral towards care and the actual treatment. This in turn requires a clearly defined referral process, agreements on case management, and the availability of supportive facilities and social support systems beyond the health care system. Finally, the multidisciplinary challenge here is to combine clinical strategies with regard to PPS manifestations on the one hand with public health strategies with regard to deprivation and social care on the other hand.

AIM OF THIS THESIS

The overall aim of the present thesis is to demonstrate the feasibility of an innovative screen-and-advice instrument, for routine screening and subsequent referral to tailored care of pregnant women with psychopathology, psychosocial problems and substance use.
Firstly, this dissertation addresses how and by whom PPS risk management should be performed, with regard to screening and subsequent guidance to specialised care, if indicated. Secondly, this dissertation outlines recommendations for a targeted prevention of poor perinatal health related to PPS, by investigating the role of PPS in the pathway to the preterm birth, birth weight and small for gestational age.

To that purpose five research questions are answered:

1. What is the prevalence of psychopathology, psychosocial problems and substance use during pregnancy in a large Dutch urban area? (chapter 2)
2. Is the Mind2Care screen-and-advice instrument a reliable and valid instrument for routine use in obstetric care? (chapters 2, 3, and 4)
3. Is the antenatal screening for depressive and/or anxiety symptoms biased by worries surrounding the first ultrasound examination? (chapter 5)
4. How many pregnant women identified as being at risk for PPS after screening eventually receive specialized treatment? (chapter 6)
5. What is the role of psychopathology, psychosocial problems and substance use in the pathway to adverse pregnancy outcomes? (chapters 7 and 8)

STUDY POPULATION IN THIS THESIS

Study area

The studies presented in this thesis were conducted in several regions in The Netherlands: the larger city of Rotterdam, Breda, Apeldoorn, and the rural region of Meppel.
Rotterdam is the second largest city in The Netherlands, with more than 610,000 inhabitants. Rotterdam has the highest proportion of non-western inhabitants (48%), with the following four non-western groups being most prevalent: Surinamese (9%), Turkish (8%), Moroccan (7%), and Dutch Antillean (4%).[31] This city has also the highest number of deprived neighbourhoods, with 10% of pregnant women having a low socio-economic status (<20th percentile).[32] Of the approximately 8,000 newborns per year, with 10% being small for gestational age (<10th percentile)*.[31,32]
Breda is a non-deprived middle sized city with nearly 175,000 inhabitants, of which 22% is of non-western ethnicity (3% Moroccan, 2% Turkish, 2% Surinamese, 2% Dutch Antillean).

Five per cent of pregnant women have a low socio-economic status. The birth rate in Breda is 2,000 per year, with 6% small for gestational age babies.
The non-deprived middle sized city of Apeldoorn has 156,000 inhabitants. Of the 15% non-western inhabitants, 3% is of Turkish ethnicity and less than 1% is of Moroccan, Surinamese, and Dutch Antillean ethnicity. In Apeldoorn nearly 1,600 children are born per year, of which 5% have a small for gestational age.
The rural region of Meppel, includes the small city of Zwolle, and the villages Meppel, Staphorst and Steenwijkerland. All together, this rural region counts 21,000 inhabitants, of which a little more than 10% is of non-western ethnicity. In this rural area nearly 2,800 newborns are born per year, of which 3% have a small for gestational age.[31,32]

Study cohort

This thesis describes results based on the Mind2Care instrument in more than 2300 pregnant women.

** At the time of data collection the commonly used 10th percentile reference values accounted for approximately 7.5% of the Dutch newborn. Hence, the prevalence of SGA in Rotterdam exceeded the average Dutch prevalence of SGA, as expected in such a deprived urban area.*

MEASURE

The Mind2Care questions cover the following domains:
• social and demographic background (e.g. maternal age, ethnicity, educational level)
• obstetric characteristics (e.g. gestational age, gravidity, parity)
• psychiatric problems (e.g. depressive symptoms assessed with the Edinburgh Depression Scale, psychotropic medication use)
• psychosocial problems (e.g. insufficient social support, relational problems)
•substance use (e.g. smoking, alcohol consumption, illicit drug use)
The latter 3 are the primary outcomes of the Mind2Care.
The Mind2Care questionnaire is added as appendix (chapter 11).

OUTLINE OF THIS THESIS

Chapter 2 describes the prevalence of psychopathology, psychosocial problems and substance use among urban pregnant women as measured by the Mind2Care instrument. The feasibility and psychometric properties of the instrument are tested under routine care conditions.

Chapter 3 compares the performance of the self-report digital Mind2Care instrument with the professional's paper based R4U checklist. Screen instruments are compared for their detection of PPS risk factors and for their identification of women-at-risk for adverse pregnancy outcomes.

Chapter 4 describes the formally validation of four triage models for mental disorders of the DSM-IV axis I and II for routine use in obstetric care, including a number of Mind2Care items. Structured Clinical Interviews of the DSM-IV axis I and II disorders (SCID I and II) are conducted as gold standard.

Chapter 5 tests whether the Mind2Care results are influenced by general worries surrounding the routine ultrasound during early pregnancy.

Chapter 6 examines the path from screening to treatment among urban pregnant women at risk for PPS. Reasons for dropout and risk factors related to dropout during screening, indication assessment, referral towards care and the utilisation of care are assessed.

Chapter 7 describes the role of depressive symptoms in the pathway to the adverse pregnancy outcomes preterm birth and small for gestational age by a formal mediation analysis. Several urban background risks are taken into account.

Chapter 8 examines the role of depressive symptoms, psychosocial problems, substance use, and the accumulation of PPS conditions in relation to inequalities in preterm birth and birth weight in urban and rural areas.

Finally, **Chapters 9 and 10** summarise and discuss the main findings and conclusions of this thesis. The implications and recommendations for clinical practice and future research are provided.

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CHAPTER 2

An innovative screen-and-advice model for psychopathology and psychosocial problems among urban pregnant women: an exploratory study

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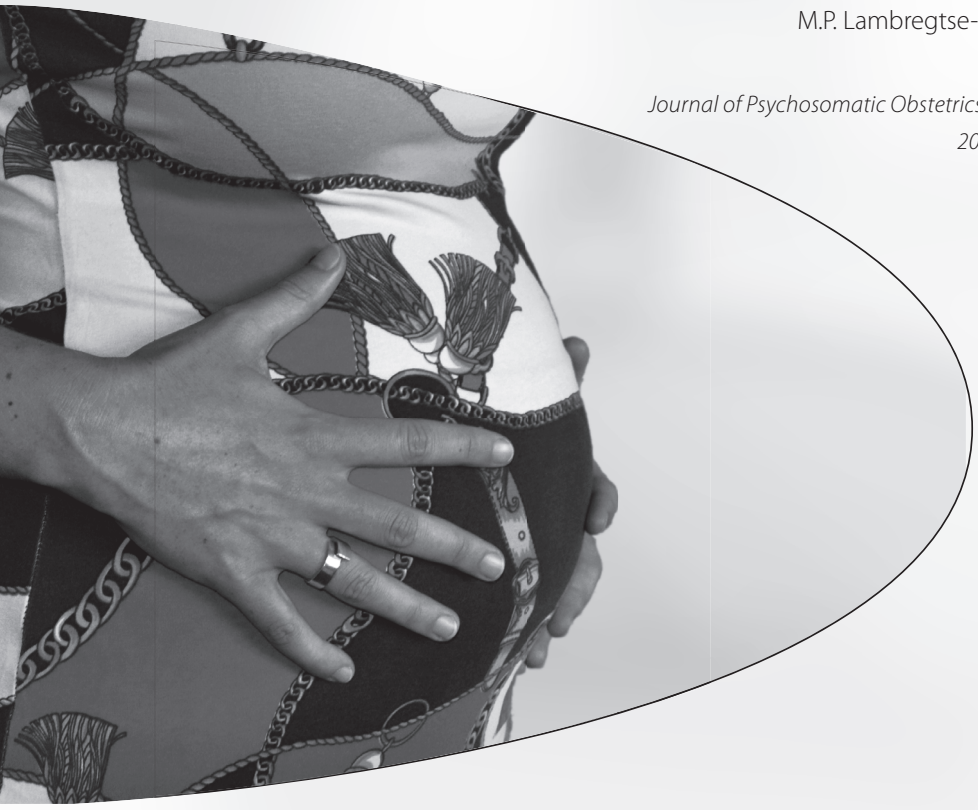
Journal of Psychosomatic Obstetrics & Gynecology,
2012; 33(1): 7–14.



ABSTRACT

Background: Increased adverse pregnancy outcomes related to psychiatric and psychosocial problems can be observed for urban areas when compared to national averages. We developed a personal digital assistant (PDA)-based self-report screening model that produces tailored intervention advices. After having adapted the model to local care pathways, we tested the reliability, validity and feasibility of the model in routine antenatal care.

Methods: Observational study among pregnant women in a Dutch urban area included women with a booking visit. Women answered questions posed by the PDA tool while waiting for their appointment. If the tool suggested specific interventions (screen result), this was discussed during booking visit. A randomly selected subsample of participants completed the questionnaire again at a subsequent pregnancy check (retest). After the study was conducted, prenatal caregivers and assistants were interviewed for feasibility judgments. Psychometric and diagnostic performance of this approach was established.

Results: Response rate among invited pregnant women was 94% on weighted average (n = 621). Internal reliability ranged 0.88–0.90, test-retest reliability ranged 0.64–1.00. Positive predictive value was 86% and negative predictive value was 97%. No interpractice psychometrical differences were observed. Migrant women more often received an intervention advice than native women ($p < 0.001$). The approach was well accepted among prenatal caregivers for its time efficiency and patient-friendliness.

Conclusion: Psychometric properties of our screen-and-advice tool were favorable under routine conditions, and the feasibility of this integral approach appeared good. The technical flexibility renders the model suitable for broader application. Local care pathways can easily be incorporated. We suggest implementation of this model in prenatal care in urbanized settings in order to make tailored mental healthcare broadly available.

INTRODUCTION

While pregnancy is cheerful for most, in 5–10% women, clinically relevant psychiatric disturbances are present,[1] of which mood disorders are most common.[1-3] Sources for psychopathological and psychosocial problems, which include substance abuse (further referred to as "mental health problems"), vary. Pregnancy induced hormonal and physical changes,[4, 5] stress, life events[5] and environmental risks such as poverty[6] are prevalent exposures. Subsequent outcomes are affected in terms of preterm birth, low birth weight, negatively influenced compliance of preventive and curative care and postpartum persistence of mental health morbidity.[2, 7-9]

Perinatal outcomes in urbanized areas are usually lower than the national averages. The parallel low socio-economic status and the deprived living environment of urban areas represent a permanent mental health risk for all, pregnant women included. In Rotterdam, the Netherlands, the pregnant population is comparable to Melbourne (Australia), Birmingham and London (UK) in terms of cultural diversity and deprivation.[6, 10-13] Adverse pregnancy outcomes are about similar in Rotterdam and Birmingham, and characterized by high perinatal mortality rates due to preterm birth, low birth weight and congenital malformations.[6, 13]

Despite the high prevalence of mental health problems during pregnancy, maternal mental health is not a systematic part of prenatal care.[14, 15] Several factors contribute to lack of detection and treatment: professional's lack of awareness and expertise, negative expectations of both clients and professionals,[16] reluctance of professionals to take responsibility for case management, and to guide women-at-risk towards tailored care.[15] If not asked specifically, women are often not inclined to report mental health complaints,[14] partly from shame or perceived stigmatization, partly from ignorance, partly because they feel that pregnancy is supposed to be surrounded by positive emotions.[1]

A wide range of several screening instruments for detecting antenatal psychopathology have been proposed, in particular for detecting depression and anxiety. Examples of efforts in this pursuit are: the Edinburgh Depression Scale (EDS),[17] Beck's Depression Inventory,[18] the State-Trait Anxiety Inventory,[19] the Hospital Anxiety and Depression Scale[20] and the Pregnancy Depression Scale.[21] In addition, screening instruments for the detection of antenatal psychosocial problems are available, e.g. the prenatal psychosocial profile,[22] and other tools detect alcohol abuse, e.g. CAGE, T-ACE and AUDIT.[23] Despite the need among prenatal caregivers for a comprehensive screening instrument for psychopathology and psychosocial problems,[15,16] so far systematic comprehensive instruments and protocols are absent in prenatal care.

Current screening instruments leave the tailoring of available interventions and/or referral to the discretion of prenatal caregivers. In order to more fully comply to the Wilson and Jungner criteria for adequate screening,[24] we developed a screen-and-advice approach (GyPsy in Dutch, derived from Gynecology and Psychiatry) to (i) overcome the practicalities of routine screening in this context and to (ii) connect tailored intervention advices to the screening

results. The approach introduces a personal digital assistant (PDA) for smart data collection and generation of optional advices, as a support of a routine booking visit.
Three features of GyPsy are unique: (i) the comprehensive approach of screening for psychopathology and psychosocial problems, including substance abuse, (ii) the 1-to-1 link of screen-detected cases to care pathways and (iii) the flexibility of the digital model regarding thresholds and intervention options, allowing for adaptation of the model to local healthcare systems.
The aim of the study was to explore the reliability, validity (predictive value) and feasibility of the GyPsy approach under routine practice conditions in Rotterdam, the Netherlands.

METHODS

Screen-and-advice model

From January 2008 to December 2009, first we developed a self-report questionnaire for comprehensive and systematic screening of both antenatal psychopathology and psychosocial conditions among pregnant women. Secondly, we incorporated available local care pathways in Rotterdam into the model, as tailored intervention advices for all women above the screen threshold.
The self-report questionnaire contains 33 items, covering four domains: socio-demographic (e.g. maternal age and ethnicity), obstetric (e.g. current gestational age and parity), psychiatric domain (existing of the EDS[17] and e.g. the use of psychotropic medication) and a psychosocial domain (e.g. substance use and social support). The EDS is a 10-item self-report questionnaire validated in Dutch for screening in pregnant women[25] and measures anxiety and depressive symptoms.[26] The item response range is 0–3, the total item score range is 0–30. A score ≥13 indicates clinically relevant antenatal depressive symptoms[1,25] and a score ≥9 indicates mild depressive symptoms.[1]
Depending on the risk profiles that can result from the screening, local care pathways can be linked to the model to propose specific interventions on a 1-to-1 base to screen-detected cases. Local care pathways are defined by activities (prevention, treatment and support) and a setting, where the precise choice of caregiver and setting may depend on local services. For instance, primary prevention can be considered for women in complete remission after a depressive episode in the past or secondary (or even tertiary) preventive interventions for women with current depressive complaints or substance abuse. The nature of the intervention can range from short-term individual counselling to group sessions or admission to a psychiatric ward, and from a mono-disciplinary approach (e.g. treatment of depression) to integral approaches (e.g. interventions related to psychopathology, psychosocial problems and substance abuse as combined). Similarly, various disciplines can be involved in this model, such as prenatal caregivers, psychiatrists and social workers.

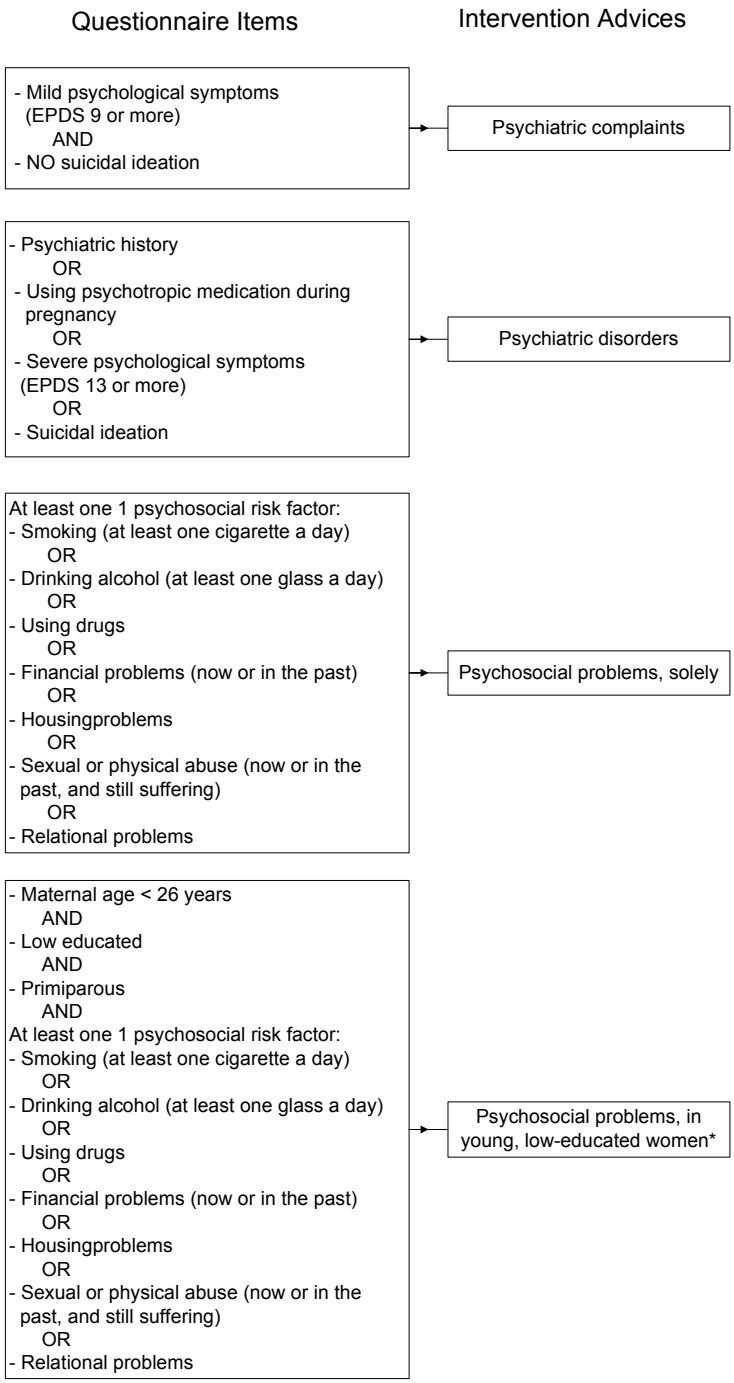


Figure 1 Screen-and-advice algorithm: entry-criteria for the four pregnancy-specific mental health interventions, available in Rotterdam.
***Dutch equivalent** of the Nurse-Family Partnership program from David Olds[27]

We adapted the screen-and-advice model to the local care pathways of Rotterdam, by incorporating four pregnancy-specific mental healthcare programs. Two programs focus on psychiatric support [BeBe and professional psychiatric support (PPS)], where milder cases with current symptoms receive BeBe, and the more severe cases receive PPS. The combined BeBe and PPS is suggested if mild symptoms coincide with a severe, yet non-manifest psychiatric background. The other two programs (Prezorg and Voorzorg in Dutch, translated into PreParent and PreCare) focus on psychosocial support, where PreCare (the equivalent of the American program Nurse-Family Partnership)[27] is additive to PreParent in the more severe cases.

The self-report questionnaire was programmed on a PDA (handheld computer) using a patient-friendly interface. An additionally programmed algorithm translated the item responses into intervention advices for any of the four programs (see Figure 1). Prenatal caregivers only had access to the advices provided (screen result), not to the preceding answers given to individual questions. Unlike health measures such as the SF-36,[28] the GyPsy is a classification tool; hence, GyPsy sum scores have no use in this context.

The advantage of tailored PDA-generated advices is that caregivers without specific training are able to screen for mental health problems and guide high-risk women to tailored care, independent of the level of expertise and knowledge about mental health problems. Other advantages of PDA's relate to the digital aspect. Digital screening is recommended if sensitive questions are asked, e.g. sexual abuse or drug abuse during pregnancy,[29,30] as it is supposed to increase valid answers. The adaptive character of digital screening allows for time efficiency: short-cuts are built-in and additional questions are asked where needed. Finally, local care pathways can be incorporated into the model, and the algorithm and its cut-off scores can be adapted upon request.

Practices & patients

To examine the performance of the GyPsy screen-and-advice model, we conducted an explanatory study from January 2010 to November 2010. We consecutively included all pregnant women with a booking visit at the obstetric clinic of a university hospital (Erasmus Medical Centre, practice EMC), an equal number of women at community midwifery practices in severely deprived areas [Midwifery Rotterdam East and West (MEW)] and 105 women at a community midwifery practice in a Rotterdam suburb (Barendrecht, MBA) representing a non-deprived area conform existing national criteria[6]. These three practices provide a representative sample of the (sub)urban pregnant population of Rotterdam and cover the range from low (MBA), moderate (MEW) to high (EMC) risk for mental health problems, in terms of cultural and socio-economical diversity. Exclusion criteria were inability to read Dutch or severe cognitive impairment. At the time of this study, the tool was available in Dutch only, because most treatments and supportive programs are available in Dutch only. Translation and intercultural adaptation of these treatments is pending.

In the Netherlands, pregnancy and delivery are monitored by independent midwives in the first echelon. Based on national guidelines, women are referred to obstetricians in a general hospital (second echelon) or in an academic referral centre (third echelon) if complications occur or interventions during pregnancy or delivery are required. A subset of high-risk women receives care through obstetricians from the onset.

In all settings, midwives and obstetricians are supported by so called "practice assistants".

In our study, routine practice was essentially kept unchanged and the PDA procedure was added prior to the booking visit. The practice assistants identified pregnant women with booking visits on consultation lists. Women were introduced to the PDA as a tool to check problems otherwise asked for during a booking visit. They were informed that the result of the PDA-questionnaire could be an intervention suggestion that subsequently was discussed with the caregiver. It was explained that the answers to the individual questions were coded and unavailable to the prenatal caregiver.

After instruction, the PDA-questionnaire was subsequently completed at a quiet place in the waiting room. Upon completion of the questions, the PDA translated the risk profile into an intervention advice, which emerged on the screen. The client took the PDA with her and showed the advice (screen result) to the prenatal caregiver during the booking consultation. The caregiver discussed the advice (if any), and, if agreed upon, referred the woman or provided other specific care.

The Medical Ethics Board of the Erasmus Medical Centre regarded informed consent redundant as the four interventions were all part of local routine care, requiring the same criteria to be fulfilled but now checked by a potentially better device, the PDA. Any screen refusal was accepted, comparable to the opting-out approach of routine screening for HIV during pregnancy. Dutch Civil Law allows for screening only if opting-out is explicit (in Dutch: the WBO and WGBO Act).

The tool was piloted in a cohort of 55 pregnant women at the obstetric department of practice EMC to check feasibility, readability of the screen, interpretation of the questions, and to establish seamless uptake in the booking protocol. The approached women were only high risk for obstetrical reasons. The screen-and-advice tool appeared understandable and unambiguous according to these respondents.

Psychometrics

To establish test-retest reliability, we randomly (SPSS tool) selected 20% (n = 65) of the EMC participants. This subset completed the same questionnaire again during a subsequent pregnancy check (median interval 13 weeks). The potential for retesting was deliberately not announced at onset. Invited women, however, were explicitly informed on the strict research purpose of this voluntarily second test. Respondents were asked to bear the situation at the initial booking in mind.

Criterion validity of the screen part of the GyPsy rests on positive and negative predictive value. In this case, a straightforward definition of the true status of client (gold standard) is unavailable, and the true status cannot be obtained by an independent alternative tool applied to all respondents. Therefore, we used the caregivers' revealed acceptation or rejection of the advice as evidence (reference standard) on the positive predictive value in cases who received an intervention advice. Similarly, we used information on the presence at any stage of manifest psychopathological or psychosocial disturbances as the best available evidence (reference standard) to establish negative predictive value among cases who did not receive an intervention advice. Information was obtained from discharge letters, peer letters and medical records. Missed cases were regarded as false negative, unless clinical evidence pointed unequivocally to an onset of the mental health problems after the screening period. As the time frame of confirmation of a positive versus a negative case is very different, and as referred patients may change caregiver, the information sources are different. In this context, false positive screen-detected cases are regarded as less clinically relevant compared to false negative cases. Being false positive will readily emerge from subsequent antenatal visits, and we assume few side effects from being at scrutiny for mental healthcare.

The calculation of predictive value was only possible for EMC participants, because the midwife registration did not allow for sufficient complete identification and tracking of their participants.

After the inclusion period, we interviewed all involved prenatal caregivers (one obstetrician, four midwives) and practice assistants (four) on the practical implications of the screen-and-advice tool. The interview included questions about the handing out of the tool with instructions, the required expertise, feasibility of this approach and pros and cons of discussing the advised interventions with the pregnant women.

Statistical analysis

Internal reliability of the EDS was expressed through Cronbach's α coefficient. Test-retest reliability was established through the intraclass correlation coefficient, Cohen's κ and Kendall's τ-b. Criterion validity was primarily determined by diagnostic negative predictive value. Positive predictive value was reported as secondary measure. To examine risk profiles and to describe feasibility judgements, we used conventional descriptive and comparative statistics, where the actual test chosen depended on data distribution. Posthoc Bonferroni adjusted pair wise comparisons were performed to identify any group related difference. All analyses were performed using the Statistical Package for Social Science, version 17.0.2.

RESULTS

Participation rate

As shown in Table 1, the screen-and-advice tool was offered to 40.8% of all pregnant women with a booking visit at the practice EMC. Major reasons for non-offering were patients arriving too late for booking visit or arriving at the emergency unit, temporary lack of practice assistant's support, and rarely, non-adherence of personnel to the protocol.

In total, 22 women were excluded, 21 due to insufficient command of the Dutch language and one due to mental retardation. Thirty women refused participation or did not complete the screening, due to internal conflicts with cultural beliefs, like the belief that mental problems are taboo (37%).

In total, data from 621 booking visits were included: 259 from practice EMC, 257 from practice MEW, and 105 from practice MBA, which allowed for all required comparisons (power 0.80 and p value <0.05).

Table I. Participation rate among pregnant women with a booking visit at three antenatal practices in Rotterdam.

	Practice Cohorts			
	EMC	**MEW**	**MBA**	**Total**
Booking visits during inclusion period, emergencies included (n)	696	n.a.	n.a.	
Booking visits approached for participation[a]	284 (40.8)	284	106	
Exclusions[a]	12 (4.2)	10 (3.5)	0	
Refusal or missings[a]	13 (4.6)	17 (6.0)	1 (1.0)	
Participants[a]	259 (91.2)	257 (90.5)	105 (99)	621 (93.5)

EMC, Erasmus Medical Centre
MEW, Midwifery practice Rotterdam East and West
MBA, Midwifery practice Barendrecht
[a] *Given as number, percentage*

Risk profiles and intervention advices

Characteristics and risk profiles of the three populations appeared comparable (Table 2). Participants were about 30 years old; the majority was Dutch and had a partner. Significant inter-practice differences existed regarding age, level of education, regular employment, mean gestational age at booking visit and gravidity. Regarding risk factors, prevalence of psychotropic medication and mean EDS score differed significantly.

Despite different risk profiles, no significant inter-practice differences existed in the number or type of intervention advices. About half of the participants were found screen-positive, receiving the advice for one or more of the four interventions involved (EMC 48.3%; MEW 42.4%; MBA 44.8%). Over 25% received an advice related to psychiatric complaints or disorders, and about another 25% received an advice related to psychosocial problems (Table 3). Ten percent of all women were found screen-positive for both interventions related to

Table II. Sociodemographical and obstetrical background, and psychiatric and psychosocial risk factors covered by the GyPsy screen-and-advice model, in 3 practice cohorts (n=621)

	Practice Cohorts				
Items	**EMC (n=259)**	**MEW (n=257)**	**MBA (n=105)**	**Test statistic**	**Significance**
Sociodemographical background					
Maternal age, y (mean ± SD)	31.2 ± 5.4[1]	29.9 ± 5.2[2]	30.8 ± 4.7	F = 4.05	0.018
Ethnicity[a] (n, %)				x^2 = 16.80	< 0.001
- Dutch	111 (42.9)	137 (53.3)	70 (66.7)		
- Moroccan	21 (8.1)	24 (9.3)	6 (5.7)		
- Turkish	20 (7.7)	14 (5.4)	2 (1.9)		
- Surinamese or Antillian	44 (17.0)	39 (15.2)	8 (7.6)		
- Other	48 (18.5)	34 (13.2)	14 (13.3)		
Level of education (n, %)				x^2 = 18.48	0.001
- Low	69 (26.7)[1]	47 (18.3)[2]	14 (13.4)[2]		
- Medium	83 (32.1)	77 (30.0)	39 (37.1)		
- High	75 (29.0)	114 (44.4)	49 (46.7)		
Partnered (n, %)				x^2 = 5.38	0.250
- Yes, living together	225 (86.9)	221 (86.0)	98 (93.3)		
- Yes, not living together	22 (8.5)	25 (9.7)	3 (2.9)		
- No	11 (4.2)	8 (3.1)	4 (3.8)		
Paid Job (n, %)	178 (68.7)[1]	211 (82.1)[2]	76 (72.4)	x^2 = 13.83	0.001
Obstetrical background					
Gestational age, w (mean ± SD)	16.9 ± 9.7[1]	10.1 ± 3.8[2]	11.7 ± 6.5[2]	F = 53.29	< 0.001
Gravidity (n, %)				x^2 = 40.48	< 0.001
1	76 (29.3)[1]	132 (51.4)[2]	38 (36.2)		
2	93 (35.9)	74 (28.8)	36 (34.3)		
3	39 (15.1)	27 (10.5)	23 (21.9)		
4	26 (10.0)	15 (5.8)	6 (5.7)		
5 or more	25 (9.7)	9 (3.5)	2 (1.9)		
Psychiatric risk factors					
Psychiatric history (n, %)	51 (19.7)	42 (16.3)	19 (18.1)	x^2 = 0.72	0.700
Psychotropic medication past (n, %)	23 (8.9)	12 (4.7)	7 (6.7)	x^2 = 3.38	0.184
Psychotropic medication during pregnancy (n, %)				x^2 = 9.74	0.045
- Yes, untill pregnancy was known	6 (2.3)	5 (1.9)[1]	2 (1.9)[2]		
- Yes, still	9 (3.5)	1 (0.4)	6 (5.7)		
- No	240 (92.7)	241 (93.8)	95 (90.5)		
Mean EDS score (mean ± SD)	6.7 ± 6.2[1]	5.5 ± 2.2[2]	6.4 ± 5.6	F = 3.14	0.044

Table II continued

Items	Practice Cohorts				
	EMC (n=259)	MEW (n=257)	MBA (n=105)	Test	Significance
Psychosocial risk factors (n, %)					
Smoking[b]	59 (22.8)	51 (19.8)	19 (18.1)	$x^2 = 1.61$	0.448
Alcohol[c]	4 (1.6)	9 (3.5)	1 (0)	$x^2 = 3.03$	0.220
Drugs	8 (3.1)	7 (2.7)	4 (3.8)	$x^2 = 0.32$	0.851
Insufficient support[d]	12 (4.6)	9 (3.5)	1 (1.0)	$x^2 = 2.85$	0.248
Financial problems[e]	50 (19.3)	32 (12.5)	16 (15.2)	$x^2 = 4.28$	0.117
Unstable housing	14 (5.4)	11 (4.3)	6 (5.7)	$x^2 = 0.44$	0.802
Abuse[f]	7 (2.7)	3 (1.2)	4 (3.8)	$x^2 = 2.68$	0.262
Relational problems[g]	18 (6.9)	13 (5.1)	3 (2.9)	$x^2 = 3.10$	0.213

EMC, Erasmus Medical Centre
MEW, Midwifery practice Rotterdam East and West
MBA, Midwifery practice Barendrecht
[a] *A woman is considered of non-Dutch ethnicity if she or at least one of her parents is born outside the Netherlands*
[b] *Smoking at least one cigarette a day*
[c] *Drinking at least one glass of alcohol a day*
[d] *Insufficient support by partner or environment*
[e] *Currently or in the past*
[f] *Sexual abuse or domestic violence currently or in the past*
[g] *Relational problems with partner/family/friends*
Superscripts 1, 2 and 3 represent significant interpractice differences according to post hoc Benferroni-adjusted pairwise comparison

psychiatric disorders and interventions related to psychosocial problems. Additional analysis showed that migrant women received significantly more advices than native women (x^2 = 13.34, $p < 0.001$), and significantly different types of intervention advices (x^2 = 18.56, p = 0.001) (data available from authors).

Table III. Intervention advices generated by the GyPsy screen-and-advice model, in 3 practice cohorts (n=621)

Intervention advice[a]	Practice Cohorts			
	EMC (n=259)	MEW (n=257)	MBA (n=105)	Total (n=621)
Psychiatric complaints	4 (1.5)	6 (2.3)	1 (1.0)	11 (1.8)
Psychiatric disorders	69 (26.6)	65 (25.3)	28 (26.7)	162 (26.1)
Psychosocial problems solely	86 (33.2)	64 (24.9)	29 (27.6)	179 (28.8)
Psychosocial problems, in young, low-educated women	8 (3.1)	7 (2.7)	2 (1.9)	17 (2.7)
Yes, any	125 (48.3)	109 (42.4)	47 (44.8)	281 (45.2)
No, none	134 (51.7)	148 (57.6)	58 (55.2)	340 (54.8)

EMC, Erasmus Medical Centre
MEW, Midwifery practice Rotterdam East and West
MBA, Midwifery practice Barendrecht
Data are given as number (%)
[a] *Testing 'yes, any' across thee practices x^2=1.794, p = 0.0408, testing separate advices across three practices x^2 = 5.216, p = 0.734*

Psychometrics

The EDS proved to have high internal reliability in all practices, with Cronbach's α ranging from 0.88 (practice MEW) to 0.90 (practice EMC), unrelated to level of education or ethnicity. Of 65 selected for retest, 17 (26.2%) were no longer pregnant (miscarriage, termination of pregnancy, or had already given birth), and five women (7.7%) undertook pregnancy checks elsewhere. Test-retest reliability of the remaining 43 women (66.2%) ranged 0.80–1.00 (ICC); 0.85–1.00 (Kendall's τ); 0.64–0.94 (Cohen's κ) with the poorest retest score for the past use of psychotropic medications. Calculation of Cohen's κ could not be calculated for the items antenatal alcohol consumption, antenatal use of recreational drugs and insufficient support by partner or environment. Instead, we calculated the proportion of agreement for these three items, resulting in agreement in respectively 100%, 95.1% and 97.7% of cases.

Retrospective examination of discharge letters, peer letters and medical records of the 123 negative-screened EMC participants showed that four women had mental health problems during the screen period, leading to a negative predictive value of 96.7%. During booking consultation of the 136 positive-screened EMC participants, 19 were not at risk for mental health problems, leading to a positive predictive value of 86.2%. Hence, we cannot judge the validity of patients from MEW and MBA.

Eight of nine interviewed practice assistants and caregivers indicated that the use of this tool required less than 5 minutes extra time per woman. Practice assistants spent less than 5 minutes on including and instructing pregnant women on the practical use of the handheld computer. The caregivers spent less than 5 minutes to the discussion of the advised interventions, if applicable. This was experienced not to exceed the effort if the same intervention had come up after history taking. Time to complete the questionnaire rarely exceeded 10 minutes for pregnant women. About half of the midwives preferred better prior education on the content of the screen-and-advice tool and the implied relation of a particular score profile to an intervention. Overall, prenatal caregivers agreed that this screen-and-advice model is a useful complement to prenatal care.

DISCUSSION

The GyPsy screen-and-advice model with predefined cut-off scores for tailored mental healthcare in pregnancy showed high internal reliability, high test-retest reliability, high discriminatory value in terms of positive and negative predictive value and good feasibility, providing evidence that the GyPsy screen-and-advice model is valid under routine practice conditions.

The GyPsy tool was offered to only 40% of all pregnant women, whereas full coverage was the aim. Failure was primarily due to lack of time of the practice assistants or delayed arrival of the client, for which selection bias seems unlikely. Once offered, response rate to the tool

was high with an average of 94%, which suggests that pregnant women accept the tool in routine practice.

To improve implementation in the future, we advocate the following measures. First, in a hospital setting with large numbers of patients, the supportive role of practice assistants should be made an explicit task. This role can be replaced by research nurses or instructed administrative personnel. Second, in case of routine implementation of the tool, pregnant women with booking visits could be invited 15 minutes prior to the start of their consultation to avoid late arrival leading to lack of time to complete the questionnaire. The pros and cons of offering the questionnaire at home via a web-based tool should be investigated.

Other studies support the high prevalence of pregnant women with mental health problems in urban areas.[31–35] Such high rates, however, might challenge the existing capacity to deal with all screen-detected or referred cases. The required capacity, however, is much less than the prevalence rate. Current thresholds of our screen-and-advice tool were designed to be sensitive and aimed at women with increased risk for adverse outcome during pregnancy and delivery, with an intentional second stage judgment by the caregiver. Screen-positives are possibly eligible for intervention. The second stage discussion with the prenatal caregiver a few minutes after completing the questionnaire has two aims. First, it creates a window of opportunity for checking sensitive problems during a booking visit, which otherwise are left unnoticed. Second, it provides a natural opportunity to put aside the advice if the burden of treatment exceeds the anticipated gains (e.g. in minor cases or cases with a history of treatment failure). Screen-positivity is thus confirmed without delay on the spot.

Limited diagnostic and treatment capacity was not a constraint in the four Rotterdam programs, but limited capacity could be a serious problem in other local care systems elsewhere requiring cut-off adaptation to ensure treatment of the worst cases.

Negative and positive predictive value appeared high. Due to the absence of a simple comprehensive gold standard to define a case, the positive predictive value may be lower than was obtained in this study.

Our expectation that women in more deprived areas have more mental health problems than those in less deprived areas was not confirmed. In our urban population, the diversity of background characteristics among the three practice populations is unrelated to the uniform and rather high level of mental health problems. A few non-exclusive explanations are possible. First, the added risk of low-socioeconomically status and deprivation might not be that strong in pregnant women, if moderate mental health problems are at issue. It is, for instance, known that alcohol abuse shows a strong positive association with higher socio-economic class. Second, women with higher educational level or coming from non-deprived areas might more easily admit mental health problems or even complain about their mental health. However, our tool could be unsuitable for women from the lowest socio-economic strata.

The observed overlap in intervention advices for both psychiatric disorders and psychosocial problems does not suggest redundancy or inefficiency, but rather underlines that these two categories of problems cannot be considered independent, nor from an etiological point of view, neither from a therapeutic perspective. Treating a depressive disorder has little impact when one is homeless.

Nearly 20% of screen-detected true cases appeared already under treatment for mental health problems, which suggests the model to be inefficient (rather than invalid). Generally, the booking visit checks current medical status, but some clinical domains receive little systematic attention. Mental health problems and psychiatric pharmaceutical treatment are known to suffer from underreporting, and our instrument may add to the awareness of perinatal caregivers. Also, active psychiatric treatment often needs to be adopted during pregnancy to accommodate new needs, as pregnancy can affect mental health. Hence, redundancy of detection is not the issue, but an existing therapeutic history requires careful reconsideration of treatment options. For this purpose, we will add questions to label the women who are already under treatment, and change the wording of the intervention into an alert for prenatal caregivers.

The feasibility of the model was good. For digital screening, we used PDA-devices with on-demand support from practice assistants. The straightforward application of the model and unambiguous cut-off score contributed to acceptability from the caregiver's viewpoint. Time efficiency was apparent: response time rarely exceeded 10 minutes. The adaptive questioning and the instant presentation of results on the screen add to this efficiency.[36–38] Digital surveys have been advocated for sensitive data,[29,30] such as illicit drug use and sexual or physical abuse. Our study confirms this preference by showing high compliance to answering sensitive questions. This is maybe the result of the "discretion" of the instrument where only final intervention advices are presented to prenatal caregivers. Asking for sensitive questions during a face-to-face interview might be too intrusive during the first contact between a pregnant woman and her prenatal caregiver.

Compared to current passive recording of mental health problems, digital screening undoubtedly requires extra time. Although the effectiveness of the early detection is not studied in this paper, we believe that the clinical relevance is likely to be superior since mental health problems are not detected systematically under current standard arrangements. Therefore, systematic detection of these problems (and initiation of the appropriate actions once being screen-positive) is an improvement compared to the current situation. Nevertheless, a formal study on the effectiveness of early detection-with-intervention is urgently needed, preferably through a well-sized randomized design to reveal both small to moderate effects and the secondary effects of the increased awareness.

The technical flexibility allows for the implementation of the tool elsewhere. We assume interventions will also be available elsewhere although precise entry-criteria may differ and entitlement will differ among countries. Even if access to pregnancy-specific mental care is

limited, the model can be adapted to the available local care, where for example general mental healthcare and social services can be offered to the worst off. Even in that case, our systematic approach contributes to decreasing healthcare inequalities which often arise in the urban context.

At this stage, we have no follow-up data available. Our intent was to test the performance psychometrics of the model, and systematic use under practice conditions first, before moving to the subsequent follow-up process.

In the future, we will implement the screen-and-advice model at large, enabling routine screening of mental health problems for all pregnant women. We intend to also develop a postnatal version of the model so that structured postpartum mental healthcare protocols become available. We demonstrated a comprehensive screen-and-advice model for psychopathology and psychosocial problems, including substance abuse, during pregnancy, which takes advantage of new proven technologies. We believe our approach offers a high potential for routine application of mental healthcare in urban environments where risk levels are high.

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CHAPTER 3

Patient versus professional based psychosocial risk factor screening for adverse pregnancy outcomes

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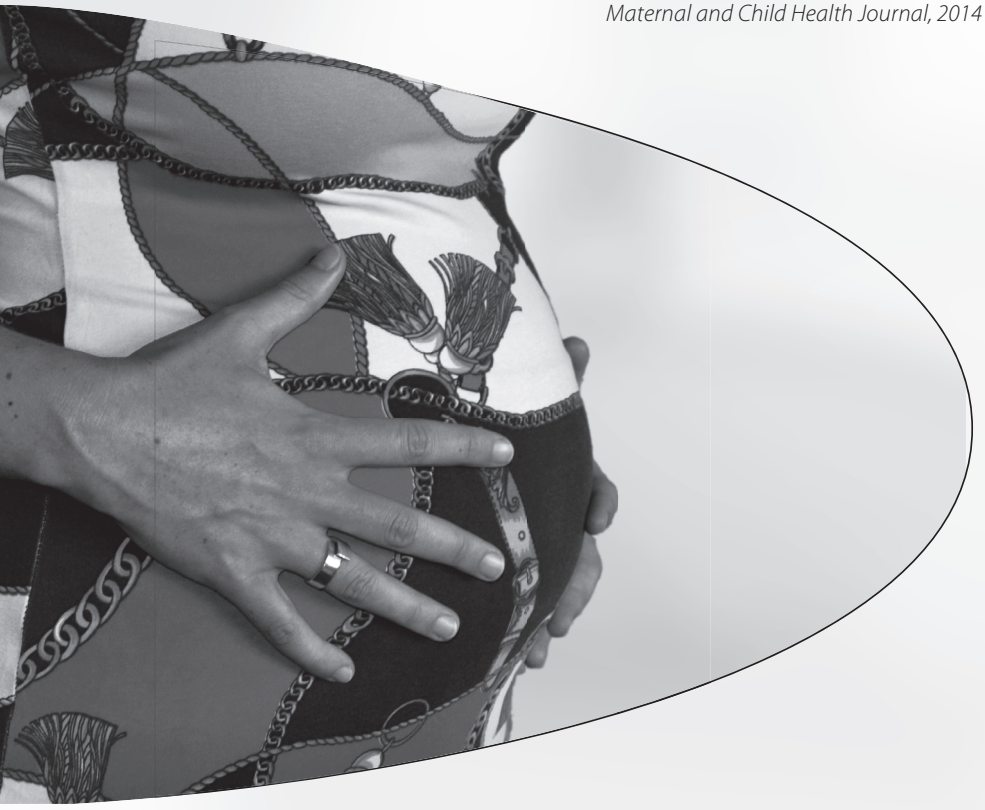
Maternal and Child Health Journal, 2014 Mar 1, in press



ABSTRACT

To identify Psychopathology, Psychosocial problems and substance use (PPS) as predictors of adverse pregnancy outcomes, two screen-and-advice instruments were developed: Mind-2Care (M2C, self-report) and Rotterdam Reproductive Risk Reduction (R4U, professional's checklist). To decide on the best clinical approach of these risks, the performance of both instruments was compared.

Observational study of 164 pregnant women who booked at two midwifery practices in Rotterdam. Women were consecutively screened with M2C and R4U. For referral to tailored care based on specific PPS risks, inter-test agreement of single risks was performed in terms of overall accuracy and positive accuracy (risk present according to both instruments). With univariate regression analysis we explored determinants of poor agreement (<90 %). For triage based on risk accumulation and for detecting women-at-risk for adverse birth outcomes, M2C and R4U sum scores were compared. Overall accuracy of single risks was high (mean 93 %). Positive accuracy was lower (mean 46 %) with poorest accuracy for current psychiatric symptoms. Educational level and ethnicity partly explained poor accuracy ($p<0.05$). Overall low PPS prevalence decreased the statistical power. For triage, M2C and R4U sum scores were interchangeable from sum scores of five or more (difference <1 %). The probability of adverse birth outcomes similarly increased with risk accumulation for both instruments, identifying 55–75 % of women-at-risk.

The self-report M2C and the professional's R4U checklist seem interchangeable for triage of women-at-risk for PPS or adverse birth outcomes. However, the instruments seem to provide complementary information if used as a guidance to tailored risk-specific care.

OBJECTIVE

Conventional antenatal risk assessment focuses on medical and obstetric risk factors only.[1, 2] Several recent cohort studies, however, have stressed the equal importance of non-medical and non-obstetric risk factors, e.g. non-Western ethnicity, smoking and depression during pregnancy, as predictors of poor perinatal health.[3–7]

As the Netherlands show high rates of perinatal mortality and morbidity[1, 8] with accumulation of medical and non-medical risk factors as important contributors,[9] risk guided individualized care is a key target.[1] The Erasmus Medical Centre developed two antenatal screen instruments in parallel: the patient based Mind2Care (M2C) screen-and-advice instrument (formerly known as the "GyPsy instrument")[10] and the professional based Rotterdam Reproductive Risk Reduction checklist (R4U).[1] M2C is a validated self-report personal digital assistant (PDA)-based instrument, developed for screening and subsequent treatment allocation for psychopathology, psychosocial problems and substance use (together 'PPS'). R4U is a standardised general risk checklist for obstetric caregivers, to screen for a wide range of risk factors related to adverse outcomes, in particular preterm birth (PTB) and small for gestational age (SGA).[11]

Both instruments address PPS. M2C is more extensive and relies on self-reportage, while R4U is brief but may benefit from the face-to-face professional's judgement. Both instruments can lead to tailored care, based on the specific PPS risk profile. Regarding accumulation of PPS risk, both instruments apply sum scores for triage.

To decide on best clinical use, we performed a head-to-head comparison. For referral to tailored care, based on specific PPS risks, inter-test agreement of single M2C and R4U risk factors was established. Agreement was hypothesized to depend on the literal phrasing of the M2C and R4U questions and responses, women's characteristics, the interviewer (individual midwife), and women's satisfaction with either instrument.

For triage and for early identification of women-at-risk for adverse outcomes, we established the inter-test equivalence of M2C and R4U sum scores. Instruments were hypothesized to be substitutable.

METHODS

Design

This longitudinal study was conducted from September to October 2011 and from January to April 2012 among all Dutch speaking pregnant women with a booking visit at two midwifery practices in Rotterdam, the Netherlands. Study approval was obtained from the Medical Ethical Board of the Erasmus Medical Center (MEC-2011-229). The study confirmed the ethical standards following the Declaration of Helsinki and its later amendments.

Data Collection

After written informed consent, women completed the M2C questionnaire on a PDA prior to the booking visit. During booking visit, the community midwife completed the R4U checklist by interviewing the same women. All midwives were trained to complete the R4U interview, and were blinded for the M2C results.

After booking visit, women completed a 15-item survey to rate their satisfaction with both instruments (including clarity, time investment, handiness, anonymity and privacy) and their preference for one of the instruments (and the corresponding method: self-report versus professional's interview).

Patient characteristics included maternal age, socioeconomic status, ethnicity, educational level, parity and the presence of a partner during booking visit.

Birth outcomes obtained from medical records included PTB, SGA, low APGAR scores and congenital malformations (together defined as 'Big 4 conditions', as they relate to 85% of perinatal mortality),[12] interventions during delivery, and maternal complications.

Outcome Measures

Inter-test agreement included for each risk factor the observed prevalence and the number of missing responses on both instruments, the overall accuracy, positive item agreement, item disagreement, positive accuracy, and comparability of question and response options. Overall accuracy included response agreement for single risk factors (2x2 analysis: yes or no on both instruments; and 3x3 analysis: yes or no or missing on both instruments).

Positive item agreement (M2C+ R4U+) included a positive response on both instruments for a single risk factor. Item disagreement included a positive response on one instrument and a negative response on the other instrument (M2C+ R4U- and M2C-R4U+). Positive accuracy was calculated as positive item agreement divided by positive item agreement and item disagreement.

Overall accuracy below 90% and a positive accuracy below 60% were pre-determined as poor inter-test agreement. These cut-offs were derived from the kappa's cut-offs of 0.6 for moderate agreement and 0.8 for substantial agreement.[13] As we expected overall agreement to be very high, we set the cut-off at 0.90.

To compare the triage performance of both instruments, inter-test equivalence was examined through comparing the proportion of women-at-high-risk for PPS identified by M2C versus R4U for different sum scores. This was repeated for the early identification of women-at-risk for adverse outcomes.

Statistical Analysis

Sample size was based on estimated prevalence of common risks (e.g. 15% depressive symptoms) and on the anticipated 90% overall accuracy derived from previous studies with M2C[10] and R4U solely (unpublished R4U data, presented at the International Confederation

of Midwives 29th Triennial Conference, June 2011, Durban, South Africa). We aimed at 115 valid responses.

Conventional descriptive statistics were used to describe the study population. PPS prevalence, missing responses, item agreement and item disagreement were reported as counts. Overall accuracy and positive accuracy were quantified with 2x2 tables (or 3x3 tables in case of missing responses) and expressed as proportions.

Associations between poor accuracy and literal phrasing of questions and response options, women's characteristics, the individual interviewer, and women's satisfaction and preferences were explored with univariate logistic regression analyses. Associations with a p value below 0.05 were regarded as significant. The statistical power did not allow regression analysis for poor positive accuracy.

For triage, M2C and R4U sum scores were compared with X–Y plots, to check whether differences, if any, were systematic or not.

All analyses were performed using the Statistical Package for Social Science, version 20.0.

RESULTS

Study Population

As Figure 1 shows, 270 women had a booking visit, of which 16% were excluded (n = 44), and 27% refused participation (n = 61), mainly for perceived lack of usefulness of the study (n = 31), and lack of time (obstetric caregiver n = 12; pregnant woman n = 10). Refusers were older, more often of non-Western ethnicity and had a lower gestational age at booking (all $p<0.05$, data available upon request). As one woman was excluded due to missing responses, 164 women were included in analysis. Birth outcomes were available for 116 women (71%), with lack of consent for follow-up as main reason for unavailability (n = 31).

Table 1 shows that the median maternal age was 29 years, 47% were highly educated, 55% were of Western ethnicity and 55% were nulliparous. Big 4 conditions were present in 14% of which 9% SGA. About 30% of women had an induced labour, 20% had an assisted delivery and 38% received some kind of analgesia during delivery.

Inter-Test Agreement

Table 2 shows the inter-test agreement of single PPS risk factors as measured by both instruments. The observed prevalence of each risk was generally equal, except for 'current psychiatric symptoms' (M2C n = 30; R4U n = 6). Missing responses were infrequent and relatively equally distributed over both instruments.

Overall accuracy was generally high (mean 93%; range 71–100%). Accuracy was lower than 90% for the risk factors: low income, hospital admission for psychiatric disorder, current psychiatric symptoms and periconceptional alcohol consumption. Psychosocial risk factors were

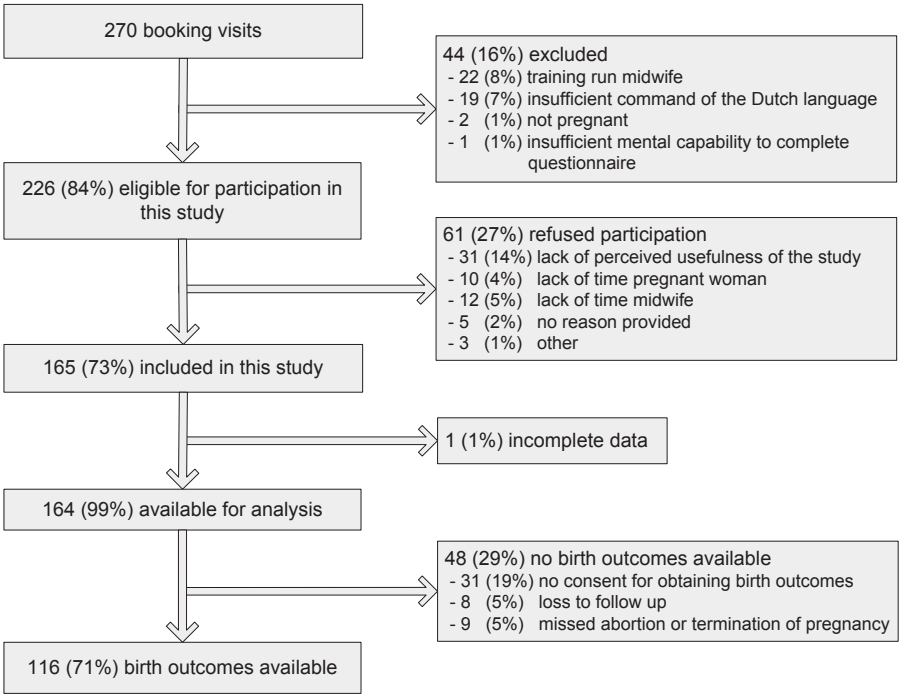


Figure 1 Study population

more often detected by M2C than by R4U (higher counts of disagreement M2C+ R4U-), while intoxications were more often detected by R4U (higher counts of disagreement M2C- R4U+). The proportion positive accuracy, defined as positive responses on both instruments, among any positive response, was lower than the overall accuracy (mean 46%; range 13–100%). Ten risk factors showed a positive accuracy below 60%: housing problems, relational problems, physical or sexual abuse, unintended pregnancy, (previous) hospital admission for psychiatric disorder, psychotropic medication use, current psychiatric symptoms, smoking during pregnancy, periconceptional alcohol consumption and periconceptional illicit drug use.

Poor overall accuracy appeared unrelated to differences in literal phrasing of questions and response options, e.g. despite low income questions and response modes being literally equal in both instruments, the overall accuracy appeared low. Hospital admission for psychiatric symptoms had comparable questions (++) and response modes which were alike (+), but the overall accuracy appeared high.

Exploratory univariate regression analysis (Table 3) showed that low overall accuracy of the risk factors 'low income', 'periconceptional alcohol consumption', 'hospital admission for psychiatric disorder' and 'current psychiatric symptoms' were associated with educational level and ethnicity ($p<0.05$). These univariate associations pointed in different directions for each

Table 1. Characteristics of pregnant women who booked at two midwifery practices in Rotterdam, the Netherlands

	Participants (n = 164)				Participants (n = 116)	
Determinants	*n*	%	164	*Birth outcomes*	*n*	*%*
Maternal age (years)[a]	29	(26 ; 33)		Big 4 condition[f]	16	14
Educational level[b]				Preterm birth[g]	0	0
low	36	22		Small for gestational age[h]	11	9
moderate	51	31		Induced labour	33	28
high	77	47		Assisted delivery[d]		
Socioeconomic status[c]				none	92	79
< 20th percentile	69	42		vaginal instrumental delivery	12	10
20th - 80th percentile	42	26		emergency caesarean section	12	10
≥ 80th percentile	53	32		Analgesia during delivery		
Living in a deprived area	57	35		none	72	62
Ethnicity[d]				pethidine, remifentanyl, sedativa, systemic analgisica	25	22
Dutch	91	55		epidural / spinal analgisica	19	16
Moroccan	15	9		Maternal complications		
Antillian	4	2		none	97	84
Surinamese	10	6		PE/HELLP	1	1
Turkish	11	7		haemorrhage	4	3
other non-Western	33	20		manual removal of placenta	6	5
Gestational age[e]				3rd or 4th degree perineal tear	8	7
< 8 weeks	13	8				
8-9 weeks	87	53				
≥ 10 weeks	62	38				
Nulliparity	91	55				
Partner present during booking	100	61				

[a] Data given as median (Q1;Q3)

[b] Defined as the highest education completed. 'Low' indicating primary school or special schooling, 'moderate' indicating secondary school or high school, 'high' indicating college or university

[c] Based on a z-score for socio-economic status nationally available at the website of the Central Bureau of Statistics (http://statline.cbs.nl/StatWeb/dome/default.aspx)

[d] Percentages do not add up to 100% due to rounding

[e] Percentages do not add up to 100% due to 2 missing values

[f] Big 4 conditions are defined as preterm birth (< 37 weeks of gestation), or SGA (<p10), or APGAR score < 7, 5 minutes after birth, or congenital malformations

[g] Defined as delivery before 37th week of gestation

[h] Below the 10th percentile

of the risks, without a systematic pattern, e.g. odds ratios for 'alcohol consumption' pointed in opposite directions compared to odds ratios for 'low income'.

The majority of women were satisfied with both instruments (>75%, 14% no opinion). Advantages of the self-report M2C included fast digital screening, the easy to handle instrument,

Table 2. Inter-test agreement of single risk factors as measured by the Mind2Care (M2C) and R4U screen instruments (n=164)

	Observed risk factor prevalence		Missing responses		Overall accuracy		Positive item agreement	Item disagreement		Positive accuracy[6]	Literal question and response agreement[7]	
	M2C	R4U	M2C	R4U	2x2[1]	3x3[2]	M+R+[3]	M+R-[4]	M-R+[5]			
Psychosocial risk factors	*n*	*n*	*n*	*n*	%	%	*n*	*n*	*n*	%	Q	R
Single status	7	11	0	0	97.6	97.6	7	0	4	63.6	++	++
Insufficient social support	1	1	0	0	99.4	98.8	0	1	1	n.a.	+	+++
No paid job	43	35	0	0	90.2	90.2	31	12	4	66.0	++	+++
Low income (<€1000 net monthly)	14	17	3	0	90.9	**89.0**	0	6	9	n.a.	+++	+++
Financial problems	12	9	0	1	97.0	96.3	8	4	1	61.5	++	+++
Housing problems	9	8	0	0	94.5	94.5	4	5	4	**30.8**	+++	+++
Relational problems	7	6	2	1	94.5	92.7	2	5	4	**18.2**	++	+++
Physical or sexual abuse	7	3	1	1	96.3	95.1	2	5	1	**25.0**	+	+++
Unintended pregnancy	9	10	1	1	92.1	90.9	3	6	7	**18.8**	+	++
Psychiatric risk factors												
Hospital admission for psychiatric disorder ever (pregnant women herself or first degree relative)	7	4	15	1	98.2	89.6	4	3	0	**57.1**	++	+
Use of psychotropic medication ever	5	6	0	0	97.0	97.0	3	2	3	**37.5**	+++	+++
Current psychiatric symptoms	30	6	0	2	**82.9**	**82.3**	4	26	2	**12.5**	+	+
Substance use risk factors												
Smoking periconceptionallly	34	33	0	0	93.3	93.3	28	6	5	71.8	++	++
Smoking during pregnancy	8	11	0	0	95.7	95.7	6	2	5	**46.2**	+++	++
Alcohol consumption periconceptionally	54	49	1	0	**71.3**	**70.7**	28	26	21	**37.3**	++	++
Alcohol consumption during pregnancy	0	2	1	0	98.8	98.2	0	1	2	n.a.	+++	++
Illicit drug use preconceptionally	1	3	0	2	98.8	97.6	1	0	2	**33.3**	++	++
Illicit drugs use during pregnancy	1	1	0	2	100.0	98.8	1	0	0	100.0	+++	++

[1] *Accuracy defined as 'yes' on both instruments or 'no' on both instruments; missings are considered as 'absence of risk'*

[2] *Accuracy defined as 'yes' on both instruments, 'no' on both instruments or 'missings' on both instruments*

[3] *Positive agreement M+R+ is defined as 'yes' measured by Mind2Care and 'yes' measured by R4U*

[4] *Disagreement M+R- is defined as 'yes' measured by Mind2Care and 'no' measured by R4U*

[5] *Disagreement M-R+ is defined as 'no' measured by Mind2Care and 'yes' measured by R4U*

[6] *Positive accuracy is defined as: [agreement M+R+] / ([disagreement M+R-] + [disagreement M-R+] + [agreement M+R+])*

[7] *+++ = literally equal; ++ comparable, + alike*

n.a. = not applicable

Bold *numbers indicate agreement below the predefined cut-off of 90% for overall accuracy and 60% for positive accuracy*

and clear questions. Advantages of the R4U included the face-to-face character, the number of questions and the clarity of the questions. Women preferred M2C for screening for psychosocial risks, and R4U for psychiatric risks, substance use, and for overall screening (40% no opinion). Women's satisfaction and preferences, as well as the individual midwife as interviewer showed no association with overall accuracy (data available upon request).

Table 3 (supplementary online table). Exploratory univariate regression analysis: determinants of poor overall accuracy of single PPS risk factors as measured by the Mind2Care (M2C) and R4U instrument among pregnant women (n=164)

	Overall accuracy for the risk factor							
	Low income (< €1000,- net monthly)		Periconceptional alcohol consumption periconceptionally		Hospital admission for psychiatric disorder		Current psychiatric symptoms	
Independent variable	*OR*	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
Maternal age (years)	1.10	(0.99 - 1.21)	**0.93**	**(0.86 - 0.99)**	1.02	(0.93 - 1.13)	1.06	(0.98 - 1.15)
Socioeconomic status (SES)								
< 20th percentile	**3.12**	**(1.11 - 8.79)**	0.76	(0.38 - 1.52)	1.25	(0.46 - 3.43)	**3.90**	**(1.65 - 9.23)**
≥ 20th percentile (REF)	1		1		1		1	
Ethnicity								
Western (REF)	1		1		1		1	
non-Western	**0.19**	**(0.06 - 0.62)**	**2.90**	**(1.13 - 7.46)**	0.69	(0.25 - 1.88)	**0.29**	**(0.12 - 0.69)**
Educational level								
low	**0.14**	**(0.04 - 0.56)**	**5.50**	**(1.47 - 20.54)**	**0.22**	**(0.05 - 0.89)**	0.64	(0.23 - 1.82)
moderate (REF)	1		1		1		1	
high	1.14	(0.24 - 5.32)	0.88	(0.42 - 1.84)	0.74	(0.18 - 3.10)	1.29	(0.49 - 3.37)
Parity								
0	0.73	(0.43 - 1.24)	**0.46**	**(0.22 - 0.93)**	1.05	(0.56 - 1.94)	0.88	(0.56 - 1.40)
≥1 (REF)	1		1		1		1	
Partner attended booking visit								
yes	**4.79**	**(1.65 - 13.90)**	0.38	(0.14 - 1.79)	1.58	(0.56 - 4.43)	1.60	(0.68 - 3.80)
no (REF)	1		1		1		1	

Bold *indicates significance of p<0.05*

Inter-Test Equivalence

Figure 2 shows that the proportion of women detected as 'high risk' by M2C is slightly higher than the proportion of women detected by R4U for each cut-off. If a sum score of two PPS risk factors is used as cut-off for example, M2C identified 37% of women, compared to 32% by R4U. From a sum score of five or more PPS risk factors, the difference in proportion of women identified was negligible (<1%).

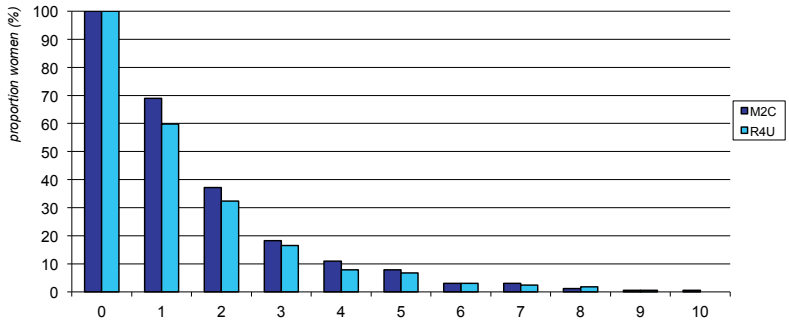


Figure 2 Inter-test equivalence of Mind2Care (M2C) and R4U sum scores. Comparison of the proportion of women identified by Mind2Care (M2C) versus R4U, by using different sum scores as cut-off (n = 164)
PPS risk factors include risk factors related to Psychopathology, Psychosocial problems and Substance use

Figure 3 shows that the proportion of women with the adverse outcomes SGA, assisted labour, pain relief during labour and maternal complication similarly increased with PPS sum score for both instruments. All adverse outcomes, however, were present among women without any PPS risk factor according to M2C and R4U. For example, panel A of Figure 3 shows that according to the M2C 36%, and according to the R4U 45% of women without any PPS risk delivered a SGA baby. The accumulation of PPS risks could identify 55% of the SGA babies

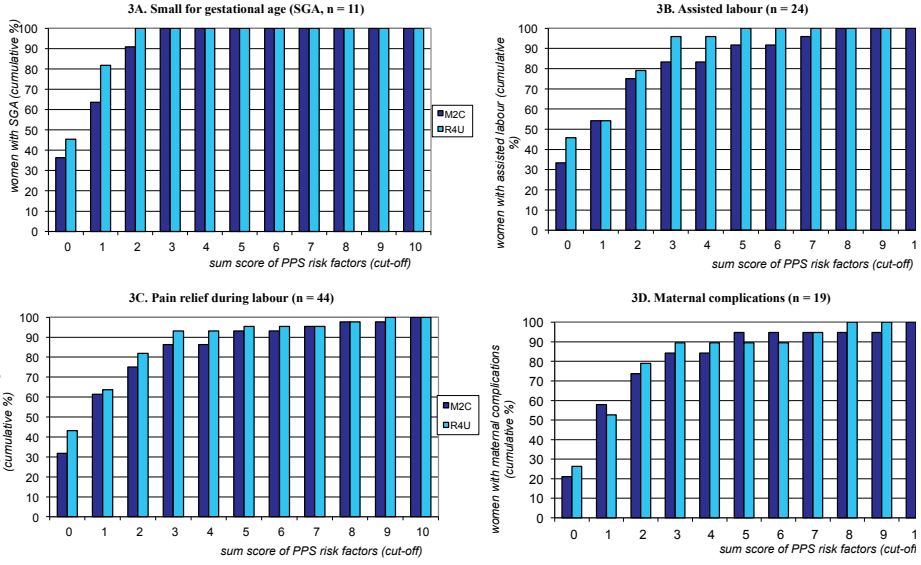


Figure 3A-D Inter-test equivalence of Mind2Care (M2C) and R4U sum scores. Comparison of the proportion of women with an adverse outcome, by using different M2C and R4U sum scores

here. Panels B, C and D show that the accumulation of PPS risks could identify respectively

54, 57 and 75% of the 'women-at-risk' for an assisted labour, pain relief during labour, and maternal complications.

CONCLUSION

Main Findings

Our head-to-head comparison of the patient based M2C instrument and the professional based R4U instrument, on how to screen and whom should screen, showed that both instruments can interchangeably be used for triage purposes, if a sum score of five is used as cut-off for high risk. M2C and R4U are also interchangeable if used for early detection of women-at-risk for adverse birth outcomes. However, if used as guidance to tailored care based on specific risks M2C and R4U are not fully interchangeable, but as we assume rather complementary instruments. Some risk factors, e.g. 'low income' and 'current psychiatric symptoms', require scrutiny and additional verification based on the poor agreement found in this study. In particular, if a specific care proposal rests on the presence of this particular risk factor.

Strengths and Limitations

Strength of this study is the systematic sampling method: a head-to-head comparison among an unselected cohort of pregnant women. Unlike most other studies[14–16] this study used a more precise definition of inter-test agreement to judge the exchangeability of the two instruments. This precise definition allows for a more detailed comparison of response patterns to M2C and R4U for individual pregnant women, instead of a global group measure of agreement. Finally, the source of inaccuracies was examined regarding pregnant women's factors and the individual midwives as interviewers.

This study is subject to several weaknesses. First, participation is biased towards slightly older women of Western ethnicity, possibly resulting in a better than average accuracy. Second, results may be subject to an order effect as the M2C instrument always preceded the R4U. While the current sequence was chosen for pragmatic purposes, the opposite sequence could have led to different responses of the women on the M2C questions. Third, major weakness of this study is the lack of an independent reference test to judge criterion validity. For some risk factors this would require unacceptable infringement of privacy, e.g. financial problems and sexual or physical abuse. For others, invasive tests would be required, e.g. blood tests for intoxications or confirmation of depressive symptoms by a psychiatrist. Due to the lack of a gold standard, we are not able to find one screen instrument to be superior over the other for the detection of single risks. This is in contrast to the findings of a comprehensive review by Lane et al.,[16] who found digital PDA-based instruments to be superior over paper-based instruments in terms of data handling and patient-friendliness. Comparisons of PDA-based

versus paper-based accuracy, however, are inconsistent.[16] Where interpretation errors of questions and response options may occur more frequently in digital self-report questionnaires, professional based interviewing is more likely to be susceptible to social desirability bias.[17]

Finally, low prevalence of positive item responses led to broad confidence intervals and decreased power to examine the association between positive accuracy and pregnant woman and interviewer factors.

Interpretation

This study confirmed high overall agreement between digital (PDA-based) questionnaires and paper-based questionnaires, as reported in previous studies,[14, 15] with educational level as a potential predictor for poor agreement.[14] Different interpretations of the M2C and R4U questions (e.g. in terms of risk definition or thresholds) might be a likely reason for poor accuracy. To increase the clarity of the questions, the M2C instrument could be extended with assistance, e.g. pop-ups or audio-support.

Another explanation of poor inter-test agreement is the avoidance of stigma or its consequences,[17] e.g. report of illicit drug use to the child protection services, leading to custodial placement of the newborn. All our study participants, however, were aware of the study aim and could have answered 'no' on both instruments to avoid stigma or consequences, therefore leading to high (negative) inter-test agreement.

As compared to US standards, prevalence of risk factors and adverse birth outcomes were low, yet representative of the general Dutch population, except for preterm birth.[3, 9,18] Remarkably, preterm birth was absent in this cohort, in contrast to previous studies.[8, 9] Selection bias, however, is not likely here, as informed consent was asked before booking visit. The most likely explanation is chance. The presence of SGA argues against an extremely healthy population.

Due to the low prevalence of PPS our findings should be interpreted with some caution and need to be further verified in future research, e.g. by repeating such a comparative study among another and larger cohort of pregnant women with a different risk profile. Repeated measurements within women could address intra-rater reliability of measurements.

As we hypothesized, the self-report M2C instrument and the professional's R4U checklist seem interchangeable if used for triage purposes or early detection of women at risk for adverse birth outcomes based on sum scores. However, if used as guidance to tailored risk-specific care, the instruments seem to provide complementary information and
could be used in addition to each other. Awaiting further evidence, we advocate as stated in the NICE guidelines,[19] that all pregnant women should be screened for PPS and subsequently be referred to tailored care if necessary.

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CHAPTER 4

Successful five-item triage for the broad specter of mental disorders in pregnancy – a validation study

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Manuscript submitted for publication

ABSTRACT

Background: Mental disorders are prevalent during pregnancy, affecting 10% of women worldwide. To improve triage of a broad specter of mental disorders, we aimed to: 1) validate a short set of currently used psychiatric triage items, 2) explore the potential of an additional (intermediate) set of psychiatric items, 3) explore the added value of the widely used 10-item Edinburgh Depression Scale (extended set), and 4) explore the incorporation of prevalent psychosocial co-predictors (comprehensive set).

Methods: Validation study of 330 urban pregnant women. Women completed a questionnaire including 20 psychiatric and 10 psychosocial items. Psychiatric diagnosis was performed through Structured Clinical Interviews of DSM-IV axis I and II disorders (SCID-I and II). Outcome measure was defined as any current mental disorder (yes/no).
The performance of the short, intermediate, extended, and comprehensive triage models was evaluated by multiple logistic regression analysis, area under the ROC curve (AUC) and test performance, including e.g. sensitivity, specificity and the number of missed cases.

Results: Diagnostic performance of the short triage model (1) was acceptable (Nagelkerke's R^2=0.276, AUC=0.740, 48 out of 131 cases were missed). The intermediate model (2) performed better (R^2=0.547, AUC=0.883, 22 cases were missed) including the five items: traumatic experience ever, feelings of a depressed mood ever, panic attack ever, current psychiatric symptoms and current severe depressive or anxious symptoms. Addition of the 10-item Edinburgh Depression Scale or the three psychosocial items unplanned pregnancy, alcohol consumption and sexual/physical abuse (models 3 and 4) further increased R^2 and AUC (>0.900), with 23 cases missed. Missed cases included pregnant women with a current eating disorder, psychotic disorder and first onset anxiety disorders.

Conclusions: For a valid detection of the broad specter of prevalent mental disorders during pregnancy, at least the intermediate set of five psychiatric items should be implemented in routine obstetric care. For a brief yet comprehensive triage, three psychosocial items should be added as independent contributors.

BACKGROUND

Pregnancy and childbirth are sensitive periods in which mental disorders can arise or relapse.[1] The prevalence of mental disorders during pregnancy varies from e.g. 13% major depressive disorder, to 1% bipolar disorders, 1% substance use disorder, 2% panic disorder, 4% post- traumatic stress disorder, 9% generalized anxiety disorder, 1% obsessive-compulsive disorder, 4% eating disorder, and 6% personality disorders.[1,2] Despite the high prevalence and subsequent short and long term adverse health outcomes for both mother and child,[3-5] mental health is not always part of routine prenatal care.[6] Consequently detection and treatment rates of pregnant women with mental disorders are low. Reasons include professional's lack of expertise and education, reluctance to take responsibility for case management, and avoidance of stigmatisation of both women and professionals. If not asked specifically, women are not inclined to report mental health symptoms spontaneously.[6,7]

In the city of Rotterdam, obstetricians and psychiatrists agree on a structured triage for mental disorders during pregnancy. Besides the general history, pregnant women with mental disorders are guided to psychiatric consultation on behalf of a short set of three psychiatric triage items: hospital admission of the woman for psychiatric disorder ever, hospital admission of a first-degree relative for psychiatric disorder ever, or psychotropic medication use ever. This selection was based on previous studies that consistently showed that psychiatric history is the strongest predictor for future psychiatric disorders.[1,8] For triage purposes, we aim at the most serious disorders, for which psychiatric admission or medication use is needed. We additionally ask for hospital admission of a first-degree relative as a general marker for increased vulnerability for psychiatric disorders, and more specifically because of the strongly increased risk for postpartum psychosis in women with a first-degree relative suffering from bipolar disorder.[9]

To further facilitate obstetrical professionals in the triage of mental disorders during pregnancy, several screen instruments have been developed worldwide. Most instruments show limitations in diagnostic coverage. First, most instruments, such as the commonly used Edinburgh Depression Scale, focus specifically on the most common disorders depression and anxiety only.[10-14] Second, personality disorders are not included, despite that these disorders are prevalent during pregnancy and are known to worsen health outcomes and complicate treatment in case of comorbid diagnosis.[15] Third, comorbid conditions such as insufficient social support and substance use are claimed to be strong independent co-predictors for mental disorders[16, 17] but are rarely incorporated in screening or triage.

A trade-off exists between a) the comprehensiveness of instruments, including mental disorders, and comorbid psychosocial stressors or substance abuse, and b) brevity, including a limited number of items, but with a rather high correlation to the broad specter of mental disorders.

To investigate the best balance of comprehensiveness and brevity for the triage of the broad specter of mental disorders of axis I and II of the DSM-IV during pregnancy, this paper aims to: 1) formally validate the currently used short set of psychiatric items, 2) explore the screen potential of an intermediate set of additional psychiatric items as suggested by clinicians, 3) explore the added value of the frequently used Edinburgh Depression Scale, and 4) explore the added value of incorporation of comorbid psychosocial items.

METHODS

Study design

From May 2012 to July 2012 we approached an unselected cohort of 512 pregnant women at low risk for mental disorders from a midwifery practice and an obstetric outpatient department of a general hospital to participate in this study. From September 2011 to July 2013, we approached a preselected cohort of 188 pregnant women at high risk for mental disorders from a tertiary hospital; including pregnant women who were referred to this hospital for psychiatric symptoms according to their general practitioner or midwife, and women with a history of psychiatric symptoms. Risk stratification was not based on a current or prior psychiatric diagnosis. All practices were located in Rotterdam, a large Dutch urban area.

Procedure

After complete description of the study to the subjects, written informed consent was obtained. Data were generated by the self-report Mind2Care screen-and-advice instrument (formerly known as GyPsy instrument)[18] and a set of seven additional psychiatric screen items. Mind2Care was primarily developed by the Erasmus Medical Center as a tool for screening and subsequent treatment allocation for psychiatric and psychosocial risk factors during pregnancy. Mind2Care includes the short set of psychiatric triage items (hospital admission of the woman for mental disorder ever, hospital admission of first-degree relative for mental disorder ever, psychotropic medication use ever), the 10-item Edinburgh Depression Scale (EDS),[19] ten psychosocial stressors, including life events and substance use (unplanned pregnancy, unwanted pregnancy, insufficient social support, relational problems, financial debts, unstable housing, sexual or physical abuse, smoking, alcohol consumption and illicit drug use), and a set of characteristics (maternal age, ethnicity, socioeconomic status, educational level, marital status, gestational age, gravidity, and parity).[18]

The intermediate set of additional psychiatric triage items was suggested by clinicians who screened more than 2300 pregnant women for mental disorders. The questions were selected and phrased on the basis of a review of the literature[1,16,20-24] and on the basis of their face validity by the research group. Seven additional items were selected: professional psychiatric treatment ever, traumatic experience ever, feelings of a depressed mood ever, panic attack

ever, current psychiatric symptoms, current severe depressive or anxious symptoms, current Table of childbirth (see table 1).

Table 1. Ten potential psychiatric items for the triage of mental disorders of the DSM-IV axis I and II during pregnanacy

Psychiatric items
Short set of triage items
Have you ever been admitted to a hospital for a psychiatric disorder?
Has a first-degree relative (father, mother, brother or sister) ever been admitted to a hospital for a psychiatric disorder?
Have you ever used psychotropic medication?
Intermediate set of triage items
Have you ever received professional treatment for psychiatric symptoms?
Have you ever experienced a major traumatic event, such as life-threatening situation, a rape or a sexual assault?
Has there ever been a period of time in which you felt depressed, down or empty, almost every day? Or that you could not enjoy activities that used to be enjoyed?
Have you ever had a panic attack?
Do you currently experience any psychiatric symptoms?
Do you currently experience severe depressive or anxious symptoms?
Do you currently experience severe fear of childbirth?

Outcome

Outcome measure was defined as any current mental disorder diagnosed through a Structured Clinical Interview of the DSM-IV axis I and axis II disorders (SCID-I and SCID-II).[21,22] SCID-I assesses major mental disorders of the DSM-IV axis I divided into seven primary classes: mood, psychotic, substance, anxiety, somatoform, eating, and adjustment disorders.

SCID-II assesses the eleven DSM-IV personality disorders divided into cluster A, B and C personality disorders. SCID responses include a 3-point rating with 1 indicating 'no', 2 indicating 'yes, subthreshold', and 3 indicating 'yes, suprathreshold'. Psychiatric diagnosis are based on the underlying SCID algorithm and scoring system. The 18 SCID classifications presented here cover all of the information available from SCID-I and II.

SCID interviews were conducted by a formally trained, certificated researcher (C.Q.) in private rooms at the outpatient departments of the participating hospitals or at the women's home. The interviewer was blinded to all previous reported data. The interviews lasted from 15 minutes for women without any mental disorder to 3 hours for women with mental disorders.

Participants

Exclusion criteria included having a miscarriage at the time of screening, being non-Dutch speaking, and insufficient mental capability to complete the Mind2Care independently. In total, 538 pregnant women fulfilled the inclusion criteria. As 206 women refused participation and two women had too many missing data, 330 women were included (Figure 1). Women did not receive a reward for participation. An a priori sample size calculation defined

that a sample of at least 120 women with mental disorder was needed to conduct statistical analysis with a power of 0.8 and 95% confidence interval.
This study was approved by the institutional review board of the Erasmus University Medical Center (MEC-2011-101).

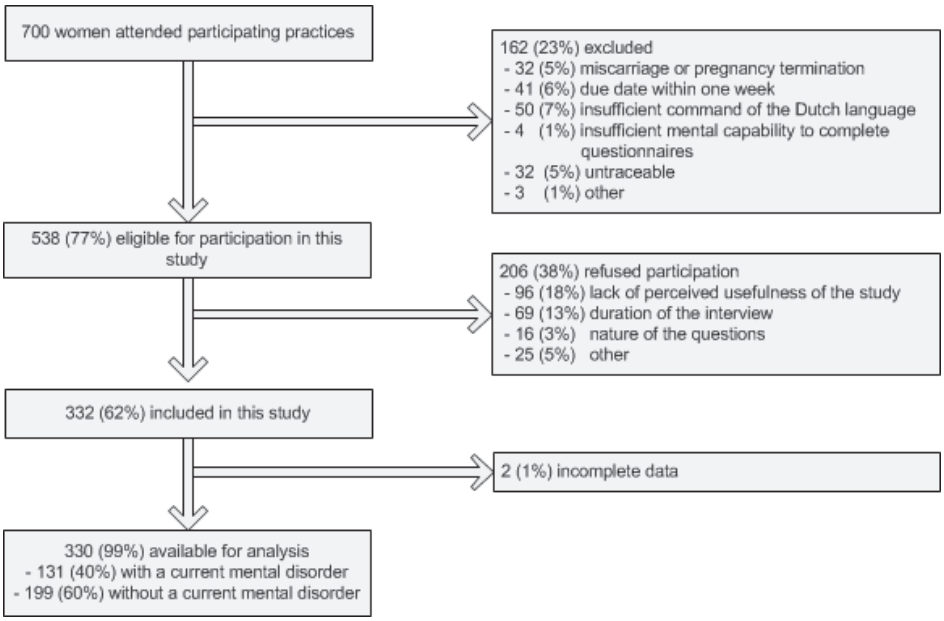


Figure 1 Study population

Statistical analysis

All analyses were performed using the Statistical Package for Social Science, version 20.0. Conventional descriptive statistics were used to describe the study population. Prevalence of characteristics, psychiatric and psychosocial triage items according to the presence of mental disorders were examined.
To validate the short, intermediate, extended, and comprehensive set of triage items, first multiple logistic regression analyses were conducted. The short set of clinically used psychiatric items were entered into model 1. Then we explored the additive potential of the intermediate set of psychiatric items in model 2, applying stepwise backwards regression. The Edinburgh Depression Scale was added in model 3 (extended set). Finally we tested the additive value of psychosocial items, including life events and substance use (model 4, comprehensive set of items). At this stage, we deliberately did not adjust for women's characteristics, as we focused on the performance of different sets of items in a heterogeneous population of pregnant women. Women's characteristics were, however, entered in a fifth model to explore the sensibility of the triage models. Sensibility was explored to ensure

validity under routine care conditions, without the exceptions of any subgroup, for example low educated women. Associations following multiple regression analyses were expressed through adjusted odds ratios and 95% confidence interval. Associations with a p-value below 0.05 were regarded as statistically significant. Model fitness was assessed by chi-squared and Nagelkerke's R-squared statistics.

Discriminant validity of the four triage models was examined with the area under the Receiver Operator Characteristics (ROC) Curve. The Area Under the Curve (AUC) was calculated for all four models, with a value of 0.70 representing acceptable discrimination, 0.80 representing excellent discrimination, and 0.90 representing outstanding discrimination. Test performances in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated using a cut-off of 0.4. The cut-off of 0.4 was chosen as it reflects the prevalence of mental disorders in our sample.

RESULTS

Table 2 reports the prevalence of current mental disorders of the DSM-IV axis I and axis II in the study population. Fourty per cent of women had a current mental disorder, with mood, anxiety and personality disorders being most prevalent.

Table 3 shows the prevalence of characteristics and triage items for the total group of women, and separately for women with and women without a current mental disorder. Women with mental disorders were more often of non-Western ethnicity (44% versus 32%), less often high educated (27% versus 41%), and more often single as compared to women without mental disorders (8% versus 3%, all $p<0.05$). All psychosocial and psychiatric triage items were more prevalent among women with a current mental disorder, except for unstable housing (9% versus 3%, $p=0.090$) and hospital admission of a first-degree relative for mental disorders ever (16% versus 12%, $p=0.242$).

Table 4 shows the multivariate logistic regression models for the prediction of mental disorders. All models appeared to be legitimate ($p<0.001$), with an increasing goodness of fit by adding more items to the model, as we would expect.

Model 1 represents the short set of three psychiatric items with a Nagelkerke's R^2 of 0.276. The AUC was 0.740 (95% CI: 0.683-0.797), representing an acceptable discrimination (Figure 2). The test performance of the model at the cut-off point of 0.4 showed a high specificity and NPV (0.83 and 0.77), yet 48 out of 131 cases were missed and 34 non-cases were falsely identified as a case.

Model 2 includes the intermediate set of five psychiatric items for the detection of mental disorders during pregnancy, as nominated through a backwards stepwise regression analysis (see Table 5). Nagelkerke's R^2 was 0.547, and the AUC showed an excellent discrimination

Table 2. Psychiatric diagnosis of study participants established by SCID I and SCID II[1] (n = 330)

	Participants (n = 330)	
Psychiatric diagnosis	*n*	*(%)*
Current mental disorder (axis I or II)	131	(40)[2]
Current mental disorder on DSM-IV axis I	110	(33)
Mood disorder	57	(17)
Bipolar disorder type I or II	1	(0)
Major depressive disorder	54	(16)
Dysthymic disorder	2	(1)
Psychotic disorder	8	(2)
Substance related disorder	7	(2)
Anxiety disorder	71	(22)
Panic disorder	43	(13)
Phobias	13	(4)
Obsessive-compulsive disorder	5	(2)
Post-traumatic stress disorder	20	(6)
Generalized anxiety disorder	14	(4)
Somatoform disorder	0	(0)
Eating disorder	5	(2)
Adjustment disorder	4	(1)
Current mental disorder on DSM-IV axis II	56	(17)
Cluster A personality disorder	0	(0)
Cluster B personality disorder	33	(10)
Cluster C personality disorder	30	(9)

[1] Diagnosis based on Structured Clinicial Interview of DSM-IV disorders axis I and II (SCID I and SCID II)

[2] Including 44 women of the unselected cohort (low a priori risk for mental disorders) and 87 women of the preselected cohort (high a priori risk for mental disorders)

of 0.883 (95% CI: 0.846-0.921). Sensitivity and NPV appeared high (0.83 and 0.88). Model 2 missed 22 cases and identified 45 non-cases as cases.

Addition of the 10-item Edinburgh Depression Scale (model 3, extended set of 15 items), increased Nagelkerke's R^2 with 16% to 0.637 and the AUC to 0.918 (95% CI: 0.887-0.949), representing outstanding discrimination. Twenty-three cases were missed and 25 non-cases were falsely identified as a case.

The three psychosocial items sexual or physical abuse, alcohol consumption during pregnancy and having an unplanned pregnancy were identified as significant predictors for mental disorders during pregnancy. The addition of these psychosocial items to the five psychiatric items of model 2, increased Nagelkerke's R^2 with 12% from 0.547 for model 2 to 0.615 for model 4 (comprehensive set of items). The AUC slightly increased as well from 0.883 to 0.909, representing an outstanding discrimination, comparable to model 3.

Table 3. Prevalence of characteristics, psychosocial and psychiatric triage items according to the presence of mental disorders[1]

	Total (n = 330)		Women with mental disorder (n =131)		Women without mental disorder (n = 199)		
Socio-demographic characteristics	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*p-value*
Maternal age (years)[2]	31	(27 - 35)	32	(29 - 35)	31	(27 - 34)	0.090
Non-Western ethnicity	121	(37)	58	(44)	63	(32)	0.020
Socio economic status[3]							0.327
< 20th percentile	175	(53)	70	(53)	105	(53)	
20th - 20th percentile	119	(36)	43	(33)	76	(38)	
≥ 80th percentile	36	(11)	18	(14)	18	(9)	
Educational level							0.039
low	44	(13)	20	(15)	24	(12)	
moderate	168	(51)	75	(57)	93	(47)	
high	118	(36)	36	(27)	82	(41)	
Single status	15	(5)	10	(8)	5	(3)	0.029
Obstetric characteristics	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*p-value*
Gestational age (weeks)[2]	24	(14 - 31)	23	(16 - 32)	24	(14 - 31)	0.475
Gravidity							0.176
1	99	(30)	41	(31)	58	(29)	
2	113	(34)	36	(27)	77	(39)	
3	50	(15)	22	(17)	28	(14)	
≥4	68	(21)	32	(24)	36	(18)	
Parity							0.836
0	152	(46)	65	(50)	87	(44)	
1	110	(33)	35	(27)	75	(38)	
2	43	(13)	19	(15)	24	(12)	
3	16	(5)	8	(6)	8	(4)	
≥4	9	(3)	4	(3)	5	(3)	
Psychosocial items	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*p-value*
Insufficient social support	50	(15)	34	(26)	16	(8)	<0.001
Relational problems	47	(14)	38	(29)	9	(5)	<0.001
Financial debts	68	(21)	43	(33)	25	(13)	<0.001
Unstable housing	15	(5)	10	(9)	5	(3)	0.090
Unplanned pregnancy	133	(40)	68	(52)	65	(33)	<0.001
Unwanted pregnancy	30	(9)	20	(15)	10	(5)	0.002
Life event item	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*p-value*

Table 3 continued

	Total (n = 330)		Women with mental disorder (n =131)		Women without mental disorder (n = 199)		
Sexual or physical abuse[4]	49	(15)	43	(33)	6	(3)	<0.001
Substance use items	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*p-value*
Smoking during pregnancy[5]							0.015
No	212	(64)	76	(58)	136	(68)	
Yes, untill pregnancy was known	66	(20)	25	(19)	41	(21)	
Yes, still	52	(16)	30	(23)	22	(11)	
Alcohol consumption during pregnancy[6]							0.038
No	151	(46)	59	(45)	92	(46)	
Yes, untill pregnancy was known	167	(51)	63	(48)	104	(52)	
Yes, still	12	(4)	9	(7)	3	(2)	
Illicit drug use during pregnancy							0.018
No	308	(93)	116	(89)	192	(96)	
Yes, untill pregnancy was known	19	(6)	13	(10)	6	(3)	
Yes, still	3	(1)	2	(2)	1	(1)	
Psychiatric items	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*p-value*
Hospital admission for mental disorder ever (woman herself)	35	(11)	24	(18)	11	(6)	<0.001
Hospital admission of a first-degree relative for mental disorder ever	44	(13)	21	(16)	23	(12)	0.242
Psychotropic medication use ever	117	(35)	83	(63)	34	(17)	<0.001
Professional psychiatric treatment ever	175	(53)	105	(80)	70	(35)	<0.001
Traumatic experience ever	104	(32)	72	(55)	32	(16)	<0.001
Feelings of a depressed mood ever	169	(51)	109	(83)	60	(30)	<0.001
Panic attac ever	130	(39)	88	(67)	42	(21)	<0.001
Current psychiatric symptoms	80	(24)	70	(53)	10	(5)	<0.001
Current severe depressive or anxious symptoms	75	(23)	62	(47)	13	(7)	<0.001
Current severe fear of childbirth	70	(21)	45	(34)	30	(15)	<0.001
Edinburgh Depression Scale score[2]	3	(1 - 10)	12	(5 - 17)	2	(0 - 3)	<0.001

[1] Diagnosis based on Structured Clinicial Interview of DSM-IV disorders axis I and II (SCID I and SCID II) by a certified professional

[2] Data given as median (Q1;Q3)

[3] Based on a z-score for socio-economic status nationally available at the website of the Central Bureau of Statistics (http://statline.cbs.nl/StatWeb/dome/default.aspx)

[4] Defined as current sexual/physical abuse, or still suffering from a past history of sexual/physical abuse

[5] Defined as smoking at least one cigarette a day

[6] Defined as consuming at least one glass of alcohol a week

All items were part of the Mind2Care screen-and-advice instrument, except for: professional psychiatric treatment ever, traumatic experience ever, feelings of a depressed mood ever, panic attack ever, current psychiatric symptoms, current severe depressive or anxious symptoms, and current severe fear of childbirth

Table 4. Multivariate logistic regression analysis for four triage models for mental disorders during pregnancy

	Model 1		Model 2		Model 3			Model 4		
Psychiatric items (short set)[2]	*OR*	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*		*OR*	*(95% CI)*	
Hospital admission for mental disorder ever (women herself)										
no (REF)	1									
yes	1.23	(0.52 - 2.89)								
Hospital admission of a first-degree relative for mental disorder ever										
no (REF)	1									
yes	1.05	(0.50 - 2.19)								
Psychotropic medication use ever										
no (REF)	1	**								
yes	7.96	(4.59 - 13.80)								
Psychiatric items (intermediate set)[3]										
Traumatic experience ever										
no (REF)			1	**	1		**	1		
yes			3.00	(1.58 - 5.70)	2.78	(1.36 - 5.64)		1.89	(0.91 - 3.90)	
Feelings of a depressed mood ever										
no (REF)			1	**	1		*	1		**
yes			3.57	(1.83 - 6.96)	2.31	(1.10 - 4.85)		3.58	(1.74 - 7.39)	
Panic attac ever										
no (REF)			1	**	1		*	1		**
yes			2.59	(1.35 - 4.94)	2.50	(1.23 - 5.10)		3.57	(1.75 - 7.28)	
Current psychiatric symptoms										
no (REF)			1	**	1			1		**
yes			5.08	(2.07 - 12.46)	2.44	(0.89 - 6.68)		4.56	(1.80 - 11.53)	
Current severe depressive or anxious symptoms										
no (REF)			1		1			1		
yes			2.40	(1.00 - 5.76)	0.73	(0.25 - 2.11)		2.38	(0.95 - 5.98)	
Psychiatric items (extended set)[3]										
Edinburgh Depression Scale score[4]					1.26	(1.16 - 1.37)	**			
Psychosocial items (comprehensive set)[3]										
Sexual or physical abuse[5]										
no (REF)								1		**
yes								5.87	(1.88 - 18.27)	
Alcohol consumption during pregnancy[6]										
No (REF)								1		**
Yes, untill pregnancy was known								1.10	(0.57 - 2.15)	
Yes, still								9.13	(1.78 - 46.74)	
Unplanned pregnancy										
no (REF)								1		**
yes								3.00	(1.52 - 5.90)	

[1] Diagnosis based on Structured Clinicial Interview of DSM-IV disorders axis I and II (SCID I and SCID II)

[2] all determinants were entered

[3] stepwise backwards logistic regression, last step of the regression model is reported

[4] Including 10 items

[5] Defined as current sexual/physical abuse, or still suffering from a past history of sexual/physical abuse

[6] Defined as consuming at least one glass of alcohol a week

** $p < 0.05$, ** $p < 0.01$*

Model 1, short set of 3 items $x^2 = 75.3$, $p < 0.001$. Nagelkerke's $R^2 = 0.276$

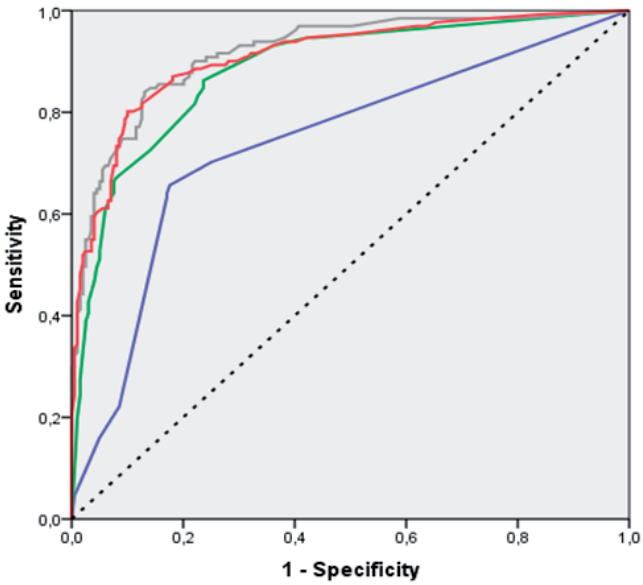
Model 2, intermediate set of 5 items, $x^2 = 171.1$, $p < 0.001$. Nagelkerke's $R^2 = 0.547$

Model 3, intermediate ste + Edinburgh Depression Scale, together: extended set of 15 items, $x^2 = 210.1$, $p < 0.001$. Nagelkerke's $R^2 = 0.637$

Model 4, intermediate set + 3 psychosocial items, together: comprehensive set of 8 items, $x^2 = 199.9$, $p < 0.001$. Nagelkerke's $R^2 = 0.615$

Similarly as compared to the addition of the 10-item Edinburgh Depression Scale (model 3), the addition of three psychosocial items, did not change the sensitivity or NPV, but increased the specificity and PPV to 0.86 and 0.80. Again, 23 cases were missed, and 2 more non-cases were falsely identified (n=27).

Finally, sociodemographic characteristics were added to explore the influence of these characteristics on the performance of the triage models. After applying stepwise backwards regression analysis, none of the characteristics contributed to the detection of mental disorders.



	AUC (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Model 1	0.740 (0.683-0.797)	0.63	0.83	0.71	0.77
Model 2	0.883 (0.846-0.921)	0.83	0.77	0.71	0.88
Model 3	0.918 (0.887-0.949)	0.82	0.87	0.81	0.88
Model 4	0.909 (0.878-0.942)	0.82	0.86	0.80	0.88

Figure 2 Area under the ROC curve and discriminant validity of four triage models for mental disorders during pregnancy

[1] **EDS:** Edinburgh Depression Scale

Additional file 1 Ten potential psychiatric items for the triage of mental disorders of the DSM-IV axis I and II during pregnancy

Additional file 2 The comprehensive set of five psychiatric items and three psychosocial items to be implemented in routine obstetric care for the triage of mental disorders of the DSM-IV axis I and II

Table 5. The comprehensive set of five psychiatric items and three psychosocial items to be implemented in routine obstetric care for the triage of mental disorders of the DSM-IV axis I and II

Comprehensive set of items
Psychiatric screen items (extended set of items)
Have you ever experienced a major traumatic event, such as life-threatening situation, a rape or a sexual assault?
• yes
• no
Has there ever been a period of time in which you felt depressed, down or empty, almost every day? Or that you could not enjoy activities that used to be enjoyed?
• yes
• no
Have you ever had a panic attack?
• yes
• no
Do you currently experience any psychiatric symptoms?
• yes
• no
Do you currently experience severe depressive or anxious symptoms?
• yes
• no
Psychosocial screen items (added to the extended set)
Did you drink any alcohol during your pregnancy?
• yes, untill I discovered that I was pregnant
• yes, I still do
• no
Are you currently experiencing or have you ever experienced any physical or sexual abuse, and do you still experience any disadvantages because of that?
• yes
• no
Were you deliberatly trying to conceive?
• yes
• no

DISCUSSION

The burden of a broad specter of mental disorders in pregnancy is considerable, and a structured triage is often lacking. Our study showed that the currently used short set of three psychiatric items perform acceptable for triage purposes. However, an intermediate set of the five psychiatric items: traumatic experience ever, feelings of a depressed mood ever, panic attack ever, current psychiatric symptoms and current severe depressive or anxious symptoms, significantly improved the performance. Further improvement can be achieved

through the addition of the 10-item Edinburgh Depression Scale or the addition of the three co-morbid conditions: alcohol consumption, physical or sexual abuse and having an unplanned pregnancy is superior. The addition of three psychosocial items could be preferred for a brief yet broad triage.

Psychiatric diagnosis was obtained with SCID I and II interviews. To our knowledge, we are the first to screen for the broad specter of DSM-IV axis I and axis II disorders during pregnancy instead of focusing on the most prevalent disorders only. As personality disorders contribute to the burden of mental disease, triage creates an opportunity for identifying disorders which are otherwise left unnoticed in the obstetric setting. The rather complex and long lasting treatment of personality disorders is often not a primary aim during pregnancy, however, the provision of some kind of maternal support is desired.

Unlike previous studies, which mostly assess psychiatric diagnoses in screen positive participants,[25-27] we obtained psychiatric diagnosis for both low and high-risk participants. Psychiatric diagnosis of all participants provides the most accurate information on the test performance of the triage models. We believe that obtaining reliable measurements of false negative and false positive rates outweighs the effort of a psychiatric assessment of all participants.

The purpose of this study was to validate a set of items for the triage of a broad specter of mental disorders antenatally. Clinical triage requires the combination of a high sensitivity, specificity, positive and negative predictive value. The emphasis is on a high sensitivity and high negative predictive value (resulting in low rates of missed cases), assuming that false-positive women are identified during an intentional subsequent confirmation by a psychiatric professional. Despite the excellent discrimination of the triage models, 23 women with a current mental disorder were missed. These women are likely to have a limited insight in their illness, because all 23 responded negatively to the question about having current psychiatric symptoms. Remarkable is that three out of five women with a current eating disorder, and two out of eight women with a current psychotic disorder were missed by the triage model, indicating a low sensitivity for these type of disorders. Seven out of the 23 missed cases included first onset psychiatric disorders in women of moderate to high education from a Western origin, without a psychiatric history and without any psychosocial stressors. Two of these women reported fetal loss or previous miscarriages as reasons for their anxiety disorder. This stresses the importance of special awareness of the psychiatric consequence of previous adverse pregnancy outcomes.

This study was subject to several limitations. First, psychiatric diagnosis addressed a current state of mental disorders and not a future state throughout pregnancy or postpartum. Repeated assessments during pregnancy and postpartum would provide valuable information on the onset of mental disorder during later pregnancy and after delivery. Nevertheless, this study included pregnant women with a mixture of gestational ages, representing the whole

antenatal period. As postpartum mental disorders often already start during pregnancy, we focused on the antenatal period only.
The study was subject to bias by research, as the acceptance rate of the study was 38%, with the duration of the interview as one of the main reasons for study refusal. The purpose of this study was to validate a set of triage items in a heterogeneous population of mixed socio-economic status, educational level and ethnicity, and not to include an unselected cohort of pregnant women. It is yet important to cross validate the performance of the item sets and their thresholds for use in clinical screening in primary care.

CONCLUSIONS

The findings in this study led to an important recommendation. For a brief triage and a subsequent referral to psychiatric care or provision of support for women with mental disorders during pregnancy, the implementation of a comprehensive set of at least five psychiatric triage items is warranted. The addition of three psychosocial items further improves the detection of mental disorders. Therefore, we strive for the implementation of this brief, yet comprehensive set of items in routine obstetric care (see Additional file 2). Nevertheless, triage alone is not enough. All identified women following triage need a psychiatric consultation for the confirmation of the psychiatric disorder and subsequent interventions.

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CHAPTER 5

Worries surrounding the first ultrasound do not bias the screening for depressive and anxiety symptoms during pregnancy

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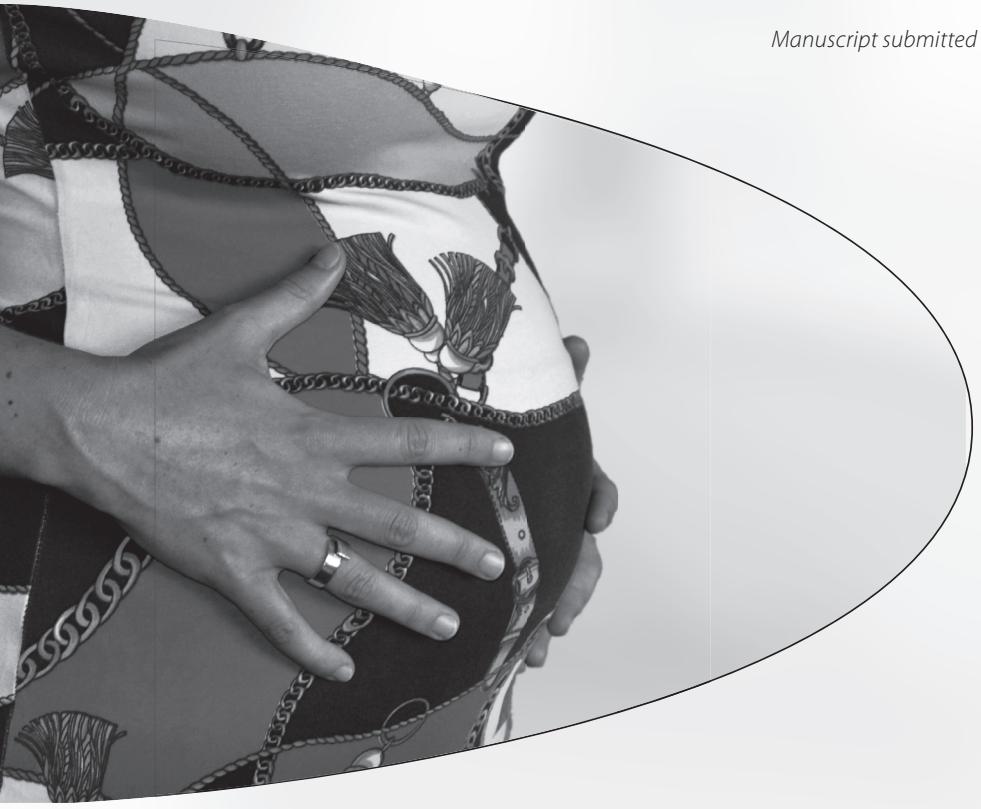
Manuscript submitted for publication



ABSTRACT

Introduction: Antenatal screening for depressive/anxiety symptoms could be biased by worries surrounding the first ultrasound. Therefore, we examined the potential influence of worries surrounding the first ultrasound on systematic screening for depressive/anxiety symptoms during pregnancy.

Materials and methods: We obtained data from 961 women screened consecutively in midwifery practices and hospitals in The Netherlands. Data included the Edinburgh Depression Scale (EDS), having had an ultrasound, and its perceived influence on women's worries.

Results: In total, 18% had EDS scores ≥10 (n=117). Among 777 women who underwent an ultrasound, existing worries before the ultrasound predicted depressive/anxiety symptoms (aOR:4.52, $p<0.001$), in contrast to worries which started after the ultrasound. Among 184 women who did not undergo an ultrasound, expected continuation of existing worries after the ultrasound predicted depressive/anxiety symptoms (aOR:15.76, $p=0.032$), in contrast to worries which were expected to subside.

Discussion: In our cohort, depressive and/or anxiety symptoms were not associated with worries induced or reduced by a first ultrasound, suggesting no bias. Antenatal screening for anxiety/depressive symptoms should therefore not depend on the timing of this ultrasound examination.

INTRODUCTION

For the detection of depressive and anxiety symptoms during pregnancy, the validated 10-item Edinburgh Depression Scale (EDS) is the most commonly used questionnaire.[1] The EDS asks for depressive and anxiety symptoms in the past 7 days and results in a sum score ranging from 0-30. An EDS score of 10 or more indicates clinically relevant symptoms.[2]
Psychiatric treatment is, however, not necessary for all women who score above this threshold. In some cases an elevated EDS score reflects transient psychiatric symptoms related to stress-inducing circumstances. We hypothesized the first ultrasound examination during pregnancy to be such a stress-inducing circumstance.
In The Netherlands, all pregnant women receive an ultrasound (US) examination during their booking visit which on average takes place around the tenth weeks of gestation. This first US is conducted to verify whether the pregnancy is intact and to determine the gestational age. This US is typically followed by a nuchal translucency scan at 11-14 weeks gestational age and a malformation scan at 20 weeks of gestational age.
The period surrounding the first US is experienced as exciting, yet uncertain, and may lead to maternal worries.[3] In a recent pilot on screening for depression during pregnancy,[4] women with depressive and/or anxiety symptoms following screening generally indicated that their high EDS score was the consequence of worries surrounding their first US, and that these worries were substantially reduced after the confirmation of a vital pregnancy. If true, one might consider an adapted timing of screening to avoid false positive cases. To our knowledge, the potential interfering role of reported worries surrounding the first US in the timing of screening for depressive and anxiety symptoms has never been examined before.
We examined the hypothesized influence of the first routine US on systematic screening for depressive and anxiety symptoms during pregnancy.

MATERIALS AND METHODS

Data were generated using the validated Mind2Care screen-and-advice instrument (formerly known as the GyPsy instrument),[4] including the Edinburgh Depression Scale (EDS),[1] substituted with questions about socio-demographic characteristics, obstetric characteristics, and experienced worries surrounding the first routine ultrasound examination. Mind2Care was developed by the Erasmus University Medical Center as a tool for screening and subsequent treatment allocation for psychiatric and psychosocial conditions during pregnancy. Prior to this study, the Mind2Care instrument was implemented from April 2011 to July 2013 consecutively in nine midwifery practices, two general hospitals and one tertiary hospital spread across a deprived urban area and a rural area in The Netherlands. All pregnant women who sufficiently mastered the Dutch language and were mentally capable to complete the ques-

tionnaire independently were invited to complete the Mind2Care on a handheld computer. As part of routine practice, 986 women completed the questionnaire prior to a pregnancy check-up. In half of the midwifery practices and hospitals women received the Mind2Care prior to their first pregnancy check-up, in the other half of the practices and hospitals women received the Mind2Care during a later check-up. Data were anonymously processed and stored in a database, and retrieved for secondary analysis.

The study was performed in accordance with the ethical standards of the Medical Ethical Board of the Erasmus University Medical Center Rotterdam [MEC 2013-522, November 13th 2013] and with the Helsinki Declaration (1975, and its later amendments).

Primary outcome measures were 1) EDS scores, with a score of 10 of more indicating clinically relevant depressive and/or anxiety symptoms; and 2) the self-reported potential/perceived influence of the US on the women's emotional state (see Table 1). Principal determinant was having had the first US at the time of screening (yes/no). Additional determinants included maternal age, ethnicity, socioeconomic status, educational level, parity, and gestational age at screening.

A posthoc sample size calculation showed that our sample was sufficient to detect proportional differences in EDS scores between women before and after US, for the group with and without pre-existing worries (alpha 5% and a power of 0.80). Completeness of data was expressed as the proportion of missing data per woman and per variable. In case of less than 10% missing values, missing values were replaced by missing imputation. In case of ≥10% missing values or missing values on ultrasound determinants, women and/or variables were excluded from analysis.

Table 1. Questions addressing the first prenatal ultrasound examination

Have you already had the first ultrasound examination?
* yes
* no
if yes
Did this ultrasound influence the way you feel?
* no, I was not worried, and I am still not worried
* yes, I was (a little) worried, but these worries have gone
* yes, I was not worried, but now I am (a little) worried
* no, I was (a little) worried, and I still am worried
if no
Do you think that the first ultrasound will influence how you feel?
* no, I am not worried, and after the ultrasound examination I will probably still not be worried
* yes, I am (a little) worried, but the worries will probably go away after the ultrasound examination
* yes, I am not worried, but after the ultrasound examination I will probably be (a little) worried
* no, I am (a little) worried, and after the ultrasound examination I will probably still be worried

Descriptive statistics were used to describe the study population, and to compare characteristics of women with vs. without an ultrasound at the time of screening. The primary association between the first US and depressive and/or anxiety symptoms (yes/no) was tested with univariate logistic regression analysis. Multiple logistic regression analyses were conducted to assess whether this association, if any, persisted after adjustment for predefined sociodemographic and obstetric characteristics. Associations following regression analyses were expressed through (adjusted) odds ratios. Associations with a two sided p-value below 0.05 were considered as statistically significant. All analyses were conducted with the Statistical Package for Social Science version 20.0.

RESULTS

Anonymous data of 986 women who were screened with the Mind2Care were available. Twenty five women were excluded, due to missing data on ultrasound related questions (n=11) or more than 10% missing values in total (n=14). Data were complete for 961 women (97%), of which 177 women had clinically relevant depressive and/or anxiety symptoms (18%).

Women's mean age was 30±5 years and the median gestational age at screening was 19 weeks (range 5-41). Women with depressive/anxiety symptoms were significantly more often of non-western ethnicity (38% vs. 20%) and of low socioeconomic status (46% vs. 38%) as compared to women without these symptoms.

Table 2 shows that 777 (81%) of women had already had an US examination at the time of screening. Having had an US was not associated with depressive/anxiety symptoms (aOR 0.99, 95% CI: 0.64-1.54, p=0.976). In 111 of the 777 women (14%) worries were reported. In 36 of these women (32%), these worries started after the US, and in 75 women (68%) these worries were already present before the US. Worries which started after the US were not associated with depressive/anxiety symptoms (aOR 1.75, 95% CI: 0.82-3.74, *p=0.147*). Pre-existing worries, however, appeared significantly associated with depressive/anxiety symptoms (aOR 4.52, 95% CI: 2.67-7.67, *p<0.001*).

Of the 184 women who had not had an US at the time of screening, 30 women (16%) reported experiencing worries, of which 27 (90%) indicated that these worries would probably subside after the US, and 3 (10%) indicated that the worries would probably still be present. Worries which were expected to subside after the US were not associated with depressive/anxiety symptoms (aOR 2.36, 95% CI: 0.84-6.64, *p=0.104*). Worries which were expected still to be present after the US did predict depressive/anxiety symptoms (aOR 15.76, 95% CI: 1.26-196.46, *p=0.032*).

Besides, women who had had an US at the time of screening (retrospectively) more often reported worries prior to the US (256/777, 33%), compared to women who had not had

Table 2. Crude and adjusted associations between the first ultrasound examination, and the (proposed) influence of this ultrasound on depressive and/or anxiety symptoms during pregnancy (n = 961)

	Total		EDS score ≥10		p-value			
	n	%	n	%		aOR[1]	95%CI	*p-value*
Ultrasound (US) during this pregnancy					*0.689*			*0.976*
yes	777	81	145	82		reference		
no	184	19	32	18		0.99	(0.64 - 1.54)	
Women with US (n = 777)								
Influence of the US					*<0.001*			
none, no worries before US / no worries currently after US	485	62	60	41		reference		*<0.001*
yes, no worries before US / worries currently after US	36	5	11	8		2.83	(1.29 - 6.21)	
yes worries before US / no worries currently after US	181	23	40	28		2.31	(1.43 - 3.70)	
none, worries before US / worries currently after US	75	10	34	23		6.42	(3.64 - 11.31)	
Current worries, started and/or continued after US					*<0.001*			*<0.001*
yes	111	14	45	31		3.70	(2.35 - 5.83)	
no	666	86	100	69		reference		
Current worries, started after US					*0.061*			*0.147*
yes	36	5	11	8		1.75	(0.82 - 3.74)	
no	741	95	134	92		reference		
Current worries, continued after US					*<0.001*			*<0.001*
yes	75	10	34	23		4.52	(2.67 - 7.67)	
no	702	90	111	77		reference		
Women without US (n = 184)								
Presumed influence of an US					*0.114*			*0.061*
none, no current worries / no expected worries after US	61	33	10	31		reference		
yes, no current worries / expected worries after US	93	51	13	41		0.84	(0.31 - 2.26)	
yes current worries / no expected worries after US	27	15	7	22		2.38	(0.70 - 8.08)	
no, current worries / expected worries after US	3	2	2	6		17.44	(1.28 - 237.59)	
Current worries, before US					*0.046*			*0.016*
yes	30	16	9	28		3.37	(1.26 - 9.03)	
no	154	84	23	72		reference		
Current worries, expected to be subside after US					*0.207*			*0.104*
yes	27	15	7	22		2.36	(0.84 - 6.64)	
no	157	85	25	78		reference		
Current worries, expected to be present also after US					*0.063*			*0.032*
yes	3	2	2	6		15.76	(1.26 - 196.46)	
no	181	98	30	94		reference		

[1] *adjusted for maternal age, ethnicity, educational level, socio-economic status, and parity*

an US (current worries 30/184, 17%). Women who had already undergone an US also more frequently reported that the US removed their worries (181/777, 23%), compared to the expectations of those women who did not undergo an US (27/184, 15%). Women who did not undergo an US more often reported (to expect) that the US would introduce worries (93/184, 51%), compared to reports by the women who had already undergone an US (36/777, 5%).

DISCUSSION

This cross-sectional naturalistic study showed that depressive and/or anxiety symptoms during pregnancy were not associated with (transient) worries induced or reduced by the first ultrasound examination. Depressive and/or anxiety symptoms appeared however more prevalent among women who reported pre-existing intrinsic worries, independent from the timing of the first US.

A strength of this first attempt to examine the hypothesized increase of false positive screen-detected cases of psychopathology is the large and heterogeneous sample of pregnant women. Our cohort represents the Dutch pregnant population.[5,6] Secondly, in this secondary analysis of existing data, neither the women nor the midwives/obstetricians were aware of the study aim during screening, ruling out information bias. The retrospective design, however, is also subject to some limitations. First, the outcome of the US was not available, as the anonymized screen data could not be linked to the patient records. This may have introduced random error, rather than bias. Second, as the median gestational age at screening with the Mind2Care was 19 weeks, some women already had had three ultrasound examinations, while others only had had the first US. Despite the fact that we examined worries surrounding the first US among all participants, this could have introduced recall bias. Third, no information on previous pregnancies was available, including fetal abnormalities or a past history of miscarriages or fetal loss. Such experience may induce worries during pregnancy and subsequently trigger maternal depression or anxiety.[7] When analyses were repeated for women with a discrepant gravidity and parity (for example G3P1) compared to the remaining group, results were similar. Fourth, the underlying reasons of reported worries were not recorded, and should be investigated in a more detailed study.

Interestingly, the presumed influence of the first US differed from the actual perceived influence of the US. This observation suggests that the timing of screening could affect women's perception of worries, and the influence of the US on these worries. Another explanation is selection towards more worried women who requested for an early US examination. Unfortunately, gestational age data at the time of the first US examination are not available.

Another interesting finding of this study is the perseverance of women's pre-existing intrinsic worries. Similar findings of maternal anxiety with regard to first trimester nuchal translucency screening have been described.[3,8]

We conclude that early antenatal screening for depressive and/ or anxiety symptoms is not biased by the timing of the first ultrasound examination. This lack of transient effects facilitates the implementation of systematic screening for depressive and anxiety symptoms in routine obstetric care.

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CHAPTER 6

Withdrawal from mental and psychosocial care during pregnancy

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Part of this chapter is published:
Journal of Psychosomatic Obstetrics and Gynecology, 2014
Aug, in press.

ABSTRACT

Psychopathology, ***P***sychosocial problems and ***S***ubstance use (***PPS***) commonly occur in pregnant women, and can have a negative impact on the course of pregnancy and the healthy development of the child. As PPS often remains undetected and untreated during pregnancy, we developed and implemented a four step screen-and-treat protocol in routine obstetric care, with: 1)***S***creening including triage and subsequent confirmation, 2)***I***ndication assessment, 3)***T***ransfer towards care, 4)***U***tilization of care.

Adherence to the protocol and risk factors associated with dropout were examined for 236 Dutch pregnant women in a deprived urban area.

Seventy-nine percent of women accepted the screening. After triage, dropout rates included 30% at confirmation, 19% during transfer, and 77% thereafter. Provided reasons for dropout were lack of time and lack of perceived benefit.

In particular smokers, multiparous women, and women of non-Western ethnicity drop out on the way towards mental and psychosocial care. For a successful implementation of the protocol in the future, with improved adherence of pregnant women to the protocol, education of women on PPS risks, motivational skills, and compulsory treatment are worth investigation.

INTRODUCTION

Psychopathology, Psychosocial problems and Substance use (referred to as 'PPS') are prevalent, frequently co-morbid conditions, with serious short and long term consequences for both mother and child.[1-3] Despite professional guidelines,[4,5] however, systematic antenatal screening is uncommon. Even if detected, PPS often remains untreated.[6] Reasons provided are insufficient expertise, perceived stigmatization, and the absence of comprehensive protocols.[6,7]

Therefore, we developed the pragmatic 'SITU screen-and-treat protocol'. This comprehensive protocol includes four subsequent steps: 1) ***S***ystematic detection, 2) ***I***ndication assessment 3) ***T***ransfer towards tailored mental and psychosocial care, and 4) ***U***tilization of care. Its acronym 'SITU' refers to the preference for local services. We implemented this protocol in a large general hospital in Rotterdam, the Netherlands. For the development of a targeted implementation strategy in the future, the protocol's performance was established by examining adherence rates for each step of the protocol and reasons for dropout.

METHODS

Study design

From January 2011 to January 2012 we developed the SITU protocol, based on existing local guidelines,[8] professional expertise, the availability of screen instruments,[3,9] and previous study results.[2,3,10]

The protocol was implemented in routine obstetric care from February to June 2012 at a general hospital serving a severely deprived area. All Dutch-speaking pregnant women were invited to participate in this study during booking visit.

Study approval was obtained from the Medical Ethical Board of the Erasmus University Medical Center (MEC-2012-060). The study conformed the ethical standards following the Declaration of Helsinki and its later amendments.

Procedure and SITU protocol

Prior to the study period, all obstetricians received information on the purpose and content of the study, and were trained for the use of the protocol by the principal investigator during a two-hour course.

The first step of the SITU protocol implies a two-stage screening: firstly, a highly sensitive triage, with a low cut-off for being 'at risk' for PPS; secondly, a confirmation of PPS existence, for which a high specificity is required.

For triage, after written informed consent, women were screened with the Rotterdam Reproductive Risk Reduction checklist (R4U)[9] during booking visit. R4U is a standardised risk

checklist to be filled out by the obstetrician. R4U contains both medical and non-medical risk factors for preterm birth and small for gestational age, including 23 PPS risk factors. All women with at least one PPS risk at triage qualified for the confirmatory stage. PPS confirmation rests on the outcome of the validated Mind2Care instrument (formerly known as the GyPsy instrument).[3] Mind2Care is a self-report digital PDA-based questionnaire, to be filled out by the pregnant women after booking visit. Mind2Care is targeted to detect psychiatric problems (e.g. current depressive symptoms as measured by the Edinburgh Depression Scale and psychotropic medication use), psychosocial problems (e.g. financial problems and sexual/physical abuse) and substance use. Mind2Care not only screens for PPS, but also generates tailored interventions advice after completion of the questionnaire. An underlying script matches the woman's responses to entry criteria of available local interventions, which are incorporated in the PDA. Intervention advices appeared on the PDA screen and were graded for severity on a scale of 0-4, representing the input for SITU step 2: indication assessment. The advice was registered in the medical record by a research assistant and discussed by the obstetrician and women during the next pregnancy check-up after a three to four week interval. Here, the obstetrician weighed the type and severity of PPS problems as indicated by the suggested advice to the suitability and willingness of the woman to get treated. If necessary and desired, the obstetrician referred women to the advised mental or psychosocial care, offered close to the place of living (SITU step 3).

After referral, research assistants monitored the actual utilisation of treatment (SITU step 4), including the receipt of an invitation for treatment, the appearance on treatment appointments, and the continuation of all treatment sessions during pregnancy and after delivery.

Four care packages were defined: 1) hospital based social work, for the provision of psychosocial support; 2) specialised psychiatric treatment for antenatal psychopathology; 3) specific psychiatric treatment for antenatal substance abuse, and 4) preventive care and education for women with subsyndromal psychiatric symptoms or mild substance use.[11]

Protocol evaluation

Adherence to the protocol was established by recording the number of dropouts per step. A dropout was defined as 'no show' or 'refusal' to comply with the screening or suggested intervention advices. Reasons for dropout were recorded by research assistants. In case of no-shows, women were called instantly or approached during a subsequent pregnancy check-up.

We related dropout to women's characteristics and the PPS risk factors involved. Information on characteristics and risk factors was drawn from medical records and the R4U screen instrument, if completed.

Statistical analyses

Dropout rates were expressed as proportions. Exploratory univariate logistic regression analyses were conducted to identify risk factors for dropout. All analyses were performed using the Statistical Package for Social Science, version 20.0.

RESULTS

Study population and dropout rates

Figure 1 shows that 15 out of the 251 women with a booking visit did not meet the inclusion criteria (6%). From the 236 eligible women, 187 women (79%) were screened for triage in step 1. Reasons for dropout were in 50% related to a caregiver's factor, in particular stated lack of time to complete the R4U, and in 50% to a patient's factor, in particular lack of perceived benefit of the screening and the possible subsequent treatment.

Of the 120 women at risk for PPS following triage, 35 women (29%) dropped out during the subsequent confirmatory screen stage, with lack of time (n=11) and lack of perceived benefit (n=15) as main reasons provided.

Indication assessment among the remaining 85 participants in SITU step 2 resulted in 46 women with severity level 0 (no risk), and 32 women with severity level 1 to 3 (low to high risk). Seven women were already under treatment for PPS (severity 2 and 3). Of the 32 high-risk women following confirmation, 6 (19%) refused referral due to lack of motivation for treatment, and 20 (77%) dropped out after referral. Here, dropout included no-show at mental care and loss to follow up. Six women received treatment. All six received psychosocial support from medical social workers at the outpatient clinic.

Factors related to dropout

Table I shows that having a non-Western ethnicity significantly increased the risk for dropout at triage (OR 1.9; 95% CI:1.0-3.6).

Multiparity tended to increase the risk for dropout at the subsequent confirmation (OR 2.3; 95% CI:1.0-5.1, p=0.051).

After triage, during confirmation and SITU step 2-4, smoking during pregnancy significantly increased the risk to dropout on the way towards mental and psychosocial care (OR 3.1; 95%CI:1.2-7.8).

DISCUSSION

This first attempt to improve antenatal PPS risk management with our four-stage protocol, clearly demonstrates that despite high initial adherence, pregnant women gradually drop

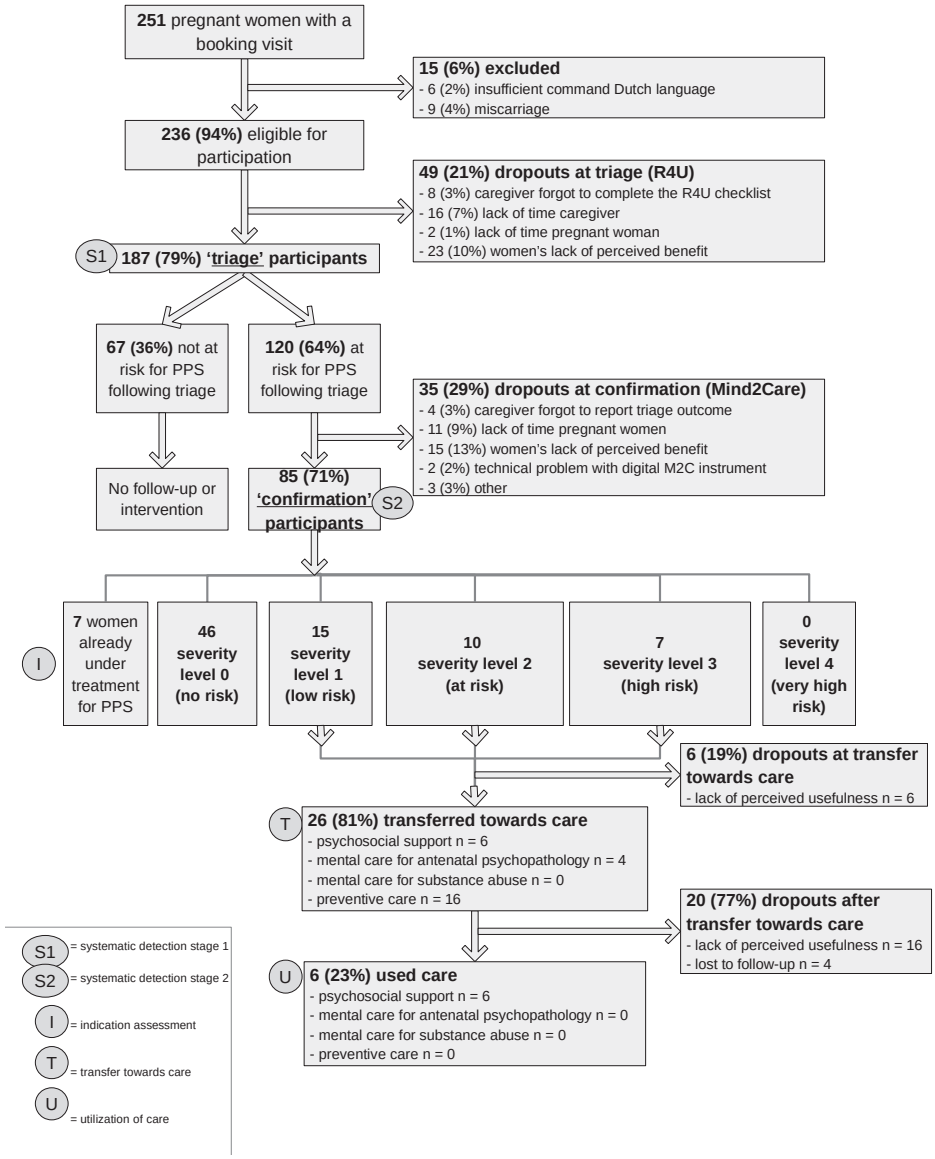

Figure 1 Adherence to the "SITU protocol" in the obstetric setting of a large urban secondary hospital in Rotterdam, the Netherlands

out in the way towards care; in particular multiparous women and women of non-Western ethnicity. Smokers quit the protocol when offered treatment for smoking cessation or treatment for co-morbid psychiatric or psychosocial conditions.

As this pilot was carried out under routine care conditions, we believe the results are representative for the current state of antenatal care. In addition, our comprehensive approach encompassed psychopathology, psychosocial problems and substance use, which reflects

Table 1 Characteristics and risk factors for dropping out of the SITU protocol (total, n = 236); exploratory regression analyses

	Total (n = 236)	Dropout at triage (n = 49)					Dropout at confirmation (n = 35)					Dropout at any point after triage (n = 61)				
	n	n	(%)	OR[a]	(95% CI)	p-value	n	(%)	OR[a]	(95% CI)	p-value	n	(%)	OR[a]	(95% CI)	p-value
Characteristics																
Maternal age (years)						0.384					0.930					0.971
≤ 25	44	8	(16%)	0.5	(0.2 - 1.3)		12	(34%)	1.0	(0.4 - 2.7)		21	(34%)	1.7	(0.5 - 3.0)	
25 - 30 (REF)	66	16	(33%)	1			10	(29%)	1			16	(26%)	1		
31 - 35	68	17	(35%)	1.0	(0.5 - 2.3)		6	(17%)	0.7	(0.2 - 2.3)		12	(20%)	0.9	(0.3 - 2.6)	
≥ 36	44	8	(16%)	0.7	(0.3 - 1.8)		7	(20%)	0.9	(0.3 - 2.9)		12	(20%)	1.0	(0.3 - 2.9)	
Ethnicity						0.049					0.235					0.455
Western (REF)	118	20	(41%)	1			16	(46%)	1			31	(51%)	1		
Non-Western	118	29	(59%)	1.9	(1.0 - 3.6)		19	(54%)	1.6	(0.7 - 3.6)		30	(49%)	1.3	(0.6 - 2.7)	
Socioeconomic status						0.247					0.202					0.207
≤ 20th percentile	132	31	(63%)	1.5	(0.8 - 2.8)		23	(66%)	1.7	(0.8 - 3.9)		38	(62%)	1.6	(0.8 - 3.3)	
> 20th percentile (REF)	104	18	(36%)	1			12	(34%)	1			23	(38%)	1		
Parity						0.796					0.051					0.103
nulliparity (0; REF)	108	23	(47%)	1			12	(34%)	1			26	(43%)	1		
multiparity (≥ 1)	126	24	(49%)	1.1	(0.6 - 2.1)		23	(66%)	2.3	(1.0 - 5.1)		35	(57%)	1.8	(0.9 - 3.8)	
Gestational age						0.463					0.770					0.796
first trimester	133	28	(57%)	1.0	(0.4 - 2.3)		20	(57%)	0.7	(0.3 - 1.9)		12	(21%)	0.9	(0.3 - 2.2)	
second trimester (REF)	47	9	(18%)	1			8	(23%)	1			36	(59%)	1		
third trimester	43	12	(24%)	1.6	(0.6 - 4.4)		7	(20%)	0.8	(0.2 - 2.8)		13	(23%)	1.2	(0.4 - 3.8)	
PPS factor present[b]																

Table 1 continued

	Total (n = 236)	Dropout at triage (n = 49)					Dropout at confirmation (n = 35)					Dropout at any point after triage (n = 61)				
	n	n	(%)	OR[a]	(95% CI)	p-value	n	(%)	OR[a]	(95% CI)	p-value	n	(%)	OR[a]	(95% CI)	p-value
Single status	n.a.						5	(14%)	1.6	(0.5 - 5.3)	0.438	6	(10%)	0.8	(0.3 - 2.6)	0.721
Relational problems	n.a.						2	(6%)	0.6	(0.1 - 2.9)	0.510	3	(5%)	0.4	(0.1 - 1.6)	0.182
Insufficient social support	n.a.						3	(9%)	1.5	(0.3 - 6.6)	0.594	4	(7%)	1.0	(0.2 - 4.1)	0.961
Domestic violence	n.a.						0	(0%)	n.a.			0	(0%)	n.a.		
Financial problems	n.a.						6	(17%)	1.4	(0.5 - 4.1)	0.550	10	(16%)	1.5	(0.5 - 4.1)	0.479
Housing problems	n.a.						1	(3%)	0.8	(0.1 - 8.0)	0.852	1	(2%)	0.3	(0.1 - 3.1)	0.318
Hospital admission for psychiatric disorder ever[c]	n.a.						1	(3%)	0.2	(0.0 - 2.0)	0.195	3	(5%)	0.4	(0.1 - 1.6)	0.182
Use of psychotropic medication ever	n.a.						1	(3%)	0.4	(0.0 - 3.3)	0.388	3	(5%)	0.7	(0.2 - 3.3)	0.665
Current psychiatric complaints	n.a.						1	(3%)	0.6	(0.1 - 5.5)	0.648	2	(3%)	0.6	(0.1 - 3.9)	0.623
Smoking during pregnancy	n.a.						8	(23%)	0.9	(0.4 - 2.5)	0.937	20	(33%)	3.1	(1.2 - 7.8)	0.015
Alcohol consumption during pregnancy	n.a.						1	(6%)	n.a.			2	(3%)	n.a.		
Illicit drug use during pregnancy	n.a.						0	(0%)	n.a.			0	(0%)	n.a.		

n.a. not applicable

[a] *unadjusted odds ratio's following univariate logistic regression analysis*

[b] *PPS: psychopathology, psychosocial problems or substance use during pregnancy, reference category is 'no'*

[c] *pregnant woman herself or a first degree relative*

the actual everyday challenge of obstetric caregivers, especially in deprived areas with high PPS prevalence.

The relatively small sample restricts a more detailed analysis, yet potential targets for future implementation strategies are identified.

In line with previous studies,[7,12-14] several barriers to care have been identified, including women's lack of time and lack of perceived direct benefit. Lack of time is a broad concept and includes child related factors (e.g. picking up children from school), and work related factors (e.g. taking time off for extra hospital visits). Lack of time, however, can also be provided as a socially desirable answer, actually meaning e.g. lack of motivation or even the fear of custody loss.[15]

As far as we know, parity has not been identified as predictor for dropout at screening during pregnancy before. Yet, multiparity is a plausible predictor. Women who already have delivered a baby, may be likely to underestimate the benefit of improving antenatal conditions, because they may believe they 'already know' everything about pregnancies.

The predictor non-Western ethnicity might be subject to underlying mechanisms such as language barriers[16] and cultural aspects. August et al[17] underlined the importance of language concordance in the communication between patients and caregivers, especially among foreign born women. In case of a so called poor patient-caregiver fit pregnant women are less prone to discuss problems, in particular on behalf of their mental health,[17] and caregivers are less prone to elicit problems[18] and counsel women for e.g. lifestyle treatment.[19]

An important question may be whether the proposed interventions match the women's expectations, especially in women with poor insight in their mental illness, and a poor willingness to receive treatment. Given the serious consequences of PPS for maternal and foetal health, education of women on PPS risks, motivational skills, and compulsory treatment are worth investigation.

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CHAPTER 7

The role of depressive symptoms in the pathway of demographic and psychosocial risks to preterm birth and small for gestational age

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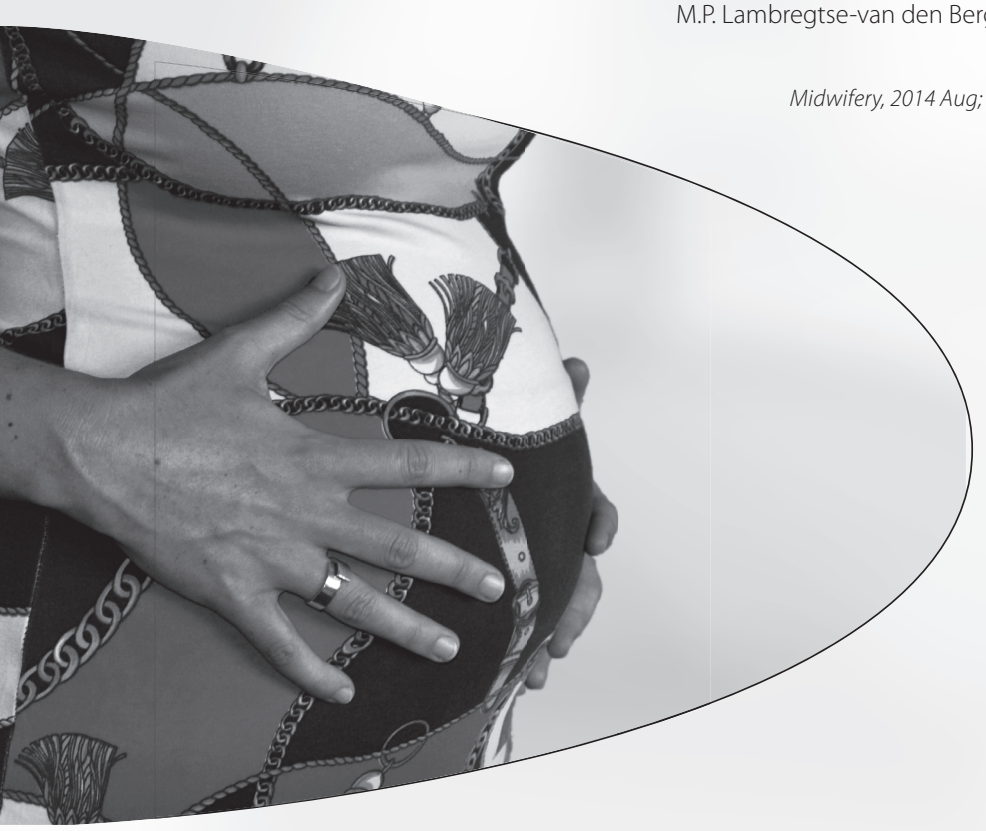
Midwifery, 2014 Aug; 30(8):919-925.



ABSTRACT

Objective: Depressive symptoms during pregnancy are associated with preterm birth (PTB) and small for gestational age (SGA). Depressive symptoms and PTB and SGA, however, share similar demographic and psychosocial risk factors. Therefore, we investigated whether depressive symptomatology is an independent risk factor, or a mediator in the pathway of demographic and psychosocial risks to PTB and SGA.

Design: Multicentre follow-up study.

Participants and setting: Pregnant women (n = 1013) from midwifery practices, secondary hospitals and a tertiary hospital in three urban areas in the Netherlands.

Measurements: Initial risk factors and depressive symptoms were assessed with the Mind2Care instrument, including Edinburgh Depression Scale (EDS) during early pregnancy. Pregnancy outcomes were extracted from medical records. A formal mediation analysis was conducted to investigate the role of depressive symptoms in the pathway to PTB and SGA.

Findings: A univariate association between depressive symptoms and PTB (OR:1.04; 95% CI:1.00-1.08) was observed. After adjusting for the risk factors educational level and smoking in the mediation analysis, this association disappeared. One educational aspect remained associated: low education OR: 1.06; 95%CI: 1.02-1.10.

Key Conclusions: Depressive symptomatology appeared no mediator in the pathway of demographic and psychosocial risks to PTB or SGA. The presumed association between depressive symptoms and PTB seems spurious and may be explained by demographic and psychosocial risk factors.

Implications for practice: For the prevention of PTB and SGA, interventions directed at demographic and psychosocial risk factors are likely to be of primary concern for clinicians and public health initiatives. As depressive symptoms and PTB and SGA share similar risk factors, both will profit.

INTRODUCTION

Adverse pregnancy outcomes, like preterm birth (PTB, <37 weeks of gestation) and small for gestational age (SGA, <10th percentile) have short and long-term consequences for both mother and child.[1-3] As PTB and SGA are related to 80% of perinatal deaths, the prevention of PTB and SGA has become a key target.[4-6]

Many risk factors have been associated with PTB and SGA, including a set of initial demographic and social risk factors, e.g. non-Western ethnicity, young maternal age (<20 years), smoking and nulliparity,[7-10] and more specific risks such as depressive symptoms during pregnancy.[11,12]

Depressive symptoms and the adverse pregnancy outcomes PTB and SGA share many initial demographic and social risks, as e.g. non-Western ethnicity, young maternal age, smoking and nulliparity also have been identified to be strong predictors for depressive symptoms during pregnancy.[13]

This common explanatory background raises the question whether depressive symptoms increase the risk of PTB and SGA as an independent risk factor (covariate), or whether depression is part of the causal pathway from initial demographic and social risk factors (X) towards these adverse outcomes (Y).

Depressive symptoms cannot only interfere in this pathway as a mediator, but also as a confounder or moderator (effect modifier). We speak of a mediator if initial risk factors (X) cause depressive symptoms during pregnancy, and depressive symptoms consecutively lead to PTB and SGA (Y), we speak of a confounder if depressive symptoms cause both X and Y. We speak of a moderator if depressive symptoms alter the relation of X to Y at different levels of the variable of interest.[14] With a formal mediation analysis the explicit role of depressive symptoms can be tested.

The more depression acts as a true mediator, the more important is the screening for and treatment of depressive symptoms during pregnancy. If depressive symptoms, however, do not mediate the demographic and social pathway to PTB and SGA, it may be more efficient to screen for initial risk factors and to focus on relevant interventions in that regard, rather than to screen for depressive symptoms alone, if the primary goal is to prevent the associated adverse pregnancy outcomes. With a formal mediation analysis, the role of depressive symptoms in the pathway to PTB and SGA was tested in a multicentre follow-up study.

METHODS

Data were generated using the Mind2Care screen-and-advice instrument (formerly known as GyPsy instrument),[15] including the validated Edinburgh Depression Scale (EDS),[16] demographical, obstetrical, social, and psychiatric risk factors including substance use, for adverse

pregnancy outcomes. This instrument was developed by the Erasmus Medical Centre and the Rotterdam Municipality in 2008. Mind2Care has good psychometric properties with a positive predictive value of 86% and a negative predictive value of 97%.[15] As recommended by the ACOG[17] and the NICE guidelines,[18] this digital screen instrument aims to detect mental health problems among pregnant women and to provide tailored intervention advices for women-at-risk instantly.

In this multicentre follow-up study, the Mind2Care instrument was implemented from October 2009 to April 2011 in three Dutch urban areas, covering the three levels of care: three midwifery practices in Rotterdam (primary level of care), two general hospitals in Apeldoorn and Breda (secondary level of care) and the Rotterdam academic hospital (tertiary level of care). In the Netherlands, obstetric health care has a unique organisation. All healthy women with no history of medical or obstetrical complications are monitored by independent midwives (primary level of care). If complications occur or interventions are required during pregnancy or delivery, women are monitored by obstetricians at a general hospital (secondary level of care) or an academic hospital (tertiary level of care).

The Mind2Care-procedure started at the booking visit or any subsequent pregnancy check-up before the 20th week of gestation. A physician's assistant asked all pregnant women to complete the Mind2Care questionnaire on a personal digital assistant (handheld computer) in the waiting room in privacy, as part of routine practice.

Exclusion criteria for participation in this study were insufficient command of the Dutch language and insufficient mental capability to complete the questionnaire independently, as judged by the physician's assistants. As this study was part of routine care, the number of excluded women was not recorded in all practices. Based on similar studies with Mind2Care in Rotterdam we estimate that 3% of women were excluded due to a language barrier and 0.2% due to an insufficient mental capability.

Participants with more than 10 missing data in total, or with missing data on the Edinburgh Depression Scale were excluded too (n=59).

Adverse pregnancy outcomes of interest included preterm birth (<37 weeks of gestation) and small-for-gestational-age (birth weight <p10, adjusted for gestational age at birth, parity and gender of the baby). Postpartum, adverse pregnancy outcomes were extracted from medical records.

The set of initial demographic and (psycho)social risk factors was measured by Mind2Care and included socioeconomic status (based on postal/ZIP-code; <20th percentile / 20th-80th percentile / ≥80th percentile; <20th is low), ethnicity (Dutch / Mediterranean / Antillean/Surinamese / Asian / Black / other European / other non-European; further grouped into Dutch / non-Dutch), educational level (low/moderate/high), maternal age (continuous; 16-20 / 21-25 / 26-30 / 31-35 / 36-40 / 41-45), gestational age (continuous), primigravidity (yes/no), nulliparity (yes/no), psychiatric history (yes/no), history of psychotropic medication use (yes/no), smoking (yes/no), alcohol consumption (yes/no), and illicit drug use (yes/no).

Socioeconomic status data was obtained from the Dutch Social and Cultural Planning Office.[19]

Depressive symptoms during pregnancy were considered as a potential mediator of the effect of initial risk factors on PTB and SGA, and were measured by the EDS, as a part of the Mind2Care questionnaire. The EDS is a ten item self-report checklist with a total score range of 0-30. Women with EDS scores of 12 or more were regarded as having clinically relevant depressive symptoms.[16]

The Medical Ethical Board of the Erasmus University Medical Centre (Rotterdam), the Gelre Teaching Hospital Apeldoorn and the Amphia Hospital (Breda) exempted this study from IBR approval, since the screening was already part of routine care, now conducted by the Mind2Care instrument, including opting-out. In The Netherlands, screening is allowed under Dutch Law if opting-out is made explicit to the participant (in Dutch: the WBO and WGBO Act). Post-hoc data collection of health outcomes from medical records is allowed provided analysis is anonymised.

Conventional descriptive statistics were used to describe the study population. Prevalence of initial risk factors, depressive symptoms and the adverse pregnancy outcomes PTB and SGA were compared for each level of care. The distribution of risks and adverse outcomes among women with clinically relevant depressive symptoms (EDS score ≥12) were presented. As a general reference for the prevalence of risk factors and depressive symptoms we used two large Dutch cohort studies (Generation R and ABCD study)[20,21] and for the prevalence of PTB and SGA we used national reference data as stated on the Dutch Perinatal Registry website.[22]

Associations between initial demographic and psychosocial risk factors (X), the potential mediator depressive symptoms during pregnancy (M) and the outcome measures PTB and SGA (Y) were examined with univariate regression analysis. All initial risk factors associated with depressive symptoms and PTB or SGA at a 0.10 level were selected for inclusion in a formal mediation analysis.[23] As a classic mediation analysis requires a continuous measure for the mediator,[24] we used EDS score as continuous measure for depressive symptoms.

Mediation analysis exists of three steps. First, the association between initial risk factors and an adverse outcome (PTB or SGA) is tested (X→Y, *path* C). Second, the association between initial risks and the mediator (depressive symptoms) is tested (X→M, *path* A). Third, the association between the mediator and the adverse outcome is tested, adjusted for the initial risks (M→Y|X, *path* B). If all associations of path A, B and C are significant ($p<0.05$), mediation is present, and the effect size of the mediator can subsequently be explored (X→Y|M, *path C', so called 'total effect'*).[24] If the total effect disappears after introduction of the mediator, complete mediation is present. If the total effect decreases to a non-zero level, but becomes non-significant after introduction of the mediator, partial mediation is present.[25,26]

Mediation analyses were conducted using the indirect macro of Preacher and Hayes.[24] All analyses were performed using the Statistical Package for Social Science, version 17.0.2.

FINDINGS

As shown by Figure 1, 1335 women completed the Mind2Care-questionnaire. As clinical outcomes were available for 1072 women and 59 women had more than 10 missing values in total or having any missing values on the EDS, data of 1013 women were analysed.

Table 1 presents an overview of the initial risk factors, depressive symptoms and the adverse pregnancy outcomes PTB and SGA among the study participants. All factors, except smoking, illicit drug use, and psychiatric history differed significantly between the three groups. Participants from the tertiary level of care show the highest risk regarding demographic risk factors, smoking and illicit drug use. Women from the primary care level most often reported alcohol consumption during pregnancy (36%) but showed low risks overall. Over 20% of all participants had a psychiatric history, with the highest prevalence among women from the secondary care level (23%). Current clinically relevant depression as measured by the EDS (cut-off ≥12) was prevalent in 15% of the total study population.

Adverse outcomes were prevalent with overall 11% PTB and 11% SGA. Preterm birth was most prevalent in the secondary care level (14%) and least prevalent among women from the tertiary level of care (7%), even for spontaneous PTB (secondary level 8%, primary level 7% and tertiary level 3%, data not shown). Congenital malformations and low APGAR scores after birth both were present among 3% of participants, and perinatal mortality occurred among 1.5%. Forty-seven percent of women had an induced delivery and 38% of women had an instrumental delivery or secondary caesarean section. Analgesia were provided during 55% of all deliveries, with highest prevalence among women from the secondary level of care (74%). Maternal complications including pre-eclampsia/HELLP, postpartum haemorrhage, manual removal of the placenta and 3rd or 4th degree sphincter rupture were observed in 5%

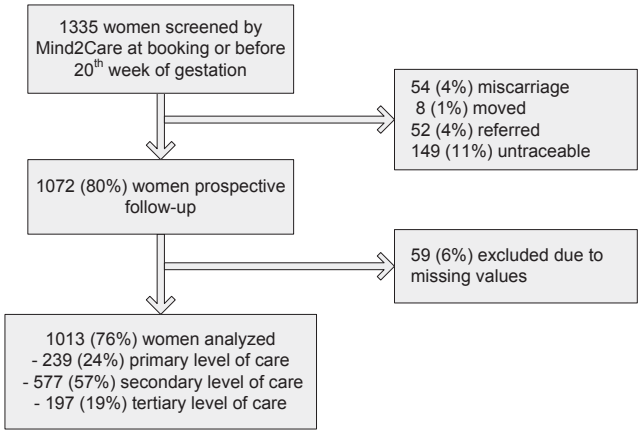


Figure 1 Study profile among three urban pregnant cohorts in the Netherlands.

Table 1. Overview of initial demographic, obstetric and social risk factors, EDS scores, and adverse pregnancy outcomes among study participants in three urban areas in the Netherlands, covering the three levels of care (n=1013)

	Study participants								
	primary level of care (n = 239)		secondary level of care (n = 577)		tertiary level of care (n = 197)		total (n = 1013)		
Independent initial risks (X)	n	%	n	%	n	%	n	%	%[a]
Socio-economic status *									
< 20th percentile	81	33.9	75	13.0	94	47.7	250	24.7	*20*
20th - 80th percentile	50	20.9	423	73.3	72	36.5	545	53.8	*14*
≥ 80th percentile	108	45.2	79	13.7	31	15.7	218	21.5	*11*
Ethnicity *									
Dutch	152	63.6	520	90.1	81	41.1	753	74.3	*11*
Mediterranean	23	9.6	23	4.0	40	20.3	86	8.5	*33*
Antillean/Surinamese	18	7.5	0	0.0	26	13.2	44	4.3	*16*
Asian	18	7.5	9	1.6	7	3.6	34	3.4	*21*
Black	3	1.3	2	0.3	3	1.5	8	0.8	*13*
Other European	12	5.0	12	2.1	20	10.2	44	4.3	*23*
Other non-european	13	5.4	11	1.9	20	10.2	44	4.3	*25*
Educational level *									
low	36	15.1	141	24.4	58	29.4	235	23.2	*23*
moderate	78	32.6	154	26.7	57	28.9	289	28.5	*16*
high	114	47.7	233	40.4	62	31.5	409	40.4	*9*
Maternal age[b *]	30	(18-42)	32	(17-44)	32	(19-44)	31	(17-44)	*n.a.*
Nulliparous women *	132	55.2	203	35.2	70	35.5	405	40.0	*15*
Smoking during pregnancy	42	17.6	126	21.8	47	23.9	215	21.2	*20*
Alcohol consumption during pregnancy*	85	35.6	161	27.9	36	18.3	215	21.2	*13*
Illicit drug (ab)use during pregnancy	3	1.3	8	1.4	6	3.0	17	1.7	*47*
Psychiatric history	40	16.7	133	23.1	36	18.3	209	20.6	*33*
(History of) psychotropic medication *	11	4.6	73	12.7	18	9.1	102	10.1	*37*
Potential mediators (M)									
EDS score[c]	5	± 4.8	6	± 4.8	7	± 6.0	6	± 5.1	*n.a.*
Current depressive symptoms (EDS 12 or more) *	29	12.1	77	13.3	43	21.8	149	14.7	*n.a.*
Dependent adverse pregnancy outcomes (Y)									
Preterm birth[d *]	21	8.8	78	13.5	13	6.6	112	11.1	*21*
Small for gestational age[e *]	17	7.1	59	10.2	59	29.9	109	10.8	*12*

[a] Percentages of independent initial risks and dependent adverse pregnancy outcomes among women with an EDS score ≥ 12 (n = 149)

[b] Data given as median (min-max)

[c] Data given as mean ± sd

[d] Defined as delivery before 37th week of gestation

[e] Defined as below the 10th percentile

[*] Indicates a significant difference between the three level of care groups (p<0.05)

n.a. not applicable

Percentages do not always count up to 100% due to missing responses

of participants, with the lowest prevalence among women from the secondary care level (2%) (data available from authors).

Since PTB and SGA were of primary interest, we included those two outcomes in further analyses only.

Univariate logistic regression analyses (Table 2) showed that the initial risk factors, ethnicity, educational level, smoking, illicit drug use, psychiatric history, psychotropic medication use, and level of care were associated with depressive symptoms (continuous EDS score) during pregnancy (all $p < 0.05$). Regarding adverse pregnancy outcomes, educational level and maternal age were significantly associated with PTB at a 0.05 level. Smoking, past psychotropic medication use and psychiatric history were, however, associated with PTB at a 0.10 level. For SGA, maternal age, parity, smoking and level of care were significant predictors ($p<0.05$), with no factors in the range $0.05 < p < 0.10$.

Regarding the association between antenatal depressive symptoms and adverse pregnancy outcomes, EDS score was significantly associated with PTB only (OR 1.04; 95% CI 1.00;1.08, p-value < 0.05). Therefore, mediation analysis was conducted only for this specific adverse outcome.

The initial risk factors educational level, smoking, past psychotropic medication use and psychiatric history were associated with both EDS score and preterm birth at a 0.10 level and therefore qualified for inclusion in the mediation analysis. Of this set of initial risk factors, past psychotropic medication use and psychiatric history could potentially lead to overcorrection as both may be related to depression and were hence excluded from primary analysis. This potential overcorrection was checked in a secondary mediation analysis.

Figure 2 shows the pathways of the mediation model. Path C shows that educational level (X) significantly predicts preterm birth (Y) (low educated OR 1.06; 95% CI 1.02;1.10, adjusted for high educational level and smoking). Path A shows that pregnant women with a low educational level (X) also have an increased risk to develop depressive symptoms (M) (OR 3.57; 95% CI 1.99;6.40, adjusted for smoking). Highly educated women have decreased risks for depressive symptoms (OR 0.36; 95% CI 0.21;0.61, adjusted for smoking). Smoking, adjusted for educational level, was not associated with depressive symptoms during pregnancy.

Path B shows that EDS score (M) is no longer associated with PTB (Y) after adjusting for the initial risk factors (X) (OR: 1.00; 95% CI 1.00;1.01). Conform the mediation protocol, this implies that depressive symptoms do not mediate the association between initial risks and PTB. In addition, adjusting for EDS scores in path C' barely changes the associations between the initial risk factors and preterm birth of path C (path C': low educational level OR: 1.06; 95% CI 1.02;1.10, high educational level OR: 0.97; 95% CI 0.94;1.01).

Secondary mediation analysis with the initially excluded risk factors (past) psychotropic medication use and past psychiatric history confirms the absence of EDS score as a mediator in the pathway to preterm birth. Both risk factors decrease the impact of educational level

Table 2. Association between initial demographic, obstetric and social risk factors and the potential mediator, and the adverse pregnancy outcomes preterm birth and SGA among 3 cohorts of urban pregnant women (n=1013); univariate logistic regression analyses.

	Potential mediator (M)		Dependent adverse pregnancy outcomes (Y)		
Independent initial risk factors (X)	**EDS score[a]**		**Preterm birth**		**SGA[b]**	
	crude b	90% CI	crude OR	90% CI	crude OR	90% CI
Low socio-economic status	0.60	-0.13;1.33	0.86	0.54;1.38	1.44	0.94;2.23
Ethnicity						
Dutch (REF)	**1**		1		1	
non-Dutch	**1.49**	0.77 ; 2.20	1.01	0.65 ; 1.59	1.50	0.98 ; 2.29
Educational level						
low	**1.29**	0.71 ; 1.86	1.49	0.91 ; 2.43	1.73	0.99 ; 2.99
moderate (REF)	**1**		**1**		1	
high	**-1.09**	-1.59 ; -0.58	**0.60**	0.36 ; 0.99	0.99	0.58 ; 1.69
Maternal age (years)						
16-20	1.16	-1.66 ; 3.98	0.79	0.10 ; 6.22	0.59	0.08 ; 4.62
21-25	1.18	-0.03 ; 2.34	1.01	0.47 ; 2.18	0.85	0.41 ; 1.75
26-30	0.08	-0.68 ; 0.83	1.15	0.71 ; 1.87	0.97	0.62 ; 1.53
31-35 (REF)	1		**1**		**1**	
36-40	0.84	-0.07 ; 1.75	**1.79**	1.05 ; 3.02	**0.47**	0.24 ; 0.93
41-45	0.54	-1.61 ; 2.69	0.90	0.20 ; 3.98	**0.00**	0.00 ; 0.00
Parity						
primiparous	0.32	-0.32 ; 0.97	1.40[c]	0.94 ; 2.08	**0.54**	0.35 ; 0.83
multiparous (REF)	1		1		**1**	
Smoking						
no (REF)	**1**		1		**1**	
yes, untill pregnancy known	0.68	-0.27 ; 1.62	1.12	0.56 ; 2.25	1.31	0.65 ; 2.65
yes, still	**0.84**	0.07 ; 1.61	1.63[c]	0.96 ; 2.77	**2.20**	1.44 ; 3.37
Alcohol during pregnancy						
no (REF)	1		1		1	
yes	0.05	-0.72 ; 0.82	1,14	0.71 ; 1.82	0.99	0.61 ; 1.61
Illicit drug use during pregnancy						
no (REF)	**1**		1		1	
yes	**4.18**	1.74 ; 6.61	1.74	0.49 ; 6.16	1.80	0.51 ; 6.36
Psychiatric history						
no (REF)	**1**		1		1	
yes	**4.00**	3.27 ; 4.74	1.55[c]	0.99 ; 2.43	0.85	0.51 ; 1.42
(History of) psychotropic medication						
no (REF)	**1**		1		1	
yes	**4.72**	3.71 ; 5.72	1.72[c]	0.98 ; 3.02	1.24	0.67 ; 2.30
Level of care						
primary (REF)	**1**		1		**1**	
secondary	**0.77**	0.01 ; 1.54	1.62	0.98 ; 2.70	1.49	0.85 ; 2.61
tertiary	**1.11**	0.15 ; 2.08	0.73	0.36 ; 1.51	**2.63**	1.42 ; 4.88
Potential mediator (M)						
EDS score			**1.04**	1.00 ; 1.08	0.99	0.95 ; 1.03

[a] continuous variable, indicating a measure of depressive symptoms as measured by the Edinburgh Depression Scale

[b] small for gestational age

[c] indicates an association at a p<0.10 level

*Numers printed **bold** indicate significance of association at p<0.05*

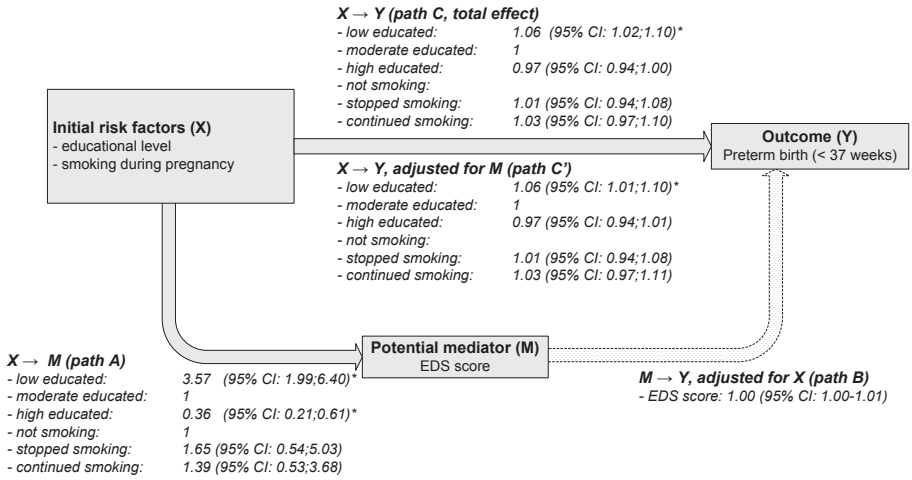


Figure 2 Mediation model of the causal pathway to preterm birth, including the direct pathway of educational level and smoking to preterm birth and the indirect pathway of educational level and smoking through depressive symptoms during pregnancy (n = 1013)
Associations are expressed through adjusted odds ratio's and 95% confidence intervals, calculated by 1000 bootstrapping resamples.
*** indicate** significance of association at p<0.05 level, some of the 95% confidence intervals contain the number 1 due to rouding.

and smoking on depression, but do not affect the impact of educational level and smoking on preterm birth (data available upon request).

DISCUSSION

Depressive symptoms are not a mediator in the pathway of demographic and psychosocial risks factors to PTB and SGA. Low educational level enhances depressive symptoms during pregnancy, and also the risk of PTB. The observed association between depressive symptoms and PTB, however, is spurious. Preterm birth is most likely directly induced by initial background risks, rather than indirectly, through antenatal depressive symptoms.

This large prospective study is subject to several limitations. First, we did not adjust for psychiatric treatment status at the time of screening. A direct effect of successful psychiatric treatment on EDS score could have diluted the effect of EDS score on PTB at a later stage. Psychiatric treatment, however, rarely starts at time of screening and usually dates from well before conception. Successful treatment then will be reflected in a low EDS score during screening, rather than in a diminished effect of a high EDS score on later events.

Second, an overrepresentation of pregnant women with psychiatric complaints could be present within this study, since the participating hospitals are known to provide pregnancy-related psychiatric treatment. However, our study represents three different pregnant cohorts collected during routine prenatal practice, with comparable prevalence of psychopathology

and psychosocial problems in all three levels of care. The routine implementation of the screening in all cohorts allowed for a natural estimate of prevalence, with very high response rate and little bias through selective participation.

Third, antenatal depressive symptomatology was based on self-reported symptoms (EDS score), and not on a formal DSM-IV diagnosis of depression. Both methods have their own merits. A formal diagnosis of depression should guide patient treatment. Despite its strong association with clinical depression, high EDS scores cannot undoubtedly be regarded as distinct disease. The EDS score is more sensitive in detecting a minor depression and subsyndromal depressive symptoms. A formal clinical diagnosis is an entity at the extreme end of mood disturbances where risks and protective factors act on the full spectre of the disturbances, from very mild to extreme.

Finally, obstetric risk factors such as previous preterm birth and infectious diseases[27] were deliberately not addressed in this study. This could have resulted in dilution of the power of the total mediation model. We intended, however, not to create a prediction model for PTB and SGA. Since demographic and psychosocial risks are prevalent in Dutch urban areas, we specifically examined the role of depressive symptoms in the pathway of demographic and psychosocial risk factors to the adverse pregnancy outcomes.

This study introduces a formal mediation analysis to judge on the presence of either a direct or an indirect pathway to PTB and SGA. Few studies allow for a comparison, as in the presence of an association between antenatal depression and adverse pregnancy outcomes the causality is usually taken for granted. Our study contradicts conclusions from at least two meta-analysis reporting an association between antenatal depression and PTB and SGA.[11,12] Besides a different statistical approach in our study, another explanation for contradicting outcomes are the slightly different defined outcomes. As reported by Grote et al and Alder et al, most studies focus on low birth weight, rather than SGA, and some studies focus on spontaneous preterm birth specifically.[11,12] In addition, crosscultural variability of the prevalence of antenatal depression in relation to PTB and birth weight exists.[12]

The results of our study are supported by the report of Dunkel Schetter and Glynn, however, which stated that most studies find no association between antenatal depression and PTB.[28]

The findings in this study support the need to reduce background inequalities in terms of demographic and psychosocial risks to decrease the risk for depressive symptoms and for adverse pregnancy outcomes, such as PTB.[29,30]

Among our study population initial demographic and psychosocial risk factors, depressive symptoms and the adverse pregnancy outcomes PTB and SGA were prevalent, yet comparable to the prevalence of risks measured in other international studies.[1,6,22] Even the high rate of alcohol consumption during pregnancy in the more highly educated, overall Dutch population in the primary level of care has been reported before.[31]

Compared to national and international averages, the prevalence of adverse foetal outcome among our study population is high, especially for preterm birth and SGA. However, these numbers are comparable to rates reported by other authors.[4,32]

More research is needed beyond statistical analysis to conclude on the mediating role of antenatal depressive symptoms. A thorough analysis of the biochemical pathways (e.g. HPA axis) between EDS and PTB or SGA is a likely candidate. However, this pathway is general and related to initial risks too. Hence it suffers from the same interpretative ambiguity as EDS. Perhaps most information will be provided from follow-up studies of women getting depressed during pregnancy, where disease severity measurements can be related to child outcome.

Maternal depression and the adverse pregnancy outcomes PTB and SGA are major public health issues. This study supports the need to measure and, to the extent possible, ameliorate initial demographic and psychosocial background risks among pregnant women, since both depressive symptoms during pregnancy and PTB and SGA share the same initial risks, and will both profit. This mechanistic view does not invalidate depression treatment during pregnancy. Mental health problems during pregnancy can have severe and long-term consequences, like suicide and adverse effects on maternal-child attachment.[33] However, if our findings are confirmed, the preventive interventions directed at demographic and psychosocial risk factors are likely to be of primary concern for clinicians and public health initiatives.[34]

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CHAPTER 8

Contribution of psychopathology, psychosocial problems and substance use to urban and rural differences in birth outcomes

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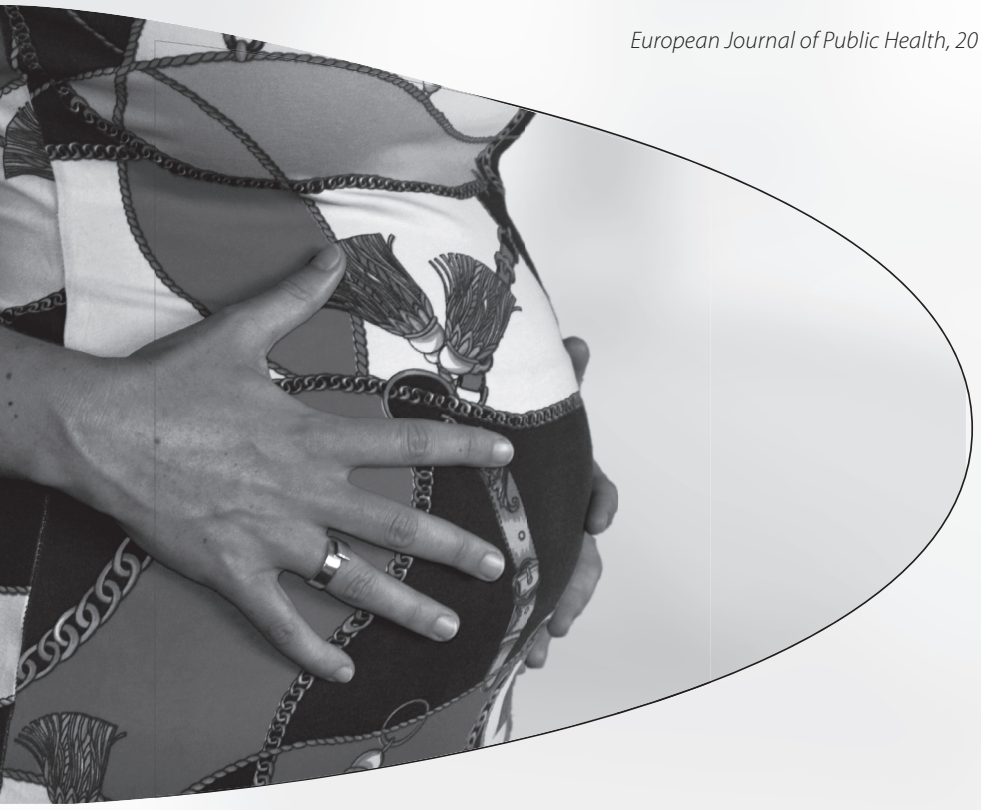
European Journal of Public Health, 2014 juni, in press



ABSTRACT

Background: Urban residence contributes to disparities in preterm birth and birth weight. As urban and rural pregnant populations differ in individual Psychopathological, Psychosocial and Substance use (PPS) risks, we examined to which extent preterm birth and birth weight depend on the (accumulative) effect of PPS risk factors and on demographic variation..

Methods: Follow-up study from 2010 to 2012 among 689 urban and 348 rural pregnant women. Urbanity was based on the population density per ZIP code. Women completed the validated Mind2Care instrument, which includes the Edinburgh Depression Scale, and demographic, obstetric and PPS questions. Pregnancy outcomes were extracted from medical records.
With regression analyses we assessed crude and adjusted associations between residence and birth outcomes, adjusted for available confounding or mediating factors.

Results: Preterm birth was significantly associated with segregation, maternal age (<25 years and ≥35 years), primiparity, smoking during pregnancy, and the accumulation of risks, but not with residence (urban 4%, rural 7%, p=0.16).
Mean birth weight was significantly lower for urban babies (crude β: -174, p<0.001). Adjusting for potential confounders and mediators, non-Western ethnicity, parity, and smoking during pregnancy significantly decreased birth weight besides residence. The accumulative effect of PPS risk factors significantly decreased birth weight. (β: -58 grams per risk factor, p<0.001).

Conclusion: Preterm birth was not associated with residence. The lower birth weight of urban babies remains significant after adjusting for urban risks, such as non-Western ethnicity and the PPS risk factor smoking. The accumulation of multiple (moderate) PPS risks accounts partly for the urban effect.

INTRODUCTION

Preterm birth (PTB) and low birth weight (LBW) are two important adverse birth outcomes, affecting more than 10% of women and their new-borns worldwide.[1,2] Both conditions are leading causes of perinatal and infant mortality,[3,4] chronic disease in later life,[5] and result in high health care costs.[1,6]

Among other well-known risks factors, such as preeclampsia and ethnicity contributing to adverse birth outcomes,[2,6] the influence of geographical disparities is relatively understudied. Regarding geographical disparities in perinatal health, there are contrasting findings on the contribution of urban and rural residence.[7-13] In the international literature, rural populations generally have the highest prevalence of adverse birth outcomes, of deprivation and of individual risk factors, such as a non-indigenous ethnicity, low socioeconomic status, and maternal depression.[8,10,13,14] Some studies however, find the opposite, in particular studies from The Netherlands.[7,15]

One explanation for the contrasting findings is that they are confounded or mediated by underlying individual risks, since urban and rural populations differ in many respects, e.g. demographic composition, and environmental exposures.[1,6,16,17] More specific and often co-occurring risk factors concerning Psychopathology, Psychosocial problems, and Substance use (PPS) are also associated with PTB and LBW,[14,15,18]in particular in case of risk accumulation.[19] Geographical disparities in PPS risk factors exist too. Therefore, urban-rural disparities in birth outcomes may not only be affected by geographic risks, but also by (the accumulation of) PPS risks.

The observed perinatal health disparities urge for targeted improvement strategies. Increased insight into the contribution of specific (treatable) risk factors for adverse birth outcomes in combination with screening and subsequent referral to targeted interventions could reduce these disparities.

To our knowledge, there are no studies that systematically investigated the (accumulative) effect of PPS risk factors in relation to geographic disparities in birth outcomes.

We aimed to investigate to which extent PTB and birth weight depend on the (accumulative) effect of individual PPS risk factors in urban and rural areas or on geographic and demographic variation.

METHODS

Data was obtained from the validated Mind2Care screen-and-advice instrument (M2C, formerly known as the GyPsy instrument),[20] including the Edinburgh Depression Scale (EDS),[21] and a set of risk factors for psychiatric disorders during pregnancy, including substance use, demographic, obstetric, and psychosocial factors. M2C was specifically developed by the

Erasmus Medical Center as a tool for screening and subsequent treatment allocation for PPS risks during pregnancy, as these often escape detection.[22]

In Rotterdam, one of the major cities in The Netherlands, M2C was implemented from June 2010 to June 2012, in three midwifery practices and a general hospital. All pregnant women with a booking visit at these clinics were approached for this study. The midwifery practices were located in a severely deprived, a less deprived and a non-deprived area. The hospital served a severely deprived area. Together, 40% of all urban Rotterdam pregnant women were served by a participating practice.

In Meppel, a small rural city, M2C was implemented from April 2012 to May 2012 in four midwifery practices and the local general hospital. All pregnant women residing in this city and the adjacent rural agricultural area who attended the clinics during the study period were approached for this study.

All participating women completed the M2C-questionnaire on a personal digital assistant (PDA) prior to their pregnancy check-up, as part of routine practice. In total, 1076 (88%) of the 1230 eligible women were screened with M2C (Figure 1). 11% refused participation and 1% was excluded due to a language barrier. M2C data was complete for 1037 women (96%), as data on residence or ≥10 M2C questions was missing for 39 women. Postpartum, follow-up information and birth outcomes were extracted from medical records. Birth outcomes were unavailable for 25% of women (n=259). Main reasons included miscarriage or pregnancy

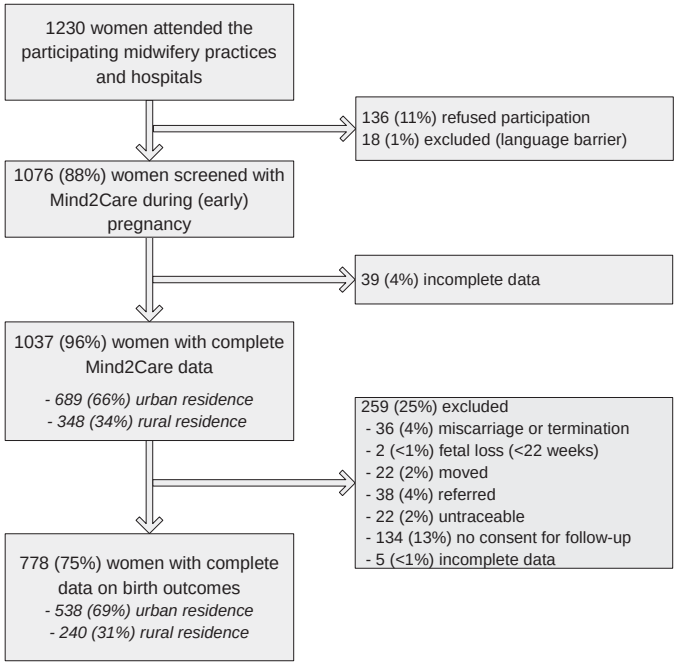


Figure 1 Study population

termination (4%), referral outside the study region (4%), and lack of consent for follow-up (13%). Outcomes of 778 women were analysed. Women with incomplete data on birth outcomes were more often of rural residence, non-Western ethnicity, and low educational level compared to women with complete data (42% vs. 31%, 33% vs. 23%, and 28% vs. 21%, $p<0.05$, data available upon request).

Study approval was obtained from the Medical Ethical Board of the Erasmus University Medical Center Rotterdam [MEC-2013-162].

Birth outcomes included PTB (<37 weeks of gestation), small for gestational age (SGA, < 10th percentile based on national percentile distributions[23]), and birth weight (BW, grams). The definition of urban and rural residence was based on the population density per ZIP code, as classified in the 2011 consensus of the Dutch Central Bureau of Statistics (CBS).[24] Urban residence was defined as residence in a ZIP code area with more than 1500 household per km^2 and rural residence was defined as residence in a ZIP code area with fewer than 1500 households per km^2. A dichotomous definition was used to ensure sufficient power for statistical analysis. ZIP code and individual risk factors were measured with M2C.

Individual risk factors included demographic factors (socioeconomic status, segregation, ethnicity, educational level, maternal age, and single status), obstetric factors (gestational age, gravidity and parity), **p**sychosocial stressors (insufficient social support, relational problems, financial debts, housing problems, and physical/sexual abuse), **s**ubstance use (smoking, alcohol consumption, and illicit drug use) and **p**sychopathology related factors (depressive symptoms and psychotropic medication use). Demographic and obstetric factors were regarded as individual risk factors related to geographical composition. Psychosocial stressors, substance use and psychopathology related factors were regarded as individual PPS risks.

Socioeconomic status was measured by proxy (z-score for socioeconomic status for each ZIP code), and was obtained from the Dutch Social and Cultural Planning Office.[25] Segregation was qualified as the distribution of non-Western immigrants among all other residents per ZIP code within one borough. The index can be interpreted as the proportion of non-Western immigrants that would have to move from the ZIP code areas in order to achieve a uniform distribution over the borough. Segregation indexes were calculated conventionally by using data on population size and composition from the CBS Web site and the formula of Taylor et at.[26,27]

Depressive symptoms during pregnancy were measured by the EDS, a validated ten item self-report checklist with a total score range of 0-30.[21] Women with EDS scores of 10 or more were regarded as having clinically relevant depressive symptoms.[28]

Risk accumulation was expressed through a weighted sum score of all separate PPS risks representing the overall PPS risk load. Based on the study of Timmermans et al,[19] PPS risk factors accounted for 1 point, except for the continuation of substances, which accounted for 2 points. The sum score ranged from 0 to 13, where 0 represented absence of any risk.

As a general reference for the prevalence of demographic risk factors, PPS risks, and birth outcomes we used two large Dutch cohort studies (Generation R and ABCD study)[29,30] and national reference data as stated on the websites of the Dutch Social and Cultural Planning Office and the Dutch Perinatal Registry.[23,25]

Urban and rural differences in birth outcomes and in individual risks, and crude associations between individual risk factors and birth outcomes were assessed with chi-squared tests, student's t-tests and Mann-Whitney-U tests. The crude association between residence and birth outcomes were examined with univariate logistic and linear regression analyses. Multiple stepwise regression analyses were conducted to assess the association between residence and adverse birth outcomes, adjusted for all available confounding or mediating individual risk factors. All birth outcomes and individual demographic risk factors with a p-value below 0.10 following descriptive statistics were included in the multiple stepwise regression model, with model 1 including demographic risk factors, model 2 including demographic and PPS risk factors, and model 3 including the accumulative effect of PPS risks. All models were adjusted for gestational age at birth.

Associations following univariate and multiple regression analyses were expressed through unadjusted respectively adjusted odds ratios or betas (95% CI) and p-value. Associations with a p-value below 0.05 were regarded as statistically significant. All analyses were performed using the Statistical Package for Social Science, version 20.0.

RESULTS

Table 1 shows birth outcomes differed across residence, with significantly lower birth weights in urban areas (mean weight 3385 vs. 3533 grams, $p<0.01$). Prevalence of PTB and SGA were comparable between urban and rural babies (urban PTB 4% vs. rural PTB 7%, $p=0.16$; urban SGA 7% vs. rural SGA 5%, $p=0.42$). As SGA is a standardised measure of birth weight, SGA was not included in further analysis.

A number of demographic factors were associated with residence too. Urban pregnant women were more likely to be of low socio-economic status, non-Western ethnicity, and high educational level, and were more often single (all $p<0.01$). The distribution of non-Western immigrants was higher among urban residents (median segregation index 0.30 versus 0.17, $p<0.001$). Urban women were also more often of primigravidity and primiparity, and had, due to the study design, a lower gestational age at screening (median 9 weeks vs. 26 weeks) ($p<0.05$).

Of the PPS risk factors, financial debts and alcohol consumption during early pregnancy had a higher prevalence among urban women (9% vs. 5%; 20% vs. 11%, $p<0.05$). Urban women had more depressive symptoms (17% vs. 13%) and rural women were more likely to continue psychotropic medication use during pregnancy (3% vs. 1%, both $p<0.05$). Accumulation of

Table 1. Prevalence of adverse birth outcomes, demograhic, obstetric, psychosocial, substance use and psychiatric determinants of women from an urban versus a rural residence in the Netherlands (n=1037)

	Urban women (n = 538)		**Rural women (n = 240)**		
Adverse birth outcomes	*n*	*(%)*	*n*	*(%)*	*p-value*
Preterm birth (< 37th week of gestation)	23	(4)	16	(7)	0.158
Birth weight (grams)[1]	3385	(557)	3533	(594)	0.001
Small for gestational age (< 10th percentile)	35	(7)	12	(5)	0.416
	Urban women (n = 689)		**Rural women (n = 348)**		
Demographic determinants	*n*	*(%)*	*n*	*(%)*	*p-value*
Low socio economic status (< 20th percentile)	293	(43)	76	(22)	<0.001
Segregation index[2]	0.30	(0.18 - 0.30)	0.17	(0.06 - 0.37)	<0.001
Ethnicity					<0.001
Dutch	410	(60) [a]	340	(98) [b]	
Moroccan	53	(8) [a]	0	(0) [b]	
Turkish	23	(3) [a]	0	(0) [b]	
Antillian	51	(7) [a]	0	(0) [b]	
Surinamese	39	(6) [a]	0	(0) [b]	
Eastern Europe	24	(3) [a]	1	(0) [b]	
other non-Western	89	(13) [a]	7	(2) [b]	
Educational level					<0.001
low	144	(21) [a]	90	(26) [a]	
moderate	209	(30) [a]	143	(41) [b]	
high	336	(49) [a]	115	(33) [b]	
Maternal age[1]	30	(5)	30	(5)	0.360
Single status	26	(4)	3	(1)	0.007
Obstetric determinants					
Gestational age at screening (weeks)[2]	9	(8 - 12)	26	(19 - 34)	<0.001
Gravidity					0.017
1	320	(46) [a]	131	(38) [b]	
2	212	(31) [a]	111	(32) [a]	
3	99	(14) [a]	62	(18) [a]	
4+	58	(8) [a]	44	(13) [b]	
Primiparity	386	(56)	145	(42)	<0.001
Psychosocial stressors					

table 1 continued

Insufficient social support	15	(2)	3	(1)	0.126
Relational problems	31	(4)	11	(3)	0.302
Financial debts	63	(9)	17	(5)	0.015
Housing problems	36	(5)	10	(3)	0.082
Physical or sexual abuse	11	(2)	6	(2)	0.879
Substance use					
Smoking during pregnancy[3]					0.114
No	568	(82)	291	(84)	
Yes, until pregnancy was known	77	(11)	27	(8)	
Yes, continued during pregnancy	44	(6)	30	(9)	
Alcohol consumption during pregnancy[4]					<0.001
No	552	(80) [a]	309	(89) [b]	
Yes, until pregnancy was known	136	(20) [a]	39	(11) [b]	
Yes, continued during pregnancy	2	(0) [a]	0	(0) [a]	
Illicit drug use during pregnancy					0.061
No	678	(98)	347	(100)	
Yes, until pregnancy was known	8	(1)	1	(0)	
Yes, continued during pregnancy	3	(0)	0	(0)	
Psychiatric determinants					
Clinically relevant depressive symptoms (EDS ≥ 10)[5]	120	(17)	44	(13)	0.047
Continued use of psychotropic medication during pregnancy	6	(1)	9	(3)	0.029
Accumulation of PPS risks[6]					
Sum of PPS risk determinants[7]					<0.001
0 to 2	395	(57) [a]	280	(80) [b]	
3 to 4	212	(31) [a]	59	(17) [b]	
5 or more	82	(12) [a]	9	(3) [b]	

For categorical data a chi-squared test was performed

[1] Data given as mean (sd), student's t-test was used

[2] Data given as median (Q1-Q3), Mann Whitney U test was used

[3] Defined as at least one cigarette a day

[4] Defined as at least one glass a week

[5] EDS: Edinburgh Depression Scale

[6] PPS indicates Psychiatric determinants, Psychosocial determinants, and Substance use determinants

[7] All individual PPS risk factors account for 1 point, including quitting substance use during pregnancy. Continuation of substance use accounts for 2 points. Range 0-13

[a,b] Each subscript letter denotes significant difference at a 0.05 level between groups according to the posthoc Bonferoni adjusted pairwise comparison

PPS risk was highest among urban women (urban 12% sum score of 5 or more vs. 3% rural, p<0.001). The demographic profiles, the prevalence of PPS risk factors and the prevalence of adverse birth outcomes were representative for Dutch urban and rural populations.

Table 2 shows that a lower birth weight was associated with low socioeconomic status (SES), non-Western ethnicity, primigravidity, multigravidity, primiparity, financial debts, physicial and sexual abuse, contined smoking during pregnancy, and the accumulation of PPS risks (all p<0.05). Maternal age was associated with low birth weight at a p<0.10 level and therefore included in the multivariate regression model too.

PTB was associated with segregation, low and high maternal age (<25 years and ≥35 years), primiparity, smoking, and accumulation of PPS risks (all p<0.05, data available upon request). Since the prevalence of PTB did not significantly differ between urban and rural women, PTB was not included in further analysis.

Table 2. Crude association between individual risk factors and birth weight in grams among urban and rural pregnant women in the Netherlands (n = 778)

	Birth weight (n = 778)		
Demographic determinants	*mean*	*(sd)*	*p-value*
Low socio economic status[1]	3346	(590)	0.002
Segregation index			0.117
< 0.25	3389	(608)	
≥ 0.25	3455	(549)	
Maternal age			0.074
< 25 years	3372	(516)	
25-35 years	3443	(572)	
≥ 35 years	3450	(651)	
Ethnicity			0.001
Dutch	3467	(589)	
Moroccan	3496	(450)	
Turkish	3239	(688)	
Antillian	3151	(490)	
Surinamese	3219	(460)	
Eastern Europe	3480	(475)	
other non-Western	3288	(469)	
Educational level			0.187
low	3366	(657)	
moderate	3423	(545)	
high	3465	(548)	
Single status	3473	(547)	0.853

table 2 continued

Obstetric determinants			
Gravidity			0.002
1	3344	(583)	
2	3515	(496)	
3	3501	(624)	
4+	3413	(637)	
Primiparity	3345	(581)	<0.001
Psychosocial stressors			
Insufficient social support	3536	(432)	0.620
Relational problems	3366	(565)	0.300
Financial debts	3231	(731)	0.043
Housing problems	3388	(473)	0.596
Physical and sexual abuse	3195	(505)	0.034
Substance use			
Smoking during pregnancy[2]			<0.001
No	3460	(551)	
Yes, untill pregnancy was known	3465	(506)	
Yes, continued during pregnancy	3072	(735)	
Alcohol consumption during pregnancy[3]			0.834
No	3424	(577)	
Yes, untill pregnancy was known	3460	(555)	
Yes, continued during pregnancy	3488	(279)	
Illicit drug use during pregnancy			0.349
No	3432	(573)	
Yes, untill pregnancy was known	3313	(462)	
Yes, continued during pregnancy	n.a.	n.a.	
Psychiatric determinants			
Clinically relevant depressive symptoms (EDS ≥ 10)[4]	3431	(584)	0.817
Continued use of psychotropic medication during pregnancy	3519	(420)	0.171
Accumulation of PPS risks[5]			
Sum of PPS risk determinants			0.020
0 to 2	3447	(566)	
3 to 4	3216	(640)	
5 or more	3339	(489)	

[1] Below the 20th percentile

[2] Defined as at least one cigarette a day

[3] Defined as at least one glass a week

[4] EDS: Edinburgh Depression Scale

[5] PPS indicates Psychiatric determinants, Psychosocial determinants and Substance use determinants

[6] All individual PPS risk factors account for 1 point, including quitting substance use during pregnancy. Continuation of substance use accounts for 2 points

Table 3. Crude and adjusted association between residence and birth weight, adjusted for demographic and obstetric determinants, and risk factors related to PPS: Psychopathology, Psychosocial stressors and Substance use (n = 778)

	Model 0		**Model 1**		**Model 2**		**Model 3**	
Determinants	*B*	*95% CI*	*B*	*95% CI*	*B*	*95% CI*	*B*	*95% CI*
Demographic determinants								
Residence								
Urban area	-173.97	(-240.98 ; -106.96) **	-130.58	(-201.47 ; -59.69) **	-138.81	(-210.24 ; -67.39) **	-77.96	(-168.74 ; -12.83) *
Rural area (REF)	0		0		0		0	
Socio economic status (SES)								
low (< 20th percentile)			-30.65	(-95.98 ; 34.68)	-17.54	(-82.91 ; 47.84)	-29.29	(-95.00 ; 36.42)
moderate-high (REF)			0		0		0	
Maternal age (years)			-1.67	(-8.41 ; 5.07)	-2.27	(-9.14 ; 4.60)	-1.82	(-8.61 ; 4.96)
Ethnicity								
Western (REF)			0		0		0	
non-Western			-82.56	(-161.34 ; -3.77) *	-98.28	(-178.53 ; -18.04) *	-81.18	(-160.31 ; -2.06) *
Obstetric determinants								
Parity								

Table 3. continued

	Model 0	Model 1		Model 2		Model 3	
primiparity		-135.24	(-199.67 ; -70.81) **	-142.65	(-207.43 ; -77.88) **	-135.87	(-200.42 ; -71.33) **
multiparity (REF)		0		0		0	
Psychosocial stressors							
Insufficient social support							
no (REF)				0			
yes				79.00	(-191.61 ; 349.62)		
Relational problems							
no (REF)				0			
yes				79.93	(-104.60 ; 264.46)		
Financial debts							
no (REF)				0			
yes				5.42	(-130.11 ; 140.96)		
Housing problems							
no (REF)				0			
yes				-49.03	(-211.55 ; 113.49)		
Physical and sexual abuse							
no (REF)				0			
yes				-167.48	(-421.86 ; 86.90)		
Psychiatric determinants							
Clinically relevant depressive symptoms (EDS ≥ 10)[1]				0			
no (REF)				91.30	(-0.79 ; 183.39)		
yes							

Table 3. continued

	Model 0	Model 1	Model 2		Model 3	
Continued use of psychotropic medication during pregnancy						
no (REF)		0				
yes		157.50	(128.77 ; 443.78)			
Substance use						
Smoking during pregnancy[2]						
no (REF)		0				
yes, untill pregnancy was known		11.93	(-102.19 ; 126.06)			
Yes, continued during pregnancy		-230.14	(-351.04 ; -109.23) **	**		
Consuming alcohol during pregnancy[3]						
no (REF)		0				
yes, until pregnancy was known		-32.10	(-117.22 ; 53.02)			
Yes, continued during pregnancy		83.78	(-521.27 ; 688.82)			
Illicit drug use during pregnancy						
no (REF)		0				
yes, until pregnancy was known		48.73	(-261.21 ; 358.66)			
Yes, continued during pregnancy		-539.16	(-1444.44 ; 366.11)			
Accumulation of PPS risks[4]						
Sum of PPS risk determinants[5]					-57.79	(-106.03 ; -9.55) *

All models are adjusted for gestational age at birth

** indicates signifance at a 0.05 level, ** indicates significance at a 0.01 level*

[1] *EDS: Edinburgh Depression Scale*

[2] *Defined as at least one cigarette a day*

[3] *Defined as at least one glass a week*

[4] *PPS indicates Psychiatric determinants, Psychosocial determinants and Substance use determinants*

[5] *All individual PPS risk factors account for 1 point, including quitting substance use during pregnancy. Continuation of substance use accounts for 2 points*

Crude analysis (table 3) showed that urban babies had a 174 gram lower birth weight than rural babies (95% CI:-240;-107 gram, adjusted for gestational age at delivery). This significant effect decreases to a 130 and 138 gram lower birth weight ($p<0.01$) after adjusting for individual demographic factors in model 1 and PPS risk factors in model 2. Non-Western ethnicity and primiparity significantly decreased birth weight (-83 grams, 95% CI:-161;-4 and -135 grams, 95% CI: -200;-70). Both factors remained significantly associated with birth weight after adjusting for PPS risk factors. Of the PPS risk factors, only smoking significantly contributed to a lower birth weight (-230 grams, 95% CI: -351;-109). The accumulation of PPS risks contributed to a decrease in birth weight with 58 grams for each risk factor (95% CI: -106;-10, $p<0.05$).

DISCUSSION

This multicentre follow-up study showed that urban babies have a 174 gram lower birth weight than rural babies. After adjusting for available mediators and confounders, non-Western ethnicity, primiparity, and the PPS risk factor smoking decreased birth weight besides urban residence. However, the accumulation of multiple PPS risk factors contributed to the urban effect with a 58 grams lower birth weight for each risk factor.

A strength of this study is the fairly large population-based sample comparing a small rural area with a large urban city, with representative prevalence of risk factors and perinatal outcomes for Dutch large rural and urban populations. However, whilst our results may be generalizable in this context, more data is needed to explore whether the same observation holds for medium size cities. A second strength is the use of prospective data derived from routine practice settings.

Besides residence and demographic factors, a comprehensive set of PPS risk factors were included in the analysis, allowing for an examination of the contribution of PPS risks to disparities in birth outcomes.

PTB was slightly more prevalent in the rural setting, which is in line with previous findings.[8-10] The Canadian Study by Lisonkova et al.,[11] however, found rural women to be less likely to deliver preterm. In contrast to a number of previous studies,[8-10,12] but in line with the study of Hillemeier et al.,[13] crude mean birth weight appeared lower in the urban area. Five explanations possibly contribute to these contrasting findings.

Firstly, positive selection could have introduced bias to our study. Data on birth outcomes were more often incomplete for rural women and low educated non-Western women. As non-Western ethnicity and rural residence were adversely associated with birth weight, we expect our findings to be an underestimation of the true urban-rural disparity in birth weight rather than an overestimation. In addition, rural women had a substantially higher gestational age during screening, which could have decreased the proportion of (early)

preterm deliveries in our study. As the prevalence of (early) PTB and mean birth weights in our urban and rural population were comparable to national and European outcomes, we assume selection bias to be limited.[23,25,31]

Secondly, the causal pathway of risks leading to PTB and LBW is likely to be equal across countries. International differences in the prevalence of the underlying demographic and PPS risks in urban and rural areas could, however, explain the urban-rural disparities in PTB and LBW prevalence. Risk factors for LBW are most prevalent in our urban sample, which is in line with previous Dutch studies.[7,19] In non-Dutch studies, however, these risk factors are most prevalent in rural samples.[8,9,11]

Thirdly, our results can be distorted by the use of a dichotomous definition of residence. The rural area includes rural areas adjacent and rural areas not adjacent to urban areas. In this context we must be aware of heterogeneity of rural communities. Most remote rural areas currently are low income and low educated as the better educated population tends to migrate to urban environments for better perspectives. However, rural areas adjacent to larger cities may profit from 'back migration' of people taking the disutility of commuting for granted for living in a healthier environment. This may result in better birth outcomes in rural areas adjacent to an urban area than in rural areas not adjacent to an urban area.[10,12]

However, as recommended by Strutz et al.,[8] we choose the geographical area level definition suited best to the population under study.

Fourthly, most studies on the urban/rural effect were conducted in the 80s and 90s. It is likely that urban and rural populations have been changed over the last three decades in terms of poverty, infrastructure, prenatal care, and population composition. Changes in this respect occurred in both the rural area and the metropolitan cities.

Finally, comparability with other studies is limited if selective sampling has been applied (e.g. non-Hispanic white women only) and PPS risks were not of primary interest.

This study is subject to several limitations. Firstly, individual risk factors were derived from the self-report M2C questionnaire. Self-reportage can introduce misclassification in our results. However, the same is true with professional based screening. Due to lack of an ethically approved gold standard for e.g. financial debts and sexual or physical abuse, self-report is the most feasible alternative for those risk factors. Secondly, since we focused on PPS, a major limitation of this study is the lack of some important predictors for PTB and LBW, such as preeclampsia, previous PTB, maternal BMI and infectious disease.[2,6] This could have led to omitted variable bias and may decreases the generalizability of our results in routine obstetric care.

In the future, community service factors such as access to care and the quality of the physical environment such as noise and air pollution could be added to the set of risk factors, as the individual residence effect appeared strong in this study. A multi-level study could be beneficial for an exploration of the underlying mechanism through which residence and

individual risk factors are linked, and lead to adverse birth outcomes. Our dataset was too small to investigate such effects.

Whilst we started with the assumption of individual PPS risk factors to explain geographical inequalities in perinatal outcomes, this study shows that the strong residence effect is partly explained by the accumulation of PPS risks and, except for smoking, not by individual PPS risk factors. In addition, rural areas seem not per definition at low risk for adverse birth outcomes. Following this argument, the M2C instrument should routinely be implemented in antenatal care. This has large implications for prenatal care, as risk management starts from a uniform approach, rather than based on clinical assumptions.

We believe that the sacrifice of time for screening and health promotion targeted on PPS risks leading to adverse birth outcomes, in particular smoking, outweighs the benefits of detecting and possibly preventing adverse birth outcomes.

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CHAPTER 9

General discussion

This thesis discusses the feasibility, reliability and validity of a systematic first approach to improve the perinatal health for pregnant women with psychopathology, psychosocial problems and substance use, and their children. The Mind2Care screen-and-advice instrument was the primary tool for this systematic approach. The instrument was applied under routine care conditions, in both the primary obstetric care setting and in hospitals.
In our systematic approach, we focused on how screening for PPS should be performed (regarding timing, instrument, screen methodology, and triage principle), and what difficulties are faced in the guidance of women-at-risk to specialized care. The potential impact of successful screening was investigated by examining the role of PPS conditions in the pathway to adverse pregnancy outcomes.
This chapter discusses the principal findings of the conducted studies, followed by methodological issues, clinical and research implications, and a final conclusion.

PRINCIPAL FINDINGS

1. What is the prevalence of psychopathology, psychosocial problems and substance use during pregnancy in a large Dutch urban area?
Chapter 2 demonstrates that approximately 25% of the urban pregnant women experience psychiatric problems, psychosocial problems or use substances during pregnancy.
Co-existence of psychiatric symptoms, psychosocial problems and/or substance use was evident in about 10% of women. Not all such women need a referral to specialized PPS care, as current thresholds for being entitled as 'screen-positive' are low (high sensitivity), and previously unsuccessful treatment or ongoing treatment were not taken into account with our approach.

2. Is the Mind2Care screen-and-advice instrument a reliable and valid instrument for routine use in obstetric care?
The Mind2Care screen-and-advice instrument was developed and validated from 2008 to 2013. Chapter 2 demonstrates that the Mind2Care appears to be a feasible tool in the routine obstetric care according to both pregnant women and obstetric caregivers, as it allows for a fast and easy screening, with a response rate of 94%. The psychometric properties of the instrument appeared favorable under routine care conditions, with high internal reliability and high test-retest reliability.
Chapter 3 further demonstrates high inter-method reliability. The digital patient based Mind2Care instrument and the professional's paper based R4U checklist can interchangeably be used for the identification of general high-risk levels for PPS and for adverse pregnancy outcomes, if a PPS sum score of 5 is used as cut-off. For the detection of specific PPS risk

factors, both instruments provide rather complementary information. In this study there was no gold standard available to define the 'truth'.
In the study of chapter 4 a formal validation of Mind2Care and R4U items was established by using Structured Clinical Interviews of the DSM-IV axis I and II mental disorders as gold standard. For a valid detection of DSM-IV axis I and axis II disorders, at least the following five-items should be incorporated in triage: 1) the experience of a traumatic event ever, 2) period of a depressed mood ever, 3) panic attack ever, 4) having any psychiatric symptoms currently, 5) manifest severe depressive or anxious symptoms. For a more comprehensive set of triage items, the psychosocial Mind2Care items 'alcohol consumption during pregnancy', 'current or past physical or sexual abuse', and 'having an unplanned pregnancy', or the widely used 10-item Edinburgh Depression Scale can be added.

3. Is the antenatal screening for depressive and/or anxiety symptoms biased by worries surrounding the first ultrasound examination?
Chapter 5 shows that the results of the Edinburgh Depression Scale are not affected by the timing of the first ultrasound examination during early pregnancy. Intrinsic worries, unaltered by the ultrasound, were significantly associated with depressive and anxiety symptoms, in contrast to (temporary) worries induced or reduced by the first prenatal ultrasound examination.

4. How many pregnant women identified as being at risk for PPS after screening eventually receive specialized treatment?
In chapter 6 we introduced a four-step model, including 1) a two stage screening (with R4U for triage and Mind2Care for subsequent confirmation), 2) indication assessment, 3) referral towards specialized care, and 4) the utilisation of specialized care. Women's and caregiver's adherence to this model was examined in the routine obstetric care setting.
We observed that after triage, women gradually drop out on the way to specialized care (up to 77%), in particular women of non-western ethnicity, multiparous women and smokers.

5. What is the role of psychopathology, psychosocial problems and substance use in the pathway to adverse pregnancy outcomes?
The pathway to preterm birth was investigated with a formal mediation analysis, showing that the previously found association between depressive symptoms and the adverse outcome preterm birth can be attributed to shared background risks, such as a low educational level. In contrast to our expectations, depressive symptoms appeared no mediator in the pathway towards adverse outcomes (chapter 7). A comparison of urban versus rural birth outcomes shows that the individual PPS risk factor 'smoking', and the accumulation of PPS risks contribute to a lower birth weight of urban babies, with a decrease in birth weight of 58 grams for each PPS risk factor present (chapter 8).

METHODOLOGICAL CONSIDERATIONS

Sample

Our epidemiological findings generally fit the international literature on the topic of psychopathology, psychosocial problems and substance use. Socio-demographic and obstetric characteristics of the study participants are representative for the Dutch pregnant population.[1,2] International population comparison, however, is often difficult to establish, and some differences are difficult to interpret.

The prevalence of individual risk factors, psychopathology, psychosocial problems, and substance use is comparable to the existing epidemiological literature.[3-7]

Regarding the psychosocial domain, differences in prevalence are prominent between studies from the USA and studies from the Netherlands. While the prevalence of psychosocial risks are high in Dutch urban areas and low in rural areas, the reverse is true in the USA.[3,6,7-9] We believe that this is a true difference. In the Netherlands, the most deprived areas are located in large cities, while in the USA a substantial proportion of the rural population is even more deprived, unlike the Dutch situation.[2,3,10] The process of migration and urbanization differs in various countries, and is likely to be one of the major underlying explanations of the contrasting prevalence.

The prevalence of substance use during pregnancy is uncertain in all studies, due to voluntary participation in screening and the intrinsic difficulties of non-invasive measurements.[11] Invasive measurements such as blood or urine tests would however lead to selective participation and ethical concerns in case of unannounced testing.

Instrument

Routine screening for psychiatric symptoms is recommended by international guidelines.[12,13] In these guidelines subsequent treatment of screen-positive women is not integrated in comprehensive screen-and-advice protocols with regard to psychopathology, psychosocial problems and substance use. No formal description of (local) actions following screening is provided, and the availability of and entry criteria for interventions differ for each region. With the Mind2Care screen-and-advice instrument, an innovative systematic approach was introduced. Risk management here includes a comprehensive screening for co-existing PPS conditions, and the provision of tailored intervention advices. A limitation of the inclusion of co-existing PPS condition, is the lack of a comprehensive gold standard for a formal validation of the instrument.

Contextual measures are taken into account, allowing for a broad use of the instrument. Intervention advices are tailored to the women's risk profile and locally available care pathways. The flexible digital character of the Mind2Care allows for easy adaption of local care pathways into the model, and specific thresholds for being entitled as 'screen-positive' can be adapted.

To improve perinatal mental health, a systematic approach must address risk management and contextual measures simultaneously. This is, however, not enough as the chain of screening, indication-assessment, referral, and treatment still appears to be weak (chapter 6).
Successful implementation of screening also requires active engagement of key professionals and patients, and changes in the perinatal health care system, e.g. financial fees or invoices and inclusion of public health strategies, such as individual and group education of deprived populations on perinatal and mental health.

Impact of PPS on adverse pregnancy outcomes

The influence of depressive symptoms on adverse pregnancy outcomes is a topic of international interest.[14,15] The same is true for specific psychosocial problems and substance use, in particular social support and smoking.[16-18] Data on the role of depressive symptoms or the accumulation of co-existing PPS conditions in the pathway to adverse pregnancy outcomes is limited and difficult to compare.[7,14,15,19] Reasons are different statistical analyses (formal mediation analysis, path analysis, descriptive statistics), different outcome definitions (SGA, low birth weight, birth weight), and differences in populations (socio-demographic or obstetric background characteristics).
The studies in this thesis stress the importance of taking into account background characteristics and the accumulative effect of co-existing PPS in the pathway to adverse pregnancy outcomes, with smoking as the largest contributor to a decreased birth weight. The effect of previous adverse pregnancy outcomes should also be taken into account, e.g. in relation to perceived worries and the risk of anxiety during the current pregnancy or in order to develop predictive models for adverse outcomes, because previous adverse pregnancy outcomes are known predictors for subsequent adverse outcomes.

Study design

Observational studies are suitable to address e.g. the PPS prevalence, the validity of the Mind2Care instrument and the role of depressive symptoms in the pathway to adverse birth outcomes. To investigate the cost-effectiveness of screen-and-treat protocols in the future, a randomized controlled trial would be a superior design.
Repeated measurements of PPS during pregnancy may on the one hand detect late onset or a relapse of PPS or on the other hand remission of PPS at later stages in pregnancy or postpartum. Single measurements could have diluted our study results, in particular for studies addressing the association between ultrasound related worries and psychiatric symptoms, and between PPS conditions and pregnancy outcomes.

CLINICAL AND RESEARCH IMPLICATIONS

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

- Psychopathology, psychosocial problems and substance use are prevalent comorbid conditions during pregnancy, in particular but not exclusively, in large urban areas. Therefore, all pregnant women should routinely be screened for PPS during early pregnancy, independent of their presumed risk level. As screening alone is not enough, women with PPS should subsequently be referred to tailored mental or psychosocial care facilities, based on their risk profile and locally available care.
- The digital Mind2Care screen-and-advice instrument was feasible and well received by both professionals and pregnant women. Reliability measures appeared favourable under routine care conditions. Therefore, the Mind2Care instrument could be implemented in routine obstetric care for the provision of a reliable detection of PPS during pregnancy.
- For a valid screening for DSM-IV axis I and axis II mental disorders, at least a short set of five psychiatric triage items should be implemented in obstetric care, including a traumatic event ever, a period of depressed mood ever, a panic attack ever, current psychiatric symptoms, manifest depressive or anxious symptoms. For a more comprehensive triage, the 10-item Edinburgh Depression Scale or the three psychosocial triage items 'alcohol consumption during pregnancy', 'current or past physical or sexual abuse', and 'having an unplanned pregnancy' should be added to the short set. False-negative cases following screening with both the short and the comprehensive triage model, indicated that a history of fetal loss or a history of miscarriages were the trigger for a mental disorder. Therefore, the predictive value of triage items concerning obstetric history should be investigated in the future, and could subsequently be added to the Mind2Care questionnaire.
- Patient based screening and professional based screening can interchangeably be used for the identification of women-at-high-risk for PPS or at-high-risk for adverse pregnancy outcomes. For the guidance of pregnant women to tailored PPS care based on the presence of specific PPS conditions, patient based versus professional based screening is not fully interchangeable, but, as we assume, rather complementary. Therefore, we believe that screening for PPS during pregnancy should take place in two stages: 1) a sensitive triage stage to identify women-at-risk either patient of professional based, 2) a confirmatory stage for indication assessment, including verification and prioritisation of the specific PPS risks identified during triage.
- Screening for depressive and anxiety symptoms is not biased by worries (expected to be) introduced by or subsided after the first prenatal ultrasound examination. These psychiatric symptoms are however significantly associated with intrinsic worries, which are unaltered by the first ultrasound examination. The timing of screening should therefore

not depend on the timing of the first prenatal ultrasound, but rather on the subsequent verification or treatment of psychiatric symptoms.

- Despite the introduction of a stepped SITU model, including a two stage Screening, Indication assessment, referral Towards care, and the actual Utilisation of care, women gradually drop out on the way to mental or psychosocial care; in particular women of non-western ethnicity, multiparous women and smokers. Therefore, future implementation strategies should focus on a) cultural aspects such as perceived stigmatization or a poor patient-caregiver fit in terms of language concordance and social class, b) education of pregnant women with regard to risk perception, in particular for smoking during pregnancy, and c) improvement of motivational techniques for obstetric caregivers. Furthermore, the role and degree of assertive outreach and compulsory treatment should be explored in this setting, depending on the severity of the present PPS conditions.
- The previously described association between depressive symptoms and the adverse outcomes preterm birth and small for gestational age can be attributed to shared background risks, such as a low educational level. For a targeted prevention of preterm birth and small for gestational age, one should measure and, to the extent possible, ameliorate background risks in pregnant women. As depressive symptoms during pregnancy and adverse pregnancy outcomes share the same background risks, both will profit. These findings should be cross validated in a larger pregnant population, and the role of psychosocial conditions could also be explored in this context.
- Dutch urban babies have a significant lower birth weight than rural babies. The background risks non-Western ethnicity and nulliparity, the individual PPS risk factor smoking, and the accumulation of multiple PPS risk factors, partly account for this urban effect. Therefore, the prevention of preterm birth and low birth weight should be targeted to the accumulative effect of multiple PPS and background risks, which are prevalent in large urban areas in The Netherlands.

FINAL CONCLUSION

Systematic antenatal risk management of prevalent and co-existing psychopathology, psychosocial problems and substance use should consist of a stepped protocol including 1) a highly sensitive triage for the detection of women-at-high risk for PPS or adverse pregnancy outcomes either patient or professional based, 2) a confirmatory stage for indication assessment, risk verification and prioritisation of the detected PPS risks during triage, 3) referral to care, and 4) the actual provision of care.

The innovative patient based Mind2Care screen-and-advice instrument is a reliable and valid instrument for screening and subsequent referral of women with PPS in routine antenatal care. As the screening for depressive and anxiety symptoms is not biased by women's worries

surrounding the first prenatal ultrasound examination, the timing of the screening should not depend on the timing of the first ultrasound.

Even with such a stepped protocol PPS risk management is challenging in daily practice. Active engagement of professionals and patients is likely to be one of the key factors for successful screening and referral to interventions.

For a targeted prevention of adverse pregnancy outcomes, one should focus on maternal background characteristics and the accumulation of PPS risk factors. Due to shared risks, both maternal depressive symptoms, and adverse pregnancy outcomes are likely to profit from such preventive strategies.

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CHAPTER 10

Summary / Samenvatting

SUMMARY

Despite the high prevalence of psychopathology, psychosocial problems and substance use (together 'PPS') during pregnancy and the related adverse outcomes for both mother and child, there is a lack of systematic detection and subsequent referral towards care of women with PPS.

To improve perinatal mental and psychosocial health for both mother and child, a systematic multidisciplinary approach encompassing risk management, contextual measures, and active engagement of professionals and patients, is urgently needed. As a response, the Mind2Care screen-and-advice instrument, for the detection and subsequent treatment allocation for pregnant women with PPS, was developed and studied in this thesis. The main aims of the present thesis were phased as five research questions and included: 1) What is the prevalence of psychopathology, psychosocial problems and substance use during pregnancy in a large Dutch urban area? 2) Is the Mind2Care screen-and-advice instrument a reliable and valid instrument for routine use in obstetric care? 3) Is the antenatal screening for depressive and/or anxiety symptoms biased by worries surrounding the first ultrasound examination? 4) How many pregnant women identified as being at risk for PPS after screening eventually receive specialized treatment? 5) What is the role of psychopathology, psychosocial problems and substance use in the pathway to adverse pregnancy outcomes?

In **Chapter 2**, the prevalence of PPS among urban pregnant women was presented, as measured by the Mind2Care instrument. Approximately one out of four pregnant women experienced PPS conditions, with comorbid presence of psychiatric symptoms and/or psychosocial problems and/or substance use being present in 10% of women.

In **Chapters 2, 3 and 4** the reliability and validity of the Mind2Care instrument were examined. The performance of the digital self-report Mind2Care instrument appeared favourable under routine care conditions, and resulted in a high internal reliability (0.88-0.90) and a high test-retest reliability (0.64-1.00) (**Chapter 2**). A formal validation of four triage models, including items of the psychopathology domain of the Mind2Care, the Edinburgh Depression Scale, and psychosocial items was carried out in **Chapter 3.** For a valid detection of DSM-IV axis I and axis II mental disorders in pregnancy at least the short set of the following five items should be implemented for triage: 1) the experience of a traumatic event ever, 2) period of a depressed mood ever, 3) panic attack ever, 4) having current psychiatric symptoms, 5) current severe depressive or anxious symptoms. The widely used 10-item Edinburgh Depression Scale, or the three psychosocial items 'alcohol consumption during pregnancy', 'current or past physical or sexual abuse', and 'having an unplanned pregnancy', could be added to this model for a more comprehensive triage. Women with a current mental disorder who were missed by the triage model (false-negative cases) included women with eating disorders, psychotic disorders, and moderately to highly educated women of a Western origin with a first onset anxiety disorder. Of the latter, some cases reported a history of fetal loss or

previous miscarriages as the main reasons for their anxiety. In **Chapter 4**, the inter-method reliability of patient based (self-report) versus professional based screening in the detection of PPS during pregnancy was assessed for a) the guidance of women to tailored PPS care, based on the presence of specific PPS conditions, and b) for triage with regard to PPS, and adverse pregnancy outcomes. For triage with regard to PPS, both screen methods can be applied if a sum score of 5 PPS risk factors is used as cut-off for high risk. For triage with regard to adverse pregnancy outcomes, both methods can be applied too, as the accumulation of PPS risk factors for both methods is similarly associated with the adverse outcomes. For the guidance of pregnant women to tailored PPS care based on the presence of specific PPS conditions, patient based versus professional based screening is rather complementary than interchangeable. Therefore, we believe that screening for PPS during pregnancy should take place in two stages: 1) a sensitive triage stage to identify women-at-risk, either patient or professional based, 2) a confirmatory stage for indication assessment, including verification and prioritisation of the identified risks.

In **Chapter 5**, the presumed influence of the first prenatal ultrasound examination on the screening for psychiatric symptoms was assessed. Prevalence of clinically relevant depressive and anxiety symptoms were compared for women who had had, and women who had not had their first ultrasound examination. Women who reported to experience worries at the time of screening had more clinically relevant psychiatric symptoms than women who reported not to experience worries, in particular women who experienced intrinsic worries, unaltered by the ultrasound. Worries which were reported or expected to be induced or reduced by the first ultrasound examination were not associated with psychiatric symptoms. In conclusion, the timing of screening for psychiatric symptoms is not biased by the timing of the first prenatal ultrasound examination.

In **Chapter 6**, we examined how many pregnant women-at-risk for PPS following screening eventually received specialized PPS treatment after the introduction of the multidisciplinary SITU protocol, included a two stage Screening, followed by Indication assessment, referral Towards specialized care, and the actual Utilisation of specialized care. Women's and professional's adherence to this model was examined in routine obstetric care. Reasons for dropout and risk factors related to dropout were assessed. After the first screen stage, women gradually dropped out on the way to specialised PPS care (30% during the second screen stage, 19% during transfer, 77% thereafter), in particular women of non-western ethnicity, multiparous women and smokers. This suggests that cultural aspects and risk perception are underlying mechanisms for dropout. As both women and professionals indicated that lack of time and perceived lack of benefit as main reasons for non-adherence, we assume that education of pregnant women on the consequences of PPS during pregnancy and improvement of motivational techniques for obstetricians may increase adherence.

Chapters 7 and 8, investigated the role of PPS in the pathway to the adverse pregnancy outcomes preterm birth, low birth weight and small for gestational age. A formal mediation

analysis with depressive symptoms and related background risks was carried out in **chapter 7**. The previously described association between depressive symptoms and small for gestational age was not confirmed (**chapter 7**). The presumed association between depressive symptoms and preterm birth disappeared after adjustment for shared background risks, such as a low educational level. Depressive symptoms appeared no mediator in the pathway towards adverse outcomes. In **Chapter 8**, the role of depressive symptoms, psychosocial problems, substance use, and the accumulation of PPS conditions was examined in relation to inequalities in preterm birth and birth weight in urban and rural areas. After adjusting for gestational age at birth, the background risks non-western ethnicity and nulliparity, and the individual PPS condition smoking during pregnancy, the mean birth weight of urban babies was 100 gram lower than the mean birth weight of rural babies. PPS accumulation also decreased birth weight with 58 grams for each PPS condition. For a targeted prevention of preterm birth, low birth weight and small for gestational age, one should aim at prevalent background risks, and at the accumulative effect of multiple PPS risks, which are both prevalent among urban pregnant women in The Netherlands.

In **Chapter 9**, the main findings and conclusions of this thesis were summarised and discussed. The present studies showed that the SITU model can be used as a framework for a systematic delivery of PPS risk management, including a two stage screening (triage and confirmation), indication assessment, referral towards PPS care, and the utilisation of PPS care. Nevertheless, even if this SITU protocol is used as a framework, PPS risk management is challenging in daily practice. For a targeted prevention of preterm birth, low birth weight, and small for gestational age, one should aim at the accumulative effect of PPS risks factors, and one should measure, and if possible, ameliorate prevalent background risks. As both adverse pregnancy outcomes and PPS risks such as depressive symptoms during pregnancy share the same background risks, both will profit.

SAMENVATTING

Ondanks de hoge prevalentie en nadelige foetale en maternale gevolgen van psychopathologie, psychosociale problemen en middelengebruik tijdens de zwangerschap (samen 'PPM'), maakt PPM geen deel uit van de routine obstetrische zorg.
Voor de verbetering van de perinatale mentale en psychosociale gezondheid is een systematisch multidisciplinaire aanpak vereist, inclusief risicomanagement, context beoordeling en actieve betrokkenheid van professionals en patiënten. Als respons is het digitale Mind2Care screen-en-advies instrument ter detectie en zorgtoeleiding-op-maat voor zwangeren met PPM ontwikkeld en getest in deze thesis. De hoofddoelen van deze thesis zijn vertaald in vijf onderzoeksvragen en luidden: 1) Wat is de prevalentie van psychopathologie, psychosociale problemen en middelengebruik in een grootstedelijk gebied in Nederland? 2) Is het Mind-2Care screen-en-advies instrument een betrouwbaar en valide instrument bij gebruik in de routine obstetrische zorg? 3) Wordt de screening op depressieve klachten en angstklachten verstoord door zorgen omtrent de eerste prenatale echo? 4) Hoeveel zwangere vrouwen met een hoog risico op PPM op basis van screening ontvangen uiteindelijk gespecialiseerde zorg? 5) Wat is de rol van PPM in het ontstaan van nadelige zwangerschapsuitkomsten?
In **hoofdstuk 2** werd de prevalentie PPM onder zwangeren uit een grootstedelijk gebied weergegeven, zoals gemeten met het Mind2Care instrument. Een op de vier zwangeren voldeed aan de PPM criteria, waarbij er in 10% van deze zwangeren sprake was van comorbide psychopathologie en/of psychosociale problematiek en/of middelengebruik.
In de **hoofdstukken 2, 3 en 4** werd de betrouwbaarheid en validiteit van het Mind2Care instrument onderzocht. Het toepassen van het digitale zelf-rapportage instrument bleek bevredigend en haalbaar in de routine obstetrische zorg en resulteerde in een hoge interne betrouwbaarheid (0.88-0.90) en een hoge test-hertest betrouwbaarheid (0.64-1.00) (**hoofdstuk 2**). **Hoofdstuk 3** beschreef een formele validatie van vier triage modellen, inclusief items uit het psychopathologie domein van de Mind2Care, de Edinburgh Depression Scale en psychosociale items uit de Mind2Care. Voor een valide detectie van DSM-IV as I en as II stoornissen tijdens de zwangerschap zou ten minste een korte set van vijf items in de routine zorg geïmplementeerd moeten worden voor triage: 1) traumatische gebeurtenis ooit, 2) depressieve periode ooit, 3) paniekaanval ooit, 4) actuele psychische klachten, 5) ernstige depressieve klachten of angstklachten op dit moment. De veel gebruikte 10-item Edinburgh Depression Scale, of de drie psychosociale items 'alcohol consumptie tijdens de zwangerschap', 'mishandeling of misbruik momenteel of in het verleden' en een 'ongeplande zwangerschap' kunnen aan de korte set worden toegevoegd voor een meer alomvattende triage. Zwangeren met een actuele psychiatrische stoornis die werden gemist door het triage model (fals-negatieven) zijn zwangeren met eetstoornissen, psychotische stoornissen en gemiddeld tot hoog opgeleide Westerse vrouwen met een nieuwe ontwikkelde angststoornis. Van

deze laatste groep rapporteerde een aantal vrouwen een voorgeschiedenis met miskramen en/of foetale sterfte als reden voor hun angst.

In **hoofdstuk 4** werd de inter-methode betrouwbaarheid van zelfrapportage (door de patient) versus professionele screening op PPM (door de verloskundige) in kaart gebracht, met oog op a) de toeleiding van zwangeren naar PPM zorg-op-maat gebaseerd op de aanwezigheid van specifieke PPM risicofactoren en b) triage in het kader van PPM en van nadelige zwangerschapsuitkomsten. Voor triage in het kader van PPM kunnen beide screenmethoden uitwisselbaar worden gebruikt, wanneer een som score van vijf PPM risicofactoren wordt gekozen als afkapwaarde voor 'hoog risico'. Ook voor triage in het kader van nadelige zwangerschapsuitkomsten kunnen beide screenmethoden gebruikt worden. De cumulatie van PPM risicofactoren is voor beide methoden op dezelfde wijze geassocieerd met nadelige uitkomsten. Voor de toeleiding van zwangeren naar PPM zorg-op-maat gebaseerd op specifieke PPM risicofactoren zijn zelfrapportage en professionele screening eerder complementair aan elkaar dan uitwisselbaar. Wij pleiten daarom dat de screening op PPM tijdens de zwangerschap in twee stappen zou moeten plaatsvinden: 1) een sensitieve triage voor de identificatie van hoog risico zwangeren, ofwel op basis van zelfrapportage ofwel op basis van professionele screening en 2) een confirmatie stap inclusief indicatiestelling, verificatie en prioritering van de gedetecteerde risicofactoren.

In **hoofstuk 5** wordt de veronderstelde invloed van de eerste prenatale echo op de screening voor psychiatrische symptomen onderzocht. De prevalentie van klinisch relevante depressieve klachten en angstklachten werd vergeleken voor vrouwen die wel een eerste prenatale echo hadden gehad en vrouwen die dat nog niet hadden gehad. Klinisch relevante psychiatrische symptomen kwamen vaker voor onder vrouwen die zorgen ten tijde van de screening op depressieve klachten en angstklachten rapporteerden, in het bijzonder onder vrouwen die intrinsieke zorgen ervoeren, onbeïnvloed door de eerste prenatale echo. Zorgen die werden uitgelokt of weggenomen door de eerste prenatale echo waren niet geassocieerd met psychische klachten. De timing van de screening op depressieve klachten en angstklachten is niet verstoord door de timing van de eerste prenatale echo.

In **hoofdstuk 6** werd in kaart gebracht hoeveel zwangeren met een hoog risico op PPM volgens screening er uiteindelijk gespecialiseerde zorg ontvingen na introductie van een multidisciplinair SITU protocol. SITU bestaat uit een tweestaps Screening, gevolgd door Indicatiestelling, Toeleiding naar zorg en Uitvoering van Zorg. De naleving van het protocol door zwangeren en professionals werd onderzocht in de routine obstetrische zorg. Redenen voor uitval uit het protocol en risicofactoren gerelateerd aan uitval werden in kaart gebracht. Na de eerste screenstap vielen zwangeren trapsgewijs uit op weg naar gespecialiseerde zorg (30% tijdens de twee screenstap, 19% tijdens toeleiding naar zorg en 77% daarna), in het bijzonder zwangeren met een niet-Westerse etniciteit, multipare vrouwen en rokers. Dit suggereert dat culturele aspecten en de risicoperceptie onderliggende mechanismen zijn voor uitval uit zorg. Zowel zwangeren als professionals gaven 'tijdgebrek' en 'geen winst' als

redenen voor het niet naleven van het protocol. Ter reductie van de uitval uit geïndiceerde PPM zorg tijdens de zwangerschap pleiten wij daarom voor het informeren van zwangeren over de consequenties van PPM tijdens de zwangerschap en voor het verbeteren van motivatietechnieken van verloskundigen / gynaecologen.

De **hoofdstukken 7 en 8** beschrijven de rol van PPM in het ontstaan van de nadelige zwangerschapsuitkomsten vroeggeboorte en een laag geboortegewicht. Een formele mediatie analyse in **hoofdstuk 7** onderzoekt de invloed van depressieve symptomen en gerelateerde achtergrondrisico's in het ontstaan van deze nadelige uitkomsten. De eerder beschreven associatie tussen depressieve klachten en een laag geboortegewicht werd niet bevestigd. De veronderstelde associatie tussen depressieve symptomen en vroeggeboorte verdween na het corrigeren voor gedeelde achtergrondrisico's, zoals een laag opleidingsniveau. Depressieve symptomatologie bleek geen mediator in deze associatie. In **hoofdstuk 8** werd de rol van depressieve klachten, psychosociale problemen en middelengebruik en de cumulatie van PPM condities onderzocht in relatie tot de ongelijke verdeling van vroeggeboorten en het geboortegewicht in stedelijke en niet-stedelijke gebieden. Na het corrigeren voor zwangerschapsduur tijdens de geboorte, de achtergrondrisico's niet-Westerse etniciteit en nulliparitеit en de PPM conditie roken, was het gemiddelde geboortegewicht van pasgeborenen in stedelijke gebieden 100 gram lager dan pasgeborenen in niet-stedelijke gebieden. PPM cumulatie verlaagt het geboortegewicht ook met 58 gram voor iedere aanwezige PPM conditie. Voor een doelgerichte preventie van vroeggeboorte en laag geboortegewicht moet men zich richten op prevalente achtergrondrisico's en het cumulatie effect van multipele PPM risico's, met name, maar niet uitsluitend, in stedelijke gebieden.

Hoofdstuk 9 vat de hoofdbevindingen en conclusies van dit proefschrift samen en bediscussieerd deze. Dit proefschrift toont aan dat het SITU model als kader kan worden gebruikt voor een systematische aanpak van PPM. Echter, zelfs wanneer er gebruik wordt gemaakt van een dergelijk kader blijkt PPM risicomanagement een uitdaging in de routine obstetrische zorg. Voor een doelgerichte preventie van vroeggeboorte en een laag geboortegewicht moet men zich enerzijds richten op het cumulatieve effect van PPM risicofactoren en anderzijds op prevalente achtergrondrisico's. Daar zowel nadelige zwangerschapsuitkomsten als PPM risico's zoals depressieve klachten tijdens de zwangerschap dezelfde achtergrondrisico's delen, zullen beiden profiteren van een dergelijk preventief focus.

CHAPTER 11

Appendix

Mind2Care questionnaire

MIND2CARE QUESTIONNAIRE

Dear Madam,

You are pregnant. This is a happy occasion for most women. We also know that for some women this is not (completely) the case. This is why we would like to ask you some questions about your wellbeing. The answers will not be seen by the midwife or obstetrician. He or she can only see if extra help should be considered. It will take about 10 minutes. There are no "good" or "false" answers. The answers are related to your situation.

If you would rather not answer a question, just press "Next". If you can't read a question completely, you can scroll down with the arrow in the low corner on the right to read the whole question.

1. ZIP-code

What is your ZIP-code?
(Numbers only, for example: 3033)

2. Maternal age

How old are you?

3. Date of birth

What is your date of birth?
(ddmmyy, for example: February 20 1980 = 200280)

4. Gestational age

Do you know (approximately) for how many weeks you have been pregnant?
□ Yes
□ No
post-question script: if (gestational age = yes) go to 'Gestational age in weeks'

5. Estimated gestational age

For how many weeks do you think you have been pregnant?
□ Less than 28 weeks
□ Between 28 and 32 weeks
□ More than 32 weeks
□ I really do not know
post-question script: go to 'gravidity'

6. Gestational age in weeks

For how many weeks have you been pregnant?

7. Gravidity

How many pregnancies have you experienced?
post-question script: if (gravidity = 1) go to 'Country of birth'

8. Parity

How many times have you given birth?
(this only concerns pregnancies over 16 weeks)
post-question script: if (parity = 0) go to 'Country of birth'

9. Number of children

How many living children do you have?
(do not include stepchildren, adopted children or foster children)

10. Unintended pregnancy

Which argument applies best for you?
□ I was consciously trying to conceive
□ I was not consciously trying to conceive, but I'm happy to be pregnant
□ I wanted to become pregnant in the future, but not at this moment in my life
□ I did not want to become pregnant at this moment of my life, neither in the future

11. Country of birth

What is your country of birth?
□ The Netherlands
□ Indonesia / the Moluccas
□ Cape Verde
□ Morocco
□ Netherlands Antilles / Aruba / Curacao
□ Surinam
□ Turkey
□ Other
post-question script:
if (country of birth = other) go to 'Other country of birth'
if (country of birth <> Surinam) go to 'Mother's country of birth'

12. Surinam

Are you:
□ Creole
□ Hindu
□ Other
post-question script: go to 'Mother's country of birth'

13. Other country of birth

In which country were you born?

14. Mother's country of birth

In which country was your mother born?
□ The Netherlands
□ Indonesia / the Moluccas
□ Cape Verde
□ Morocco
□ Netherlands Antilles / Aruba / Curacao
□ Surinam
□ Turkey
□ Other
post-question script:
if (mother's country of birth = other) go to 'Other country of birth, mother'
if (mother's country of birth <> Surinam) go to 'Father's country of birth'

15. Surinam mother

Is your mother:
□ Creole
□ Hindu
□ Other
post-question script: go to 'Father's country of birth'

16. Other country of birth, mother

In which country was your mother born?

17. Father's country of birth

In which country was your father born?
□ The Netherlands
□ Indonesia / the Moluccas
□ Cape Verde
□ Morocco
□ Netherlands Antilles / Aruba / Curacao
□ Surinam
□ Turkey
□ Other
post-question script:
if (father's country of birth = other) go to 'Other country of birth, father'
if (father's country of birth <> Surinam) go to 'Level of education'

18. Surinam father

Is your father:
□ Creole
□ Hindu
□ Other
post-question script: go to 'Level of education'

19. Other country of birth, father

In which country was your father born?

20. Level of education

What is the highest education you have completed?
□ Primary school
□ Special schooling
□ Secondary school
□ High school
□ College
□ University

21. Job

Do you have a paid job?
□ Yes
□ No

22. Smoking

Have you been smoking during your pregnancy?
□ Yes, until I discovered that I was pregnant
□ Yes, I still do
□ No
post-question script: if (smoking = no) go to 'smoking before pregnancy'

23. Number of cigarettes

How many cigarettes do/did you smoke?
□ 20 or more a day
□ 10-19 a day
□ 5-9 a day
□ 3-4 a day
□ 1-2 a day
□ Less than one a day

24. Smoking before pregnancy

Did you smoke before you became pregnant?
□ Yes
□ No

25. Alcohol

Have you been drinking any alcohol during your pregnancy?
□ Yes, until I discovered that I was pregnant
□ Yes, I still do
□ No
post-question script: if (alcohol = no) go to 'alcohol before pregnancy'

26. Amount of alcohol

How much alcohol do/did you drink?
□ More than 3 glasses a day
□ 1-3 glasses a day
□ 1 glass a day
□ 4-6 glasses a week
□ 1-3 glasses a week
□ Less than one glass a week

27. Alcohol before pregnancy

Did you drink any alcohol before the pregnancy?
□ Yes
□ No

28. Drugs

Have you been using any recreational drugs during your pregnancy?
□ Yes, until I discovered that I was pregnant
□ Yes, I still do
□ No
post-question script: if (drugs = no) go to 'drugs before pregnancy'

29. Type of drugs

Which type of recreational drugs do/did you use? (more than one answer possible) (answering scale: daily / weekly / monthly)
□ Marihuana/ hash
□ Cocaine
□ Heroin
□ XTC
□ Other
post-question script:
if (type of drugs <> other) go to 'drugs before pregnancy'

30. Other drugs

Which other type of recreational drugs do/did you use?

31. Drugs before pregnancy

Did you use any recreational drugs before you became pregnant?
□ Yes
□ No

32. Partner

Do you have a partner at this moment?
□ Yes, my partner and I are living together
□ Yes, we are living apart
□ No, I do not have a partner
post-question script: if (partner = no) go to 'support by friends and family'

33. Support of partner.

Do you have the feeling that you get enough moral support from your partner?
□ Yes
□ No

34. Support by friends and family

Do you have that feeling that you get enough moral support from your friends and family?
□ Yes
□ No

35. Low income

Is your net family income less than €1.000 per month?
□ Yes
□ No

36. Financial problems

Do you, or did you have any financial problems or debts?
□ Yes
□ No

37. Unstable housing

Do you have a stable housing situation?
□ Yes
□ No

38. Sexual abuse or domestic violence

Are you experiencing any sexual abuse or domestic violence at this moment?
□ Yes
□ No
post-question script: if (sexual abuse or domestic violence = yes) go to 'relational problems'

39. Sexual abuse or domestic violence in the past

Have you experienced any sexual abuse or domestic violence in the past?
□ Yes
□ No
post-question script: if (sexual abuse or domestic violence in the past = no) go to 'relational problems'

40. Disadvantages

Do you still experience any disadvantages?
□ Yes
□ No

41. Relational problems

Are you experiencing any problems with relationships at the moment?
(for example with your partner, family and/or friends)
□ Yes
□ No

42. EDS introduction

The next 10 questions are about how you have felt IN THE PAST 7 DAYS.
Click the answer which describes best how you felt.

43. EDS (1)

I have been able to laugh and see the funny side of things
□ As much as I always could
□ Not quite so much now
□ Definitely not so much now
□ Not at all

44. EDS (2)

I have looked forward with enjoyment to things.
□ As much as I ever did
□ Rather less than I used to
□ Definitely less than I used to
□ Hardly at all

45. EDS (3)

I have blamed myself unnecessarily when things went wrong.
□ Yes, most of the time
□ Yes, some of the time
□ Not very often
□ No, never

46. EDS (4)

I have been anxious or worried for no good reason.
□ No, not at all
□ Hardly ever
□ Yes, sometimes
□ Yes, very often

47. EDS (5)

I have felt scared or panicky for no very good reason.

□ Yes, quite a lot
□ Yes, sometimes
□ No, not much
□ No, not at all

48. EDS (6)

Things have been getting on top of me.

□ Yes, most of the time I haven't been able to cope at all
□ Yes, sometimes I haven't been coping as well as usual
□ No, most of the time I have coped quite well
□ No, I have been coping as well as ever

49. EDS (7)

I have been so unhappy that I have had difficulty sleeping.

□ Yes, most of the time
□ Yes, sometimes
□ Not very often
□ No, not at all

50. EDS (8)

I have felt sad or miserable.

□ Yes, most of the time
□ Yes, quite often
□ Not very often
□ No, not at all

51. EDS (9)

I have been so unhappy that I have been crying.

□ Yes, most of the time
□ Yes, quite often
□ Only occasionally
□ No, never

52. EDS (10)

The thought of harming myself has occurred to me.

□ Yes, quite often
□ Sometimes
□ Hardly never
□ Never

53. Mental health history

Have you ever been admitted to a psychiatric ward for psychiatric problems?

□ Yes
□ No

post-question script: if (mental health history = no) go to 'Psych medication'

57. Mental health history which

What kind of problems where you admitted for? (more than one answer possible)

□ Anxiety symptoms
□ Symptoms of depression
□ Psychotic problems
□ Addiction
□ Eating problems
□ Other

post-question script: if (mental health history which <> other) go to 'Psych medication'

58. Mental health history other

For what kind of other problems were you admitted for?

59. Family history

Has your father, mother, brother or sister ever been admitted to a psychiatric ward for psychiatric problems?

□ Yes
□ No
□ I don't know

60. Psych medication

Did you use any psychiatric medication during your pregnancy?

□ Yes, until I discovered that I was pregnant
□ Yes, I still do
□ No

post-question script: if (psych medication = no) go to 'psychmed'

61. Medication which

What kind of medication? (more than one answer possible)

□ Antidepressant
□ Sleep medication
□ Tranquilizers
□ Antipsychotics
□ Others

post-question script: if (medication which <> other) go to 'psychmed'

62. Medication other

Which other kind of psychiatric medication did you use?

63. Psychmed

Did you use any psychiatric medication before you became pregnant?

□ Yes
□ No

64. Current treatment

Are you currently receiving treatment for psychiatric problems?

□ Yes
□ No

65. End (example 1)

Based on your answers we can conclude that you have a few or no psychological or social problems.
Thank you for your cooperation.
If you have any questions concerning this questionnaire, you can ask your midwife or obstetrician. We wish you a good and healthy pregnancy!
Please give the PDA-device to your midwife or obstetrician.

CHAPTER 12

Authors and affiliations

About the author

PhD Portfolio

Word of thanks (dankwoord)

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ABOUT THE AUTHOR

As the mother of the author, I'm very proud to write this part of her thesis.
On February 26th 1988 Chantal Quispel was born in the 'Groene Hart' Hospital in Gouda. At a gestational age of 41 weeks and 3 days, she was born waving (her hand came first). She was a gorgeous baby who could win anyone over with her adorable look.
Chantal grew up as an only child in the small village of Bergambacht in the South-Western part of the Netherlands. She always had a lot of friends, more boys than girls, since she preferred to play soccer over the real girls stuff.
She has always been a busy girl. During high school, she worked at the elderly home on Saturdays and was trained to be a dance/sports instructor on her 'free' Sundays. After she graduated high school in 2006, she was admitted to the study of medicine at the Erasmus University Rotterdam, by passing the tests of the 'decentrale selectie'. It took her a week of her vacation and an extra ticket to fly back home, but she reached her goal. If she has set her mind on something, she will go for it for a 200%. Even during her early childhood it was obvious that she wanted to become a doctor someday. All family members were subjected to her consultations and candy treatments, over and over again.
During her medicine study she was (and still is) busy with extracurricular activities. She provided first aid resuscitation classes to medical students, joined the Mind2Care research group, and continued her work as a zumba, step, street dance and fitness instructor for four nights a week at the center for fitness and physiotherapy in Bergambacht.
In October 2010, she started as a PhD candidate in the field of perinatal mental health. She worked hard and travelled a lot to present her work at international conferences, which fueled her passion for travelling. Since March 10th 2014, she has started her internship and is planning to finish her medical training in the beginning of 2016. I'm very happy and proud to become a grandmother in November and I hope that the baby will be just as lovely as his mother (and father off course).
Also speaking for her father, we are truly very proud of her and we know for sure that she will be a very competent and compassionate doctor.

Gina Quispel

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD candidate:	Chantal Quispel
Erasmus MC departments:	Psychiatry and Obstetrics & Gynaecology
Research school:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	October 2010 – March 2014
Promotors:	Prof. dr. Witte J.G. Hoogendijk
	Prof. dr. Gouke J. Bonsel
Copromotor:	Dr. Mijke P. Lambregste-van den Berg

PhD training

General and specific courses

Year	*ECTS*	*Course*
2011	1.5	SCID I and SCID II training
2011	5.7	NIHES: Public Health Research – A, B, C
2011	1.9	NIHES: Regression Analysis
2011	4.3	NIHES: Study Design
2011	0.3	Introduction in SPSS Data Entry
2011	0.3	CPO mini course: good clinical practice

International conferences

Year	*ECTS*	*Conference*
2013	1.5	Perinatal Mental Health Meeting, Chicago, U.S.A. **oral presentation**
2013	0.6	Perinatal Mental Health Meeting, Chicago, U.S.A. **poster presentation**
2013	1.5	International conference of the International Society of Psychosomatic Obstetrics and Gynecology (ISPOG), Berlin, Germany **oral presentation** (joint presentation with Tom Schneider)
2013	1.2	Annual conference of the Society for Gynecologic Investigation (SGI), Orlando, U.S.A. **2 poster presentations**
2012	1.5	Annual conference of the European Public Health Association (EUPHA), Malta, **oral presentation** (Ferenc Bojan Young investigator's Award session)
2012	1.5	International conference of the Marcé Society, Paris, France, **oral presentation**
2011	1.5	Annual conference of the Society for Gynecologic Investigation (SGI), San Diego, U.S.A. **poster presentation**

National conferences (presentations)

Year	*ECTS*	*Conference*
2013	1.0	Symposium 'Klaar voor een Kind', Rotterdam: **oral presentation**
2013	1.0	Symposium 'Regionaal Consortium Zuid-West Nederland', Rotterdam, **oral presentation**
2012	1.0	Symposium 'Interculturele geboortezorg', Rotterdam: **oral presentation**
2012	0.6	NCVGZ Dutch Annual Public Health Conference, Amsterdam: **poster presentation**
2012	1.0	Annual midwifery conference 'Kennispoort Verloskunde', Utrecht: **oral presentation**
2011	1.0	Symposium 'Grootstedelijke Perinatale Gezondheid'), Rotterdam: **oral presentation**
2011	0.6	NCVGZ Dutch Annual Public Health Conference, Amsterdam: **poster presentation**
2011	1.0	Annual Conference of the Dutch Association of Psychiatry 'Voorjaarscongres Psychiatrie', Amsterdam: **oral presentation** (joint presentation with Tom Schneider)

National conferences (attendance)

Year	*ECTS*	*Conference*
2013	0.3	Biannual Conference of 'de Veilige Kribbe', Rotterdam
2012	0.3	Biannual LKPZ Conference, Amsterdam
2011	0.3	Biannual Conference 'de Veilige Kribbe', Rotterdam
2010	0.3	Biannual LKPZ Conference, Oegstgeest

Lecturing

Year	*ECTS*	*Lecture*
2012	1.0	NIHES: urban perinatal health (joint lecture with Tom Schneider)
2011	1.0	Training 'Voorlichters Perinatale Gezondheid' – *Antenatal mental disorders*
2011	1.0	Training 'Voorlichters Perinatale Gezondheid' - *Labour*

Supervising

Year	*ECTS*	*Student / Project*
2013	0.6	Minor substance use and addition, onderzoeksstage (4 students), Hogeschool Rotterdam
2013	0.3	Minor department of psychiatry, scriptie (3 students)
2012	4.0	Mariet Haverkamp, Master's thesis (76 weeks), Midwifery Academy Rotterdam
2012	0.3	Minor circle of life, sciptie (3 students), Erasmus MC
2012	1.4	Mirelle van den Berg keuzeonderzoek student (24 weeks), Erasmus MC

2012	1.4	Marjolein Kaan, keuzeonderzoek student (24 weeks), Erasmus MC
2011	1.6	Christianne Zuijderhoudt, keuzeonderzoek student (35 weeks), Erasmus MC
2011	1.5	Mieke Hennekam, keuzeonderzoek student (21 weeks), Erasmus MC
2011	2.5	Angela Ko-Sasson, onderzoeksstage (40 weeks), Midwifery Academy Rotterdam
2011	4.0	Arina Regterschot, Master's thesis (76 weeks), Midwifery Academy Rotterdam
2011	2.0	PMG project Hogeschool Rotterdam (16 students)

Other

Year	*ECTS*	*Student*
2013	2.0	Forming the Mind2Care steering committee
2013	1.5	Chapter in handbook 'Psychiatrie en Zwangerschap' - *Screening en zorgtoeleiding van zwangeren met psychopathologie, psychosociale problemen en middelengebruik*
2011	2.5	Examencommissie Voorlichters Perinatale Gezondheid, Zorgcampus, Rotterdam
2011	4.3	Organisation of the GyPsy mini symposium, and obtaining a 'netwerksubsidie' from ZonMw, Erasmus MC, Rotterdam

DANKWOORD

Het dankwoord, dat is het eenvoudigste deel van mijn proefschrift om te schrijven dacht ik. Nu het zo ver is valt dat best tegen.

Allereerst wil ik alle zwangeren en praktijken bedanken voor hun deelname aan het Mind-2Care onderzoek. In het bijzonder wil ik alle zwangeren bedanken die bereid waren het psychiatrische interview te ondergaan; en Sarina Koevoet en Anky Jansen van verloskundigenpraktijk Rotterdam Oost.

Mijn (co)-promotoren en (dagelijks) begeleiders wil ik bedanken voor hun ondersteuning en waardevolle feedback de afgelopen jaren.

Dr. Lambregtse-van den Berg en drs. Schneider, beste Mijke en Tom. Het onderzoeksavontuur begon met het barings-VO vijf jaar geleden, waar ik Jinke en jou (Tom) vroeg of ik eens een echte bevalling mocht zien. Je nodigde mij uit om aan te sluiten bij de 'GyPsy' onderzoeksgroep van Mijke. Het hek was van de dam: iedere vrijdagochtend om 08.00uur overleg, keuzeonderwijs, keuzeonderzoek en uiteindelijk promotieonderzoek. Met een grote glimlach kijk ik terug op onze prettige samenwerking.

Mijke, ik bewonder je doorzettingsvermogen en de manier waarop je de kliniek, research, het LKPZ en een jong gezin combineert. Ondanks je volle agenda ben je altijd bereid om kritisch naar mijn stukken te kijken. Ik vind het bijzonder dat ik vanaf het begin bij de ontwikkeling van de GyPsy/Mind2Care betrokken mocht zijn en dat ik de kans heb gekregen het instrument en mijzelf verder te ontwikkelen.

Tom, wat ik het meest aan je waardeer zijn je betrokkenheid, eerlijkheid en nuchtere kijk op alle zaken in het leven. Met veel plezier kijk ik terug op onze heerlijke relativerende cappuccino's, je adviezen en onze uitstapjes met Mijke en Leontien naar o.a. de Haaienzaal en Berlijn: de cocktails, de dansvloer, sightseeing in de getto gewapend met 1,5 meter Ritter Sport chocola en de ellenlange treinreis terug.

Professor Bonsel, beste Gouke, je enthousiasme, toewijding en creativiteit zijn bewonderenswaardig. Je hebt mij veel geleerd over onderzoek, alles daaromheen en de voordelen van stroopwafels en koffie. Ik moest even wennen aan de uitgebreide in een rood doktershandschrift geschreven feedback, maar deze kritische blik heeft dit proefschrift naar een hoger niveau getild.

Professor Hoogendijk, beste Witte, ondanks dat je iets later bent aangesloten bij de onderzoeksgroep heb ik je bijdrage zeer op prijs gesteld: je prettige persoonlijkheid, opbouwende kritiek, het benadrukken van de essentie in manuscripten en opbeurende mailtjes wanneer er weer eens een paper werd afgewezen.

Professor Steegers, beste Eric, hartelijk dank voor de opbouwende kritiek op mijn papers en de mogelijkheid dat ik dit onderzoek in de eerste plaats kon uitvoeren. Ik kijk met veel plezier terug op de samenwerking, de wedstrijd van de Orlando Magics en de gastvrijheid tijdens de borrels.

Graag wil ik alle co-auteurs bedanken voor hun bijdrage aan de artikelen in dit proefschrift en de commissie voor het kritisch lezen van mijn werk.
De KveK, HP4All, WMH onderzoekers, we hebben heel wat overlegd de afgelopen jaren. Dank voor jullie gezelligheid en de goede herinneringen. De etentjes en feestjes houden we er in! Mieke, je bent een echte doorzetter. Ik waardeer onze luchtige en serieuze gesprekken. Ingrid, de filmpjes vond ik super leuk om te maken en we gaan snel weer eens lunchen. Semiha, onze (vooral op de terugweg spannende) trip naar het stoffige Malta, waarbij we iedere ochtend een nieuwe route naar het congres vonden zal ik niet snel vergeten. Sevilay (Cindy), wat heb ik een heerlijke tijd met je gehad: NIHES, veel lachen, het verkennen van de niet-Nederlandse keuken, twee keer Amerika, sightseeing samen met Kirsten, Anke en Amber, 11 kilo shoppen… It was amazing!
Esther, Jetty, Jody, Erik, Ilse, Najma, bedankt voor jullie theetjes, etentjes, cocktails en andere gezellige momenten tussen het werk door.
Mijn kleine, maar hechte familie: bedankt voor jullie geduld en steun. Hoe sterk onze band is bleek weer uit het feit dat jullie in het roerige jaar 2013 onvoorwaardelijk voor Kevin en mij klaarstonden.
Tot slot de belangrijkste: Kevin. Je hebt mij flink laten schrikken die woensdag in januari. Daarentegen heeft het onze band nog meer versterkt en is gebleken dat wij als team alles aankunnen. Ik ben heel blij dat het nu zo goed met je gaat en dat er zelfs een kleine op komst is. Ik wil je bedanken voor je geduld, liefde, steun, nuchterheid en relativeringsvermogen. Je bent de beste aanstaande papa die er is.