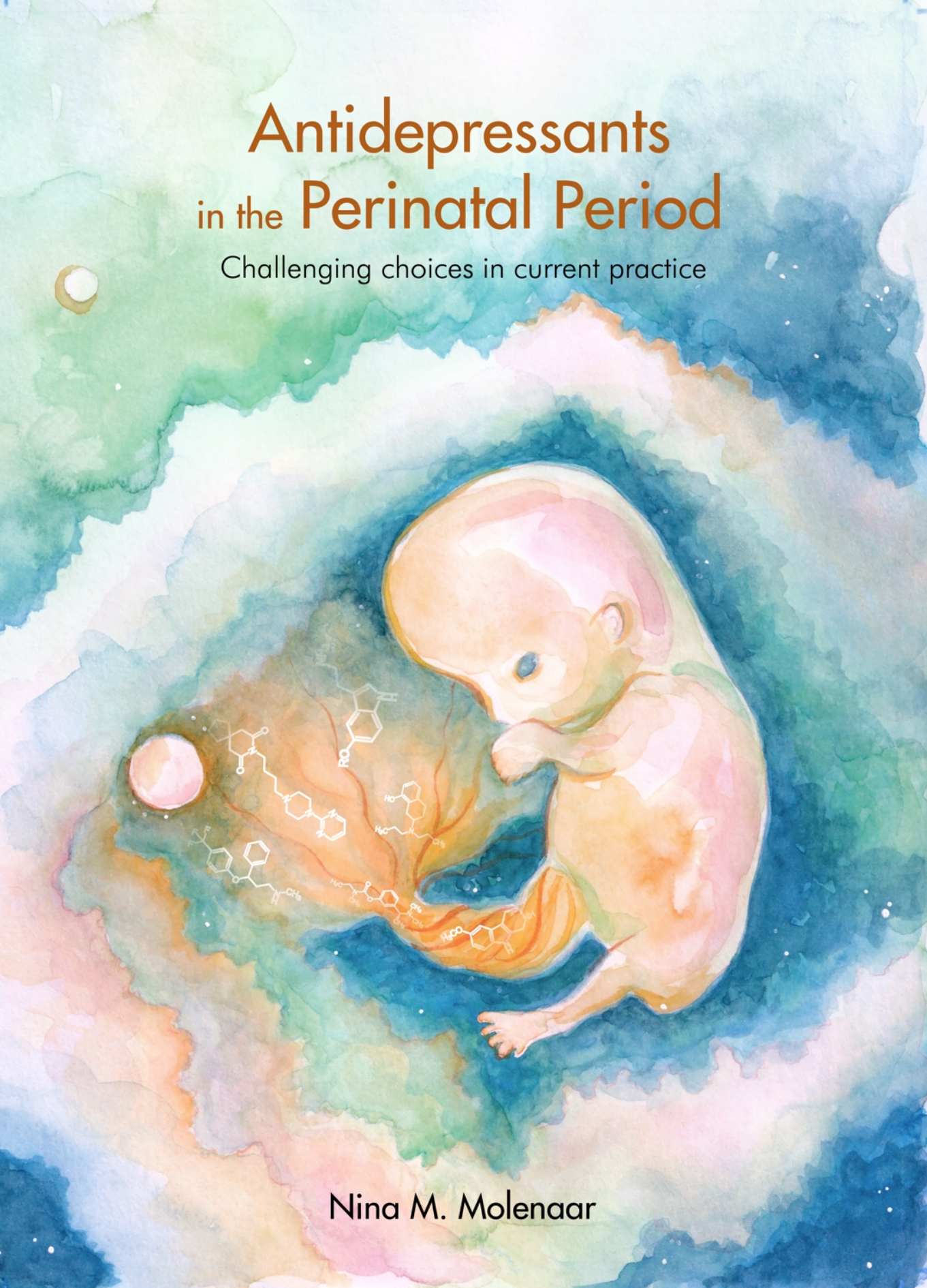
Antidepressants in the Perinatal Period

Challenging choices in current practice



Nina M. Molenaar

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The studies described in this thesis were performed at the Department of Psychiatry, Erasmus Medical Center, Rotterdam, the Netherlands; the Department of Psychology, Utrecht University, Utrecht, the Netherlands; and the Department of Psychiatry, University of Amsterdam, Amsterdam, the Netherlands.

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CHAPTER 1

Introduction

INTRODUCTION

Mental illness during the perinatal period is common and can affect both the mother and her unborn child. Especially perinatal depression, defined as depression arising in the period from conception to the end of the first postnatal year, is common, affecting up to 12% of pregnant women (1). Additionally, women with a history of major depression are at increased risk for development of a depressive episode in the perinatal period (2). Prevention and management of mental illness in the perinatal period remains an area of discussion. Next to psychotherapy, administration of psychotropic medication is, according to clinical guidelines, a recommended treatment option (3). Among these, antidepressants are the most frequently prescribed psychotropic drugs during pregnancy (4), and selective serotonin reuptake inhibitors (SSRIs) in particular (5). However, treatment with antidepressant medication in the perinatal period has been under debate for the past decades. Researchers have been reporting conflicting results on the safety of antidepressants during pregnancy for the unborn child, leading to contradictory headlines in the media.

- Antidepressants linked to premature birth -
[The New York Times, April 7th 2014]

- Relation between antidepressants and autism is wake-up call -
[de Volkskrant, December 14th 2015]

- Antidepressants during pregnancy are fine -
[Algemeen Dagblad, January 24th 2016]

- Good news about antidepressants in early pregnancy -
[Futurity, April 19th 2017]

- Using antidepressants during pregnancy may affect your child's mental health -
[ScienceDaily, September 7th 2017]

- Taking antidepressants during pregnancy may lead to fetal brain changes -
[Time, April 9th 2018]

Depression and pregnancy

Depression (major depressive disorder) is a serious mood disorder, characterized by either a depressed mood most of the day or a markedly diminished interest or pleasure in all, or almost all, activities most of the day, or both, for a minimal duration of two weeks. Additionally, people experience at least 3-4 of the following symptoms: significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate or recurrent thoughts of death potentially with suicidal thoughts or attempts. Depression is a common mental disorder and the leading cause of disability worldwide (6). In high-income countries, up to 15% of people experience at least one major depressive episode in their life (7). Women in the Western world are affected twice as often as men (8). Pregnancy does not alter the risk of depression: it's neither protective nor provocative. However, a depressive episode during pregnancy also involves the unborn child and treatment options may differ from those in a non-pregnant population.

Potential risks of antidepressants during pregnancy

There is much debate about the risks that antidepressants during pregnancy pose for the (unborn) child. An accumulation of studies has examined associations of antidepressant use during pregnancy with adverse child outcomes and the results of most of these studies have been aggregated in meta-analyses (9). Increased risks were observed for cardiovascular malformations (especially with paroxetine) (10), persistent pulmonary hypertension of the neonate (PPHN) (11), preterm delivery and lower birth weight (12) and psychiatric disorders in the offspring (e.g. mood disorders, autism spectrum disorder and behavioral disorder including attention deficit hyperactivity disorder) (13). These findings could not always be confirmed by other studies (14-17). A recent systematic review justly pointed out that verification of accurate and comparable between-group ascertainment is needed before definitive conclusions can be made (18). Even if the negative child outcomes are truly caused by antidepressants, the question remains how clinically important these findings are. For example, one study observed that exposure to antidepressants increased the risk of PPHN from 1.2 per 1000 liveborns to 3 per 1000 liveborns (11). Although the risk is doubled, in absolute numbers the overall risk of PPHN after antidepressant exposure during pregnancy remains low. One could argue that, considering these low numbers, the benefits of treatment with antidepressants outweigh the risks.

Potential risks of untreated mental illness during pregnancy

Although antidepressant use during pregnancy might induce adverse child outcomes, untreated mental illness during pregnancy is not free of risk for the child either. Untreated maternal depression and anxiety has been associated with premature delivery and low birth weight (19-22). In the long-term, maternal mental illness during pregnancy increases the risk of behavioral, emotional, cognitive and motor problems in childhood (23-26) and psychiatric disorders in adolescence (27, 28). Research examining the origins of these increased risks led scientists to propose models such as the 'fetal programming hypothesis' (29) or the 'developmental programming hypothesis' (30, 31). According to these models, the fetus or infant makes adaptive responses to the health and physical state of the mother, thereby altering important physiological and metabolic processes that can endure into adulthood. The hypothalamic-pituitary-adrenal (HPA) axis is one of the major candidate systems that could be altered by adverse intrauterine exposures, especially since plasticity of the HPA axis is high during early fetal development (24, 32). The exact underlying mechanisms of HPA axis alteration in the offspring are still unclear, although previous studies have attempted to examine potential pathways involved. High levels of maternal cortisol reaching the fetus could either be the result of extreme maternal stress, overriding the capacity of placental 11ß-hydroxysteroid-dehydrogenase enzyme type 2 (11ß-HSD-2) to convert cortisol into the inactive metabolite cortisone and thereby accumulating cortisol, or the result from altered expression of 11ß-HSD-2 in the placenta, as maternal psychopathology and stress during pregnancy have been associated with down regulation of 11ß-HSD-2, leading to active transfer of maternal cortisol into fetal circulation (33-35). Additionally, genetic factors and postnatal environmental factors such as parenting may play a role (36, 37).

Knowledge gaps in current research

The validity of findings can be questioned based on the limitations in research designs frequently used. Most of previously mentioned associations originate from retrospective observational studies with a lack to distinguish the effects of antidepressants from other shared risk factors, notably their indications depression and anxiety. Information on important confounders such as smoking behavior, socio-economic status, co-medication and co-morbidity are often not available. As a result, affected pregnant women and their health care professionals face complex decisions regarding initiation, continuation or discontinuation of antidepressants in the perinatal period. Questions often arise about the necessity and effectiveness of the medication during this specific period and about possible alternative treatment options. Although a significant number of women decide to discontinue antidepressants during pregnancy (38), to avoid potential damage to their

unborn child, no studies have examined the effectiveness of an alternative treatment option for pregnant women in which the antidepressant could be safely tapered without recurrence of depression. Therefore, in 2015 we started a randomized controlled trial (RCT) called ***Stop or Go***, to study the safety and efficacy of preventive cognitive therapy with guided tapering of antidepressants during pregnancy. This national study was initiated from the Erasmus Medical Center, University of Utrecht and University Medical Center Groningen.

Aims of this thesis

Since much has already been written about the relation between antidepressants during pregnancy and increased risks in the offspring, the aim of this thesis is to evaluate translation of previous findings into current practice. We examine international differences in management of antidepressants during the perinatal period and observe the Dutch situation at greater detail. Additionally, we examine a clinical sample to identify risk factors for recurrence of depression in the perinatal period in women taking antidepressants. Last, we examine the influence of (untreated) symptoms of psychopathology and stress on child outcomes from a biological perspective.

To that purpose the following research questions will be answered:

1. What do internationally available guidelines recommend when it comes to treatment of perinatal depression and/or the perinatal use of antidepressants (chapter 3)?
2. Are Dutch gynecologists and midwifes aware of the Dutch guideline on antidepressant use during pregnancy and do they adhere to this guideline (chapter 4)?
3. In what way have Dutch perinatal dispensing patterns of antidepressants developed over time and to what extent was the introduction of the guideline of influence (chapter 5)?
4. With what design can we examine the efficacy and safety of discontinuation of antidepressants during pregnancy (chapter 6)?
5. Which women with antidepressant use during pregnancy have recurrence of depression in the perinatal period (chapter 7)?
6. Is maternal psychopathology and stress during pregnancy associated with long-term HPA axis activity in the offspring (chapter 8)?

Study populations

Women that were included in the studies presented in this thesis originated from one of the following:

1. The **PHARMO-perined** cohort: the PHARMO Database Network is a dynamic cohort of participants that includes, among other information, drug-dispensing records from community pharmacies for more than three million individuals in the Netherlands (approximately 25% of the Dutch population), collected since 1998. Perined is a national registry that contains validated and linked data from four independent databases: the national obstetric database for midwives (LVR-1), the national obstetric database for gynecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/pediatric database (LNR). The registry contains information about care before, during and after delivery as well as maternal and neonatal characteristics and outcomes of 95% of 175.000 pregnancies annually in the Netherlands, with a minimal gestational age of 16 weeks. Linkage between the two databases is based on the birth dates of the mother and the child and their approximate address (39). We identified a cohort of 153,952 Dutch pregnancies from 1999 to 2015 with data available on the 12-month period before conception and 12 months after delivery.

2. The **Stop or Go** study: both a Randomized Controlled Trial (RCT) and an observational cohort (2015-present) of women with antidepressant use at the start of their pregnancy. Women were recruited during their first prenatal visit in midwifery practices (first echelon care) and hospitals (second and third echelons care), through general practitioners (GPs) or through advertisement in (social) media. The recruitment network was built to reach women on a population level and consisted of 51 hospitals, of which eight were academic hospitals, and over 120 midwifery practices. For recruitment through GPs, an alert was installed in Expertdoc (www.expertdoc.nl), an information system used by approximately two thirds of the GPs in the Netherlands. Further on, maximal effort was made to reach out to women in person; advertisement was placed in a magazine specific for women in their early pregnancy (Wij Zwanger, print circulation of 150.000) and on social media (facebook, instagram). Multiple newspaper articles were published drawing attention to the study and websites and forums posted calls to increase recruitment. Once recruited, experienced study researchers performed the counseling. Eligible for inclusion were women taking antidepressants at the start of their pregnancy. In the RCT, women were

randomized to either continuation of antidepressants during pregnancy or guided discontinuation of antidepressants with added preventive cognitive therapy during pregnancy. Women in the observational cohort made their own decision regarding continuation or discontinuation of antidepressants. The study did not provide treatment guidance to women in the observational cohort. Women and their children are followed until 5 years after delivery. As follow-up of the RCT has not yet been completed, this thesis will only report on outcomes of the observational cohort. However, the study protocol of the RCT will be discussed.

3. The **Generation R** study: a population-based prospective cohort study. The study is designed to identify early environmental and genetic causes and causal pathways leading to normal and abnormal growth, development and health from fetal life, childhood and young adulthood. In total, n=8880 mothers were enrolled during pregnancy with deliveries from April 2002 to January 2006 (40). For this thesis, only mother-child couples that participated in the pre- and postnatal follow-up were considered. For analysis of long-term HPA axis activity, hair collection of the child at 6 years of age was required. Hair collection did not start immediately at onset of the Generation R data collection. Thus, n=2,546 formed the study population for the current thesis.

Outline of this thesis

In **Part I** of this thesis we focus on treatment with antidepressants in the perinatal period. A general introduction on antidepressants is provided in **chapter 2**. The aim of this chapter is to gain insight in the history and development of the different types of antidepressants available and use of them in current society. In **chapter 3** we present an international review on guidelines on treatment of perinatal depression with antidepressants. The aim of this study is to compare international guidelines to guide clinicians in best clinical practice. In **chapter 4** we focus on the Dutch guideline on the use of antidepressants during pregnancy. Gynecologists and midwives throughout the Netherlands were questioned about the guideline and their adherence to it. We show guideline adherence among health care professionals and characteristics associated with adherence. The objective of **chapter 5** is to assess perinatal dispensing patterns of antidepressants in the Netherlands over time. We use population-based information on medication dispensing and dispensing patterns over 16 years (1999-2015). We examine whether medication dispensing rates increase in accordance with trends observed in other developed countries and the effect of the introduction of the Dutch guideline.

The focus of **Part II** is the Stop or Go study. In **chapter 6** we present the background for initiating this study and the protocol according to which this study (mainly the RCT) is performed. Outcomes of this RCT will not be reported in the current thesis. However, all measurements in the observational cohort were similar to the measurements in the RCT. In **chapter 7** we therefore examine the first results from the observational cohort of Stop or Go. We aim to identify patient characteristics associated with depressive recurrence in the perinatal period.

Part III of this thesis focuses on the influence of maternal mental illness during pregnancy, when not sufficiently treated, on child outcome from a biological perspective. In **chapter 8** we investigate the influence of maternal mental illness and stress on HPA axis activity in children 6 years of age using the Generation R cohort. Finally, in **chapter 9** we discuss implications of this thesis and recommendations for future research.

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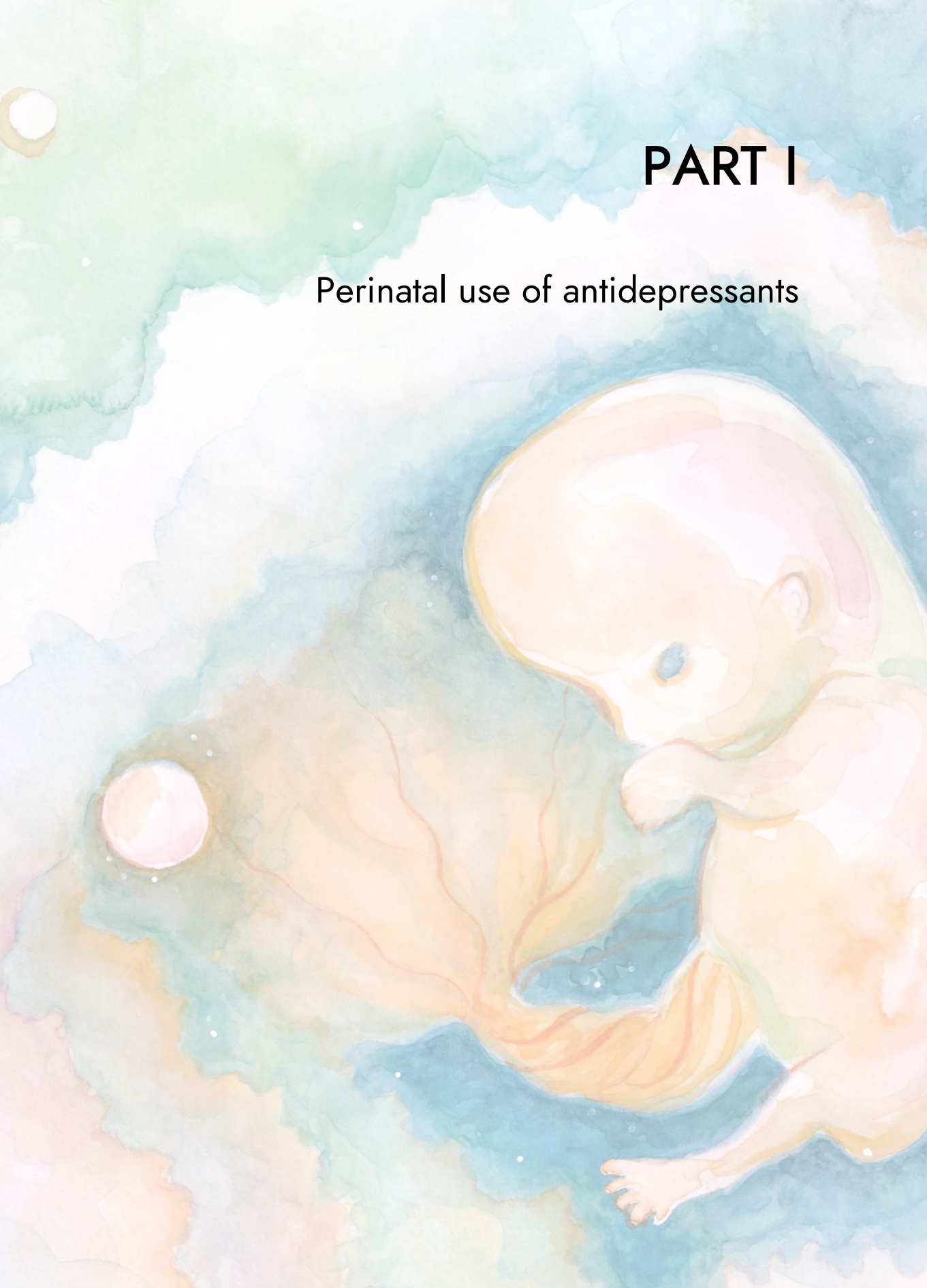
PART I

Perinatal use of antidepressants



CHAPTER 2

Antidepressants: history and current use

A brief history of depression and antidepressants

The history of depression is long, although over time it has been known under different names. In ancient Greece, Hippocrates described a distinct disease with mental and physical symptoms as melancholia, derived from "melas" (black) and "kholé" (bile). Compared to what we call depression nowadays, melancholia contained a wider array of symptoms: sadness, dejection, despondency, fear, anger, delusions and obsessions (1). In 1621, Robert Burton published the book "The anatomy of melancholy", in which several underlying theories were described and treatment methods such as sufficient sleep and a healthy diet were suggested (2). In 1856, Louis Delasiauve, a French psychiatrist, first used the word depression to refer to psychiatric symptoms (3). From that time on, the term depression started to gain use in medical papers. The first Diagnostic and Statistical Manual of Mental Disorders (DSM-I) in 1952 contained the diagnosis 'depressive reaction', defined as an excessive reaction to internal conflict or an identifiable event. The term Major Depressive Disorder (MDD) was introduced in the seventy's and incorporated in the DSM-III in 1980 (4).

Before the official introduction of what we now call antidepressants, other substances were used for a similar effect. In the eighteen hundreds, St. Johns Wort was used to relieve symptoms of depression. Around 1850, opium was approved as treatment for melancholia and in the 1930s amphetamines were introduced. Nowadays, St. Johns Wort is mostly known for its drug interactions, opioids are mostly prescribed for pain relieve and amphetamines are used in the treatment of attention deficit hyperactivity disorder (ADHD) and as a recreational drug. The discovery of the first 'real' antidepressant drug took place in 1951 when chemists had developed an antitubercular drug called isoniazid, later followed by iproniazid, which initiated side effects such as euphoria and increased appetite (5, 6). These effects were then successfully studied in a clinical trial with depressed patients by Loomer et al. and as a result iproniazid, classified as a monoamine oxidase inhibitor (MAOi), became the first official pharmacological treatment of depression. This discovery was quickly followed by a successor, also more or less invented by accident. Dr. Ronald Kuhn was examining imipramine for the treatment of schizophrenia. While it lacked antipsychotic properties, it turned out to have antidepressant abilities. Imipramine, a tricyclic antidepressant (TCA), with the name of this category based on the three benzene ring molecular core, was approved for treatment of MDD in 1959 (7). Meanwhile, researchers were studying underlying mechanisms of depression and attention was drawn to depleted concentrations of, among others, serotonin (8). Eli Lilly (a pharmaceutical company) began to develop drugs specifically aiming at this underlying mechanism. In 1975, Wong et al. published a first report on a selective serotonin reuptake inhibitor (SSRI), in this case fluoxetine. While fluoxetine was being tested, another SSRI, Zimelidine, was developed and first sold in Europe in 1982.

However, within a year and a half of its introduction, it was withdrawn from the market due to heavy side effects. In the successive years, fluvoxamine and fluoxetine entered the markets, later followed by the other SSRIs.

After introduction of MAOi's, TCAs and SSRIs, several other antidepressants have been developed and approved. In 1989 the FDA approved the use of bupropion (an aminoketone) for treatment of MDD (9). Venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI), first came on the market in 1993 (7). The most recent antidepressant to have been approved (2013) is vortioxetine, a serotonin modulator and stimulator. Despite the variety of antidepressants available, not all patients respond to treatment with the currently available antidepressants. Therefore, research continues to focus on finding new drugs that target different receptors (10).

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs): mechanisms of action

The main focus of this thesis lies on two major antidepressant drug classes: selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). There are currently six SSRIs marketed: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. SNRIs currently registered as antidepressants are venlafaxine and duloxetine.

Selective serotonin reuptake inhibitors (SSRIs)

Serotonin has many important functions and can be found in the enteric nervous system, the central nervous system (CNS) and in blood platelets. Serotonin and serotonin receptors are important in the regulation of many brain functions and in critically important functions of many human organ systems outside the CNS (11). In the CNS, serotonin is mostly produced in neurons originating in the midline of the brainstem, where axons form a neurotransmitter system reaching most parts of the CNS. On a microlevel, serotonin is released into the synapse (a gap between two neurons) and recognized by receptors of the postsynaptic cell. When research discovered associations between low serotonin concentrations and depressive symptoms (12), the pharmaceutical industry started focusing on developing medicines specifically targeting those concentrations. SSRIs decrease the reuptake of serotonin in the serotonergic presynaptic terminals by inhibition of the serotonin transporter, leading to increased synaptic concentrations of serotonin. However, a definitive theory of how these changes lead to anti-depressive and anti-anxiety effects is unknown.

Serotonin norepinephrine reuptake inhibitors (SNRIs)

SNRIs have the same mechanism of action as SSRIs except for the selectiveness for the serotonin receptor. SNRIs also inhibit the reuptake of the neurotransmitter norepinephrine, leading to an increase of both serotonin and norepinephrine in the synapse. Dual inhibition of serotonin and norepinephrine reuptake can offer advantages over other antidepressant drugs by treating a wider range of symptoms (13, 14).

Current use in daily practice

Although the name suggests otherwise, antidepressants are not only prescribed for depressive disorders. A recent study in Canada has looked at treatment indications for antidepressants in primary care between 2006 and 2015 (15). During the study period, 101.759 prescriptions of antidepressants were written. Only 55.2% of the prescriptions was prescribed for depression; 18.5% was prescribed for anxiety disorders, 10.2% for insomnia, 6.1% for pain and 4.1% for panic disorders. Over time, the percentage of antidepressants prescribed for depressive disorders decreased significantly.

Over the years, an incredible increase in the use of antidepressants is visible. In the Netherland, antidepressant use increases with approximately 1.5% each year, currently resulting in an estimated 6.5% of the population using antidepressants (16). In 2011-2014, 12.7% of persons aged 12 and over in the United States reported antidepressant use in the last month compared to 7.7% in 1999-2002 (17). In the United Kingdom a rise was observed from 6.2% in 1995 to 13.0% in 2011 (18). The increase in antidepressant prescriptions was largely driven by a rise of SSRI prescriptions; TCA prescriptions remained relatively stable. Additionally, many patients continue to take medication for a longer period: over 60% of American continue medication for 2 years or more and 14% continues medication for 10 years or more (17). Women in their reproductive ages are three times as likely to use antidepressants compared to men (17).

Use of antidepressants in the perinatal period

In case of a pregnancy, decisions regarding the use of antidepressants are complex. When antidepressants were still new and rising, teratogenicity was largely unknown and clinical practice undocumented. As research has advanced, guidelines started to emerge. In part I of this thesis we focus on guidelines on management of antidepressants in the perinatal period and adherence to the Dutch guideline, accompanied by prescription patterns observed in a 16-year time period in the Netherlands. In part II we describe the set-up and first results of the Stop or Go trial, giving insight in the efficacy of antidepressants in the perinatal period.

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CHAPTER 3

Guidelines on treatment of perinatal depression with antidepressants: an international review

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ABSTRACT

Objective: Several countries have developed Clinical Practice Guidelines (CPGs) regarding treatment of perinatal depressive symptoms and perinatal use of antidepressant. We aimed to compare guidelines to guide clinicians in best clinical practice.

Methods: An extensive search in guideline databases, MEDLINE and PsycINFO was performed. When no guidelines were (publicly) available online, we contacted psychiatric-, obstetric-, perinatal- and mood disorder societies of all first world countries and the five largest second world countries. Only CPGs adhering to quality criteria of the AGREE instrument and including a systematic review of evidence were included. Data extraction focused on recommendations regarding continuation or withdrawal of antidepressants and preferred treatment in newly depressed patients.

Results: Our initial search resulted in 1,094 articles. After first screening, 40 full-text articles were screened. Of these, 24 were excluded for not being an official CPG. In total sixteen CPGs were included originating from 12 countries. Eight guidelines were perinatal specific and eight were general guidelines.

Conclusions: During pregnancy, four guidelines advise to continue antidepressants, while there is a lack of evidence supporting this recommendation. Five guidelines do not specifically advice or discourage continuation. For new episodes, guidelines agree on psychotherapy (especially cognitive behavioral therapy) as initial treatment for mild to moderate depression and antidepressants for severe depression, with a preference for sertraline. Paroxetine is not preferred treatment for new episodes but switching antidepressants for ongoing treatment is discouraged (three guidelines). If mothers use antidepressants, observation of the neonate is generally recommended and breastfeeding encouraged.

INTRODUCTION

Depression is a common mental disorder and the leading cause of disability worldwide (1). In high-income countries, up to 15 % of people experience at least one major depressive episode in their life (2, 3). Women in the Western world are affected twice as often as men (4). Perinatal depression (considered here as depression arising in the period from conception to the end of the first postnatal year) affects up to 15 % of women; a recent meta-analysis showed a pooled prevalence of 11.9 % of all pregnancies, without significant differences between prevalence estimates for the prenatal and postnatal periods (5).

Several management options are available for depressive disorders (6). Most patients, 65-80 %, will be treated by a general practitioner (7-12), who are instructed to use a stepped care management approach (13). Especially in mild to moderate depression, these approaches recommend psychotherapy as first line treatment, before starting antidepressants. However, in current practice around 70 % of cases are primarily treated with antidepressants (9, 14-16). Subsequently, many patients continue to take medication for a longer period; for example, over 60 % of Americans continue medication for 2 years or more and 14 % continues medication for 10 years or more (17). Women in their reproductive ages are three times as likely to use antidepressants compared to men (17). In case of a pregnancy, decisions regarding the use of antidepressants are complex.

Although antidepressants are generally considered safe to use during pregnancy, this remains controversial (18). Antidepressant use has been associated with an increased risk for cardiovascular malformations (19), persistent pulmonary hypertension of the neonate (20), poor neonatal adaptation (21), preterm delivery, lower birth weight (22) and psychiatric disorders in offspring (23)

Untreated perinatal depression is not risk free either. Children of women who suffered from depression during pregnancy have an increased risk of premature delivery, low birth weight, gestational hypertension (24, 25) and perinatal death (26). Perinatal depression can also lead to behavioral, emotional, cognitive and motor problems in early childhood (27, 28). Postnatal depression may influence the mother-infant relationship, which can lead to poor infant development and outcomes (29, 30). Together, decisions regarding the prevention and treatment of perinatal depression (including the use of antidepressants) are complex.

To facilitate this decision-making, several countries have developed 'Clinical Practice Guidelines' (CPGs), to guide clinicians in choosing the most efficacious and least harmful intervention. According to the Institute of Medicine, CPGs are based on a systematic review of evidence and include recommendations to optimize patient care (31). The objective of this study was to review the content of the internationally available

guidelines on the treatment of perinatal depression and the perinatal use of antidepressants.

METHODS

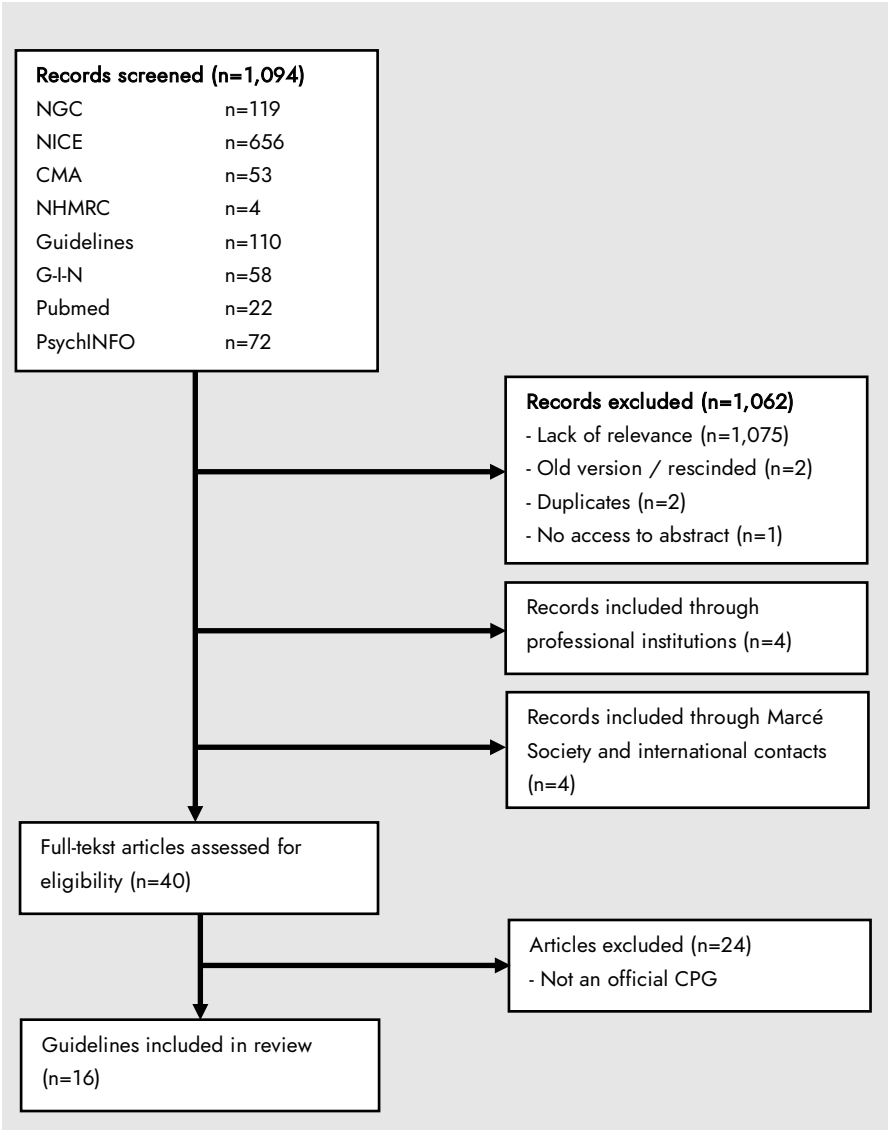
Identification of guidelines

We initially performed an extensive search in databases for clinical practice guidelines using the terms 'pregnancy', 'mood disorders', 'depression' and/or 'antidepressants'. The following databases were searched: National Guideline Clearinghouse (US AHRQ), National Institute for Health and Care Excellence (UK): Evidence services, Canadian Medical Association Infobase: Clinical Practice Guidelines (CPG), Guidelines, National Health and Medical Research Council (NHMRC) (Australia): Clinical Practice Guidelines and the Guidelines International Network (G-I-N). Secondly, we searched MEDLINE (accessed via PubMed) using a combination of free text terms (antidepressant, pregnancy, antenatal period, depression, prenatal period, mental health), limiting the results with a filter to retrieve guidelines only. Thirdly, we searched PsycINFO using a combination of title keywords (depression OR mental health OR mood disorder AND guideline), since PsycINFO does not have a search limit for guidelines and would otherwise retrieve too many hits.

Consecutively, we identified all professional societies of obstetricians and gynecologists and all professional societies of psychiatrists for countries for which we did not yet retrieve a guideline. For feasibility reasons we limited our search to societies of first world countries and the largest second and third world countries. First world refers to 'so called developed, capitalist, industrial countries, roughly, a bloc of countries aligned with the United States after World War II, with more or less common political and economic interests' (source: nationsonline.org). These include 25 countries: USA, Canada, Australia, New Zealand, Japan, Korea, UK, France, Germany, Belgium, the Netherlands, Spain, Italy, Portugal, Turkey, Greece, Luxembourg, Israel, Austria, Switzerland, Ireland, Sweden, Norway, Iceland and Denmark. In addition, we searched for guidelines in large second and third world countries including Brazil, China, India, Mexico and South-Africa. When no guidelines were (publicly) available online, we contacted perinatal and mood disorder societies and send two reminders to non-responders.

Last, we sent out an email to the members of the Marcé society (an international society for perinatal health) and to our international contacts asking for information on missing guidelines, independent on country of origin.

Figure 1. Flowchart of the article selection process



NGC: National Guideline Clearinghouse; NICE: National Institute for Health and Care Excellence; CMA: Canadian Medical Association Infobase; NHMRC: National Health and Medical Research Council; G-I-N: Guidelines International Network; CPG: Clinical Practice Guideline.

Selection of guidelines

Only CPGs, defined as statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options, were selected. These should adhere to the quality criteria of the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument (www.agreetrust.org). To avoid documents not meeting these quality criteria, consensus statements and guidance papers were excluded from this review. There were no limits for publication date or language. CPGs that did not comment on the perinatal management of mood disorders and/or on the perinatal use of antidepressants were excluded. Only the latest or more complete version of a guideline was selected when several versions of the same guideline were available.

Data extraction

Data extraction focused on recommendations before, during, and after pregnancy. Recommendations were investigated both for newly arising symptoms of depression and for pre-existent antidepressant use. We included recommendations regarding management of pre-existent antidepressant use, preferred treatment in newly depressed patients and breastfeeding with antidepressants. Recommendations were scored as follows: (blanc) no mention of the measure in the guideline, (0) measure mentioned in the guideline but without a clear direction of the recommendation (no positive or negative advice), (+) measure advised by guideline or (-) measure discouraged by guideline.

RESULTS

Our guideline database search strategy produced a set of 1,000 articles. Our Pubmed search added another 22 articles and our PsycINFO search 72. Of these 1,094 articles, 1,062 were excluded after screening on title and abstract (Figure 1). Our search strategy through the professional societies, the Marcé Society and international contacts resulted in an additional eight articles. After thorough assessment, 24 articles were excluded for not being an official CPG. This resulted in a total of 16 guidelines originating from 12 countries (6, 32-46). Additionally, we received information on the absence of a national guideline from the following countries: Austria, Belgium, France, Israel, Luxembourg, Mexico, Portugal, South-Africa, Sweden, Switzerland and Turkey. Guidelines from India and Israel are in progress.

Table 1 shows the specifics and recommendations of these guidelines. Eight guidelines were exclusively on perinatal management; the remaining guidelines were

general guidelines on treatment of depression but included a section on perinatal recommendations.

Pre-pregnancy

Three guidelines discourage switching antidepressants. The Dutch Society of Obstetrics and Gynecology (NVOG; the Netherlands) advises to continue antidepressants if the patient is psychiatrically stable.

With regard to initial therapy for new depressive symptomatology, the American Psychiatric Association (APA; USA), Centre of Perinatal Excellence (DOPE; Australia) and National Institute for Health and Care Excellence (NICE; UK) guideline give detailed recommendations. All three advise psychotherapy as initial treatment. In more severe cases of depression, the COPE and NICE guidelines advise antidepressants as initial therapy.

Pregnancy

During pregnancy, four guidelines advise to continue antidepressants. Five other guidelines mention the possibility of continuation but do not specifically advice or discourage continuation. Three guidelines discourage switching antidepressants during pregnancy. In contrast, the Danish guideline promotes switching when unfavorable antidepressants (paroxetine and fluoxetine) are used.

Most guidelines agree on psychotherapy as initial treatment for mild to moderate depression and antidepressants as initial therapy for severe depression. Only the American College of Obstetricians and Gynecologists (ACOG; USA) guideline recommends antidepressants as preferred initial therapy instead of psychotherapy and independent of symptom severity.

There is general consensus that potential harms and benefits of antidepressants during pregnancy should be discussed by the clinician with the patient. This way, patients can make well-informed decisions on preferred treatment.

Management around delivery

Most guidelines recommend a hospital delivery, which is standard in most countries. In the Netherlands and Canada, home births are still common; therefore, these guidelines explicitly mention a hospital delivery with additional observation as preferred option.

Postpartum observation of the neonate is generally recommended but the length of observation is variable (ranging from 12 hours to 3 days). The BC guideline (Canada) recommends more intense monitoring of the neonate, including pulse oximetry for early detection of persistent pulmonary hypertension and on indication neonatal serum levels of antidepressants.

Table 1. Summary of guideline recommendations pre-, during and post-pregnancy and perinatal medication recommendations

				Pre-pregnancy					Pregnancy				Postpartum					Medication recommendations	
	Country of origin	Year of publication	Perinatal specific	Pregnancy planning	Continue AD	Switch AD	Psychotherapy for new depression	Medication for new depression	Continue AD	Switch AD	Psychotherapy for new depression	Medication for new depression	Continue AD	Switch AD	Breastfeeding	Psychotherapy for new depression	Medication for new depression	Preferred medication	Non-preferred medication
ACOG	USA	2008	√								0	+							paroxetine
APA	USA	2010		+			+	0	0		+	+			+	0	0		paroxetine
BC	Canada	2014	√	+		-			0	-	+	+	+		+				paroxetine
BMU	China	2015									+	+							
CANMAT	Canada	2016		+							+	+			+	+	+	sertraline, (es)citalopram	paroxetine, fluoxetine
COPE	Australia	2017	√				+	+			+	+			+	+	+		
Danish	Denmark	2014	√						+	+	+				0			sertraline, citalopram	paroxetine, fluoxetine
DGPPN	Germany	2017							+		0	0							paroxetine, fluoxetine
NFOG	Norway	2015	√			-			+	-	+			+	+				paroxetine
NHS	Spain	2014																fluoxetine	paroxetine
NICE	UK	2014	√	+			+	+	0	0	+	+	0	0	+	+	+		
NVOG	Netherlands	2012	√		+	-			0				+		+				paroxetine
MOH	Singapore	2012							0		+	+				+	+		
RANZCP	Australia & N. Zealand	2015		+							+					+	+		paroxetine, fluoxetine, venlafaxine
SIGN	UK	2012	√						+	-	+	+			+	+	+		paroxetine
VA/DoD	USA	2016									+					+		sertraline	paroxetine, fluoxetine

√ yes, + advised by guideline, - discouraged by guideline, 0 mentioned but no steering recommendation
ACOG: American College of Obstetricians and Gynecologists; APA: American Psychiatric Association; VA/DoD: Department of Veterans Affairs/Department of Defense; BC: British Columbia Reproductive Mental Health Program & Perinatal Services British Columbia; BMU: Beijing Medical University; CANMAT: Canadian Network for Mood and Anxiety Treatments; COPE: The Centre of Perinatal Excellence; RANZCP: Royal Australian and New Zealand College of Psychiatrists; NICE: National Institute for Health and Care Excellence; SIGN: Scottish Intercollegiate Guidelines Network; Danish: Danish Psychiatric Society, Danish Society for Obstetrics and Gynecology, Danish Paediatric Society and Danish Company for Clinical Pharmacology; DGPPN: German Society for Psychiatry and Psychotherapy, Psychosomatics and Neurology; NVOG: Dutch Society of Obstetrics and Gynecology; NFOG: Nordic Federation of Societies of Obstetrics and Gynecology; NHS: Spanish ministry of health, social services and equality; MOH: Ministry of Health, Singapore.

Postpartum

BC (Canada) and NVOG (Netherlands) specifically recommend continuation of antidepressants to prevent relapse of depressive symptoms. For new episodes, most guidelines agree on psychotherapy as initial treatment for mild to moderate depression and consideration of antidepressants as initial therapy for severe depression. Most guidelines agree on encouraging breastfeeding, independent of the kind of antidepressant medication the patient is taking. The Nordic Federation of Societies of Obstetrics and Gynecology (NFOG; Norway) advises switching medication when breastfeeding with unfavorable medication. Sertraline is named as favorable medication mainly due to its low level in breast milk and infants' serum.

Medication preference

Recommended medication preferences are often not pregnancy stage specific. In general, guidelines agree on avoiding paroxetine during pregnancy, since use of paroxetine is associated with increased risk of congenital cardiovascular malformations in the newborn (19). In addition, the ACOG guideline (USA) recommends fetal examination by echocardiography if the fetus is exposed to paroxetine during early pregnancy.

Five guidelines marked fluoxetine as 'unfavorable', due to its long half-life and its presence in breast milk. Remarkably, the NHS (Spanish ministry of health, social services and equality; Spain) mentions fluoxetine as preferred medication.

There is general consensus on sertraline as preferred medication by the guidelines mentioning preferences for the postpartum period, mainly due to its favorable profile during lactation (47). Canmat (Canadian) and the Danish guideline also mention citalopram as preferred medication because of its minimized risk during lactation and available data on effectiveness during the postpartum period (48).

DISCUSSION

For new depressive episodes there is general consensus within guidelines for what is considered 'best clinical practice'. Guidelines recommend, independent of pregnancy stage, to discuss all potential treatment options available and their potential harms and benefits during and after pregnancy. Most guidelines agree that psychotherapy, especially Cognitive Behavioral Therapy (CBT), should be considered as initial treatment for mild to moderate depression, both during pregnancy and the postpartum period. Psychotherapy, such as CBT or interpersonal therapy, has a robust treatment effect for depressive disorder during pregnancy (49) and research to other treatment options like bright light therapy is still ongoing (50). In more severe cases, antidepressants are preferred treatment options,

although, until this date, there are no controlled studies on the effects of psychotropic medication for antepartum mental disorders (49); the consequence of ethical constraints of conducting clinical trials with pregnant participants. Paroxetine is not a first-choice treatment option, considering its possible increased risk for congenital heart malformations. Preferred medications during the perinatal period include sertraline and citalopram. Breastfeeding is encouraged with sertraline as preferred medication.

More complicated is the management of pre-pregnancy use of antidepressants and continuation during pregnancy. Unfortunately, evidence on the risks and benefits of tapering antidepressants during pregnancy is limited. One naturalistic study (n = 201) of women with long standing depression (mean duration of illness 15.4 years) showed a significant increased risk of relapse in pregnant women who discontinued their medication, compared to continuing medication (44 (68 %) vs. 21 (26 %)) (51), while another naturalistic study (n = 778) showed no clear difference in relapse rates of depression (16 % in total) between women continuing or discontinuing antidepressants (52). Randomized controlled trials are currently lacking with only one RCT in progress (53). Four guidelines advise continuation of antidepressants during pregnancy, which is remarkable given the scarce evidence. Unfortunately, none of the guidelines discusses treatment options for patients with current depressive symptomatology despite antidepressant use.

Most guidelines acknowledge the importance of personalized medicine. For suitable decision-making, the following should be taken into consideration: psychiatric history and indication for antidepressant medication, current psychiatric symptoms, previous attempts of tapering medication, availability of alternative treatment options such as preventive psychotherapy and the presence of a social support network. Moreover, clinical algorithms need to be developed to improve decision-making. Currently, a pilot study is being executed to investigate if a patient decision aid (PDA) tool can reduce decision-making difficulty and lead to better treatment outcomes in pregnant women with antidepressant use (54).

Overall, the guidelines have good quality (55), but most CPGs were not specifically developed for pregnant women and contained limited information on the measures of implementation and audit of the proposed measures. In our review, only eight guidelines were perinatal specific. Moreover, as pointed out by Santos et al. (55), guidelines do not disclose recommendations on emerging clinical questions and on new available evidence.

For this review, we did not include Clinical Consensus Statements (CSSs) because they were not developed in accordance with clinical practice guidelines. CSS reflect the expert views of a panel of individuals who are well-versed on the topic of interest while carefully examining and discussing the scientific data available. These consensus

statements might give different recommendations than stated in the CPGs. For example, an Austrian CSS suggests tapering of antidepressants two weeks before the due date to reduce neonatal adaptation problems (56). None of the CPGs mention this option, possibly because of available evidence suggesting reduction of exposure to SSRI's at the end of pregnancy has no significant effect on improving neonatal health (57). In clinical practice CSSs and other guiding documents are frequently used instead of the formal guidelines and might contain a higher level of detail.

In summary, this overview of information might be helpful for the development of new CPGs. Clearly there is a need for up-to-date and perinatal specific CPGs and CSSs to help clinicians and patients in decision-making. It is challenging to develop these CPGs because evidence-based medicine, personalized medicine and legal liabilities need to be balanced.

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CHAPTER 4

Antidepressants during pregnancy: Guideline adherence and current practice amongst Dutch gynecologists and midwives

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ABSTRACT

Background and objectives: Prescription rates of antidepressants during pregnancy range from 2-3 % in The Netherlands to 6.2 % in the USA. Inconclusive evidence about harms and benefits of antidepressants during pregnancy leads to variation in advice given by gynecologists and midwives. The objective was to investigate familiarity with, and adherence to the Dutch multidisciplinary guideline on Selective Serotonin Reuptake Inhibitor (SSRI) use during pregnancy by gynecologists and midwives in the Netherlands.

Methods: An online survey was developed and send to Dutch gynecologists and midwives. The survey consisted mainly of multiple-choice questions addressing guideline familiarity and current practice of the respondent. Also, caregiver characteristics associated with guideline adherence were investigated.

Findings: A total of 178 gynecologists and 139 midwives responded. Overall familiarity with the Dutch guideline was 92.7 %. However, current practice and advice given to patients by caregivers differed substantially, both between gynecologists and midwives as well as within both professions. Overall guideline adherence was 13.9 %. Multivariable logistic regression showed that solely caregiver profession was associated with guideline adherence, with gynecologists having a higher adherence rate (OR 2.10, 95 % CI 1.02–4.33) than midwives.

Key conclusion: Although reported familiarity with the guideline is high, adherence to the guideline is low, possibly resulting in advice to patients that is inconsistent with guidelines and unwanted variation in current practice.

Implications for practice: Further implementation of the recommendations as given in the guideline should be stimulated. Additional research is needed to examine how gynecologists and midwives can be facilitated to follow the recommendations of the clinical guideline on SSRI use during pregnancy.

INTRODUCTION

Worldwide, prescription rates of Selective Serotonin Reuptake Inhibitors (SSRIs) during pregnancy vary from 3.7% in the UK (1) to 6.2 % in the USA (2). In the Netherlands, approximately 2 % to 3 % of all women each year take antidepressant medication during their pregnancy (3, 4).

The use of antidepressants during pregnancy is still controversial. Studies on risks of short- and long-term effects report conflicting results. Some studies found increased risks for pregnancy-induced hypertension (5), cardiovascular malformations (6), persistent pulmonary hypertension of the neonate (PPHN) (7), poor neonatal adaptation (8), preterm delivery and lower birth weight (9), poor motor development (10) and autism spectrum disorders in the offspring (11). Several other studies failed to confirm these findings (12-14). An explanation for these conflicting results is that most of these results originate from retrospective observational studies with a lack to distinguish the effects of antidepressants from other shared risk factors, notably their indications depression and anxiety.

On the other hand, leaving depression or anxiety disorders untreated may be hazardous to the (unborn) child as well. The preventive effect of SSRIs for relapse of depression during pregnancy is indistinct. Two observational studies compared relapse rates in women who discontinued their medication with women who continued their medication (15, 16). One showed a significant increased risk of relapse in women who discontinued their medication (68 % vs. 26 %), but the other study failed to find such a difference. If women suffer from depression or anxiety during pregnancy, this could lead to, among other things, preterm birth and low birth weight (17) and behavioral, emotional, cognitive and motor problems in early childhood (18, 19). Again, the observational character of these studies preclude definite answers as continuation or discontinuation are not likely to be randomly occurring. Therefore, to date it is still impossible to make definitive statements about the harm/benefit ratio of continuing or discontinuing antidepressants during pregnancy.

In the Netherlands, maternity care is organized in a so-called primary, secondary and tertiary care model. The primary care, for obstetric low-risk women, is led by midwives and General Practitioners (GPs). Secondary care consists of obstetricians and clinical midwives in general hospitals, and tertiary care comprises obstetricians and clinical midwives in academic hospitals (20). Together with midwives, GPs and obstetricians, several other health care professionals, such as psychiatrists, psychologists, pediatricians and clinical pharmacologists, can be involved in the care during pregnancy and could be consulted on the use of antidepressants during pregnancy. In order to avoid conflicting advice to the patient, the Dutch Federation of Obstetrics and Gynecology (NVOG) has developed a multidisciplinary guideline in 2012 regarding the use of SSRIs during

pregnancy (21). This guideline gives, among others, the following advice: Pre-pregnancy continuation of SSRIs if women are stable on this medication and psychiatric indication is correct, a hospital delivery under supervision of a midwife or gynecologist, a postpartum hospital stay of at least 12 hours and continuation of SSRIs postpartum to prevent postnatal depression. It is stated that there is insufficient evidence on the possible benefit of discontinuing SSRIs during pregnancy, with or without non-pharmacological alternatives, compared to the possible risk of relapse of depression to advice pregnant women to discontinue medication.

Given that gynecologists and midwives have an important role in informing pregnant women on use of antidepressant medication, the objective of this study was to investigate if gynecologists and midwives were familiar with the multidisciplinary guideline as published in 2012, and what their routine care is regarding pregnant women using SSRIs. In addition, we tested if caregiver characteristics, such as gender and age, were associated with guideline adherence.

METHODS

Study design and procedure

For this cross-sectional study a short online survey for gynecologists and midwives was developed. The survey was developed after a review of the scientific literature to identify caregiver characteristics associated with guideline adherence in general (22-27). Before widely distributing the survey, we conducted a pilot (n = 56) and modified some textual ambiguities.

The following sociodemographic and professional variables were identified: Age, sex, place of employment (conurbation versus rural), years of professional experience, self-reported annual number of pregnant patients treated by the caregiver and self-reported annual number of pregnant patients on antidepressants. If caretakers treated no pregnant patients, they were routed to the end of the survey and excluded from analysis. To study guideline adherence, caregivers were first asked if they were familiar with the guideline (no / yes). Subsequently they received questions addressing their current practice, based on recommendations from the guideline. Participants were asked to rate on a Likert scale with 4 categories (never / sometimes / most of the time / always) how often they would give certain advice possibilities, such as continuing or discontinuing antidepressants, to patients. Further, the need for multidisciplinary consultation (no / yes, but only if there is a serious case / yes, always), secondary care (no / yes, one consultation / yes, during the whole pregnancy) and extra prenatal screening (no / yes (specification if yes)) and indicated hospital delivery (no / yes) and/or postpartum hospital stay (no /

duration <6 hours / duration of 6-12 hours / duration >12 hours) was questioned. Finally, caregivers were asked about their personal opinion on potential iatrogenic effects of antidepressants during pregnancy (no / yes) and their confidence in results from scientific research (no / yes). It took approximately five minutes to complete the survey.

The Erasmus Medical Center, Utrecht University and University Medical Center Groningen are currently performing a randomized controlled trial, 'Stop or Go' (28), to investigate the effectiveness of preventive cognitive therapy with guided tapering of antidepressants during pregnancy for relapse of depression as compared to continuation of antidepressants during pregnancy. The current survey was conducted as part of that study. Ethical approval for the present study was received from the local ethics committee of Utrecht University.

Study population

The survey was sent by e-mail to all 1012 gynecologists and 421 gynecologists in training that were registered at the Dutch Federation of Obstetrics and Gynecology (NVOG), including gynecologists that are not currently active or do not work within the field of obstetrics. They received a reminder after two weeks. To reach the 3150 midwives in the Netherlands (as measured at January 2015 (29)) we placed a call on the website of the Royal Dutch Federation of Midwives (KNOV), and sent an invitation to all general e-mail addresses of midwifery practices as could be found on the internet and reached out through the network from the 'Stop or Go' study. It was not possible to send all midwives a personal invitation.

By clicking on a link to the survey, caregivers implicitly consented to participate. The initial e-mail explained that all answers were processed anonymously.

Statistical analysis

Descriptive statistics were used to outline caregiver characteristics, familiarity with the guideline and current practice. Differences between gynecologists and midwives were tested using chi-square tests.

Logistic regression was used for the evaluation of the univariable and multivariable associations of caregiver characteristics with guideline adherence. We developed two composite outcome variables based on the answers on the current practice questions representing guideline adherence.

1) Overall guideline adherence. Overall adherence to the guideline was defined as caregivers advising patients to continue antidepressants, both pre-pregnancy and during pregnancy, while not advising patients to discontinue medication; indicating a need for multidisciplinary consultation; indicating no need for secondary care or extra

prenatal examination; and indicating a need for hospital delivery and postpartum hospital stay with a minimum of 12 hours.

2) Guideline adherence during pregnancy. Since consultation pre-pregnancy is not routine care for obstetricians and midwives, a second composite variable representing guideline adherence was developed, equal to the overall guideline adherence variable but excluding caregiver advice pre-pregnancy.

Next to these two composite outcome variables we selected three additional dependent variables for multivariable logistic regression: 3) Familiarity with the guideline, 4) caregiver advice to continue antidepressants during pregnancy (Likert scale dichotomized into never/sometimes and often/always), and 5) caregiver advice to discontinue antidepressants during pregnancy (yes / no).

We selected the following independent variables: Gender, type of caregiver, place of employment, years of professional experience, self-reported annual number of pregnant patients on antidepressants treated by caregiver, familiarity with the guideline, caregiver's opinion on potential harmfulness of antidepressants during pregnancy and caregiver's confidence in results from scientific research.

Univariable associations between our dependent variables and all the independent variables were computed. Variables with a *p*-value <0.10 were entered into a multivariable logistic regression model. Independent variables with a two-sided *p*-value < 0.05 in the multivariable model were defined as statistically significant. All associations were expressed as odds ratios (OR) with 95% confidence intervals (95%CI).

All statistical analyses were performed with SPSS, version 21.0.

RESULTS

Baseline characteristics

A total of 178 gynecologists and 139 midwives fully completed the questionnaire. Baseline characteristics of both groups are shown in Table 1. Based on reports of Nivel, the Netherlands institute for health services research, we were able to compare age and gender in our sample with that of the total caregiver population (29, 30). Our sample of gynecologists was overrepresented by women (72.5 % in our sample vs. 55.8 % in the total caregiver population). The study sample of midwives matched on age and gender with the target population. Self-reported percentage of pregnant women with antidepressants treated by gynecologists was 11.7 %, as compared to 10.6 % by midwives (*p*=0.01).

Table 1. Baseline characteristics of health care professionals

	Gynecologists (n=178)	Midwives (n=139)
Gender, female (%)	129 (72.5)	136 (97.8)
Age in years, mean (SD)	43.9 (9.4)	37.9 (10.8)
Place of employment (%)		
Conurbation	78 (43.8)	56 (40.3)
Rural	100 (56.2)	83 (59.7)
Years of professional experience, mean (SD)	14.5 (8.9)	13.2 (9.8)
Self-reported number of pregnant women seen by individual caregiver, per year (SD)	428.6 (284.3)	282.1 (169.2)
Self-reported number of pregnant women with antidepressants seen by individual caregiver, per year (SD)	50.2 (48.7)	29.8 (35.4)
Self-reported percentage of pregnant women with antidepressants (%)	11.7	10.6

Current practice

Table 2 shows the results on the current practice questions. Most caregivers were familiar with the guideline (overall 92.7 %; 97.8 % of gynecologists and 86.3 % of midwives, $p<0.01$). Caregivers reported to act differently on multidisciplinary consultation, indication for secondary care and extra prenatal screening, and advice on hospital delivery and/or postpartum hospital stay. These differences were seen both within the professions as well as between the professions. 14.5 % of the respondents considered antidepressant use as an indication for extra prenatal screening, mostly additional advanced ultrasound investigation (80.4 %). Most caregivers (80.3 % of the gynecologists and 84.2 % of the midwives) indicated to advice a postpartum hospital stay of at least 12 hours or of 6 to 12 hours.

40.4 % of gynecologists and 61.9 % of midwives ($p<0.01$) considered antidepressants potentially harmful during pregnancy. Just over half of the participants (55.6 % of gynecologists and 54.0 % of midwives) would trust results from scientific research to direct their actions with regard to prenatal antidepressant use.

Table 3 shows the results from the multivariable logistic regression on guideline familiarity. Less familiarity with the guideline was not only associated with type of caregiver, but also with an increasing number of years of professional experience (OR 0.93, 95%CI 0.88–0.99) and a lower confidence in results from scientific research (OR 3.71, 95%CI 1.38–9.99).

We also evaluated participants' rating of advice possibilities to patients pre-pregnancy and during pregnancy using antidepressants. Opinions of both gynecologists and midwives on continuing medication, lowering dose and consultation options vary

widely. Figure 1 shows most caregivers (76.6 % to 83.1 %) always give some form of advice to patients using antidepressants, both before and during pregnancy. The full data on participants rating of advice possibilities can be found in the data supplement.

Guideline adherence

Overall self-reported guideline adherence (including advice both pre-pregnancy and during pregnancy) was 13.9 % among all caregivers (18.0 % in gynecologists and 8.6 % in midwives, Table 2). Results of the univariable analysis showed associations with self-reported annual number of pregnant patients on antidepressants seen by the individual caregiver, type of caregiver (gynecologist or midwife) and confidence in results of scientific research (Table 3). Only type of caregiver remained significantly associated in the multivariable model; gynecologists had 2.08 higher odds (95%CI 1.02–4.33) to act according to the guideline.

Self-reported guideline adherence during pregnancy (excluding advice in the pre-pregnancy period) among all caregivers was 20.5 %. Univariable analysis showed associations with a higher self-reported annual number of pregnant patients on antidepressants seen by the individual caregiver and increasing years of professional experience. Both remained significant in multivariable analysis, with OR 1.01 (95%CI 1.00-1.01) and 1.03 (95%CI 1.00-1.06) respectively.

Caregiver's advice to continue and discontinue antidepressants during pregnancy

Of all caregivers, 75.7 % often advised to continue antidepressant medication during pregnancy (Appendix 1). Univariable analysis showed associations with self-reported annual number of pregnant patients on antidepressants seen by the individual caregiver, type of caregiver, caregiver's opinion that antidepressant use during pregnancy is potentially harmful and unfamiliarity with the guideline (Table 3). Only type of caregiver remained statistically significant in the multivariable model. Midwives reported to less often advice to continue antidepressants during pregnancy (OR 5.48, 95%CI 2.95–10.21).

None of the independent variables showed a significant association at univariable analysis with advice to discontinue antidepressants.

Table 2. Current practice and opinions amongst gynecologists and midwives

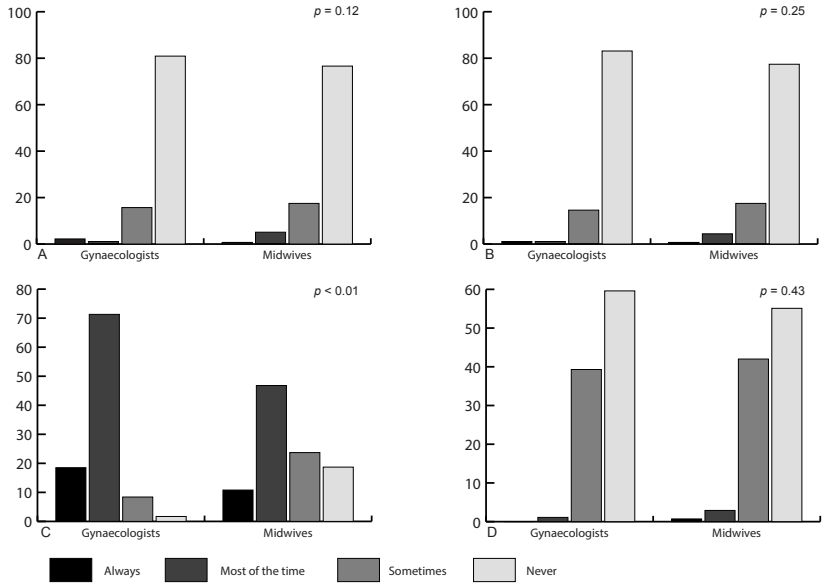
	Gynecologists (n=178)	Midwives (n=139)	*p*
Familiarity with the guideline, yes %	97.8	86.3	< 0.01
Discussed in multidisciplinary team, %			
No	13.5	10.1	0.01
Yes, but only if there is a serious case	42.1	28.8	
Yes, always	44.4	61.2	
Indication secondary care, %			
No	48.9	66.9	< 0.01
Yes, one consultation	46.1	32.4	
Yes, during the whole pregnancy	5.1	0.7	
Extra prenatal screening, yes %	13.5	15.8	0.56
Of which additional ultrasound, %	79.2	81.9	
Advice for hospital delivery, yes %	78.5	90.6	< 0.01
Postpartum hospital stay baby, %			
No hospital stay	1.1	0.7	0.82
Duration < 6 hours	0.6	0.7	
Duration of 6 to 12 hours	18.0	14.4	
Duration > 12 hours	80.3	84.2	
Opinion on harmfulness, yes %	40.4	61.9	< 0.01
Confidence in results of scientific research, yes %	55.6	54.0	0.77
Overall guideline adherence (composite variable 1), yes %	18.0	8.6	0.02
Guideline adherence during pregnancy (composite variable 2), yes %	23.0	17.3	0.21

Table 3. Univariable and multivariable associations between professional characteristics and guideline adherence / advice options

	Univariable outcome p-value	Multivariable outcome p-value	OR (95% CI)
Familiarity with the guideline			
Type of caregiver	< 0.01	< 0.01	0.15 (0.05 – 0.47)
Years of professional experience	0.01	0.03	0.93 (0.88 – 0.99)
Confidence in results of scientific research	< 0.01	< 0.01	3.71 (1.38 – 9.99)
Overall guideline adherence			
Self-reported annual number of pregnant patients on antidepressants seen by individual caregiver	0.03	0.09	NA
Type of caregiver	0.02	0.05	2.10 (1.02 – 4.33)
Confidence in results of scientific research	0.10	0.07	NA
Guideline adherence during pregnancy			
Self-reported annual number of pregnant patients on antidepressants seen by individual caregiver	< 0.01	< 0.01	1.01 (1.00 – 1.01)
Years of professional experience	0.02	0.02	1.03 (1.00 – 1.06)
Caregiver's advice to continue antidepressants during pregnancy			
Self-reported annual number of pregnant patients on antidepressants seen by individual caregiver	0.04	0.63	NA
Type of caregiver	< 0.01	< 0.01	5.48 (2.95 – 10.21)
Caregiver's opinion that antidepressant use during pregnancy is potentially harmful	< 0.01	0.14	NA
Caregiver unfamiliar with guideline	< 0.01	0.21	NA

Only variables with $p \leq 0.10$ in the univariable analysis are presented in this table. OR = odds ratio, CI = confidence interval, NA = not applicable

Figure 1. Distribution in advice frequency given by caregivers pre-pregnancy and during pregnancy



A: No advice given pre-pregnancy by caregiver. B: No advice given during pregnancy by caregiver. C: Advice given to continue antidepressants during pregnancy. D: Advice given to discontinue antidepressants during pregnancy.

DISCUSSION

This cross-sectional study investigated if gynecologists and midwives report to be familiar with the Dutch multidisciplinary guideline on the use of SSRIs during pregnancy, to adhere to this guideline in current practice, and whether specific caregiver characteristics were associated with guideline adherence. Familiarity with the guideline was high (92.7 %), however self-reported guideline adherence was low (13.9 %). Differences were seen within the caregiver professions as well as between the professions. No other caregiver characteristics showed important associations with guideline adherence.

Guideline familiarity was significantly less amongst midwives compared to gynecologists. Although the guideline is available for all caregivers involved during pregnancy, the guideline working group did not include midwives and the Royal Dutch Organization of Midwives (KNOV) did not accredit the guideline, possibly explaining this difference. Familiarity with the guideline does not directly imply extensive knowledge of

the content. Our survey showed self-reported current practice often differed between caregivers.

Advice on continuing or discontinuing antidepressants, both before and during pregnancy, differed substantially between caregivers. In practice this may result in conflicting advice from different caregivers, creating a potentially difficult situation for vulnerable women. The same variation in advice was reported previously in a survey amongst Dutch General Practitioners (GPs) (31). Pre-pregnancy advice patterns of GPs, in around 80 % of the cases the prescribers of the medication (32), are probably more relevant than those of gynecologists and midwives. Gynecologists only see a selected group for pre-pregnancy advice, for example couples with fertility problems. Experience of midwives with pre-pregnancy advice will be even smaller. Resulting advice patterns should therefore be interpreted with caution.

Caregiver's advice can be based on the guideline, on their personal opinion or on a request from the patient. The current results show that 16.9 % to 23.4 % of caregivers do not always give advice to their patient with regard to antidepressive medication. This is remarkable since antidepressant use during pregnancy justifies attention and consideration of the caregiver, amongst others due to the potential risks of antidepressants on birth outcomes and the effect of untreated symptoms on the neonate. Patients should always be informed on potential harms and benefits of medication and make a decision in consultation with the caregiver.

Opinion on harmfulness of antidepressants during pregnancy, with 49.8 % of respondents perceiving antidepressants as being potentially harmful, is very illustrative of current best evidence, which is still indistinct. This percentage is relatively low compared to previously reported opinions of GPs and pharmacists in the Netherlands in 2006; 96 % of GPs and 65 % of pharmacists believed antidepressants are associated with an increased risk of birth defects (31). A study amongst physicians of multiple hospital specialties in Latin America showed similar outcomes as ours with 49.2% of respondents considering antidepressants potentially harmful (33).

Although extra, non-standard prenatal screening is not advised, 14.5 % of the respondents considered antidepressant use as an indicator for extra prenatal screening, mostly additional advanced ultrasound investigation. Such methods are quite expensive, which in turn may results in unnecessary health care costs. Given the increase in antidepressant use during pregnancy, this may increase future health care costs. On the other hand, introduction of each pregnant patient in a multidisciplinary team, which is advised by the guideline, does often not take place. Multidisciplinary consultation of women can lead to more efficient prenatal care and uniform advice to patients, thereby possibly decreasing costs and increasing patient satisfaction.

Only 13.9 % of caregivers reported overall guideline adherence, which seems to be lower than rates in other adherence studies among various specialty areas (34), but in line with previous guideline adherence research amongst midwives (35, 36). We used multivariable regression to investigate possible independent determinants of guideline non-adherence. Characteristics were selected based on previous research, showing positive and negative associations with knowledge of and adherence to guidelines in various specialty areas (22-27). In our survey, professional-related characteristics and perceptions did not explain a significant part of variance in non-adherence. Other often reported barriers for guideline non-adherence, such as patient preference or professional's personal experience (24, 34), could play a part but were not investigated in this survey.

Limitations

Despite the significant results, there were some limitations. First of all, due to our recruitment method, it was not possible to calculate valid response rates. It was not possible to send the invitation to obstetric gynecologists only (the Dutch Federation of Obstetrics and Gynecology responded they do not register subspecialisations) or invite all midwives personally through email. This makes generalizability of our results uncertain.

The self-reported number of pregnant patients on antidepressants was high with a mean 11.3 %, as compared to the national 2-3 % as reported in previous research (3, 4). This could be an overestimation, but it is plausible that our response group actually has more experience with pregnant women using antidepressants and is therefore not representative. For example, gynecologists who work at a specialized outpatient clinic for obstetric patients with psychiatric disease will attract more patients with antidepressants. One possible consequence is that this leads to an overestimation of familiarity with and adherence to the guideline. Another possibility is that, because of their more extensive experience, these caregivers more often deviate from the guideline. Guidelines are developed using the most recent evidence but have to be updated regularly because of fast developing new findings. Recommendations from guidelines can be outdated, which is especially recognized by professionals who encounter the specific population more often.

CONCLUSION

From this cross-sectional survey it can be concluded that guideline familiarity is high, but there are large differences among gynecologists and midwives in views on managing women using antidepressants before and during pregnancy. This seems to reflect the

current state of literature, which shows inconclusive results on benefits and harms of antidepressants during pregnancy. Unfortunately, this could lead to giving advice to patients that is not in line with evidence based clinical guidelines. Qualitative research could explore reasons for guideline non-adherence and stimulate further implementation in daily clinical practice of the guideline.

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DATA SUPPLEMENT

Supplementary table 1. Advice given to patients by gynecologists and midwives pre-pregnancy and during pregnancy

	Gynecologists (n=178), %				**Midwives (n=139), %**				*p*-value
	Always	Most of the time	Sometimes	Never	Always	Most of the time	Sometimes	Never	
Advice to a patient who uses antidepressants and is planning to become pregnant									
Continue antidepressant	3.4	69.7	24.2	2.8	3.6	31.9	37.0	27.5	< 0.01
Discontinue antidepressant	0	4.5	65.7	29.8	0.7	6.5	40.6	52.2	< 0.01
Lower dose antidepressant	0.6	6.2	53.4	39.9	1.5	11.7	39.4	47.4	0.06
Switch to other antidepressant	1.1	1.1	75.8	21.9	0.7	7.2	52.2	39.9	< 0.01
Replace or add (psycho)therapy	2.2	3.4	60.1	34.3	5.8	10.9	53.6	29.7	0.02
Consultation with a psychiatrist	7.3	31.5	59.0	2.2	25.4	25.4	29.7	19.6	< 0.01
Consultation with a gynecologist					12.3	15.2	29.0	43.5	NA
No advice	2.2	1.1	15.7	80.9	0.7	5.1	17.5	76.6	0.12
Advice to a patient who uses antidepressants during pregnancy									
Continue antidepressant	18.5	71.3	8.4	1.7	10.8	46.8	23.7	18.7	< 0.01
Discontinue antidepressant	0	1.1	39.3	59.6	0	2.9	42.0	55.1	0.43
Lower dose antidepressant	0.6	3.4	48.3	47.8	1.4	6.5	45.7	46.4	0.49
Switch to other antidepressant	0.6	0	62.9	36.5	0.7	2.9	60.6	35.8	0.15
Replace or add (psycho)therapy	2.2	2.8	60.1	34.8	5.8	10.1	63.0	21.0	< 0.01
Consultation with a psychiatrist	10.1	32.6	55.6	1.7	28.3	22.5	42.8	6.5	< 0.01
Consultation with a gynecologist					25.4	24.6	36.2	13.8	NA
No advice	1.1	1.1	14.6	83.1	0.7	4.4	17.5	77.4	0.25

CHAPTER 5

Dispensing patterns of selective serotonin reuptake inhibitors before, during and after pregnancy: a 16-year population-based cohort study from the Netherlands

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ABSTRACT

Purpose: Management of mental illness in the perinatal period with antidepressants is controversial, since evidence emerged on potential harmful effects to the unborn child. However, over time the dispensing of antidepressants in the perinatal period has increased. We examined perinatal dispensing patterns over time and the role of a recently issued guideline in this regard.

Methods: We identified a 16-year cohort of 153,952 Dutch pregnancies with a delivery date between January 1999 and December 2014. Data included exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) related to phases of pregnancy (preconception, pregnancy and delivery, post-delivery). The chi-square test for trends was used. With standard logistic regression we explored the influence of patient characteristics on continuation of SSRIs during pregnancy.

Results: A persistent significant rise of dispensing rates at preconception, in pregnancy and childbed was observed, with the largest increase during pregnancy (from 0.8% in 1999/2000 to 2.1% in 2013/2014, chi-square for trend=141.735, $p<0.001$). A substantial change of practice in terms of the SSRI used (less paroxetine) and the policy towards continuation into pregnancy (more continuation over time) was visible. Concomitant use of psycholeptics halved the probability of continuation of SSRI use during pregnancy (OR 0.50, 95%CI 0.43-0.55, $p<0.01$).

Conclusions: Dispensing rates of SSRIs steadily increased last 16 years, especially during pregnancy, caused by an increase in the proportion of women continuing their medication during pregnancy. In view of the demonstrated impact of uncertainty regarding effectiveness and safety of SSRIs in pregnancy, future research should involve more detailed outcome research of SSRIs as it is, and research into viable alternatives.

INTRODUCTION

Management of mental illness in the perinatal period, defined as the entire period of pregnancy, the preconception period and the postnatal period (the first year after birth), remains an area of discussion. Approximately 25% of women experience any psychiatric disorder in this period (1, 2). Next to psychotherapy, administration of psychotropic medication is a common treatment option (3). Antidepressants are the most frequently prescribed psychotropic drugs during pregnancy (4), selective serotonin reuptake inhibitors (SSRIs) in particular (5). Over the years, an increase in prescriptions of antidepressants in the perinatal period has been observed (5-8). A large cohort from Tennessee (US) for example showed an increase of pregnancies with antidepressant use from 5.7% in 1999 to 13.4% in 2003 (5); in the United Kingdom an increase was seen from 3.5% in 2004 to 5.0% in 2010 (7). A more recent study in France, on the other hand, showed a slight decrease in the prevalence of prescriptions from 2% in 2005 to 1.7% in 2014 (9).

The use of antidepressants during pregnancy, however, has become controversial as evidence emerged on potential harmful effects to the unborn child (10). It has been associated with increased risks for cardiovascular malformations (especially paroxetine, RR=1.43; 95%CI, 1-08-1.88) (11), persistent pulmonary hypertension of the neonate (12), poor neonatal adaptation (13), preterm delivery, lower birth weight (14) and psychiatric disorders in the offspring (e.g. mood disorders, autism spectrum disorder and behavioral disorder including ADHD, HR=1.27; 95%CI 1.17-1.38) (15). A trade-off seems present, as untreated depression during pregnancy is not free of risk for the child either: multiple negative child outcomes have been reported such as premature delivery, low birth weight and perinatal mortality (16-18). In early childhood it can lead to behavioral, emotional, cognitive and motor problems (19, 20). Additionally, chronic postnatal depression influences the mother-infant relationship (21, 22).

As a result, the affected pregnant women and health care professionals face complex decisions regarding initiation, continuation or discontinuation of SSRIs in the perinatal period; the dilemma's involved are recognized (23). Internationally, guidelines agree on a limited set of recommendations, such as the universal obligation to inform patients in due time about risks and benefits of all treatment options, and the use of psychotherapy as preferred treatment in mild to moderate depression (24). But on key aspects of the dilemma, they are unclear, i.e. the first choice of an antidepressant or the need for a switch (or not) in case of pre-existing antidepressant use. A recent Dutch national survey among obstetricians and midwives showed that the advice provided to women in these instances varied considerably (25).

Despite considerable scientific efforts to obtain evidence on the risks and benefits of antidepressant use in the perinatal period, the available evidence is

unequivocal. Published studies are often retrospective and register-based, in part inevitable due to the ethical demands of research in this context. As professionals show divergent views on the undecided issues, the question is relevant what actual practice at the population level is in terms of SSRI use, what variation in medication dispensing can be observed before, during and after pregnancy, and what change over time –if any- is visible.

In this study we present population-based information on medication dispensing and dispensing patterns related to the pregnancy phases over 16 years (with delivery dates between January 1999 and December 2014) in the Netherlands. We examine whether medication dispensing rates increase in accordance with trends observed in other developed countries. In addition, we examine the effect (or not) of the introduction of the Dutch multidisciplinary guideline in 2012 on continuation of SSRI use during pregnancy (26). The guideline recommends continuing SSRIs (without switching) in the perinatal period if women are stable on this medication and psychiatric indication is correct. Furthermore, we will look at specific SSRIs used over the years. We expect a decline in paroxetine dispensing rates during pregnancy as evidence suggests increased risks of paroxetine use on child outcomes compared to other SSRIs, and as the Dutch guideline recommends switching from paroxetine to another SSRI in the preconception period when possible. Lastly, we will examine whether patient characteristics are associated with continuation or discontinuation of SSRIs during pregnancy expecting impact of higher socio-economic status and multiparity on continuation rate. During the study period no relevant change was present regarding the reimbursement scheme of dispensed psychotropic drugs in pregnancy.

METHODS

Data sources

For this population-based study, a cohort of 153,952 Dutch pregnancies was identified after probabilistic linkage between the Out-patient Pharmacy Database of the PHARMO Database Network and the Netherlands Perinatal Registry (PRN). The PHARMO Database Network is a dynamic cohort of participants that includes drug-dispensing records from community pharmacies of approximately 25% of the Dutch population, collected since 1998 (27). The PRN is a national registry that contains validated and linked data from midwives, gynecologists, general practitioners and pediatricians on 95% of all pregnancies with a minimal gestational age of 16 weeks in the Netherlands. More information on these databases and the probabilistic linkage can be found in the appendix. All pregnancies with a delivery date between January 1999 (therefore including

preconception data from 1998 onwards) and December 2014 were included. To be able to define drug dispensing in the 12-month period before conception and 12 months after delivery, women needed to be registered in the community pharmacy database of the PHARMO Database Network for both of these 12-month periods.

Drugs of interest

The out-patient drug dispensing during the 12-month period before conception until 12 months after pregnancy was extracted from the Out-patient Pharmacy Database. All the drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system (28). SSRIs were defined as products with an ATC code starting with N06AB (further defined onto the fifth level) and included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. The SSRI drug-dispensing data contained the following information per dispensing: timing of dispensing (before, during or after pregnancy, based on dispensing date), regimen and quantity dispensed. Pregnancy duration was based on ultrasound or last menstrual period, as recorded in the PRN. For all other drugs information was available on second level (the therapeutic subgroup with two digits), with timing only (before, during or after pregnancy). Note that inpatient drug provision is exceptional, limited to pregnant patients who for other reasons are hospitalized.

Analysis

Women were defined as a user of a SSRI during one of the three phases (12 months leading up to pregnancy, during pregnancy and 12 months after pregnancy) if a dispensing of at least 28 days for a given phase was registered. This definition excluded women discontinuing SSRI use in that particular phase. For trend analysis, data was divided into groups of two years (based on year of delivery) and the chi-square test for trends was used. Special attention was given to the before-after 2012 comparison, as in 2012 the SSRI guideline was introduced.

Having available user information, subdivided into three phases related to pregnancy, we could define the following seven patterns: 1) women who used SSRIs before pregnancy only, 2) women who used SSRIs both before and during pregnancy, 3) women who used SSRIs before, during and after pregnancy, 4) women who used SSRIs during pregnancy only, 5) women who used SSRIs both during and after pregnancy, 6) women who used SSRIs after pregnancy only, and 7) women who used SSRIs before and after pregnancy, but not during (recidivist). Percentages of each group were calculated per two-year time period to analyze whether dispensing pattern changed, in particular related to the introduction of the guideline.

To examine the association between general patient characteristics and discontinuation of SSRIs during pregnancy, only data of women using SSRIs in the year before pregnancy (women from the patterns 1, 2, 3 and 7) were used. Characteristics studied were year of delivery, parity, socio-economic status (determined on basis of data per zip code from the Central Bureau of Statistics (CBS), divided in low, middle and high), co-dispensing of psycholeptics (ATC codes starting with N05; including antipsychotics, anxiolytics, hypnotics and sedatives) and number of other co-medications (defined as the sum of all other pharmacy registered dispensed drugs, excluding SSRIs and psycholeptics) in the year before pregnancy. First, we determined univariable associations between the dependent variable and all the independent variables. Variables with a *p*-value <0.10 were entered into a multivariable logistic regression model. Independent variables with a two-sided *p*-value <0.05 in the multivariable model were defined as statistically significant. All associations were expressed as adjusted odds ratios (OR) with the respective 95% confidence intervals (95%CI). Statistical Package for Social Sciences (SPSS) version 25.0 was used.

RESULTS

A total of 153,952 pregnancies in the Netherlands with a delivery date between January 1999 and December 2014 were identified. The mean maternal age at delivery was 31 years (standard deviation (SD), 5) and socio-economic status was low in 28%, middle in 34% and high in 38%. Of these 153,952 pregnancies, 7,284 of pregnancies (4.7%) used SSRIs in one or multiple phases (before, during and/or after pregnancy). Mean maternal age at delivery for these pregnancies was similar (31 years (SD, 5)), socio-economic status differed slightly (shift to lower SES), with SES low in 35%, middle in 33% and high in 32% ($p < 0.01$) (supplementary table 1). There were another 536 (0.35% of all) women that received a dispensing of less than 28 days in the year before pregnancy, 63 (0.04%) women during pregnancy and 260 (0.17%) women in the year after pregnancy. These cases are excluded for further analysis.

Dispensing patterns over time

Table 1 shows SSRI dispensing rates in the year before pregnancy, during pregnancy and in the year following pregnancy, comparing 2-year groups. Dispensing rate universally is highest in the year before pregnancy (e.g. 3.9% in 2013/2014) and lowest during pregnancy (e.g. 2.1% in 2013/2014). A significant rise over the years can be observed for all phases (before pregnancy, chi-square for trend=48.411, p<0.001; during pregnancy, chi-square for trend=141.735, p<0.001; after pregnancy, chi-square for

trend=10.540, p=0.001), with the largest increase during pregnancy (from 0.8% in 1999/2000 to 2.1% in 2013/2014). The trend was not interrupted in 2012, when the guideline was introduced.

Table 1. Number of deliveries in which the women received a dispensing for a SSRI in the year before pregnancy, during pregnancy or in the year following pregnancy, per 2-year group based on delivery date.

		SSRI dispensing during		
	Total number of deliveries	The year before pregnancy (%)	During pregnancy (%)	The year following pregnancy (%)
1999/2000	6,172	170 (2.8)	50 (0.8)	133 (2.2)
2001/2002	11,625	386 (3.3)	118 (1.0)	292 (2.5)
2003/2004	14,201	437 (3.1)	181 (1.3)	388 (2.7)
2005/2006	20,684	639 (3.1)	276 (1.3)	521 (2.5)
2007/2008	28.231	935 (3.3)	425 (1.5)	742 (2.6)
2009/2010	28,220	987 (3.5)	462 (1.6)	764 (2.7)
2011/2012	22,652	906 (4.0)	493 (2.2)	681 (3.0)
2013/2014	22,167	856 (3.9)	461 (2.1)	677 (3.1)

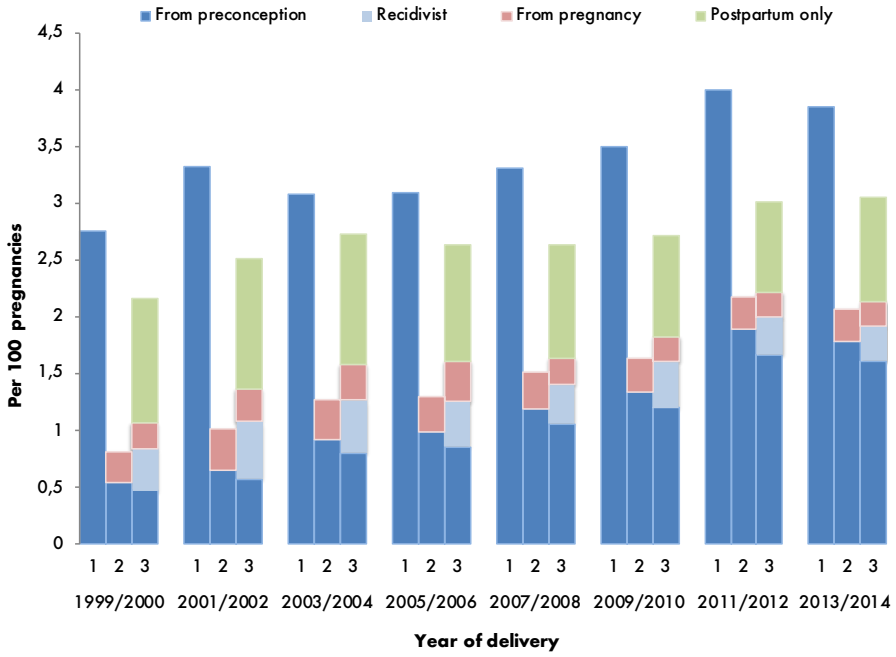
Figure 1 shows starting and stopping scenarios of SSRI use, comparing 2-year groups. In the early years of our cohort, most women using SSRIs in the year before pregnancy (2.8% in 1999/2000) discontinued SSRIs during pregnancy (81% in 1999/2000), while after 2012 only 54% discontinued medication (chi-square for trend=25.256, p<0.001), which is illustrated in figure 2. The percentage of women starting medication during pregnancy (without use in the year before pregnancy) does not alter much over the years (0.27% in 1999/2000 and 0.28% in 2013/2014). A small proportion (17.6%) of women who discontinued SSRIs during pregnancy, restarts SSRIs postpartum (recidivist, pattern 7), ranging from 19.0% in 2001/2002 to 14.9% in 2013/2014. Finally, the percentage of women who initiated SSRIs in the first year following pregnancy, without use in the year before pregnancy or during pregnancy decreased from 1.08% in 1999/2000 to 0.91% in 2013/2014. No obvious change in trend is visible after introduction of the guideline in 2012.

Concomitant use of psycholeptic was highly prevalent: Of the 5316 women using SSRIs in the year before pregnancy, 44.6% also used psycholeptics in that year. A mean number of 4.0 (SD 2.7) other co-medications were used in the year before pregnancy by this group (supplementary table 1).

Table 2 relates patient characteristics to the decision to continue SSRI use during pregnancy. All variables tested univariable were included in the multivariable model. In the multivariable model, a more recent delivery increased the odds of continuation with

10% per calendar year (OR 1.10, 95%CI 1.08-1.11, p<0.01); women with low SES were less likely to continue during pregnancy (OR 0.87, 95%CI 0.75-1.00); a higher parity increased the odds (with 15% per additional pregnancy) of continuation (OR 1.15, 95%CI 1.09-1.21, p<0.01); concomitant use of psycholeptics however halved the probability of continuation of SSRI use during pregnancy (OR 0.50, 95%CI 0.43-0.55, p<0.01). The mean number of non-psycholeptic co-medications as such was not associated with continuation of SSRIs (OR 1.00, 95%CI 0.98-1.02, p=0.92).

Figure 1. SSRIs perinatal dispensing rate per time period of interest per 100 pregnancies in the Netherlands, 1999-2014



1 = the year before pregnancy, 2 = during pregnancy, 3 = the year after pregnancy.
Complete data on all three phases was available for all women and thus the number of women at risk for each bar (1, 2 and 3) per 2 years are comparable. E.g. a woman with a delivery date in 199, who took SSRIs during all three phases (before, during, after) is represented in blue in all three bars (1, 2, 3) of the 1999 column.

Individual drugs

Of the six SSRIs dispensed, combining all years, paroxetine was the most frequently dispensed, accounting for 42.3% in the year before pregnancy, 41.3% during pregnancy and 46.0% in the year following pregnancy. However, a significant change in the selection of a particular SSRI dispensed was observed (figure 3). Over time, the absolute number

of paroxetine dispenses decreased steeply, as did the share of this particular SSRI among users. Especially citalopram and sertraline showed an increase, both absolute and relative, over time. During pregnancy, the same relative decline of paroxetine dispenses was observed, however without a concomitant absolute decrease as in general dispensing during pregnancy increased due to less discontinuation. In the year after pregnancy again both relative and absolute dispensing of paroxetine decreased again, although paroxetine still is the most often dispensed SSRI in 2013/2014.

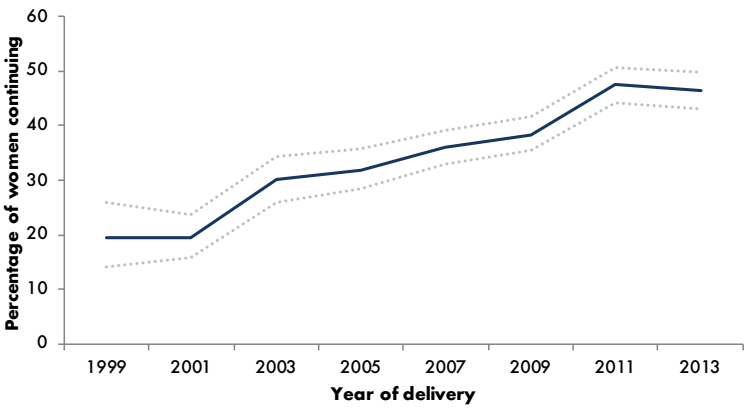
Of the (all years combined) 1986 women who used SSRIs in the year before pregnancy and who continued medication during pregnancy, 127 women (6.4%) switched from SSRI at some point before, during or after pregnancy (supplementary table 2). No change in trend over the years was observed (chi-square for trend=5.577, p=0.590).

Table 2. Univariable and multivariable associations between patient characteristics and continuing pre-conceptive SSRI use during pregnancy

	Univariable outcome		Multivariable outcome	
	cOR (95%CI)	p-value	aOR (95%CI)	p-value
Year of delivery	1.10 (1.08-1.12)	< 0.01	1.10 (1.08-1.11)	< 0.01
Parity	1.15 (1.09-1.22)	< 0.01	1.15 (1.09-1.21)	< 0.01
Socio-economic status				
Low	0.86 (0.75-0.98)	0.03	0.87 (0.75-1.00)	0.05
High	0.99 (0.87-1.13)	0.88	0.97 (0.84-1.11)	0.64
Concomitant use of psycholeptics	0.47 (0.42-0.53)	< 0.01	0.50 (0.43-0.55)	< 0.01
Number of co-medications	0.98 (0.96-1.00)	0.03	1.00 (0.98-1.02)	0.92

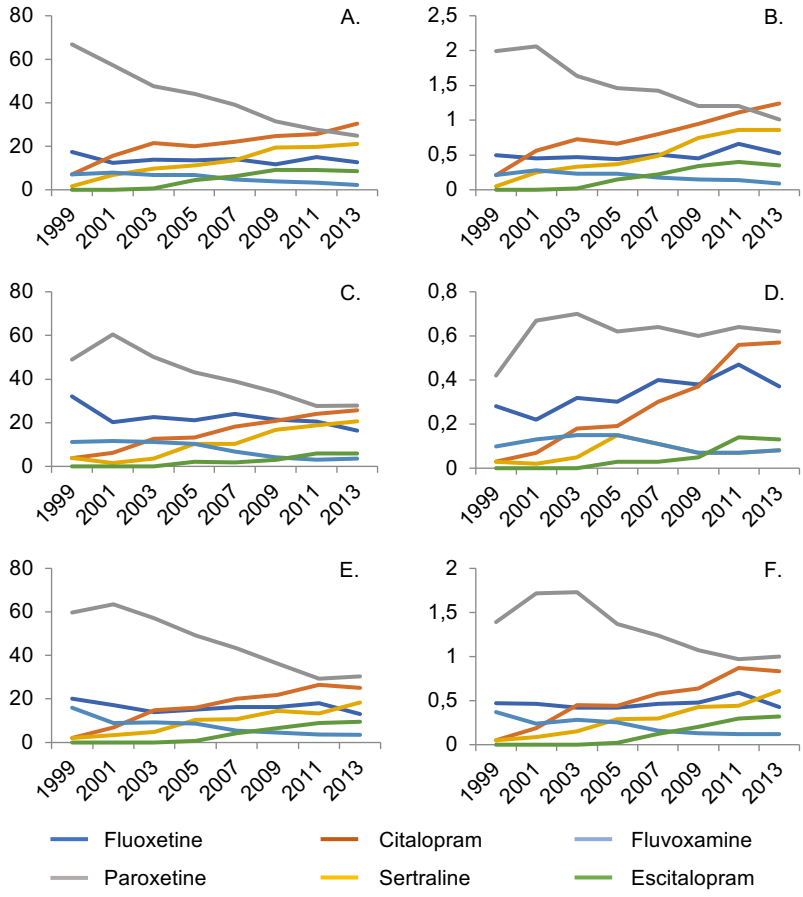
cOR = crude odds ratio, aOR = adjusted odds ratio, CI = confidence interval

Figure 2. Percentage of women with SSRI dispensing in the year before pregnancy continuing during pregnancy in the Netherlands, 1999-2014



Dotted lines represent the 95% confidence intervals.

Figure 3. Relative and absolute dispensing rates per specific SSRI before, during and after pregnancy in the Netherlands, 1999-2014



A. Relative SSRI dispensing in the year before pregnancy; B. Absolute SSRI dispensing in the year before pregnancy; C. Relative SSRI dispensing during pregnancy; D. Absolute SSRI dispensing during pregnancy; E. Relative SSRI dispensing in the year after pregnancy; F. Absolute SSRI dispensing in the year after pregnancy. Each year represents two calendar years.

DISCUSSION

This large 16-year population-based study shows a general trend of increased SSRI use in the year before pregnancy, during pregnancy and in the year following pregnancy, a substantial change of practice with regard to continuation over time (more continuation), initiated already before introduction of the 2012 guideline, and a changed pattern in terms of particular SSRI used. An increased preference for both citalopram and sertraline, at the expense of paroxetine. The latter change is a change in practice, rather than in individual patients, as switching between specific SSRIs is rare (6.4%). Higher parity and more recent delivery increased the odds of continuation, while low SES and concomitant use of psycholeptics substantially decreased the continuation rate.

To our knowledge, this study is the largest to examine trends in SSRI use related to pregnancy in the Netherlands, irrespective of drug choice. Two Dutch author groups previously reported on more selected samples. Ververs described the experience of a cohort of 29,005 deliveries between January 2000 and July 2003, which was made available from one health care insurance company (29). Here 2.2% of women used SSRIs before pregnancy, with a decrease to 1.4% in the third trimester and an increase to 2.3% in the post-delivery period. Bakker et al reported on a cohort of 14,902 pregnancies with deliveries between 1995 and 2004 available from the Interaction Database (IADB.nl) (6). Over these years, the exposure rate to SSRIs in the year preceding delivery increased from 1.2% to 2.9%. The data on the early years of our cohort fits to these observations and show that the growing trend has persisted 10 years beyond 2004. Research among the general Dutch population within the age category of 25 to 49 years (thereby including our target population) also reported an increase in SSRI use from around 2.5% in 1998 to 4.0% in 2004. After 2004 a mild decrease was seen to around 3.7% in 2010 (30). Our data did not show such a decrease, possibly because of our specific target population, but nonetheless rates in the year before pregnancy are a good match. A more recent cohort study examined SSRI prescription in several European countries over the years 2004 to 2010. Prescription rates before, during and after pregnancy in our study were comparable to Denmark (4.1%, 2.3% and 4.1% respectively) and Italy (4.4%, 1.6% and 2.4% respectively), but prescription rates in the UK were considerably higher with 8.8 to 9.6% of women using SSRIs in the year before pregnancy (7). Compared to the USA, where SSRI prescription rates during pregnancy increased from 5.7% to 13.4% in 2003, prescription rates in European countries are low (5).

A trend towards more continuation is observed over the years, without an obvious change in trend after introduction of the 2012 guideline, which recommends continuation of SSRIs if women are stable on this medication and psychiatric indication is correct (26). This recommendation is a result of insufficient evidence on benefits of SSRI discontinuation during pregnancy, with or without non-pharmacological alternatives, and inconclusive

evidence on the risk of relapse of depression when SSRIs are discontinued. A hypothesis is that the relatively low percentage of women receiving a SSRI in general compared to other countries such as the USA, indicates a more personalized drug treatment for severe psychiatric disorders in low prescription countries, therefore warranting continuation of SSRI during pregnancy to prevent relapse of severe psychiatric disorder. Interestingly, concomitant use of psycholeptics, associated with more severe psychiatric diagnosis, halved the probability of continuation of SSRI use during pregnancy. An explanation could be that women might think using multiple forms of psychotropic medication is harmful (cumulative effect); by self-tapering such women may think this benefits child outcome. Final interpretation of this interaction pattern requires more data e.g. on the severity of underlying disease. A higher parity was associated with increased odds on continuing medication. This could be explained by the high correlation of parity with age. A higher parity could indicate a longer duration of psychiatric disease and/or longer duration of antidepressant treatment; this in turn might lead to an increased perceived dependence on antidepressant treatment (31). Another explanation could be that multiparous women with previous healthy infant(s) while using antidepressants, are more likely to be willing to continue a consecutive pregnancy on SSRIs due to the assigned benefits.

There has been a major shift in specific SSRIs dispensed over the years. Where paroxetine was responsible for 58.5% of all SSRIs dispensed in 1999/2000, it only accounted for 27.6% of the SSRIs dispensed in 2013/2014. This seems to be an appropriate reaction to the increasing amount of evidence showing a higher rate of negative consequences on birth outcomes in paroxetine use compared to the other SSRIs (32-38). Overall, paroxetine remained the most frequently dispensed SSRI, while a population-based study from Denmark, Iceland, Norway and Sweden showed paroxetine was the least prescribed SSRI in the period of 2008 to 2012 (39).

Insufficient evidence on the risk of relapse of depression when discontinuing medication during pregnancy is available. The first randomized controlled trial is being executed at the moment (40), but so far only two naturalistic studies report on relapse rates in women continuing or discontinuing antidepressants during pregnancy (41, 42). Where the first study reported a significant increased risk of relapse in women who discontinued their medication compared to women continuing medication (86% vs. 26%), the second study failed to find such a difference. In our current study, only a small proportion of women restarted medication after discontinuation during pregnancy, which may reflect the relapse rate of the psychiatric disorder. The possibility of a short discontinuation period, with subsequent relapse, however cannot be ruled out.

Strengths and limitations

The size and composition of the Out-patient Pharmacy Database is a major strength of this study. It includes representative data on approximately 25% of the Dutch population, thereby allowing for fairly good estimates on the level of the Dutch population. Data was available from a year before conception until the end of the year following pregnancy. An accurate conception date could be obtained from the PRN database based on ultrasound or the last menstrual period and the exact delivery date was also present in the PRN database. However, even this dataset had its limitations. Exact timing of drug dispensing for this study was defined according to before, during and after pregnancy, enabling us to rule out the possibility that drugs dispensed just before pregnancy were still being used in the first trimester of pregnancy and so on. For some drug dispensing an unknown ATC code was registered, thereby potentially missing a small amount of SSRI dispensing leading to underreporting of SSRI dispensing among the target population.

A limitation of prescription registry data is that actual use may be less (non-compliance), or more (external sources of medication, shelf medication). Non-compliance is the most likely weakness, due to an increasing societal and professional reluctance to take/prescribe drugs during pregnancy, and psychotropic drugs in particular (43). In this study we assume the likelihood of underestimation to be very small. Last, information on pregnancies that ended before a gestational age of 16 weeks was excluded in our study as the PRN database only contains information of pregnancies of >= 16 weeks of gestation. However, SSRIs do not seem to increase risk of miscarriage (44) and in addition patterns examined in this study would not be affected.

CONCLUSION

For more than a decade SSRI use before, during and after pregnancy shows a steady increase. Rise is most prominent during pregnancy, by the combined effect of a general rise in SSRIs use, and a change towards continuation rather than quitting SSRI use if women get pregnant. Despite a substantial shift in drug preference, paroxetine is still most commonly used. In view of the demonstrated impact of uncertainty regarding effectiveness and safety of SSRIs in pregnancy, future research should involve more detailed outcome research of SSRIs as it is, and research into viable alternatives (drug, non-drug) for the use of SSRIs in pregnancy.

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APPENDIX

Data sources

The PHARMO Database Network is a dynamic cohort of participants that includes, among other information, drug-dispensing records from community pharmacies for more than three million individuals in the Netherlands (approximately 25% of the Dutch population) collected since 1998 [1]. The PRN is a national registry that contains validated and linked data from four independent databases: the national obstetric database for midwives (LVR-1), the national obstetric database for gynaecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/paediatric database (LNR) [2]. The registry contains information about care before, during and after delivery as well as maternal and neonatal characteristics (determinants) and outcomes of 95% of 175.000 pregnancies annually in the Netherlands, with a minimal gestational age of 16 weeks. The linkage method used here has been described elsewhere; it is generally based on the birth dates of the mother and the child and their approximate address (postal zip codes; covers 2000-5000 persons, 20-50 deliveries annually) [3]. The probabilistic record linkage here used techniques validated before with these datasets. Due to the favourable data characteristics in this case, accuracy is close to perfect [4, 5].

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DATA SUPPLEMENT

Supplementary table 1. Characteristics of all women with SSRI use (n=7,284) before, during and/or after pregnancy and of women with SSRI use (n=5,316) in the year before pregnancy.

	Full sample	Women with SSRI use before pregnancy
Age in years, mean (SD)	31.5 (4.7)	31.5 (4.8)
Socio-economic status		
Low	2451 (33.6)	1713 (32.2)
Middle	2420 (33.2)	1816 (34.2)
High	2371 (32.6)	1759 (33.1)
Concomitant use of psycholeptics, yes (%)	2729 (37.5)	2369 (44.6)
Number of co-medications, mean (SD)	4.0 (2.7)	4.0 (2.7)

Supplementary table 2. Specific SSRIs used before and after switch in women using SSRIs in the year before pregnancy and continuing SSRIs during pregnancy and switching at some point before or during pregnancy.

	SSRI use before switch, n (%)	SSRI used after switch, n (%)
Citalopram	30 (22.2)	34 (21.1)
Escitalopram	10 (7.4)	9 (5.6)
Fluoxetine	11 (8.1)	27 (16.8)
Fluvoxamine	5 (3.7)	12 (7.5)
Paroxetine	31 (23.0)	41 (25.5)
Sertraline	48 (35.6)	38 (23.6)

Numbers sum up to more than the number of women due to multiple SSRIs used or multiple switches.

PART II

The Stop or Go trial

CHAPTER 6

Stop or Go? Preventive cognitive therapy with guided tapering of antidepressants during pregnancy: study protocol of a pragmatic multicenter non-inferiority randomized controlled trial

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ABSTRACT

Introduction: Approximately 6.2% of women in the USA and 3.7% of women in the UK, use Selective Serotonin Reuptake Inhibitors (SSRIs) during their pregnancies because of depression and/or anxiety. In the Netherlands, this prevalence is around 2%. Nonetheless, SSRI use during pregnancy is still controversial. On the one hand SSRIs may be toxic to the intrauterine developing child, while on the other hand relapse or recurrence of depression during pregnancy poses risks for both mother and child. Among patients and professionals there is an urgent need for evidence from randomized studies to make rational decisions regarding continuation or tapering of SSRIs during pregnancy. At present, no such studies exist.

Methods / Design: 'Stop or Go' is a pragmatic multicenter randomized non-inferiority trial among 200 pregnant women with a gestational age of less than 16 weeks who use SSRIs without clinically relevant depressive symptoms. Women allocated to the intervention group will receive preventive cognitive therapy with gradual, guided discontinuation of SSRIs under medical management (STOP). Women in the control group will continue the use of SSRIs (GO). Primary outcome will be the (cumulative) incidence of relapse or recurrence of maternal depressive disorder (as assessed by the Structured Clinical Interview for DSM disorders) during pregnancy and up to three months postpartum. Secondary outcomes will be child outcome (neonatal outcomes and psychomotor and behavioural outcomes up to 24 months postpartum), and health-care costs. Total study duration for participants will be therefore be 30 months. We specified a non-inferiority margin of 15% difference in relapse risk.

Discussion: This study is the first to investigate the effect of guided tapering of SSRIs with preventive cognitive therapy from early pregnancy onwards as compared to continuation of SSRIs during pregnancy. We will study the effects on both mother and child with a pragmatic approach. Additionally, the study examines cost effectiveness. If non-inferiority of preventive cognitive therapy with guided tapering of SSRIs compared to intended continuation of SSRIs is demonstrated for the primary outcome, this may be the preferential strategy during pregnancy.

INTRODUCTION

Depressive disorder and anxiety disorders are the primary indications for the use of Selective Serotonin Reuptake Inhibitors (SSRIs). Worldwide, the SSRI prescription rate during pregnancy ranges from 6.2% in the USA (1), to 3.7% in the UK (2). The actual Dutch nationwide estimated use of SSRIs during pregnancy is about two percent (3, 4); while in the Rotterdam area this number is even as high as five percent (5). Nonetheless, SSRI use during pregnancy is still controversial. On the one hand SSRIs may be toxic to the intrauterine developing child, while on the other hand, relapse of depression and/or anxiety during pregnancy poses risks for both mother and child (6).

The preventive effect of SSRIs for relapse of depression during pregnancy seems equivocal. One naturalistic study showed a significant increased risk of relapse in pregnant women who discontinued their medication compared to continuing medication (68% vs. 26%), while another naturalistic study showed no clear difference relapse rates of depression (16% in total) between pregnant women continuing or discontinuing antidepressants (7, 8).

Pregnancy-related complications both exist for women using SSRIs during pregnancy and women with untreated depression/anxiety during pregnancy, posing a dilemma for the treating physician who considers SSRI withdrawal. For example, studies found significantly increased risks for preeclampsia among women who use SSRIs and increased risks for pregnancy-induced hypertension in women with depression/anxiety during pregnancy compared to healthy controls (9, 10).

Whether or not SSRIs are of direct influence on the newborn, both short- and long-term, is another unresolved issue. For example, a recent meta-analysis showed an increased risk for cardiovascular malformations (RR = 1.36) and septal heart defects (RR = 1.40) with use of SSRIs (11). These findings were however not supported by a recent Nordic cohort study, which – after a sibling-controlled analysis – found no substantial increase in prevalence of overall cardiac birth defects for any SSRI (OR = 0.92) (12). Another example of evidence of a potential direct toxic effect is the association of SSRI use with persistent pulmonary hypertension (PPHN) of the neonate. A large cohort study from the Scandinavian national health registers showed a twofold-increased risk of PPHN with exposure later than gestational week 20 (OR = 2.1) (13). However, this risk appeared more modest (OR = 1.51) in a large cohort study from 46 US states (14).

Several other effects of SSRIs during pregnancy have been described, such as a higher risk of poor neonatal adaptation (OR = 5.07), respiratory distress (OR = 2.20), tremors (OR = 7.89), preterm delivery and small for gestational age, lower birth weight and lower Apgar scores at 1 and 5 minutes after birth (15, 16). Long-term effects on children are less often investigated. One systematic review found an adverse effect on children's motor development but not on emotional or behavioral development (17). Two

large studies reported on the association between maternal SSRI use and childhood autism spectrum disorders, but found conflicting results (18, 19).

On the other hand, leaving depression or anxiety disorders untreated may be hazardous to the unborn child as well. At present, it is well known that children of women who suffered from anxiety or depression during pregnancy have an increased risk of adverse perinatal health outcomes, and behavioral, emotional, cognitive, and motor problems in early childhood (20, 21). It is also shown that the infant cortisol stress response is altered if the mother suffered from depression during pregnancy (22). One meta-analysis showed an association of depression during pregnancy with preterm birth and low birth weight (23). Another more recent meta-analysis showed that depression during pregnancy is associated with premature delivery, but did not find associations with birth weight, neonatal intensive care unit admissions, preeclampsia, gestational age or Apgar scores (24).

Overall, in clinical practice and literature, pregnant women express a strong preference for non-pharmacologic treatment of depression over antidepressant medication (25). Hence, cognitive behavioral therapy (CBT) could be a good alternative for SSRI use during pregnancy. According to a recent meta-analysis there is strong evidence that CBT interventions are effective for preventing depressive relapse during the perinatal period (26). A recent follow-up study showed that preventive cognitive therapy (PCT) has long-term effects in preventing depressive relapse in patients with recurrent depression for over 5.5-10 years after the sessions ended (27, 28). This preventive psychological strategy therefore seems promising in preventing depressive relapse, presumably also during pregnancy. Moreover, a recent study in the UK among non-pregnant patients showed that tapering antidepressants with therapy was as effective as continuation of antidepressants (Hazard Ratio 0.89) (29). Nevertheless, further investigation is necessary to assess effectiveness of tapering antidepressants with added PCT during the perinatal period.

In conclusion, pregnant women and their clinicians face a dilemma, which is widely experienced in current practice (30). At present, there are no suitable data available to guide evidence-based decisions on SSRI continuation or discontinuation during pregnancy (31). Both the National Institute for Health and Clinical Excellence in the United Kingdom (NICE) guideline (32), and American Psychiatric Association (APA) (33) therefore recommend to discuss both possibilities with women. The recently developed Dutch multidisciplinary guideline advises to continue SSRI use during pregnancy, and furthermore advises a hospital delivery and neonatal observation based on the increased risk and the severity of the (rare) condition of PPHN and prevalence (25-30%) of children with neonatal abstinence after maternal SSRI use (34). Nonetheless, the need of randomized trials was stressed. Indeed, existing studies are observational and therefore their results do not fully allow causal inference nor definite conclusions for practice.

Trial objectives

In this randomized controlled trial (RCT), the effect of preventive cognitive therapy (PCT) with guided tapering of SSRIs in early pregnancy will be compared to continuation of SSRIs during pregnancy. We will study effects on both mother and child with a pragmatic approach. The expectation is that tapering of SSRIs with added PCT does not increase the risk of clinically relevant maternal relapse or recurrence of depression or onset of anxiety disorders during pregnancy up to three months postpartum in excess of [absolute] 15% compared to continuation of SSRIs. If so, discontinuation is deemed non-inferior with regard to relapse/recurrence risk. Furthermore, we expect that tapering of SSRIs is better than continuation of SSRIs with respect to child development. Finally, but not unimportantly, we hypothesize that discontinuation will decrease total costs per woman and child on a 3 months and projected long term base, assuming no relevant effects of discontinuation on the mother and no effects on the child are found.

METHODS / DESIGN

Design & Setting

The Stop or Go study is a pragmatic multi-center randomized controlled non-inferiority trial (RCT) in obstetric care. Women will be recruited during their first prenatal visit in midwifery practices (first echelon care) and hospitals (second and third echelons care), or through advertisement in (social) media. After inclusion, women will be randomly allocated into two groups: STOP or GO. Both groups will receive regular assessments throughout their pregnancy and up to 3 months post-partum. Permission will be asked to contact the Centre of Childhood (CJG) at 24 months after delivery for information on the development of the child. Total duration of the study for participants will therefore be 30 months. In Figure 1 an overview of the study design and main procedures is shown.

Participants

Women who are less than 16 weeks pregnant and use a SSRI primarily for depressive disorder, and are currently at least in remission or recovered (35), are invited to participate in the trial. Exclusion criteria are multiple pregnancy, as these women have a markedly increased obstetric risk, thereby threatening the homogeneity of the study population and thus potentially complicate the statistical analysis, and insufficient proficiency in Dutch or English, since our intervention is not yet available in other languages. Also, women will be excluded with severe medical conditions, such as oncology-related conditions or conditions that need urgent medical interventions, which involve treatment decisions overriding research participation. Exclusion criteria related to mental health are: current

mania or hypomania or a history of bipolar illness, suicidality and serious self-harm, any psychotic disorder (current and previous), current alcohol or drug misuse, predominant anxiety disorders and personality disorders that require psychotherapeutic treatment for more than 2 sessions a month.

Assessment of eligibility

After informed consent is obtained, a pre-assessment interview will be conducted, with the Structured Clinical Interview for DSM-disorders (SCID) (36) and the Hamilton Depression Rating Scale (HDRS) (37) to assess major DSM-IV Axis I psychiatric diagnoses and actual remission status and depressive symptoms respectively. Before randomization, study researchers will contact the medical professional who prescribed the SSRI medication to inform the professional about the study and discuss exclusion criteria as described above for study participation.

Randomization

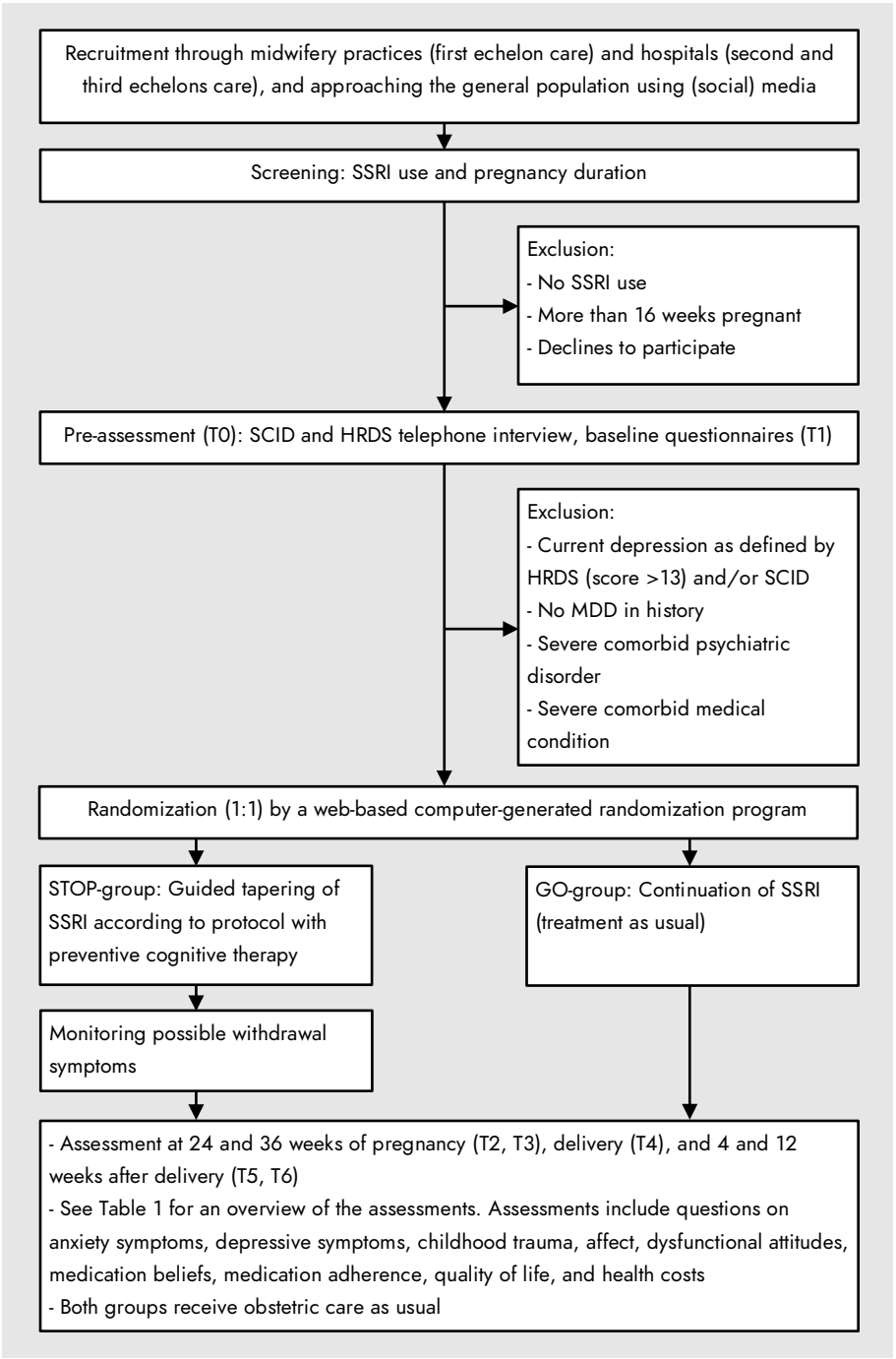
Two hundred women will be randomized in a 1:1 allocation ratio to either the intervention arm (STOP) or the care as usual arm (GO). Randomization will be done with a web based computer-generated randomization schedule (a validated TENALEA Clinical Trial Data Management System; http://www.formsvision.com/) using permuted blocks of random size with a maximum of 16 and stratified for the number of previous depressive episodes (dichotomized). Based on a recent review (35), the participants are divided into groups of participants with 3 or less previous depressive episodes, versus 4 or more. Allocation of participants is concealed for study researchers.

Interventions

1. Tapering SSRI

Women assigned to discontinuation of SSRIs will be referred to a psychiatrist trained in guiding tapering of SSRIs during pregnancy. They will plan and carry out SSRI discontinuation using an expert-based discontinuation protocol (38). The aim is to taper the use of SSRIs within four weeks, depending on patient preferences and on drug characteristics (e.g. half-life in the body). There are no restrictions on the use of medication like sleeping pills, paracetamol, and mild tranquillizers. All co-medication will be monitored during the study period.

Figure 1. Study flow chart



2. Preventive Cognitive Therapy

Trained psychologists will provide preventive cognitive therapy in the discontinuation arm. This psychological intervention has proven to be effective in relapse prevention (27, 39-42). The current manual was evaluated in previous studies (27, 38, 41, 43).

The intervention will be applied through VSee (www.vsee.nl), a HIPAA-compliant telehealth app. Several studies demonstrated that psychological intervention as applied by telephone support is effective and there is some evidence that it might be effective to decrease postpartum depressive symptomatology (44-47). Although not tested during pregnancy, there are indications that antenatal telephone or online therapy is effective and convenient (48).

The preventive psychological intervention consists of a minimum of eight weekly VSee sessions. These sessions are led by professional psychologists trained in cognitive behavioral therapy and may occur at any time of the day. The focus of the sessions is on identifying and teaching the participants to challenge dysfunctional beliefs, enhance recall of positive feelings and cognitions and a personal prevention plan is developed in which it is specified how the participant can prevent a depressive episode in the future. For each session the participant will receive some assignments of approximately 10 minutes per day. Treatment adherence will be monitored.

3. Care as usual

Women assigned to continuation of SSRIs (GO) obtain usual care. They will be instructed to consult their doctor as they regularly do, in line with the pragmatic nature of the study. All the care that is provided will be monitored.

Outcome measures

1. Mother

Primary outcome of this trial is (cumulative) incidence of relapse or recurrence of a depressive episode (as defined by the SCID-I (36)) during pregnancy and up to 12 weeks postpartum. The SCID-I is assessed at baseline (T0) and 12 weeks postpartum (T6). If – based on assessment with the HDRS at fixed time-points – relapse/recurrence is suspected, the SCID-I will be performed intermittently.

For registration of severity of depressive symptoms, the HDRS will telephonically be assessed additionally, at baseline (T0), at 36 weeks of gestation (T3), and 12 weeks postpartum (T6), and also intermittently, if necessary (37). When the HDRS at any stage turn out above cut-off scores, the participant will be called one week after initial measurement. The HDRS will be repeated to confirm or reject elevated scores. An adjusted telephonic version of the everyday problem checklist (EPCL) and pregnancy related life events will be assessed during each telephonic measurement (T0, T2, T3, T5 and T6).

Women will be asked to fill in questionnaires during five occasions: baseline (T1), 24 and 36 weeks of gestation (T2 and T3), and 4 and 12 weeks postpartum (T5 and T6). The questionnaires differ in composition at the five measurement moments, as shown in Table 1. During these occasions, participants are variably asked to report on anxiety symptoms (Dutch version of the State Trait Anxiety Inventory STAI), short and long version (49, 50)), depressive symptoms (the Dutch version of the Edinburgh Postnatal Depressions Scale; EPDS (51)), childhood trauma (Childhood Trauma Questionnaire; CTQ (52)), affect (the International Short-Form of the Positive and Negative Affect Schedule; I-PANAS-SF (53)), dysfunctional attitudes (Dysfunctional Attitude Scale; DAS (54)), medication beliefs (Beliefs about Medicines Questionnaire; BMQ (55)), medication adherence (Medication Adherence Rating Scale; MARS (56)) and Quality of Life (EQ-5D-5L (57)). Socioeconomic position, ethnicity, smoking behavior, alcohol use, family history and information on previous pregnancies and family size will be assessed using the Mind2Care questionnaire (58), a screen-and-advice instrument to detect mental health problems among pregnant women.

Health care cost data is registered using the TIC-P (59). This instrument allows reliable recall over the past six months (60). We will adapt scoring for 'normal' absenteeism and sickness leave for pregnant and recently delivered women. Care will be taken for secondary effects on child-care for other children (if present) in case of postpartum hospitalization.

Using the Discontinuation Emergent Signs and Symptoms checklist (DESS) (61), the discontinuation group will be monitored by telephone weekly during tapering, to collect information about dosages and potential symptoms of withdrawal. Both groups will receive telephonic monitoring of medication use, including psychiatric co-medication, at 24 and 36 weeks of gestation (T2 and T3) and 4 and 12 weeks postpartum (T5 and T6).

Alongside the self-report measures, several sources of biological materials will be collected during the study. At baseline, immediately after delivery and 12 weeks postpartum (T1, T4 and T6) we will collect maternal hair strands to measure cortisol levels. Hair cortisol is a validated biomarker for long-term cortisol exposure and makes it possible to create a timeline of cortisol exposure during follow-up (62). At baseline a maternal buccal swab will be collected in order to enable epigenetic and pharmacogenetic analysis. Maternal blood sampling will be performed 12 weeks postpartum (T6) to enable additional epigenetic and pharmacogenetic testing, but also for measurement of SSRI concentration and immunological factors.

2. Health care professional

We will send a Case Report Form (CRF) to the participant's obstetric caregiver, either a midwife or a gynecologist, to request information about the pregnancy and delivery.

Complications during pregnancy and delivery, such as hypertensive disorders or pregnancy, fetal growth retardation, preterm labor, induced labor and caesarean section will be registered as well as information about the neonate (e.g. Apgar scores, birth weight, congenital malformations and admission to pediatric ward).

Table 1. Assessment per measurement moment

	Method	T0	T1	T2	T3	T4	T5	T6	T7
Clinical Diagnostic Interview (SCID-I)	Int	X		…	…	…	…	X	
Depressive symptoms (HDRS)	Int	X		…	X	…	…	X	
Peripartum depression (EPDS)	SR		X	X	X		X	X	
Anxiety (STAI)	SR		X	X	X		X	X	
Affect (I-PANAS-SF)	SR		X	X	X		X	X	
Attitudes (DAS)	SR		X	X	X				
Daily hassles	Int	X		X	X		X	X	
Life events	Int	X		X	X		X	X	
Sociodemographic & -economic factors (M2C)	SR		X						
Substance use (M2C)	SR		X	X	X		X	X	
Medication use	Int	X		X	X		X	X	
Medication adherence (MARS)	SR		X	X	X		X	X	
Medication beliefs (BMQ)	SR		X						
Childhood trauma (CTQ)	SR			X					
Quality of life (EQ-5D-5L)	SR		X	X	X		X	X	
Health care consumption (TIC-P)	SR		X		X		X	X	
Pregnancy related outcomes	CG					X			
Neural development (GM)	ME							X	
Child behavior (CBCL)	SR								X
Cortisol (hair strands)	BM		X			X		X	
Buccal swab	BM		X					X	
Blood sample	BM							X	
Meconium (SSRI concentration)	BM					X			
Breast milk (SSRI concentration)	BM					X			

M2C = mind2care, Int = interview, SR = self-report, CG = caregiver, BM = biological materials, T0: pre-assessment, T1: baseline, T2: 24 weeks of gestation, T3: 36 weeks of gestation, T4: delivery, T5: 4 weeks postpartum, T6: 12 weeks postpartum, T7: 18 months postpartum

3. Child

At 12 weeks postpartum we will perform a General Movements (GM) assessment by taking video recordings at home (63). This assessment method evaluates the function of the young nervous system.

GMs are spontaneous movements that are present from early foetal life onwards until the end of the first half-year of life. GMs are complex, occur frequently and last long enough to be observed properly. If the nervous system is impaired, GMs lose their complex and variable character and become monotonous and poor (64).

For mapping of the SSRI exposure of the newborn, samples of meconium and breast milk (if breastfeeding) will be collected. SSRI in meconium will be measured by a validated method according to LCH guidelines on LC-MS/MS (65). If feasible, hair strands and a buccal swab of the newborn will be collected at 12 weeks after birth (T6).

Long-term follow-up includes the well-established, reliable and valid Child Behavior Check List 1.5-5 years, including the Caregiver Teacher Report Form (C-TRF) and the Language Development Survey (LDS) at 18 months postpartum (66). Also, permission will be asked to obtain routine data from Centers for Childhood (CJG) until 24 months (in particular on length gain, weight gain, normal development, and any information on abnormal behavioral development).

Sample size

Sample size calculation is based on the main aim of this study, which is to demonstrate non-inferiority of preventive CT with guided discontinuation of SSRIs (STOP) compared to continuation (GO), with respect to relapse or recurrence of a depressive episode up to 3 months postnatal. We will use a non-inferiority margin (tolerance threshold, 'delta') of 15%. This is based on the assumption that this excess relapse (taking into account the possibility of restoring SSRI treatment) is still in balance with the expected beneficial effects of discontinuation of SSRI for the remaining mothers. We also anticipate that this balance is acceptable for women.

With this non-inferiority margin, and the assumption that the overall absolute risk of relapse will be around 15% (67), we need 178 women, given alpha .025, power 80%, and a one-sided test. To account for some attrition, we aim to include 200 women in total. Given this sample size, we have sufficient power to demonstrate small to moderate effect sizes of .42 or over on continuous secondary outcomes. With respect to dichotomous secondary outcomes, we will be able to detect odds ratios of 1.5 or over when the base probability is .5.

Statistical analysis

Analysis will primarily be carried out according to the intention-to-treat principle, i.e. the participants will be analyzed according to their randomized allocation, regardless of the actual interventions received by the participant. Supplementary, we will perform analyses per protocol, i.e. according to actual SSRI use, irrespective of randomized arm.

The primary outcome, risk (cumulative incidence up to 3 months postnatal) of relapse of depression, will be compared between the randomized groups. Differences will be assessed statistically using a one-sided Chi-Square Test at a significance level of .025 and will be presented as a risk difference. The remainder of statistical tests will be performed two-sided at a significance level of .05.

Time to relapse will be compared between the randomized groups using survival analysis. Kaplan-Meier curves will be constructed and differences will be tested using the log-rank test. A Cox proportional hazard model will be used to calculate hazard ratios

Continuous outcomes, e.g. the General Movements scores at 3 months, will be compared between the groups using the unpaired t-test. Categorical secondary outcomes, e.g. obstetric complications, will be tested using Chi-Square Tests. For the continuous variables and categorical variables that are assessed more than twice, we will deploy linear mixed models and generalized linear mixed models respectively. These models use all available data (do not exclude persons with missing values) under the assumption of data being missing at random, and account for within-subject correlation over time. If despite randomization prognostically important factors differ between the groups, they will be adjusted for in supplemental analyses by including these factors in the pertaining regression models.

Subgroup analyses will be undertaken according to: Dutch/non-Dutch, nulliparous/multiparous, yes/no history depressive disorder and/or anxiety disorder, yes/no co-morbid anxiety symptoms or disorder. All effect parameters will be supplied with a 95% confidence interval.

Economic evaluation

In the present study we will also evaluate the outcome in the two study groups (Stop and Go) from a societal, economic perspective. It is therefore important to weigh cost savings for both groups against their clinical value. If relapse/recurrence incidence is within the predefined threshold (15%), hence non-inferiority is confirmed; a straightforward cost minimization analysis will be executed focusing on cost savings. However, successful tapering of SSRIs will reduce SSRI use for years. Hence, with a sensitivity analysis on maternal effects and costs we will project cost estimations for 10 years. We expect that the upfront investment in PCT for women with previous psychiatric disorders will then be balanced by reduced SSRI use and less healthcare consumption. A previous RCT in a non-pregnant population demonstrated that a brief CT intervention is cost effective in remitted depressed individuals that stop antidepressants, compared to continuation of antidepressants (68).

If, however, relapse/recurrence incidence is higher than the predefined tolerance threshold, thus discontinuation is clinically inferior and rejected, a cost-effectiveness analysis will be executed as primary analysis, which estimates the costs avoided per additional relapse. This is the opposite of the extra costs per prevented relapse, if the starting point would have been no SSRI, and starting SSRI would be considered. Regardless the relapse outcome, we will conduct a cost utility analysis which

estimates the impact of SSRI on the costs per Quality Adjusted Life Year (QALY), at least with a 3-month time horizon.

DISCUSSION

The use of SSRIs during pregnancy remains a clinical dilemma for both clinicians and patients. Given the increase of SSRI use among pregnant women and studies reporting conflicting results (7, 8, 11-14, 18, 19), there is dire need of randomized controlled trials investigating the use of SSRIs during pregnancy. This study will be the first to investigate the effect of preventive cognitive therapy with guided tapering of SSRIs from early pregnancy onwards as compared to continuation of SSRIs during pregnancy. Additionally, the study focuses on child outcomes and cost effectiveness.

Previous studies on relapse prevention showed promising results for tapering antidepressants with added relapse prevention (29). Preventive cognitive therapy moreover showed promising long-term effects in non-pregnant women with a history of depression (27, 28). Preventive cognitive therapy with guided tapering of antidepressants may therefore be a good alternative for SSRI use during pregnancy.

To our knowledge, no randomized controlled trials have been performed during pregnancy that investigated alternative treatment options versus SSRI use. This may be the result of the complex ethical situation of studies in pregnant women who are taking SSRIs and must be willing to either taper or continue SSRI use. Logistics of a nationwide randomized controlled trial are also difficult in a multidisciplinary setting. Although a multidisciplinary guideline exists, health care givers still have different views on best practice and therefore give different advices to their patients. This study will therefore be as pragmatic as possible, while still providing the intervention in a protocoled manner.

Results of this study will be published and will contribute to further development of (international) guidelines. The results will provide a first step in giving pregnant women an answer to the question whether it is better to stop or to continue the use of SSRIs during pregnancy.

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CHAPTER 7

Recurrence of depression in the perinatal period: Clinical features and risk factors in an observational cohort

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ABSTRACT

Introduction: Antidepressant medication for prevention of depression recurrence in the perinatal period is common, but the efficacy remains unclear and it is unknown what risk factors may play a role. The objective of the current study was to structurally describe women who experienced a perinatal recurrence of depression despite ongoing antidepressant use. Additionally, this study aimed to identify clinically measurable risk factors for recurrence of depression.

Methods: Eighty-five pregnant women with a history of depression who used antidepressants (e.g. SSRIs and SNRIs) at the start of the study were included. Clinical features, including information on psychiatric history and antidepressant use, were collected throughout the perinatal period (in this study defined as the period between 16 weeks of pregnancy up till three months postpartum). For women experiencing recurrence of depression, these features were described in detail. To identify risk factors for recurrence of depression, we performed univariable logistic regression analyses.

Results: Eight women (9.4%) experienced a recurrence of depression; two during pregnancy and six in the first 12 weeks postpartum. All women with recurrence of depression had first onset of depression during childhood or adolescence and had at least 2 psychiatric co-morbidities. Identification of predictors for recurrence of depression yielded associations with depressive symptoms (EPDS score) around 16 weeks of pregnancy (OR 1.28, 95%CI 1.08-1.52), number of psychiatric co-morbidities (OR 1.89, 95%CI 1.16-3.09) and duration of antidepressant use (OR 1.01, 95%CI 1.00-1.02).

Conclusion: Implementing adequate risk assessment in women using antidepressants during pregnancy can lead to improved individualized patient-centred care.

INTRODUCTION

Mental illness during the perinatal period, defined as the time period during pregnancy up to 3 months postpartum, is a common health problem (1), with approximately 25% of women experiencing any psychiatric disorder in this period (2). Perinatal depressive disorder is most common, with a recent meta-analysis observing a pooled prevalence of 11.9% (3). Untreated perinatal depression is not only unfavorable for the mother; it is also associated with adverse outcomes in the offspring (4). Exposure to antenatal depressive disorder is associated with increased risks of premature delivery and low birth weight (5-7) and behavioural, emotional, cognitive and motor problems in early childhood(8-10). Ante- and postnatal depression can furthermore influence the mother-infant relationship, posing increased risks for poor infant development (11-13).

Therefore, prevention or treatment of perinatal depression is important. Several treatment options are available (14), but international guidelines differ in their recommendations (15) and clinicians are frequently noncompliant(16). Antidepressant medication is an increasingly used treatment option, either for prevention of recurrence of depression or as acute treatment in newly depressed patients (17-19). Perinatal prescription rates of antidepressants vary per study setting and range from 2.1% to 13.4% (17, 19-21).

The preventive effect of continued antidepressant use in recovered women during the perinatal period remains unclear. A systematic review assessing the effectiveness of antidepressants for prevention of postnatal depression, based on observational studies, could not draw any clear conclusions due to low statistical power (22). Two studies with a naturalistic design followed women who continued or tapered antidepressants, from their first trimester throughout their pregnancy (23, 24). One study showed an increased risk of recurrence in women who discontinued their medication compared to women who continued their medication (68% vs. 26%) (23), the other study observed similar recurrence rates in women continuing or discontinuing antidepressants (16% in total) (24).

From a clinical perspective, recognizing which pregnant women using antidepressants are at risk for recurrence is vital. With this knowledge, clinicians could more accurately identify and inform patients, and subsequently arrange additional guidance when necessary. Collectively these efforts could help promote the use of individualized patient-centered care, and potentially prevent negative effects in the offspring. The purpose of the current study was to structurally describe cases with perinatal recurrence of depression out of a group of women using antidepressants in their first trimester. Clinical features of the women with recurrence were inspected and reported. Additionally, risk factors for recurrence that are easily collected during routine care, were identified.

METHODS

Setting and population

The present study was embedded in an observational cohort and a randomized controlled trial (RCT) (Stop or Go) in the Netherlands (25). The Medical Ethical Committee of the Erasmus Medical Center approved this study (MEC-2014-505).

Women were recruited during their prenatal booking visit in midwifery practices and hospitals, through general practitioners, or through advertisement in (social) media. When an eligible woman was identified, study researchers gave counselling about the RCT and observational cohort. Written informed consent was necessary for participation.

For the present study, participants were considered eligible if they (1) were less than 16 weeks pregnant, (2) used a Selective Serotonin Reuptake Inhibitor (SSRI), Selective Serotonin and Noradrenalin Reuptake Inhibitor (SNRI) or Tricyclic Antidepressant (TCA), (3) had a history of at least one depressive episode as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (26), and (4) did not have a current diagnosis of depression according to the SCID-I. Women without sufficient proficiency in Dutch or English were excluded. Participants were recruited between April 2015 and February 2018.

Perinatal recurrence of depression

We assessed relapse and recurrence, further referred to as recurrence of depression, as defined by the SCID-I, during pregnancy and up to 12 weeks postpartum. The SCID-I was assessed before 16 weeks of pregnancy (baseline assessment) and 12 weeks postpartum.

Clinical features of women with recurrence of depression

Clinical features including information on psychiatric history and antidepressant use were documented. SCID-I DSM-IV diagnoses, age of first and last onset of depression, number of depressive episodes, history of psychiatric hospital admission, psychiatric family history, antidepressant prescriber, current antidepressant dosage and number of previous discontinuation attempts were all determined before 16 weeks of pregnancy (baseline assessment).

The Edinburgh Postnatal Depression Scale (EPDS) was administered at baseline, 24 and 36 weeks of pregnancy and 4 and 12 weeks postpartum for the assessment of depressive symptoms (27, 28). The Beliefs about Medicine Questionnaire, specific version (BMQ-s) was administered at baseline (29). The BMQ-s consists of two scales assessing (1) personal beliefs about the necessity of prescribed medication for controlling one's illness (score range 5-25) and (2) concerns about the potential adverse consequences of taking medication (score range 6-30). Higher scores indicate stronger beliefs in the concepts of

the scale. During follow-up, data on healthcare use was collected using the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TIC-P) for number of visits to the general practitioner (GP), psychiatrist, psychologist, psychiatric nurse, psychotherapist and mental health care practice assistant (30).

Predictors of depression recurrence

Potential predictors for recurrence focused on sociodemographic characteristics, illness (history) and antidepressant specifications.

Included participant characteristics were age, level of education, having a paid job, parity and planned pregnancy (yes/no). Level of education was categorized in low (primary/secondary education) and higher education.

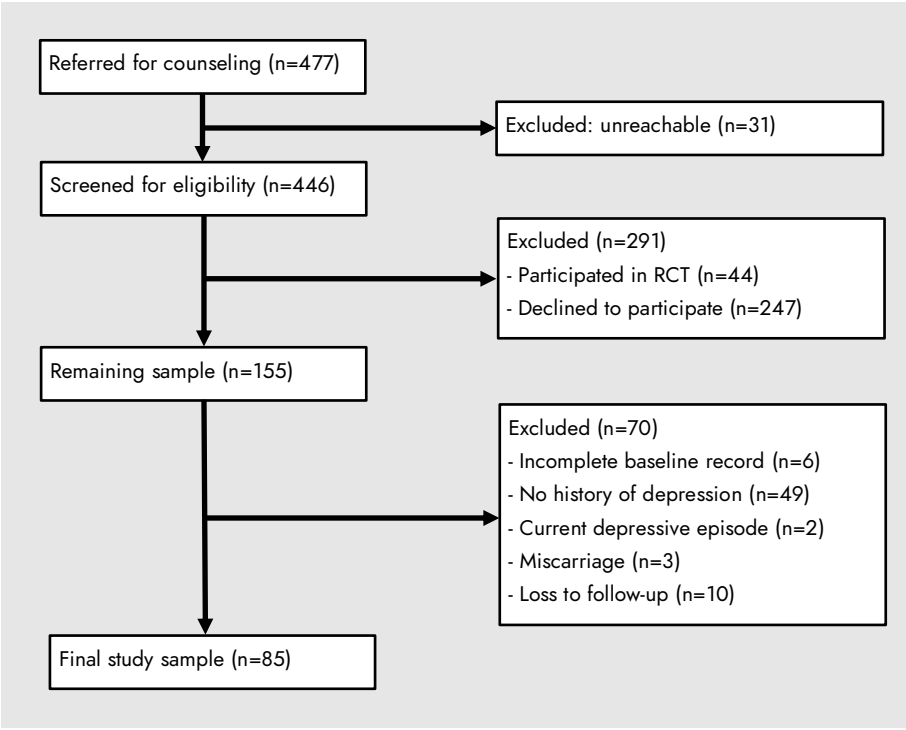
Included illness (history) determinants were EPDS score around 16 weeks of pregnancy, number of depressive episodes, number of axis I psychiatric co-morbidities (both past and present) as measured with the SCID-I and a history of psychiatric hospital admission.

Antidepressant specifications included duration of antidepressant use, number of previous tapering attempts, and dose equivalency in early pregnancy. Dose equivalency was calculated by dividing the prescribed dosage by standard initial dosages, which are: citalopram 20mg, escitalopram 10mg, fluoxetine 20mg, fluvoxamine 100mg, paroxetine 20mg, sertraline 50mg and venlafaxine 75mg. Standard dosages were based on American and Dutch pharmaceutical treatment guidelines (31, 32). During prospective follow-up, tapering and discontinuation was reported and divided into three categories: (1) no tapering, (2) intention to taper, but did not completely discontinue antidepressants during follow-up and (3) participant completely discontinued antidepressants at any point during follow-up, whether or not this discontinuation afterwards persisted throughout follow-up.

Statistical analysis

We performed a case-series study describing individual characteristics of participants. Additionally, univariable analyses were used to qualify associations between recurrence and potential predictors (previous section). We used logistic regression analyses with recurrence as the outcome variable and the predictors entered one at a time as independent variables. All associations were expressed as odds ratios (OR) with 95% confidence intervals (95%CI). All statistical analyses were performed with SPSS, version 25.0.

Figure 1. Flowchart of inclusion of participants



RESULTS

A total of 477 pregnant women were referred for further counselling for both the RCT and the observational cohort. Thirty-one women (6.5%) were unreachable for counselling, 44 (9.2%) decided to participate in the RCT and 247 (51.8%) declined to participate in both trials. Of the remaining 155 women willing to participate in the observational cohort, another 70 (14.7%) were excluded for the current study: six had an incomplete baseline record, 49 did not have a history of depressive disorder, two were currently depressed, three had a miscarriage and ten were lost to follow-up. This resulted in a total sample of 85 women (see figure 1).

Table 1 illustrates the characteristics of all participants, including those with and without depression recurrence. Eight women (9.4%) experienced a perinatal recurrence of depression, none experienced relapse. Overall, mean age was 31.7 years (SD 4.1), over half had a high level of education and for 50% it was their first pregnancy. Of all 85 women, 44 (51.8%) had one previous depressive episode and 7.1% had more than 3 episodes. Psychiatric co-morbidity was present in 71.8% of women, with panic disorder

and agoraphobia most common (both 24.7% of participants). Overall, the median duration of antidepressant use was 60 months, in which a limited number of tapering attempts were undertaken; 81.0% either did not try or only once attempted to discontinue their antidepressants. During follow-up, 12 women (14.1%) completely discontinued their medication and four (4.7%) intended to taper medication, but did not completely discontinue during follow-up.

Women with perinatal recurrence of depression

Out of eight women with a recurrence, six experienced recurrence after childbirth. Three of the women discontinued antidepressants during follow-up. A visual representation of timing of onset of recurrence can be seen in figure 2. Clinical features of individual women are listed in Table 2 (case numbers correspond with case numbers in figure 2). The mean age at first onset of depression was 16 years. None of these women had a previous episode with postpartum onset (for six women this was their first pregnancy). Four women had a positive family history of psychopathology; case 2 had a father with depression and obsessive-compulsive disorder, case 3 a brother with attention-deficit hyperactivity disorder and antidepressant use, case 7 a cousin who committed suicide and case 8 a mother, aunt and grandma with depression. All women had two or more psychiatric co-morbidities, mostly anxiety disorders. Most women received their medication through the general practitioner (GP). Overall, beliefs about necessity of their medication (BMQ-necessity) was high. However, the women with the lowest scores were also the women that discontinued their antidepressants during follow-up. The beliefs about adverse consequences were mild and homogeneous. All women had a history of (added) non-pharmacological treatment, receiving therapy for multiple years including cognitive therapy. Three women still received non-pharmacological therapy in early pregnancy.

All eight women visited the GP on average four times during study follow-up. Women had several psychiatric healthcare professionals. Five women visited a psychiatrist (mean number of visits 4.2), four a psychologist (mean number of visits 7.8), four a psychiatric nurse (mean number of visits 10.8), four a mental health care practice assistant (mean number of visits 2.0) and two a psychotherapist (mean number of visits 5). Case 7 only visited her GP (four times in total). The other women visited at least one more healthcare professional (range 1-5).

During pregnancy, the mean EPDS scores of the eight women remained stable (11.6, 12.1 and 11.1 consecutively), but increased after childbirth, when six women had onset of recurrence. Mean EPDS scores four weeks postpartum were 16.3 and 15.3 at 12 weeks postpartum. Figure 3 shows EPDS scores per case over time.

Table 1. Characteristics of women with a history of depression, with and without recurrence of depression during the perinatal period

	All (n=85)	Recurrence (n=8)	No recurrence (n=77)	OR (95% CI)
Sociodemographic characteristics				
Age, mean (SD)	31.7 (4.1)	30.8 (5.1)	31.8 (4.0)	0.95 (0.78-1.12)
High level of education, yes (%)	51 (65.4)	4 (57.1)	47 (66.2)	0.68 (0.14-3.29)
Paid job, yes (%)	65 (79.3)	6 (75.0)	59 (79.7)	0.76 (0.14-4.17)
Parity, median (range)	1.5 (1 – 11)	1 (1 – 5)	2 (1 – 11)	0.76 (0.38-1.54)
Planned pregnancy, yes (%)	64 (78.0)	7 (87.5)	57 (77.0)	0.48 (0.06-4.17)
Illness (history)				
EPDS score around 16 weeks of pregnancy, mean (SD)	6.7 (4.7)	11.6 (4.1)	6.2 (4.4)	1.28 (1.08-1.52)*
Number of depressive episodes, median (range)	1 (1 – 10)	2.5 (1 – 6)	1 (1 – 10)	1.40 (0.94-2.07)
Number of psychiatric co-morbidities, median (range)	1 (0 – 6)	2.5 (2 – 4)	1 (0 – 6)	1.89 (1.16-3.09)*
History of admission to psychiatric institute, yes (%)	12 (14.1)	3 (37.5)	9 (11.7)	4.53 (0.92-22.26)
Antidepressant specifications				
Duration of antidepressant use in months, median (range)	60.0 (4 – 252)	120 (12 – 228)	48 (4 – 252)	1.01 (1.00-1.02)*
No. of tapering attempts in history, median (range)	1 (0 – 6)	0.5 (0 – 2)	1 (0 – 6)	0.65 (0.25-1.70)
Dose equivalent at start study, mean (SD)	1.3 (0.6)	1.7 (0.7)	1.3 (0.6)	2.32 (0.84-6.42)
Tapering antidepressants during follow-up, n (%)	16 (18.8)	3 (37.5)	13 (16.9)	2.00 (0.89-4.53)
Intention to taper, did not discontinue, n (%)	4 (4.7)	0 (0.0)	4 (5.2)	
Discontinued during study, n (%)	12 (14.1)	3 (37.5)	9 (11.7)	

Columns may not sum due to missing data. SD = standard deviation, CI = confidence interval, *p-value < 0.05

Table 2. Clinical features of women with recurrence of depression in the perinatal period

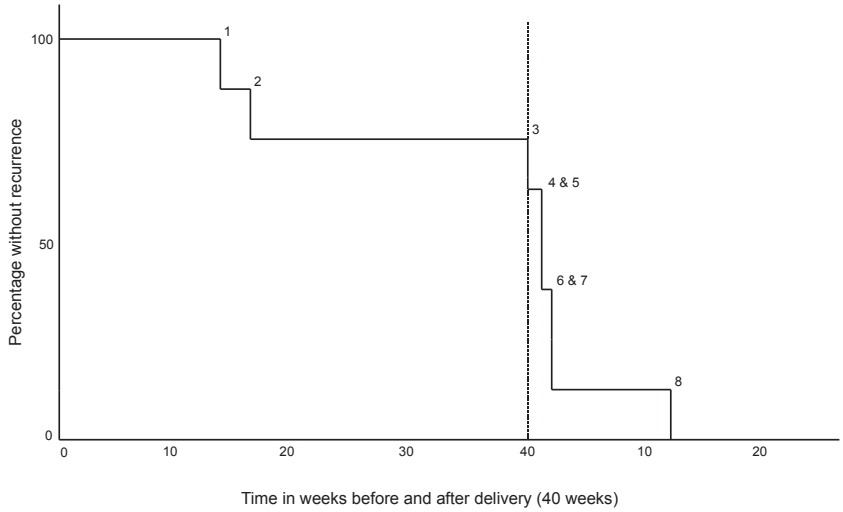
		Illness characteristics							Antidepressant specifications					Follow-up	
Case no.	Age	Parity	Age at first onset	Age at last onset	No. of episodes	Psych. co-morbidities	History of admission	Family history	Prescriber AD	BMQ nec/adv	Duration AD use	Baseline dose equiv	No. tapering attempts	Discontinued AD	No. psych care visits
1	31	1	14	14	1	2	-	-	GP	17/19	180	2.0	1	-	14
2	32	2	12	28	3	2	+	+	GP	23/21	120	3.0	1	-	18
3	37	5	17	28	3	3	-	+	GP	15/15	228	1.0	0	+	3
4	37	1	18	27	6	3	-	-	Psych	23/16	120	2.0	2	-	22
5	22	1	16	19	2	3	+	-	Psych	14/18	60	1.5	0	+	26
6	29	1	13	24	3	2	+	-	GP	21/17	96	1.0	0	-	15
7	32	1	20	27	2	2	-	+	GP	23/19	120	2.0	0	-	0
8	26	1	18	24	2	4	-	+	GP	13/18	12	1.0	1	+	15

No. = number, AD = antidepressants, BMQ = beliefs about medicines questionnaire (necessity (nec); score range 5 – 25, higher score indicates stronger belief in necessity, adverse (adv): score range 6 – 30, higher score indicates stronger belief in potential adverse consequences), (-) no/negative, (+) yes/positive, GP = general practitioner, Psych = psychiatrist

Predictors of perinatal recurrence of depression

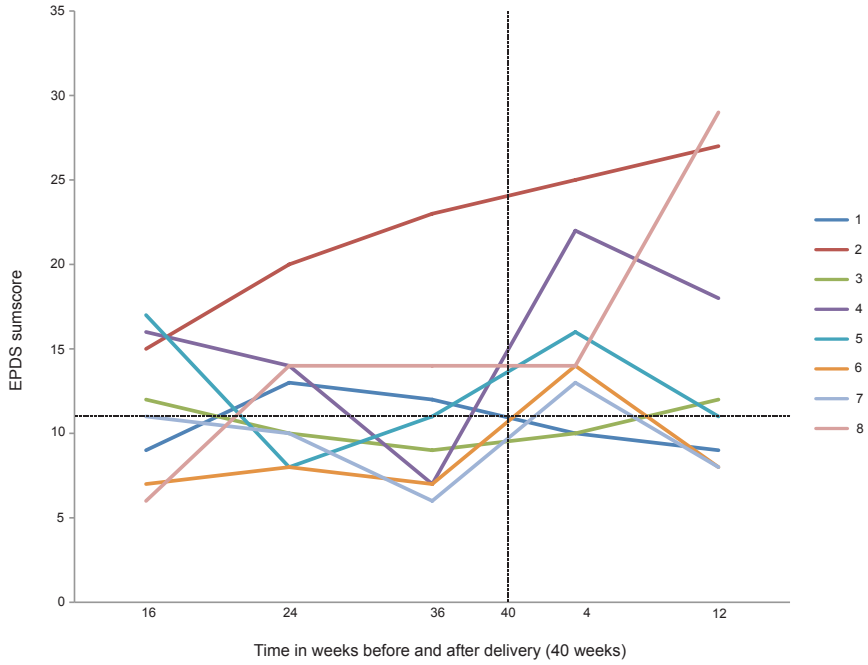
Univariable associations between the independent determinants and recurrence of depression are presented in Table 1. A higher EPDS score around 16 weeks of pregnancy (OR 1.28, 95%CI 1.08-1.52), a higher number of psychiatric co-morbidities (OR 1.89, 95%CI 1.16-3.09) and a longer duration of antidepressant use (OR 1.01, 95%CI 1.00-1.02) were associated with an increased risk of recurrence.

Figure 2. Survival curve of women with recurrence of depression in the perinatal period



Numbers in figure represent separate cases and match with case numbers listed in table 2.

Figure 3. Edinburgh Perinatal Depression Scale (EPDS) sumscore in the perinatal period



Each line represents a case with recurrence of depression. Case numbers match with case numbers listed in table 2. The horizontal dotted line represents the EPDS cut-off score.

DISCUSSION

In this prospective cohort study, 85 pregnant women with a history of depression and baseline antidepressant use were assessed for depression recurrence. In total, eight women (9.4%) experienced a recurrence of depression at follow-up. All women with recurrence had experienced their first onset of depression during childhood/adolescence and had at least two psychiatric co-morbidities. Due to the low rate of recurrence, we were only able to identify univariable predictors of recurrence. Results yielded associations for recurrence with depressive symptoms around 16 weeks of pregnancy, number of psychiatric co-morbidities and duration of antidepressant use.

Two previous observational studies investigated recurrence rates of depression in women using antidepressant during pregnancy and reported rates ranging from 68 to 16% (23, 24). Our overall recurrence rate (9.4%) is remarkably lower, despite the longer follow-up

period. Of the women discontinuing, 25% experienced recurrence compared to 7% of the women continuing. A possible explanation may be the difference in study populations. Cohen et al. (23) included women through psychiatric institutes and reported that 76.6% had three or more previous depressive episodes. In the Yonkers study (24), 38% of the women had four or more previous depressive episodes, compared to 7.1% in our population. Number of previous episodes in the general population is one of the strongest predictors for recurrence (33). Another explanation is that both previous studies reported most women had onset of recurrence in the first trimester (23, 24), whereas in our study, women with onset of recurrence in the first trimester (at start study) were excluded.

During follow-up, 14% of women completely discontinued their medication. This rate is in accordance with Dutch discontinuation rates during pregnancy as recorded in insurance and pharmacy databases (19, 34). Similar to Yonkers et al. (24), we did not find a significant effect of antidepressant discontinuation on recurrence risk.

There were some noticeable details regarding the women with recurrent depression. All eight women had a first onset of depression during childhood or adolescence, and all but one of the women had multiple depressive episodes. Age of first onset has been associated with risk of recurrence, although it is difficult to disentangle the effect of age of first onset from the number of depressive episodes, as these two are highly correlated (35). This early-onset depression has previously been associated with a more severe and chronic course of depression, often affecting women, with a longer duration of illness, more episodes, higher symptom severity, more psychiatric co-morbidity and more tendency to attempt suicide (36, 37).

Number of visits to psychiatric health care professionals during study follow-up ranged between 0 and 26 in all cases. Two women did not receive any, or only very limited, additional psychiatric healthcare, indicating that they did not receive adequate treatment for their recurrent depressive episode. This is unwanted as a review of 23 longitudinal studies found that 38% of mothers with postpartum depression (PPD) continued to have major depression during their child's first year of life and even beyond, with previous history of depression as a predictor for a chronic course of PPD (38), affecting the child as well (39). Ideally, all women would be offered additional care, even before recurrence takes place, as a recent study among adults showed that adding preventive cognitive therapy to antidepressant treatment resulted in a 41% relative risk reduction of relapse or recurrence of depression compared with antidepressants alone (40).

The analyses identified three predictors for recurrence: depressive symptoms around 16 weeks of pregnancy, number of psychiatric co-morbidities and duration of antidepressant use. In early pregnancy, five women already had an EPDS score above cut-off (27), although they did not fulfil the SCID-I criteria yet for depressive disorder. The

EPDS consists of ten questions and can thus be easily assessed in early pregnancy. International clinical guidelines encouraging routine screening for perinatal depression have been available for over a decade (41). Previous validation research of the EPDS found that a cut-off value of 11 in the first trimester, and ten in the second and third trimesters gave the most adequate combination of sensitivity, specificity, and positive predictive value (27). Clinicians may use these cut-off scores to initiate and monitor additional treatment, to prevent recurrence and decrease current symptoms of depression. The second predictor was number of psychiatric co-morbidities. Psychiatric co-morbidity has been associated with shorter time to recurrence in a non-pregnant population (42). During pregnancy, clinicians should therefore assess presence of psychiatric co-morbidities, and determine whether additional treatment targeting these co-morbidities is necessary. Lastly, a longer duration of antidepressant use was associated with recurrence. Longer duration indicates maintenance treatment, which is recommended for patients with three or more depressive episodes by international guidelines (43). However, the clinical relevance of the increased risk (OR 1.01) remains to be determined.

Strengths and limitations

A strength of the current study is that recruitment of participants took place in various settings (hospitals, midwifery practices, GP's and social media), ensuring recruitment of a representative sample. Detailed information was gathered prospectively, thereby preventing recall bias and providing insight into this specific population across the perinatal period.

However, several limitations should be noted. Due to the inclusion and exclusion criteria, only women with recurrence of depression after the first trimester were included, limiting our sample size and thereby the number of recurrences. Other vulnerable groups of women, e.g. women with a history of depressive disorder who discontinue antidepressants before pregnancy, were not observed. In the Netherlands approximately 40% of women discontinue antidepressant treatment in the year before pregnancy and even higher figures are reported in other countries (19). In the current study, women who discontinued antidepressants before pregnancy were excluded. To fully examine safety of antidepressant discontinuation, future studies should also include women discontinuing antidepressants before pregnancy. Another limitation is the limited number of women discontinuing their medication. To specifically examine the effect of discontinuation on recurrence rates, it would have been preferential to include more women discontinuing antidepressants, for example by oversampling this group. Lastly, women lost to follow-up (n=10) were excluded from the current study as information on recurrence was missing. We therefore cannot guarantee generalizability of our results.

Conclusion and future recommendations

The current study presented descriptive data on a prospective cohort of pregnant women with antidepressant use in early pregnancy and a history of depressive disorder. Three predictors for recurrence of depression were identified: depressive symptoms in early pregnancy, number of psychiatric co-morbidities and duration of antidepressant treatment. Importantly, if future studies can more robustly establish the predictive value of these variables they could easily be assessed as part of routine care procedures by clinicians. Implementing adequate and accessible risk assessment in daily practice can lead to improved individualized patient-centered care. No effect of discontinuation of risk of recurrence was observed, however, the proportion of women discontinuing medication was small and results should therefore be interpreted with caution. Future studies should aim to define additional predictors for recurrence of depression in pregnancy, assess the effects of implementing screening instruments during this phase and evaluate the effect of treatments (25) in the perinatal period in order to benefit women and (potentially) their offspring.

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PART III

Impact of mental disorders during pregnancy on the offspring

CHAPTER 8

Prenatal maternal psychopathology and stress and offspring HPA axis function at 6 years

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ABSTRACT

Introduction: Intrauterine exposures such as maternal psychopathology and stress are known to influence the physical and mental health of the offspring. One of the proposed pathways underlying these associations is dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity in the offspring. This study examined the relation of perinatal maternal symptoms of psychopathology and stress with offspring HPA axis activity at 6 years as measured by hair cortisol and cortisone concentrations.

Methods: The study was part of the population-based Generation R Study, a prospective population-based cohort from fetal life onwards. 2,546 children and their mothers formed the study population. Perinatal maternal psychopathology and stress were assessed by questionnaires in the second and third trimester. Principal components for both psychopathology and stress were created to reduce the number of explanatory variables. Child hair samples for cortisol and cortisone measurements were collected at the age of 6. Linear regression analysis, adjusted for covariates, was used to examine associations between maternal psychopathology and stress and child hair cortisol and cortisone levels.

Results: The maternal psychopathology principal component was associated with higher child hair cortisone (adjusted B = 0.24, 95%CI 0.08;0.40, p-value < 0.01). Effect estimates of the individual dimensions ranged from 0.97 (95%CI 0.21;1.73, p-value = 0.01) for interpersonal sensitivity to 1.67 (95%CI 0.86;2.47, p-value < 0.01) for paranoid ideation. In addition, children exposed to intrauterine stress, as measured by the principal component, had higher hair cortisone levels (adjusted B = 0.54, 95%CI 0.21;0.88, p-value < 0.01). Exposure to maternal psychopathology and stress was not associated with offspring hair cortisol.

Conclusion: Our results suggest that maternal psychopathology and stress during pregnancy are associated with long-term HPA axis activity of the offspring. The association of maternal psychopathology and stress during pregnancy with offspring hair cortisone levels is a novel finding. Future studies should examine whether these psychophysiological differences between exposed and non-exposed children underlie offspring morbidity associated with maternal psychopathology and stress during pregnancy.

INTRODUCTION

Many intrauterine exposures are known to influence the physical and mental health of the offspring (1, 2). Maternal psychopathology and stress during pregnancy are among the most common intrauterine exposures associated with a negative impact on the offspring's health (3, 4). Exposure to maternal psychopathology or stress during pregnancy is associated with preterm birth and low birth weight (5). In the long-term, maternal psychopathology or stress during pregnancy is related to behavioral, emotional, cognitive and motor problems in childhood (6, 7) and psychiatric disorders in adolescence (8, 9). Research examining the origins of these associations led scientists to propose models such as the 'fetal programming hypothesis' (10) or the 'developmental programming hypothesis' (2). According to these programming hypotheses, the fetus or infant adapts as a response to the health and physical state of the mother, thereby altering important physiological and metabolic processes that can endure into adulthood. The hypothalamic-pituitary-adrenal (HPA) axis is one of the major candidate systems that could be altered by adverse intrauterine exposures, especially since plasticity of the HPA axis is high during early fetal development (11, 12).

The HPA axis is the biological stress system that protects the human body from deleterious effects of acute stress. Cortisol, the end product of the HPA system, is often used to investigate HPA axis reactivity, especially in studies on psychological stress. There are several conventional methods to measure cortisol, such as saliva, blood or urine samples. These measures reflect cortisol levels at the time of sampling and are all highly influenced by daily fluctuations due to circadian rhythms and fluctuations based on homeostatic regulation (13), potentially creating methodological problems associated with collection. Conventional measures therefore reflect a 'snapshot' of HPA axis activity and may not be the most informative measure in the evaluation of long-term HPA axis activity. An increasingly used non-invasive method for detecting differences in individual's long-term stress levels is hair cortisol analysis (14-16). Cortisol extracted from hair samples reflects accumulated concentrations and can therefore give a more stable and long-term indication of HPA axis activity than saliva, blood or urine collection. Hair grows with approximately 1 centimeter per month (17), enabling assessment of mean cortisol concentrations of the last couple of months (18). Previous research showed that hair cortisol is most strongly associated with the prior 30-day integrated cortisol production measure (19), or three-day average of single-day salivary level (20), both supporting the notion that hair cortisol reflects long-term cortisol levels. Low to moderate correlations with short-term levels as single-point saliva cortisol levels were observed (20).

With the introduction of liquid chromatography tandem-mass spectrometry (LC-MS/MS) (21), the additional quantification of cortisone in scalp hair has become possible, which is metabolized from cortisol in the peripheral tissues by the 11ß-hydroxysteroid-

dehydrogenase enzyme type 2 (11ß-HSD-2), where it might act as reserve capacity for cortisol. Adding cortisone in parallel to cortisol may give even more insight into the cumulative amount of active and inactive corticosteroids in the body. Previous research showed elevated hair cortisone concentrations in young children under psychosocial stress (15). Another study even suggests salivary cortisone can provide a better reflection of systemic cortisol levels than salivary cortisol (22).

A limited number of studies have related maternal psychopathology and stress during pregnancy to changes in HPA axis functioning in the offspring, mostly in the first year of life. Maternal feelings of stress and anxiety in the last trimester of pregnancy have been measured in a prospective longitudinal study and assessed infant cortisol reactivity, measured through saliva, at 5 and 8 weeks and at 5 and 12 months of age (23); higher infant cortisol reactivity was observed in children exposed to intrauterine anxiety. Antenatal depression was analyzed in another prospective study that examined the association with infant cortisol reactivity at 2 months of age and found that infants exposed to both low and high levels of maternal depression showed greater cortisol reactivity (24). However, whether symptoms of psychopathology and stress during pregnancy affect long-term HPA axis activity in the offspring is largely unknown.

The objective of the current study was therefore to investigate whether maternal psychopathology and stress during pregnancy are associated with offspring HPA axis activity at 6 years of age. We examined several dimensions of psychopathology, including depression and anxiety, as well as different forms of experienced stress during pregnancy such as stressful life events and pregnancy-related anxiety. For long-term HPA axis activity we measured both hair cortisol and the novel biomarker hair cortisone when children were 6 years of age. We hypothesized, in line with previous short-term findings, that maternal symptoms of psychopathology and stress during pregnancy are related to heightened cortisol and cortisone levels in the offspring.

METHODS

Setting and population

The present study was embedded in an on-going population-based cohort, the Generation R Study, designed to identify early environmental and genetic causes and causal pathways leading to normal and abnormal growth, development and health from fetal life, childhood and young adulthood (25). In total, n=8880 mother were enrolled during pregnancy with deliveries from April 2002 to January 2006. The Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, approved the study. Written informed consent was obtained from all participants.

For the present explorative analysis, only children who participated in the pre- and postnatal follow-up (n=7,510) were considered (Figure 1). Of these, 1,457 children were excluded, as they did not visit the research center in childhood, when hair samples are collected. Information on maternal psychopathology and stress parameters was missing in 338 children. Hair collection did not start immediately at onset of this data collection wave and 3,161 children were not approached. The response rate for children that were approached for hair collection was 85% (26). Cortisol concentration could be quantified in 2,523 children and cortisone in 2,485 children. Extreme outliers, defined as cortisol or cortisone levels > 4SD (standard deviation), indicating contamination, were excluded. Thus, n=2,546 formed the final study population for analysis.

Maternal psychopathology

In the second trimester (at 20-25 weeks of gestation), the Brief Symptom Inventory (BSI) was administered. The BSI is a validated 53-item (5-point scale) self-report symptom inventory outlined to ascertain the psychological state of individuals in the preceding 7 days (27, 28). The BSI has nine dimensions designed to assess individual symptom groups. For this study, we used the Global Severity Index (GSI), the overall mean designed to help quantify a patient's severity-of-illness. In addition, we used the specific dimensions of the BSI: somatization, obsessive-compulsivity, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. The scores for the GSI and each dimension separately are calculated by dividing the sum of all items by the number of items. Sum scores per subscale therefore range from zero to four, with a higher score indicating more symptoms on that specific subscale.

Maternal stress

Multiple questionnaires were administered in the second and third trimester to measure different dimensions of stress, including stressful life events, long lasting difficulties, family functioning and pregnancy related stress. The Dutch-adapted version of the Social Readjusting Rating Scale (SRRS) was administered to assess the occurrence of repeated stressful life events in the preceding 12 months (29). The SRRS consists of 10 yes/no questions and items each have a certain amount of life change units (LCU). The sum score is the total of LCU's. The Long Lasting Difficulties Questionnaire (LLDQ) was administered for measurement of financial, health or social problems in the preceding 12 months (30). We used an adjusted version of the Dutch LLDQ consisting of 12 items that are scored on a 5-point scale. Maximum score per item is 3, leading to a sum score between 0 and 36. The Family Assessment Device (FAD) was administered to evaluate dimensions of family function (31). In this study, we applied the General Family functioning subscale, which consists of 12 items rated on a 4-point scale. This subscale assesses the overall health and

pathology of the family. The sum score is the mean of the items scores and therefore has a value between 1 and 4. A score above 2.17 is seen as pathological. To measure stress/anxiety concerning the pregnancy and the baby, a Dutch adapted version of the Pregnancy Outcome Questionnaire (POQ) was administered consisting of 13 items, rated on a 4-point scale, with a maximum score of 3 per item (32). The sum score is the mean of the item scores and is therefore a value between 0 and 3.

Hair cortisol/cortisone

For extraction of hair cortisol and cortisone, hair samples of approximately 100 strands were cut from the posterior vertex using small surgical scissors, as close to the scalp as possible. Hair locks were then taped to a piece of paper with the scalp end marked, and stored in an envelope at room temperature until further analysis. Briefly, the proximal 3 cm of hair samples were weighed using an electrical scale and minced. Hair samples were then washed in LC-grade isopropanol for 2 minutes at room temperature, and left to dry for at least 2 days. Deuterium labeled cortisol and cortisone were added prior to extraction. Extraction was performed using LC-grade methanol for 18 hours at 25° Celsius, in a gently shaking water basin. The extract was then transferred to a glass tube, centrifuged at 4300 g (gravity), and evaporated to dryness at 37° Celsius under a constant flow of N_2. After reconstitution in 1 ml 2% LC-grade methanol, the extract was loaded on an offline solid phase extraction plate (HLB Oasis 96-well SPE plate, Waters Chromatography), washed with 1 ml 30% LC-grade methanol, and eluted twice in 300 µl 100% LC-grade methanol. The extract was then evaporated to dryness at 50° Celsius under a constant flow of N_2 and stored at 4° Celsius until further analysis. Prior to analysis, the samples were reconstituted in 100 µl eluent (running fluid), mixed using a vortex mixer, and analyzed using LC-MS/MS (Xevo TQS, Waters Chromatography) (33).

Covariates

Potential covariates were selected based on prior research (23, 24, 33). Age, marital status, parity, gender child, ethnicity, hair color of child, education, family income, number of persons in a household and alcohol and smoking behavior were based on self-report. Marital status was dichotomized into 'married, registered partnership or living together' versus 'no partner'. Maternal ethnicity was categorized according to the classification of Statistics Netherlands (34, 35). Educational level was categorized in three levels: primary, secondary and higher education (35). Family income was defined as the total net monthly income of the household, categorized as less than € 1200 (US $1551) (below social security level), € 1200 to € 2000 (US $1551-US $2586), and more than € 2000 (US $2586) (more than modal income). Information about maternal prenatal alcohol use and smoking was based on questionnaires in each trimester.

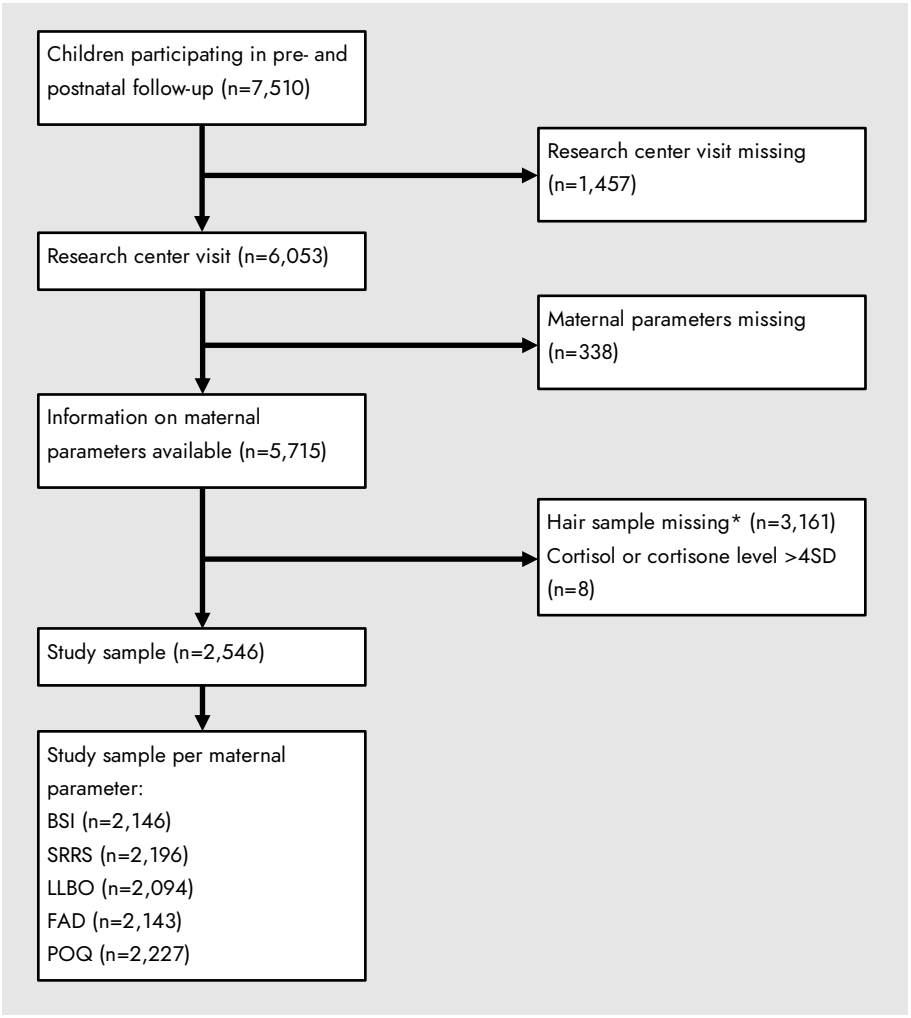
Statistical analyses

First, descriptive statistics of the study population were provided. Data was explored using histograms and calculating correlations between the different psychopathology and stress measures. The correlation of the subscales of the BSI were moderately to strongly correlated ($0.45 < r < 0.78$), while the stress parameters (SRRS, LLDQ, FAD and POQ) during pregnancy only showed weak to moderate correlations ($0.15 < r < 0.37$). Hair cortisol and cortisone measurements showed a strong correlation ($r = 0.66$).

To reduce the number of explanatory variables tested, we performed principal component analysis (PCA) in two groups: psychopathology (BSI subscales) and stress (SRRS, LLDQ, FAD and POQ). PCA is a statistical technique to convert a set of observations of possibly correlated variables into a set of values of linearly uncorrelated variables called principal components. To check if we can factorize the original variables efficiently we used the Bartlett's sphericity test and the Kaiser-Mayer-Olkin index. Both indicated our data was suitable for PCA. Subsequently, we performed principal component regression with the retrieved principal components with an eigenvalue above one. For the psychopathology group, one principal component was retrieved with component loadings of the items between 0.74 and 0.90. For the stress parameters, one principal component with item loadings between 0.64 and 0.80 was retrieved. Only when an association between the principal component and outcome variable was observed (as defined by a p-value <0.05), linear regression analysis was used to examine the relations of the individual psychopathology and stress measures with the outcome variable as to further examine the contribution of each individual measure.

Based on the 5% change-in-estimate (36), we corrected for the following confounders: marital status, parity, ethnicity, education, family income, number of people in a household and alcohol behavior. The other covariates, namely age, gender child, hair color of child and smoking behavior, did not reach a 5% change-in-estimate. On average, 4.5% of data across the covariates was missing. To avoid complete case analysis bias, we accounted for missing information on the confounders (determinants and outcomes were not imputed) by using multiple imputation methods. As recommended, imputations were based on the relations between all variables in the study (37). We report only the pooled estimates of the analysis of the 10 imputed datasets. Analysis with non-imputed data gave similar results compared to the imputed dataset. Statistical Package for Social Sciences (SPSS) version 25.0 was used for data analysis.

Figure 1. Flowchart of study sample



*Hair collection did not start immediately at onset of this research wave. The response rate for children asked for hair collection was 85%.

Table 1. Descriptive characteristics of the study population

Characteristics	n = 2,546	Characteristics	n = 2,546
Age, mean (SD)	30.5 (5.0)	Smoked throughout pregnancy	366 (15.7)
Parity, median (range)	0 (0 – 6)	Household income (%)	
Marital status (%)		< € 1200	165 (7.5)
No partner	282 (11.6)	€ 1200 – 2000	320 (14.5)
Married, registered or living together	2157 (88.4)	> € 2000	1724 (78.0)
Ethnicity (%)		Number of people in household, mean (SD)	2.2 (0.8)
Dutch	1353 (53.6)	Maternal psychopathology during pregnancy, median (range)	
Turkish	241 (9.5)	Somatization	0.3 (0 – 4)
Moroccan	161 (6.4)	Obsessive-compulsive	0.4 (0 – 3.8)
Cape Verdean	82 (3.2)	Interpersonal sensitivity	0 (0 – 3.8)
Dutch Antillean	46 (1.8)	Depression	0 (0 – 3.8)
Surinamese	196 (7.8)	Anxiety	0.2 (0 – 4)
Other Western	223 (8.8)	Hostility	0.2 (0 – 4)
Other Non-Western	223 (8.8)	Phobic anxiety	0 (0 – 3.8)
Educational level mother (%)		Paranoid ideation	0 (0 – 3.8)
Primary education / none	232 (9.5)	Psychoticism	0 (0 – 3.4)
Secondary education	1027 (42.0)	Global Severity Index	0.2 (0 – 3)
Higher education	1189 (48.6)	Maternal stress during pregnancy, median (range)	
Drinking habits (%)		Social Readjusting Rating Scale	0 (0 – 474)
Never drank in pregnancy	1064 (44.6)	Long Lasting Difficulties Questionnaire	1.0 (0 – 27)
Drank in early pregnancy	344 (14.4)	Family Assessment Device	1.4 (1 – 3.7)
Drank throughout pregnancy	975 (40.9)	Pregnancy Outcome Questionnaire	0.8 (0 – 2.4)
Smoking habits (%)		Child hair measurements, median (range)	
Never smoked in pregnancy	1755 (75.1)	Cortisol in pg/mg	1.6 (0.1 – 70.1)
Smoked in early pregnancy	217 (9.3)	Cortisone in pg/mg	7.6 (0.1 – 44.0)

Table 2. Linear regression analysis of psychopathology and stress on cortisone

Maternal predictors	Unadjusted, β (95% CI)	p-value	Partially adjusted[1], β (95% CI)	p-value	Fully adjusted[2], β (95% CI)	p-value
Principal component – psychopathology	0.22 (0.10;0.34)	< 0.01	0.18 (0.06;0.31)	< 0.01	0.18 (0.05;0.31)	< 0.01
Psychopathology (BSI)						
Overall psychopathology	1.77 (1.00;2.54)	< 0.01	1.49 (0.67;2.31)	< 0.01	1.48 (0.64;2.32)	< 0.01
Somatization	1.37 (0.76;1.99)	< 0.01	1.08 (0.41;1.75)	< 0.01	1.05 (0.37;1.73)	< 0.01
Obsessive-compulsive	0.64 (0.09;1.18)	0.02	0.55 (-0.01;1.10)	0.05	0.54 (-0.02;1.10)	0.06
Interpersonal Sensitivity	0.95 (0.36;1.53)	< 0.01	0.76 (0.16;1.36)	0.01	0.73 (0.13;1.34)	0.02
Depression	0.99 (0.38;1.60)	< 0.01	0.79 (0.16;1.43)	0.01	0.78 (0.13;1.43)	0.02
Anxiety	1.25 (0.64;1.86)	< 0.01	1.00 (0.35;1.64)	< 0.01	0.98 (0.32;1.63)	< 0.01
Hostility	1.15 (0.47;1.83)	< 0.01	0.87 (0.16;1.58)	0.02	0.87 (0.15;1.59)	0.02
Phobic Anxiety	1.47 (0.64;2.31)	< 0.01	1.16 (0.28;2.03)	< 0.01	1.07 (0.19;1.95)	0.02
Paranoid Ideation	1.36 (0.75;1.97)	< 0.01	1.14 (0.51;1.78)	< 0.01	1.15 (0.50;1.80)	< 0.01
Psychoticism	1.60 (0.76;2.43)	< 0.01	1.32 (0.45;2.20)	< 0.01	1.28 (0.39;2.16)	< 0.01
Principal component - stress	0.50 (0.26;0.73)	< 0.01	0.48 (0.21;0.74)	< 0.01	0.51 (0.23;0.79)	< 0.01
Stress						
Social Stress (SRRS)	0.01 (0.00;0.01)	0.01	0.00 (-0.00;0.01)	0.05	0.00 (0.00;0.01)	0.08
Long-lasting stress (LLBQ)	0.18 (0.09;0.26)	< 0.01	0.17 (0.08;0.26)	< 0.01	0.18 (0.09;0.28)	< 0.01
Family functioning (FAD)	0.45 (-0.16;1.05)	0.15	0.10 (-0.54;0.75)	0.76	0.04 (-0.62;0.70)	0.90
Pregnancy specific anxiety (POQ)	1.12 (0.34;1.89)	< 0.01	0.85 (0.01;1.69)	0,05	0.77 (-0.08;1.63)	0.08

BSI = Brief Symptom Inventory, GSI = Global Severity Index, SRRS = Social Readjustment Rating Scale, LLBQ = Long Lasting Difficulties Questionnaire, FAD = Family Assessment Device, POQ = Pregnancy Outcome Questionnaire. 1. Adjusted for: ethnicity, education level, parity, alcohol use. 2. Adjusted for: ethnicity, education level, parity, alcohol use, marital status, family income, number of people in household.

RESULTS

Descriptive statistics

Prenatal and postnatal characteristics of the study population are shown in table 1. Mean age of women at study inclusion was 30.5 years and the majority of women were primigravida. Due to the urban character of the study, a variety of ethnicities were present, with a little over half of the participants being Dutch. About half of the population had a higher education (48.5%). Median symptoms of psychopathology and stress during pregnancy were low, as to be expected in a population-based study.

Prenatal exposure to psychopathology and stress and child hair cortisol

The analysis of the maternal psychopathology principal component initially showed an association with child hair cortisol levels (B = 0.17, 95%CI 0.05;0.29, p-value < 0.01). However, this association was largely explained by confounding factors (adjusted B = 0.11, 95%CI -0.02;0.24, p-value = 0.10). The same was observed for the maternal stress principal component: the unadjusted association of the maternal stress principal component with child hair cortisol (B = 0.33, 95%CI 0.09;0.56, p-value < 0.01) attenuated after adjustment for confounders (adjusted B = 0.23, 95%CI -0.05;0.51, p-value = 0.11).

Prenatal exposure to psychopathology and stress and child hair cortisone

Table 2 demonstrates the results of the linear regression models of maternal psychopathology and stress during pregnancy and child hair cortisone levels. There was an association of overall maternal psychopathology during pregnancy with child hair cortisone (B = 0.22, 95%CI 0.10;0.34, p-value < 0.01), which remained present after adjustment for confounders (adjusted B = 0.18, 95%CI 0.05;0.31, p-value < 0.01). Additionally, table 2 shows that effect estimates of the different maternal psychopathology scales during pregnancy and child hair cortisone ranged from 0.54 (95%CI -0.02;1.10, p-value = 0.06) for obsessive-compulsive symptoms and child hair cortisone to 1.28 (95%CI 0.39;2.16, p-value < 0.01) for psychoticism and child hair cortisone.

The stress principal component was also associated with child hair cortisone, both before (B = 0.50, 95%CI 0.26;0.73, p-value < 0.01) and after adjustment for confounding factors (adjusted B = 0.51, 95%CI 0.23;0.79, p-value < 0.01). Subsequent analysis of all individual stress measures in relation to child hair cortisone pointed out that the association was largely driven by long-lasting difficulties (adjusted B = 0.18, 95%CI 0.09;0.28, p-value < 0.01).

DISCUSSION

In this population-based study, we found that maternal symptoms of psychopathology during pregnancy were associated with hair cortisone levels in children 6 years of age. Higher levels of symptoms on different psychopathology subscales prenatally were associated with increased levels of child hair cortisone. Additionally, we found an association of maternal symptoms of stress during pregnancy, in particular long-lasting difficulties, with child hair cortisone. In contrast, the exposure to maternal symptoms of psychopathology and stress during pregnancy was not related to child hair cortisol levels. However, the direction of the effect on cortisol, while not significant, was similar to that of cortisone.

Previous studies examining exposure to prenatal psychopathology and stress and child HPA axis functioning mostly use salivary cortisol, which is more susceptible to daily fluctuations than the hair cortisol measurement used in the present study. These prior studies have shown higher cortisol levels in children exposed to intrauterine psychopathology (24, 38). For example, a prospective study performed among 133 infants in India showed infants exposed to the highest levels of maternal depressive symptoms during intrauterine life had elevated salivary cortisol responses to immunization at 2 months of age (24). Another study among 29 mother-child pairs showed children whose mothers had pregnancy specific anxiety showed higher levels of salivary cortisol on school days at 5 years of age (38). Contrary to our expectations that were based on prior literature, we found no associations of prenatal maternal psychopathology and stress with hair cortisol levels in children 6 years of age. The discrepancy could originate from the difference in measurement method of cortisol. Salivary cortisol reflects the level at the time of sampling. In both prior studies (24, 38), cortisol was measured after induction of a stressor to measure the stress response reaction. Cortisol assessed from hair samples is a more stable long-term stress indicator, not dependent on stressors during sampling (16). Possibly, intrauterine exposure to maternal psychopathology and stress influences the immediate stress response but not long-term (basal) cortisol levels.

As expected, higher levels of hair cortisone in children exposed to intrauterine psychopathology and stress were observed in the present study. Especially long-lasting difficulties were associated with child hair cortisone levels, indicating that chronicity of stress might have a greater influence than other forms of stress such as single stressful events. Interest in the use of hair cortisone as an additional biomarker to cortisol for psychopathology and stress has recently increased. Cortisone, conversed from cortisol by the 11ß-hydroxysteroid-dehydrogenase enzyme type 2, has been shown to be higher than cortisol in hair of children (39), just as in our study, and might therefore be a more sensitive measure of HPA axis activity than cortisol. For example, one previous prospective

cohort study has examined the influence of stress in children on hair cortisone levels (15). Hair cortisone levels of 168 elementary school girls (5 to 10 years old) were measured and child-reported stress was obtained through questionnaires. Associations of increased hair cortisone and concurrent stressful events were observed. Another recent study among 62 pregnant women evaluated the association between maternal symptoms of depression, somatization and stress and maternal hair cortisol and cortisone levels and observed stronger associations with hair cortisone than with hair cortisol (40). To our knowledge, there are no studies that examined intrauterine exposure to maternal psychopathology and stress and influence on child hair cortisone levels. An explanation for our findings – increased cortisone levels but an absence of increased cortisol levels – is therefore not readily available. Further research has to examine influence of 11ß-HSD-2 activity and corticoid binding globulin (CBG) levels or affinity resulting in different concentrations of free corticosteroids and thus influencing incorporation of cortisol and cortisone into hair from the bloodstream.

Mechanisms of HPA axis alteration

The exact underlying mechanisms of HPA axis alteration in the offspring are still unclear, although previous studies have attempted to examine potential pathways involved. The fetal programming hypothesis suggests that the fetus responds to intrauterine exposure, in this case psychopathology or associated high levels of maternal cortisol, with altered physiological and metabolic processes as preparation for the anticipated postnatal environment (10). High levels of maternal cortisol reaching the fetus could either be the result of extreme maternal stress, overriding the capacity of placental 11ß-HSD-2 to convert cortisol into the inactive metabolite cortisone and thereby accumulating cortisol, or the result from altered expression of 11ß-HSD-2 in the placenta, as maternal psychopathology and stress during pregnancy have been associated with down regulation of 11ß-HSD-2, leading to active transfer of maternal cortisol into fetal circulation (41, 42). A promising biological mechanism for the fetus' response to high maternal cortisol is epigenetic programming of the HPA axis (43, 44). Candidate genes such as FK506-binding protein 51 (FKBP51) and the glucocorticoid receptor gene NR3C1 have been associated with HPA axis functioning and glucocorticoid sensitivity and susceptibility of psychiatric disorders (45-47). Altered methylation of these genes could alter the HPA axis activity in the offspring (44). Yet, not all variation can be attributed to these epigenetic findings and thus examining of other additional mechanisms is desired.

Strengths and limitations

Primary strengths of the study are the large population-based sample, the prospective nature of the study and the ability to take many confounders into account. Another strength

of the current study is the used method of the hair corticosteroid measurements, as performed with the state-of-the-art LC-MS/MS based method. A known limitation of hair corticosteroid measurement is that over time hormone levels may decrease in parts of the hair samples that are most distal from the scalp. However, we used the proximal three cm and there is agreement that the wash-out decline occurs only after a time span of 3 to 6 months (48). Despite the strengths of our study, there are some limitations that need to be discussed. We only used self-reported information of maternal psychopathology symptoms and stress during pregnancy. It was not feasible to perform diagnostic interviews in such a large cohort. In addition, not all dimensions of stress, e.g. work-related stress, were measured in the current study, even though we used multiple questionnaires to assess stress. Next, women with symptoms of psychopathology and stress during pregnancy potentially experienced symptoms of psychopathology and stress over a longer period of time after pregnancy, influencing stress levels of the offspring. The current study did not correct for postnatal psychopathology and stress and future studies should focus on the influence of chronicity of stress. Additionally, no assessment of experienced stressful events in the children in the three months before collection of the hair sample was available, which could have caused increased stress and thus cortisol levels in the children. Finally, selection bias and residual confounding cannot be ruled out, and thus results must be interpreted carefully.

Conclusion and future recommendations

In the current study an association was observed between maternal psychopathology and stress during pregnancy and hair cortisone levels in children 6 years of age, suggesting alterations in long-term HPA axis activity in children exposed to maternal psychopathology and stress during pregnancy. Altered HPA axis functioning may increase susceptibility for physical disease and mental health problems in later life (49, 50). Nevertheless, we must be careful when interpreting these results and infer causality. The use of hair cortisone as a valid biomarker should be further established and future studies should examine whether these psychoendocrinological differences between exposed and non-exposed children underlie offspring morbidity associated with maternal psychopathology and stress during pregnancy.

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CHAPTER 9

General discussion

GENERAL DISCUSSION

This thesis discusses several aspects of the use of antidepressants in the perinatal period. In **Part I** of this thesis we evaluated the translation of previous findings concerning antidepressant use in the perinatal period into current practice. We reviewed current internationally available guidelines and assessed adherence to the Dutch guideline by gynecologists and midwives. Additionally, we mapped dispensing patterns of antidepressants in the perinatal period throughout the years and examined the influence of the introduction of the guideline on dispension patterns. In **Part II** we outlined the design of a randomized controlled trial (RCT) for testing the efficacy and safety of discontinuation of antidepressants during pregnancy. We also presented our first results from the observational cohort of the Stop or Go trial, which ran parallel to the RCT. **Part III** focused on the influence of (untreated) symptoms of psychopathology during pregnancy on child outcomes from a biological perspective. Detailed descriptions on main results and shortcomings of the studies were discussed in the previous chapters. This chapter will provide a general discussion of all main findings, methodological considerations, implications for further research and a final conclusion.

MAIN FINDINGS

1. What do internationally available guidelines recommend when it comes to treatment of perinatal depression and/or the perinatal use of antidepressants?

In **chapter 3** we reviewed sixteen Clinical Practice Guidelines (CPGs) of which eight were perinatal specific. We compared recommendations regarding continuation or withdrawal of antidepressants in the perinatal period and preferred treatment options in newly depressed patients. Four guidelines advised to continue antidepressants during pregnancy and five guidelines did not specifically advise or discourage continuation. For new episodes of depression, guidelines agree on psychotherapy as initial treatment for mild to moderate depression and antidepressants for severe depression, with a preference for sertraline. Paroxetine is not preferred treatment for new episodes but switching antidepressants for ongoing treatment is discouraged by three guidelines.

2. Are Dutch gynecologists and midwives aware of the Dutch guideline on antidepressant use during pregnancy and do they adhere to this guideline?

Self-reported familiarity of Dutch gynecologists and midwives with the guideline was 92.7%. However, current practice and advice given to patients by caregivers differed substantially, both between gynecologists and midwives as well as within both professions.

Overall guideline adherence was 13.9%. We examined what caregiver characteristics influenced guideline adherence and found only profession to be of importance; gynecologists reported a higher adherence rate to the guideline (OR 2.1, 95%CI 1.02-4.33) than midwives.

3. In what way have Dutch perinatal dispensing patterns of antidepressants developed over time and to what extent was the introduction of the guideline of influence?

From 1999 to 2014 a persistent significant rise of dispensing rates of selective serotonin reuptake inhibitors (SSRIs) at preconception, in pregnancy and childbed was observed. The largest increase was observed during pregnancy: in 1999/2000 0.8% of pregnant women were using SSRIs compared to 2.1% of pregnant women in 2013/2014. Additionally, we observed a substantial change of practice in terms of the SSRI used. Over time, the relative number of paroxetine dispenses decreased steeply (from 58.5% to 27.6%), and especially citalopram and sertraline showed an increase. With time, less women using SSRIs in the year before pregnancy discontinued medication during pregnancy (from 81% in 1999/2000 to 54% after 2012). None of these patterns seemed affected by the introduction of the Dutch guideline in 2012.

4. With what design can we examine the efficacy and safety of discontinuation of antidepressants during pregnancy?

Despite considerable scientific efforts to obtain evidence on the risks and benefits of antidepressant use in the perinatal period, the evidence available is unequivocal. Published studies are usually retrospective, arguably selective, and in part inevitable due to the ethical demands of research in this context. For a better evidence-based decision on antidepressant continuation or discontinuation during pregnancy, results from randomized controlled trials (RCT) are needed. In **chapter 6** we therefore gave a detailed description on the first RCT internationally performed. The Stop or Go study is a pragmatic multi-centre non-inferiority RCT in which women were randomly allocated into two groups: STOP or GO. Women assigned to discontinuation of antidepressants (STOP) were referred to a physician for guided tapering of their antidepressants. Trained psychologists provided preventive cognitive therapy in the discontinuation arm. Women assigned to continuation of antidepressants (GO) obtained usual care. Both groups received regular assessments throughout their pregnancy and up to three months postpartum.

5. Which women with antidepressant use during pregnancy have recurrence of depression in the perinatal period?

From a clinical perspective, it is valuable to be able to recognize which pregnant women using antidepressants are at risk for recurrence of depression. With this knowledge, clinicians will be able to inform patients about their potential risks and arrange additional guidance when necessary, thereby promoting individualized patient-centered care and potentially avoiding negative effects on the offspring. In **chapter 7** we analyzed 85 pregnant women with antidepressant use at start of their pregnancy and a history of depression. Eight women (9.4%) experienced a recurrence of depression; two during pregnancy and six in the first 12 weeks postpartum. All women with recurrence of depression had first onset of depression during childhood or adolescence and had at least 2 psychiatric co-morbidities. Due to the limited number of events we chose to identify predictors for recurrence univariably. This yielded associations for recurrence with depressive symptoms around 16 weeks of pregnancy (OR 1.28, 95%CI 1.08-1.52), number of psychiatric co-morbidities (OR 1.89, 95%CI 1.16-3.09) and duration of antidepressant use (OR 1.01, 95%CI 1.00-1.02).

6. Is maternal psychopathology and stress during pregnancy associated with long-term HPA axis activity in the offspring?

In **chapter 8** we described the results from our study within the population-based Generation R cohort. Our results suggest that maternal psychopathology and stress during pregnancy are associated with long-term HPA axis activity of the offspring. We used both hair cortisol and cortisone to measure HPA axis activity and observed higher hair cortisone levels in children exposed to intrauterine psychopathology (adjusted B = 0.18, 95%CI 0.05;0.31, p-value < 0.01) and stress (adjusted B = 0.51, 95%CI 0.23;0.79, p-value < 0.01). No association with offspring hair cortisol was found.

PART I: PERINATAL USE OF ANTIDEPRESSANTS

In this thesis we demonstrated that internationally available Clinical Practice Guidelines (CPGs) had general consensus on what is considered 'best clinical practice', but differed in other recommendations throughout the perinatal period. While CPGs are developed to facilitate decision-making and optimize patient-care (1), some of the reviewed CPGs gave scarce direction for treatment management. Overall, the guidelines have good quality (2), but most CPGs were not specifically developed for pregnant women. In our review, only eight guidelines were perinatal specific. For our review, we did not include Clinical Consensus Statements (CSSs) because they are not developed in accordance with the

same quality criteria as CPGs. CSSs reflect the expert views of a panel of individuals who are well versed on the topic of interest while carefully examining and discussing the scientific data available. Recommendations by CSSs might differ from those given in CPGs. In clinical practice, CSSs and other guiding documents are frequently used instead of the formal guidelines and might contain a higher level of detail.

Adherence to the Dutch guideline was examined in more detail with a cross-sectional study amongst gynecologists and midwives. Although self-reported familiarity with the guideline was high (92.7%), self-reported guideline adherence was low (13.9%). Non-adherence can result in conflicting advice to patients from different caregivers, creating a potentially difficult situation for vulnerable women. Especially since the same variation in advice was reported previously in a survey amongst Dutch General Practitioners (GPs) (3). Compared to adherence to guidelines on not pregnancy-related topics, our observed adherence rate was substantially less (4). However, previous research examining adherence amongst midwives to obstetric guidelines showed equally low adherence rates (5, 6). In our study, professional-related characteristics and perceptions did not explain a significant part of variance in non-adherence. A limitation of our study is that often-reported barriers for guideline non-adherence, such as patient preference or professional's personal experience, were not assessed in this study (4, 7). Another limitation is the size and representativeness of our study population, since it was not possible to send an invitation to all caregivers individually.

In our last chapter of part I, we presented population-based information on antidepressant dispensing and dispensing patterns related to the pregnancy phases over 16 years (1999-2015) in the Netherlands. We observed a general trend of increased SSRI use in the year before pregnancy, during pregnancy and in the year following pregnancy, a substantial change of practice with regard to continuation over time, and a changed pattern in terms of particular SSRI used. Prescription rates before, during and after pregnancy in the Netherlands were comparable to Denmark and Italy, but prescription rates in the UK and the USA were considerably higher (9.6% in the UK in the year before pregnancy and 13.4% in the USA during pregnancy) (8, 9). A trend towards more continuation of antidepressants into pregnancy is observed over the years, without an obvious change in trend after introduction of the Dutch guideline, which recommends continuation of SSRIs if women are stable on this medication and psychiatric indication is correct. The size and composition of the pharmo-perined cohort is a major strength of this study, but we also encountered some limitations. Exact timing of drug dispensing was unknown, making it impossible to analyze subtler discontinuation patterns. A more general limitation when using an administrative dispensing database is the relation of dispensing to actual use. There might have been an overestimation of use if women do not adhere to the prescribed regimen.

PART II: THE STOP OR GO TRIAL

The Stop or Go trial was both a randomized controlled trial (RCT) and an observational cohort trial. In **chapter 6** we therefore gave a detailed description on the first RCT internationally performed on continuing or tapering antidepressant medication during pregnancy in mentally stable women with a history of depression. Previously, only observational studies examining discontinuation of antidepressants during pregnancy have been performed, as many regarded a RCT not medically-ethically justified (10, 11). Results of the Stop or Go RCT are not published in this thesis, as the study is still ongoing.

In **chapter 7**, we presented our first Stop or Go observational cohort data. In this study we followed 85 women with a history of depression and antidepressant use at start of the study. Eight women (9.4%) experienced a recurrence of depression. Our overall recurrence rate is remarkably lower than two previous studies reporting recurrence rates of depression amongst women with antidepressant use during pregnancy (43% and 16%) (10, 11). Differences in recurrence rates may be due to differences in the study populations, as mean number of previous depressive episodes was lower in our population and number of previous episodes in the general adult population has been found to be one of the strongest predictors for recurrence of depression (12). Although six out of eight women with recurrence of depression received psychiatric health care in the perinatal period, two women did not receive, or only very limited, additional psychiatric health care, indicating that they did not receive treatment for their recurrence of depression. This is unwanted as a review of 23 longitudinal studies found that 38% of mothers with postpartum depression (PPD) continued to have major depression during their child's first year of life and even beyond, with a previous history of depression as a predictor for a chronic course of PPD (13). The impact of maternal postpartum depression on the developing infant is by now well established (14). However, compared to health care seeking behavior among pregnant women with mental illness in the US, the percentage of women receiving care in the current study was high (15, 16).

To identify risk factors for recurrence of depression, we use univariable logistic regression, resulting in three predictors for recurrence of depression; EPDS score at 16 weeks of pregnancy, number of psychiatric co-morbidities and duration of antidepressant use. At baseline, five cases already had an EPDS score above cut-off (17), although they did not fulfill the criteria yet for depressive disorder according to the SCID. The EPDS consists of ten questions and can thus be easily assessed in early pregnancy. Guidelines encouraging routine screening for perinatal depression have been available for over a decade (18). Previous validation research of the EPDS found that a cutoff value of 11 in the first trimester and that of 10 in the second and third trimesters gave the most adequate combination of sensitivity, specificity, and positive predictive value (17). Methodologically the major limitation of our study was the number of recurrences during follow-up. For an

extensive prediction model with several predictors, more events would need to have taken place. Due to the limited number of events we chose to identify predictors for recurrence univariably. However, we might have missed other important risk factors and results must be interpreted with caution.

PART III: IMPACT OF MENTAL DISORDERS DURING PREGNANCY ON THE OFFSPRING

In the final part of this thesis our focus was not on treatment of mental illness during pregnancy but on (untreated) symptoms of mental illness during pregnancy and associated risks for the offspring. Previous research has found an array of adverse birth outcomes (19-22) and several underlying pathways have been proposed (23-25). In **chapter 8** we examined the effect of intrauterine exposure to maternal psychopathology and stress on long-term HPA axis functioning in the offspring. We observed that children exposed to intrauterine symptoms of psychopathology and stress had increased hair cortisone levels. Overall, hair cortisone levels have not often been investigated, but interest in hair cortisone as additional biomarker to hair cortisol has recently increased. For example, one previous prospective cohort study has examined the influence of stress in children on hair cortisone levels (26). Hair cortisone levels of 168 elementary school girls (5 to 10 years old) were measured and child-reported stress was obtained through questionnaires. Positive associations were observed between hair cortisone and stressful events over the past 6 months. Another recent study among 62 pregnant women evaluated the association between symptoms of depression, somatization and stress and hair cortisol and cortisone levels (27) and observed stronger associations with hair cortisone than with hair cortisol. In our study, we did not find associations between maternal psychopathology and stress during pregnancy and offspring hair cortisol levels. Previous studies did find increased salivary cortisol levels in children with intrauterine exposure to maternal psychopathology (28, 29). This discrepancy could, among others, originate from the difference in measurement method of cortisol (saliva versus hair). Cortisol assessed from hair samples is a more stable long-term stress indicator, not dependent on stressors during sampling. Possibly, intrauterine exposure to maternal psychopathology and stress influences the immediate stress response but not long-term (basal) cortisol levels. The most apparent limitation of our study is the measurement method of maternal psychopathology and stress. We only used self-reported information of maternal psychopathology symptoms and stress during pregnancy. It was not feasible to perform diagnostic interviews in such a large study. In addition, not all dimensions of stress, e.g. work-related stress, were measured in the current study, even though we used multiple questionnaires to assess stress.

CLINICAL AND RESEARCH IMPLICATIONS

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

- Review of the internationally available CPGs outlines the need for up-to-date and perinatal-specific CPGs to help clinicians and patients in decision-making. It is challenging to develop these CPGs because evidence-based medicine, personalized medicine and legal liabilities need to be balanced. This overview can serve as a clear starting point for further development of internationally congruent guidelines to improve consistent patient guidance independent of country and setting. The review also helps to identify gaps in current evidence, since guidelines do not disclose recommendations on emerging clinical questions. For example, none of the guidelines discusses treatment options for patients with current depressive symptomatology despite antidepressant use. Future research should focus on these gaps and on finding answers to emerging clinical questions.
- Although guideline familiarity is high, adherence amongst both Dutch gynecologists and midwives is low. This can result in treatment management recommendations that are not in line with evidence based clinical guidelines. Also, patients can encounter conflicting advice from different caregivers, which is unwanted in this vulnerable population. Qualitative research should explore reasons for guideline non-adherence and stimulate further implementation of the guideline, and thus more congruent care, in daily clinical practice. Additionally, the Dutch guideline has to be reviewed critically as the recommendations differ from recommendations of CPGs from other countries. Meanwhile, more conclusive underlying evidence has to emerge on harms and benefits of antidepressants during pregnancy in order to improve internationally available perinatal specific guidelines. Prospective (observational) research has to be initiated collecting data on not only antidepressant use but also on psychiatric history and current psychiatric features in order to adjust for confounders.
- From 1999 to 2015 there has been a substantial and significant increase in use of antidepressants in the perinatal period. Additionally, a change towards continuation rather than quitting antidepressant use if women get pregnant is observed. Despite a substantial shift in drug preference, paroxetine is still most commonly used during the perinatal period in the Netherlands, while in the Nordic countries, paroxetine is the least prescribed SSRI during pregnancy. Future research should elicit whether this implicit 'vote' in favor of antidepressant treatment is justified and if so, what these justifiable factors are. We would have to examine whether this increase in antidepressant treatment

has accomplished a decrease in perinatal psychiatric disease. Also, effectiveness of antidepressant treatment compared to non-pharmacological treatment has to be investigated in prospective settings. Differences in prescription rates between countries should be investigated based on population-based prescription rates over the past decades, as well as their connection to local policy and adherence to locally available guidelines.

- Pregnant women with antidepressant use risk recurrence of depression in the perinatal period. Three risk factors for recurrence of depression that are easily assessed by the clinicians guiding women in their pregnancy, such as midwifes, obstetricians, psychiatrists and general practitioners, are EPDS score in early pregnancy, number of psychiatric co-morbidities and duration of antidepressant use. Clinicians should use the EPDS and can use the validated cut-off scores to initiate immediate additional treatment, to prevent recurrence but also to decrease symptoms of depression and possibly anxiety or stress, which can negatively affect child outcomes. Clinicians without training in mental health care, such as midwifes and obstetricians, should refer their patients to a specialized health care professional, such as a psychiatrist or psychologist, preferable with extensive knowledge on the perinatal period. The same applies for assessing the presence of psychiatric co-morbidities; when co-morbidities are present, the clinician should discuss additional referral and treatment targeting these co-morbidities with the client. No effect of discontinuation of antidepressants on risk of recurrence was observed and this treatment option should therefore not be ruled out. Especially as alternative treatments, such as preventive cognitive therapy, could be as efficient as continuation of antidepressants. Future research has to extend knowledge on risk factors (for example social environment and partner stability) for recurrence of depression in the perinatal period and examine (preventive) non-pharmacological treatment methods.
- Children with intrauterine exposure to maternal psychopathology and stress have increased levels of hair cortisone at 6 years of age, suggesting alterations in long-term HPA axis activity. Altered HPA axis functioning may increase susceptibility for physical disease and mental health problems in later life. Before inferring causality, future research should further establish hair cortisone as a valid biomarker and our findings need to be confirmed by studies with other outcome measures related to increased HPA axis activity.

FINAL CONCLUSIONS

An increase in use of antidepressants during the perinatal period has been observed, while risk and benefits have not yet been established. International guidelines on this topic are largely incomplete and often contradictory. Additionally, adherence to the guidelines has been discovered to be low, resulting in potentially unwanted variation in daily practice. Regardless of antidepressant management, women with antidepressant use at start of their pregnancy are at risk for recurrence of depression in the perinatal period, especially if symptoms of depression (as measured with the EPDS) are present in early pregnancy and if women have psychiatric co-morbidities. Clinicians should evaluate risk of recurrence in this population in early pregnancy and act accordingly, as untreated symptoms can lead to adverse outcomes in both the mother and the offspring, such as long-term alteration of the stress regulating HPA axis activity.

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SUMMARY

SUMMARY

Mental illness during the perinatal period is common and can affect both the mother and her unborn child. Especially perinatal depression, defined as depression arising in the period from conception to the end of the first postnatal year, is common, affecting up to 12% of pregnant women. To avoid adverse outcomes and to decrease burden, prevention and management of depression in the perinatal period is of importance. An increasingly used treatment method is the administration of antidepressant medication. In **chapter 2** we provided a general introduction on the history and current use of antidepressants. Although treatment with antidepressant medication in the perinatal period has been under debate, as conflicting results on the safety and efficacy of antidepressants during pregnancy have been reported, perinatal usage has been increasing steadily.

In **chapter 3** we evaluated how international guidelines have incorporated current knowledge in their recommendations with regard to treatment of perinatal depression with antidepressants. To retrieve all relevant guidelines, we conducted an extensive search in multiple databases and included 16 Clinical Practice Guidelines originating from 12 countries. Eight guidelines were perinatal specific and eight were general guidelines. During pregnancy, four guidelines advise to continue antidepressants, while there is a lack of evidence supporting this recommendation. Five guidelines do not specifically advise or discourage continuation. For new episodes, guidelines agree on psychotherapy as initial treatment for mild to moderate depression and antidepressants for severe depression, with a preference for sertraline. Paroxetine is not preferred treatment for new episodes but switching antidepressants for ongoing treatment is discouraged. If mothers use antidepressants, observation of the neonate is generally recommended and breastfeeding encouraged. Overall, the guidelines have good quality, but most were not specifically developed for pregnant women and contained limited information on the measures of implementation and audit of the proposed measures. We recommend development of up-to-date and perinatal-specific guidelines to help clinicians and patients in decision-making.

Chapter 4 provides the results of a cross-sectional study among gynecologists and midwives regarding adherence to the Dutch guideline on antidepressant use during pregnancy. An online survey was developed, consisting mainly of multiple-choice questions addressing guideline familiarity and current practice of the respondent. A total of 178 gynecologists and 139 midwives responded. Overall familiarity with the Dutch guideline was 92.7%. However, current practice and advice given to patients by caregivers differed substantially, both between gynecologists and midwives as well as within both professions. Overall guideline adherence was 13.9%. We examined whether caregiver characteristics were associated with guideline adherence and observed that solely

caregiver profession was associated with guideline adherence, with gynecologists having a higher adherence rate (OR 2.10, 95%CI 1.02–4.33) than midwives. Further implementation of the recommendations as given in the guideline should be stimulated as this can prevent unwanted practice. Additional research is needed to examine how gynecologists and midwives can be facilitated to follow the recommendations of the clinical guideline on antidepressant use during pregnancy.

In **chapter 5** we examined perinatal dispensing patterns of selective serotonin reuptake inhibitors (SSRIs) over time and the role of the Dutch guideline in this regard. We identified a 16-year cohort of 153,952 Dutch pregnancies with a delivery date between January 1999 and December 2014. Data included exposure to SSRIs related to phases of pregnancy (preconception, pregnancy and delivery, post-delivery).
A persistent significant rise of dispensing rates at preconception, in pregnancy and childbed was observed, with the largest increase during pregnancy (from 0.8% in 1999/2000 to 2.1% in 2013/2014, x2 for trend=141.735, p<0.001). A substantial change of practice in terms of the SSRI used (less paroxetine) and the policy towards continuation into pregnancy (more continuation over time) was visible. Concomitant use of psycholeptics halved the probability of continuation of SSRI use during pregnancy (OR 0.50, 95%CI 0.43-0.55, p<0.01). Given that evidence on safety so far is inconclusive, future research should focus on effective alternatives for the use of SSRIs in pregnancy and on updated guidelines for patient-tailored advice.

In **chapter 6** we outline the protocol of the Stop or Go study: a pragmatic multicenter non-inferiority randomized controlled trial. As the use of antidepressants during pregnancy is still controversial, there is an urgent need among patient and professionals for evidence from randomized studies to make rational decision regarding continuation or tapering of antidepressants during pregnancy, as no such studies exist so far. In the Stop or Go study, pregnant women with a gestational age of less than 16 weeks who use SSRIs or serotonin noradrenalin reuptake inhibitors (SNRIs) without clinically relevant depressive symptoms are included. Women allocated to the intervention group will receive preventive cognitive therapy with gradual, guided discontinuation of antidepressants under medical management (STOP). Women in the control group will continue the use of antidepressants (GO). Primary outcome of the trial is (cumulative) incidence of relapse or recurrence of maternal depressive disorder (as assessed by the Structured Clinical Interview for DSM disorders) during pregnancy and up to three months postpartum. Secondary outcomes include continuous outcomes such as symptoms of depression and anxiety. Additionally, child outcomes will be assessed.

In **chapter 7**, we report the first results of the prospective observational Stop or Go cohort study. The study presented data on a cohort of pregnant women with antidepressant use at start of their pregnancy and a history of depressive disorder. Women were followed throughout pregnancy and up to three months postpartum and assessed for recurrence of depression. Of the 85 women included in the study, eight women experienced recurrence of depression of whom two during pregnancy and six in the first weeks after childbirth. Characteristics of these women are described in detail in the chapter. Three predictors for recurrence of depression were identified that could be easily assessed by treating clinicians in daily practice. A higher Edinburgh Postnatal Depression Scale (EPDS) score in early pregnancy, a higher number of psychiatric co-morbidities, such as anxiety disorders, and a longer duration of antidepressant use were associated with a higher risk of recurrence of depression. Previous research of the EPDS found that a cutoff value of 11 in the first trimester and that of 10 in the second and third trimester gave the most adequate combination of sensitivity, specificity, and positive predictive value. Clinicians can use these cut-off scores to initiate immediate additional treatment. No effect of discontinuation of antidepressants on risk of recurrence was observed. This result should be interpreted with caution, as numbers were small. Still, this result could indicate discontinuation of antidepressants during pregnancy is feasible.

In **chapter 8** we examined the influence of (untreated) symptoms of psychopathology and stress during pregnancy on child outcomes from a biological perspective. The study was part of the population-based Generation R Study, a prospective population-based cohort from fetal life onwards. We examined the relation of perinatal maternal symptoms of psychopathology and stress on the one hand with offspring HPA axis activity at 6 years on the other hand, as measured by hair cortisol and cortisone concentrations in 2,546 children. We found that maternal symptoms of psychopathology and stress during pregnancy were associated with increased hair cortisone levels in children 6 years of age. These results suggest alterations in long-term HPA axis activity in children exposed to maternal psychopathology and stress during pregnancy. Altered HPA axis functioning may increase susceptibility for physical disease and mental health problems in later life. Nevertheless, we must be careful when interpreting these results and infer causality. The use of hair cortisone as a valid biomarker should be further established and our findings need to be confirmed by studies with other outcome measures related to increased HPA axis activity.

Main findings and conclusions of this thesis and methodological considerations are reported in **chapter 9**. Afterwards, we discussed implications of current findings and recommendations for future research. We conclude that there is need for up-to-date and

perinatal-specific guidelines and adherence to these guidelines has to be increased. Screening for risk factors for recurrence of depression has to be incorporated in guidelines and clinical practice. Meanwhile, research should advance in examining effects of antidepressants, but also of untreated psychiatric symptoms, on child functioning, both short- and long-term. Alternative treatment options have to be validated and implemented in current treatment management.

NEDERLANDSE SAMENVATTING

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Psychische aandoeningen tijdens de perinatal periode komen vaak voor en kunnen zowel de moeder als haar ongeboren kind beïnvloeden. Vooral perinatal depressie, gedefinieerd als depressie die optreedt in de periode vanaf de conceptie tot het einde van het eerste postnatale jaar, komt vaak voor en treft tot 12% van de zwangere vrouwen. Om nadelige resultaten te voorkomen en de belasting te verminderen, is preventie en behandeling van depressie in de perinatale periode van belang. Een steeds vaker gebruikte behandelmethode is het toedienen van antidepressiva. In **hoofdstuk 2** hebben we een algemene inleiding gegeven over de geschiedenis en het huidige gebruik van antidepressiva. Hoewel tegenstrijdige resultaten over de veiligheid en werkzaamheid van antidepressiva tijdens de zwangerschap zijn gemeld is het perinatale gebruik gestaag toegenomen.

In **hoofdstuk 3** hebben we onderzocht hoe internationale richtlijnen de huidige kennis hebben verwerkt in hun aanbevelingen met betrekking tot de behandeling van perinatale depressie met antidepressiva. Om alle relevante richtlijnen op te halen, hebben we een uitgebreide zoekactie uitgevoerd in meerdere databases en hebben we 16 klinische richtlijnen opgenomen uit 12 landen. Acht richtlijnen waren specifiek voor de perinatale periode en acht waren algemene richtlijnen. Tijdens de zwangerschap adviseren vier richtlijnen om antidepressiva te continueren, terwijl er een gebrek aan bewijs is om deze aanbeveling te ondersteunen. Vijf richtlijnen adviseren niet specifiek om te continueren of ontmoedigen dit zelfs. Richtlijnen zijn het eens over het aanbieden van psychotherapie als eerste behandeling bij het nieuw optreden van milde tot matige depressie en het aanbieden van antidepressiva voor ernstige depressie, bij voorkeur sertraline. Bij een nieuwe depressie heeft paroxetine niet de voorkeur, maar het wisselen van antidepressiva voor een doorlopende behandeling wordt afgeraden. Als moeder antidepressiva gebruiken, wordt observatie van de pasgeborene over het algemeen aanbevolen en wordt het geven van borstvoeding aangemoedigd. Over het algemeen zijn de richtlijnen van goede kwaliteit, maar de meesten zijn niet specifiek ontwikkeld voor zwangere vrouwen en bevatten beperkte informatie over implementatie en het nazien van de voorgestelde maatregelen. We raden aan om up-to-date richtlijnen te ontwikkelen specifiek voor de perinatal periode om clinici en patiënten te helpen bij het nemen van beslissingen.

Hoofdstuk 4 geeft de resultaten van een cross-sectionele studie onder gynaecologen en verloskundigen met betrekking tot het naleven van de Nederlandse richtlijn over antidepressiva gebruik tijdens de zwangerschap. Er was een online enquête ontwikkeld, die voornamelijk bestond uit meerkeuzevragen over de bekendheid van de richtlijn en de huidige praktijkvoering van de respondent. Er hebben in totaal 178 gynaecologen en 139

verloskundigen gereageerd. De bekendheid met de Nederlandse richtlijn was 92.7%. Huidige praktijkvoering en adviezen aan patiënten door de zorgverleners verschilden echter aanzienlijk, zowel tussen gynaecologen en verloskundigen als binnen beide beroepsgroepen. Algehele naleving van de richtlijn was 13.9%. We onderzochten of kenmerken van de zorgverlener geassocieerd waren met het naleven van de richtlijn en vonden dat alleen het beroep van de zorgverlener geassocieerd was met het naleven van de richtlijn, waarbij gynaecologen deze vaker naleefden (OR 2.10, 95%CI 1.02-4.33) dan verloskundigen. Verdere implementatie van de aanbevelingen in de richtlijn moet worden gestimuleerd, omdat dit ongewilde praktijkvoering kan voorkomen. Aanvullend onderzoek is nodig om te onderzoeken hoe gynaecologen en verloskundigen gefaciliteerd kunnen worden in het volgen van de aanbevelingen van de klinische richtlijn over antidepressivagebruik tijdens de zwangerschap.

In **hoofdstuk 5** onderzochten we perinatale afgiftepatronen van selectieve serotonine heropname remmers (SSRI's) door de jaren heen en de invloed van de Nederlandse richtlijn hierop. We identificeerden een 16-jarig cohort van 153.952 Nederlandse zwangerschappen met een bevallingsdatum tussen januari 1999 en december 2014. Gegevens omvatten blootstelling aan SSRI's gerelateerd aan de verschillende fasen van zwangerschap (preconceptioneel, zwangerschap en bevalling en na de bevalling).
We namen een aanhoudende significantie stijging waar in de afgiftepatronen tijdens preconceptie, zwangerschap en bevalling, met de grootste stijging tijdens de zwangerschap (van 0.8% in 1999/2000 tot 2.1% in 2013/2014, x2 voor trend = 141.735, p<0.001). Een aanzienlijke verandering in de soort SSRI's die werden gebruikt was zichtbaar (minder paroxetine) en een verandering met betrekking tot het continueren tijdens de zwangerschap (meer continuatie door de jaren heen). Gelijktijdig gebruik van psycholeptica halveerde de kans op continuatie van SSRI gebruik tijdens de zwangerschap (OR 0.50, 95%CI 0.43-0.55, p<0.01). Aangezien bewijs over de veiligheid tot nu toe nog tegenstrijdig is, moet toekomstig onderzoek zich richten op effectieve alternatieven voor het gebruik van SSRI's tijdens de zwangerschap en op bijgewerkte richtlijnen voor advies op maat.

In **hoofdstuk 6** schetsen we het protocol van de Stop or Go studie: een pragmatische, gerandomiseerd, multicenter, niet-inferioriteitsstudie. Aangezien het gebruik van antidepressiva tijdens de zwangerschap nog steeds controversieel is, is er bij patiënten en professionals een dringende behoefte aan bewijs uit gerandomiseerde onderzoeken om rationeel te beslissen over voortzetten of afbouwen van antidepressiva tijdens de zwangerschap, omdat dergelijke studies tot nu toe niet bestaan. In de Stop or Go studie worden zwangere vrouwen met een zwangerschapsduur van minder dan 16 weken die

een SSRI of een serotonine noradrenaline heropnameremmer (SNRI) gebruiken zonder klinisch relevante depressieve symptomen geïncludeerd. Vrouwen in de interventiegroep ontvangen preventieve cognitieve therapie met geleidelijke, medisch begeleide stopzetting van antidepressiva (STOP). Vrouwen in de controlegroep blijven de antidepressiva gebruiken (GO). Primaire uitkomst van de studie is (cumulatieve) incidentie van terugval of recidief van depressieve stoornis (zoals beoordeeld door het gestructureerde klinische interview voor DSM-stoornissen) tijdens de zwangerschap en tot drie maanden na de bevalling. Secundaire uitkomsten omvatten continue uitkomsten zoals symptomen van depressie en angst. Aanvullend worden kind uitkomsten gemeten.

In **hoofdstuk 7** rapporteren we de eerste resultaten van de prospectieve observationele Stop or Go cohortstudie. De studie presenteerde gegevens over een cohort van zwangere vrouwen met antidepressivumgebruik aan het begin van hun zwangerschap en een depressieve stoornis in de voorgeschiedenis. Vrouwen werden gevolgd gedurende de zwangerschap en tot drie maanden na de bevalling en beoordeeld op recidief van depressie. Van de 85 vrouwen die deelnamen aan de studie, ervoeren acht vrouwen een recidief van depressie, van wie twee tijdens de zwangerschap en zes in de eerste weken na de bevalling. De kenmerken van deze vrouwen worden in detail beschreven in het hoofdstuk. Drie voorspellers voor recidief van depressie werden geïdentificeerd die gemakkelijk gemeten konden worden door clinici in de dagelijkse praktijkvoering. Een hogere Edinburgh Postnatal Depression Scale (EPDS) score in de vroege zwangerschap, een hoger aantal psychiatrische comorbiditeiten, zoals angststoornissen, en een langere duur van antidepressiva gebruik waren geassocieerd met een hoger risico op recidief van depressie. Eerder onderzoek van de EPDS wees uit dat een afkapwaarde van 11 in het eerste trimester en die van 10 in het tweede en derde trimester de meest adequate combinatie van gevoeligheid, specificiteit en positief voorspellende waarde gaf. Artsen kunnen deze afkapwaarden gebruiken om een onmiddellijke aanvullende behandeling te starten. Er werd geen effect gevonden van afbouw van antidepressiva met op risico van recidief. Dit resultaat moet voorzichtig geïnterpreteerd worden, aangezien de aantallen in deze studie klein waren. Toch zou het resultaat er op kunnen wijzen dat het staken van antidepressiva tijdens de zwangerschap mogelijk is.

In **hoofdstuk 8** onderzochten we de invloed van (onbehandelde) symptomen van psychopathologie en stress tijdens de zwangerschap op kind uitkomsten vanuit een biologisch perspectief. De studie was onderdeel van de populatie gebaseerde Generation R Study, een prospectieve populatie gebaseerd cohort vanaf het foetale leven. We onderzochten de relatie tussen perinatale maternale symptomen van psychopathologie en stress enerzijds en HPA-as activiteit in de nakomelingen op 6-jarige leeftijd anderzijds,

gemeten door cortisol en cortison concentraties in het haar, in 2.546 kinderen. We vonden dat maternale symptomen van psychopathologie en stress tijdens de zwangerschap geassocieerd waren met verhoogde haar cortison concentraties bij kinderen van 6 jaar oud. Deze resultaten suggereren veranderingen in de HPA-as activiteit op lange termijn bij kinderen die worden blootgesteld aan maternale psychopathologie en stress tijdens de zwangerschap. Veranderde werking van de HPA-as kan de gevoeligheid voor fysieke ziekte en geestelijke gezondheidsproblemen op latere leeftijd vergroten. Niettemin moeten we voorzichtig zijn bij het interpreteren van deze resultaten en het afleiden van causaliteit. Het gebruik van haar cortison als valide biomarker moet verder worden vastgesteld en onze bevindingen moeten worden bevestigd door studies met andere uitkomstmaten die verband houden met verhoogde HPA-as activiteit.

De belangrijkste bevindingen en conclusies van dit proefschrift en de methodologische overwegingen worden gerapporteerd in **hoofdstuk 9**. Nadien bespraken we de implicaties van de huidige bevindingen en gaven aanbevelingen voor toekomstig onderzoek. We concluderen dat er behoefte is aan up-to-date richtlijnen specifiek voor de perinatale periode en dat de naleving van deze richtlijnen moet worden verhoogd. Screening op risicofactoren voor recidief van depressie moet worden opgenomen in richtlijnen en in huidige praktijkvoering. Ondertussen moet verder onderzoek worden uitgevoerd naar de effecten van antidepressiva, maar ook van onbehandelde psychiatrische symptomen, op het functioneren van kinderen, zowel op de korte als de lange termijn. Alternatieve behandelingsopties moeten worden gevalideerd en geïmplementeerd in de huidige praktijk.

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Nina Molenaar
Erasmus MC, Department of Psychiatry
PhD period: August 2014 – July 2018
Promotors: W.J.G. Hoogendijk, C.L.H. Bockting
Supervisors: M.P. Lambregtse-van den Berg, A.M. Kamperman

PhD training and activities	Year	Hours	ECTS
Master of science in Evidence Based Practice *(Graduated cum laude)*	2015-2017	97	
Components:			
Epidemiology and Evidence Based Practice: concepts			
Epidemiology and Evidence Based Practice: designs			
Biostatistics: elementary analysis			
Systematic Reviews and Clinical Guidelines			
Longitudinal Module			
Biostatistics and Advanced Epidemiology			
Clinimetrics			
Health Economics			
Health Care System Evaluation			
Capital Selecta			
Thesis project			
	Year	Hours	ECTS
Other courses:			
SCID-I training	2014	6	
Systematic literature retrieval in Pubmed	2014		0,3
Workshop Endnote	2014		0,3
Good clinical practice (BROK)	2015		4
Workshop media contacts for researchers	2015	4	
BKO-workshop 'omgaan met groepen'	2016	4	
BKO-workshop 'teach the teacher 1'	2016	16	
3D ultrasound training	2016	20	
Research integrity	2017		0,3

	Year
Presentations:	
5 jaar POP-poli congress, JBZ/Reinier van Arkel *(poster)*	2014
Carrousel kwetsbare zwangeren, Zininkraamzorg, Dordrecht *(oral)*	2015
Hoe bevel Twente, MST, ZGT, Kring Twentse verloskundigen *(oral)*	2016
Mind2Care, Symposium Moeder en Baby united, LKPZ *(oral)*	2017
Various presentations in >50 hospitals and VSV's *(oral)*	2014-2017
International Marcé Society Biennial Scientific Meeting, India *(oral)*	2018
National and internation conferences:	
Briljante mislukkingen, ZonMw, Amsterdam	2014
Geboren in 2020, College Perinatale Zorg, Hilversum	2014
Lustrum Symposium LKPZ, Utrecht	2015
GGG-congres, ZonMw, Amsterdam	2015
Symposium Wetenschap in Beeld, Utrecht	2015
Veilige Kribbe V, LKPZ, Rotterdam	2015
Gynaecongres, NVOG, Hilversum	2015
American Psychiatric Association (APA), annual meeting, New York	2018
Supervision and teaching:	
Hamilton course for students and research assistants	2016
Lecture 'How to recognize mental vulnerability in pregnant women'	2017
Master thesis Leo Genet	2017
Master thesis Nicolle Croes	2018
Voluntary research projects: Diewertje Houtman, Emine Taytas	2018
Coaching medical student in research: V. Parden, J. de Boer, N. Geerts	2016-2018
Other:	
Organization of workshop 'Preventive Cognitive Therapy'	2015
Member of the PREGMETHICs expert meeting	2016
Weekly 3D ultrasound consultation clinic	2016

CURRICULUM VITAE

CURRICULUM VITAE

Nina Maren Molenaar was born in 1988 in Amsterdam, the Netherlands. After she graduated from secondary school at the Gymnasium Felisenum in 2006, she started her study Medicine at the Academic Medical Center (AMC) in Amsterdam. As part of her studies, she did two foreign internships: a scientific research internship at the Columbia University in New York (2011-2012) and a tropical medicine rotation in gynecology at the Chikankata Mission Hospital in Zambia (2013-2014). In her free time, she worked for several medicine-related companies such as the Dutch Cochrane Center, Europdonor and the GGD. Her interest in scientific research started during this time. She worked as a research assistant for the ABCD-study (Amsterdam Born Children and their Development) and conducted an extra-curricular research project at the Department of Experimental Surgery. She graduated from medical school in 2014 and started as a PhD-student at the Erasmus MC shortly after. During her second and third year she combined her work as a PhD-student with a master degree in Clinical Epidemiology at the University of Amsterdam (UvA) and graduated cum laude in 2017. Additionally, she did work for Stichting Mind2Care, which has developed an online screen-and-advice tool to detect vulnerable pregnant women. She functioned as coordinator of the foundation and streamlined implementation of the tool in hospitals and midwifery practices. As her primary interest lays in scientific research, Nina plans to continue her scientific career after finishing her PhD, starting with a postdoctoral position.

LIST OF PUBLICATIONS

PUBLICATIONS

L. Hooft, D.A. Korevaar, **N.M. Molenaar**, P.M.M. Bossuyt, R.J.P.M. Scholten. *Endorsement of ICMJE's clinical trial registration policy: a survey among journal editors*. Neth J Med. 2014 Sep;72(7):349-55.

N.M. Molenaar, M.E. Brouwer, C.L.H. Bockting, G.J. Bonsel, C.N. van der Veere, H.W. Torij, W.J.G. Hoogendijk, J.J. Duvekot, H. Burger, M.P. Lambregtse-van den Berg. *Stop or Go? Preventive cognitive therapy with guided tapering of antidepressants during pregnancy: study protocol of a pragmatic multicentre non-inferiority randomized controlled trial.* BMC Psychiatry. 2016 Mar 18;16:72.

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