Chapter 1

General introduction
This thesis focuses on neonatal symptoms after exposure to antidepressants in utero. These symptoms are mostly mild and self-limiting. However, symptoms are nonspecific and can also suit more severe neonatal pathology, such as perinatal infection. This may require invasive additional testing, which can be harmful and stressful for the infant and parents. Furthermore, as the etiology of neonatal symptoms is unknown, it is impossible to predict which infant will develop them or not, resulting in the hospital admission of all antidepressant-exposed infants. In this chapter, current knowledge of neonatal symptoms after exposure to antidepressants is described and knowledge gaps are identified, resulting in our research aims. Apart from neonatal symptoms, exposure to antidepressants can have other consequences, which will be discussed in this chapter. In addition, background information on the prevalence of psychiatric disorders and antidepressant use during pregnancy and postpartum is provided.

**Psychiatric disorders during pregnancy and postpartum**

**Prevalence**

Women with a history of a psychiatric disorder, especially depression, psychosis or bipolar disorder, are vulnerable for recurrence or worsening of psychiatric symptoms during pregnancy and postpartum. This attributes to the high prevalence of psychiatric disorders during this period, which is about 15% in Western countries.\(^1,2\) The vulnerability for psychiatric symptoms during pregnancy and postpartum is most likely caused by a combination of physical, hormonal, psychological and social factors.\(^3-5\) Women with a history of depression who do not use psychotropic medication have a risk of 60-80% of recurrence of depressive symptoms during pregnancy and postpartum.\(^6,7\) When women with a bipolar disorder or with a history of postpartum psychosis do not use preventative medication, the risk of psychotic symptoms during this period is 25-50%.\(^8,9\)

**Possible consequences of untreated psychiatric symptoms**

The high prevalence of psychiatric disorders during pregnancy is alarming, as these disorders and their associated psychiatric symptoms, including symptoms of depression, anxiety or psychosis, can harm both the pregnant woman and her child. For example, depression is associated with poor self-care and a high prevalence of smoking as well as alcohol and illicit drug use during pregnancy, which can harm the fetus.\(^10\) Infants of depressed or anxious women are at risk for premature birth and low birth weight, possibly mediated by elevated maternal and fetal cortisol levels.\(^11-13\) Maternal symptoms of depression and anxiety postpartum can lead to neonatal irritability, agitation, lethargy and less alertness as well as poverty of
facial expressions and can ultimately impair the attachment between mother and child. \textsuperscript{14-16} Impaired attachment is in turn a risk factor for learning and behavioural difficulties later in childhood.\textsuperscript{17,18}

**Treatment**

Due to the negative effects of psychiatric symptoms during pregnancy and postpartum on mother and infant, prevention and treatment are important. Possible treatment options include psychotherapeutic interventions, psychotropic medication or a combination of both. Evidence of the effectiveness of these therapeutic interventions during pregnancy is limited and there are no comparative studies.\textsuperscript{19}

For the treatment of psychiatric symptoms during pregnancy, several factors should be taken into consideration. These include the type and severity of psychiatric symptoms, the number of previous episodes and the history of treatment.\textsuperscript{7,20}

Of all types of psychotropic medication, selective serotonin reuptake Inhibitors (SSRIs) are the most frequently used during pregnancy. In Western countries, the prevalence of SSRI use during pregnancy is 2-9\%.\textsuperscript{21,22} In the Netherlands the prevalence is 1.8-2.8\%, which is 3150-4900 women every year.\textsuperscript{23,24}

**Possible consequences of exposure to selective antidepressants in utero**

This thesis focuses on neonatal symptoms postpartum after exposure to selective antidepressants (SADs) in utero. These include SSRIs, serotonin noradrenaline reuptake inhibitors (SNRIs) and noradrenergic and specific serotonergic antidepressant (NaSSAs).

When considering SAD use during pregnancy, possible negative consequences of its use have to be weighed against possible negative consequences of psychiatric symptoms. Apart from neonatal symptoms postpartum, other possible neonatal effects should also be taken into account. These include congenital malformations, perinatal effects and long-term effects. Maternal and pregnancy related effects are beyond the scope of this thesis.

**Congenital malformations**

There is a large body of research into possible congenital malformations after exposure to SSRIs during pregnancy. Some retrospective studies revealed a mild association (odds ratio 1.5-2.0) between the use of SSRIs and an atrium or ventricular septal defect.\textsuperscript{25,26} However, recent large cohort studies did not confirm this increased risk.\textsuperscript{27-29} Other antidepressants regularly prescribed during pregnancy, such as venlafaxine and bupropion (SNRIs) and mirtazapine (a NaSSA) are less studied. Available results do not indicate an increased risk of congenital malformations after exposure to these antidepressants.\textsuperscript{27,29}
**Perinatal effects**

Some studies showed an increased risk of persistent pulmonary hypertension of the newborn (PPHN) after exposure to SSRIs in utero.\(^3^0\) However, this was not confirmed in a recent large cohort-study that adjusted for several confounders. In this study, the absolute risk of PPHN in infants exposed to SSRIs was 0.34% versus a risk of 0.25% in non-exposed infants.\(^3^1\)

**Long-term effects**

Serotonin plays a role in the cerebral development of the fetus. Selective antidepressants alter the cerebral serotonin metabolism and may therefore affect fetal cerebral development. At this time, there are 24 prospective studies on the long-term effects of SSRI-exposure in infants up to the age of seven years.\(^3^2\)-\(^3^6\) Of these studies, 14 showed no difference in motor-, emotional- and cognitive functioning between exposed and non-exposed infants. Ten studies revealed very subtle effects on gross motor skills, language development and behavior. However, since many factors play a role in the development of infants, it is difficult to examine the specific long-term effects of exposure to SADs in utero.

**Neonatal symptoms after exposure to selective antidepressants in utero**

Infants exposed to SADs in utero can develop symptoms of restlessness postpartum, such as tremors, jitteriness, and feeding- and sleeping difficulties.\(^2^4,3^7,3^8\) Fortunately, most infants only show mild symptoms of restlessness, which are self-limiting. Severe symptoms such as convulsions are very rare.\(^2^4,3^9\) Most symptoms develop within 48 hours postpartum and fade out within two to six days.\(^2^4,3^8,4^0\)

**Pathogenesis and etiology**

The pathogenesis, i.e. the mechanism in which SAD-exposure leads to neonatal symptoms, is unknown. There are three possible originating mechanisms, namely withdrawal of antidepressants, drug toxicity or an overlap between both.\(^2^4,3^9,4^1\) The discussion on the pathogenesis is reflected by the various terms used to describe the symptoms. Some of these terms, including ‘neonatal behavioral syndrome’ and ‘poor neonatal adaptation (PNA)’ do not suggest an originating mechanism. Other terms do suggest such a mechanism, such as ‘neonatal abstinence syndrome’, and ‘neonatal withdrawal’.\(^3^9,4^2-4^4\) As neonatal symptoms indicate adaptation difficulties and the pathogenesis is unknown, we prefer the term PNA and will use this term henceforth.

The etiology, i.e. the factors that play a role in the development of PNA, are largely unknown. Only 20-30% of SAD-exposed infants develop symptoms of PNA and severity differs between infants. This suggests that the neonatal symptoms have
a multifactorial origin whereby factors apart from exposure to the antidepressant itself also play a role.\textsuperscript{24,37,38} In order to predict the risk of developing PNA, it is essential to gain insight into these factors. A suggested etiological factor is the level of serotonergic activity, as this is reported to be related to symptoms of restlessness in infants.\textsuperscript{42} Another factor that might be involved in the development of PNA is the fetal cortisol level. This level is most likely influenced by the maternal cortisol level and may result in impaired neonatal stress regulation.\textsuperscript{45,46}

**Diagnosis and management**

As symptoms of PNA are mostly mild and self-limiting, supporting measures such as frequent small feedings on demand and swaddling are sufficient in most cases. If insufficient, phenobarbital is a safe therapeutic option.\textsuperscript{24,39,42} In case of severe PNA, which is very rare, admission to a neonatal care unit (NCU) can be necessary.\textsuperscript{12,24,37,39}

Despite the mild and self-limiting character of PNA, all infants exposed to SADs during pregnancy are admitted for observation.\textsuperscript{24,37,39,47,48} This is due to the lack of knowledge with regard to risk factors for PNA and nonspecific nature of PNA symptoms; all individual symptoms of PNA, such as tremors and jitteriness, can also suit more severe neonatal pathology such as perinatal infection and metabolic disorders.\textsuperscript{24,40,49}

The nonspecific nature of PNA symptoms and absence of a marker for PNA makes the diagnostic process complex. The diagnosis is based on daily examination by a pediatrician and evaluation of the type and course of symptoms. To exclude other neonatal pathology, invasive testing may be necessary in case of indistinctness about the origin of symptoms. This can be harmful and stressful for the infant and parents.

An observational tool can be of additional value, in order to recognize, observe and objectify the development and progression of neonatal symptoms. Furthermore, such a tool may be used to screen infants for the presence of PNA. The Finnegan scoring list (FSL) is a widely used tool, although never validated for this purpose. This list was originally designed to assess symptoms of neonatal abstinence after exposure to opiates in utero.\textsuperscript{24,37,39,47,50} As symptoms of opiate abstinence are more extensive and severe, several items on the FSL may not be relevant for the assessment of PNA. Furthermore, the large amount of items and the differential weighing of items makes it time-consuming and error-prone.\textsuperscript{51,52} A validated, more feasible tool is not available.
General introduction

Objectives and outline of this thesis

There are several unknown aspects of PNA including the unknown etiology, the absence of a feasible observational tool and the lack of a guideline with respect to the observation of SAD-exposed infants. This results in differences in the type and duration of the observational period between hospitals.

Our first aim was to expand knowledge on the etiology of PNA. This is a first step in the development of a marker for PNA, which could simplify the diagnostic process. Furthermore, insight into the etiology may lead to identification of risk factors for PNA. Our second aim was to improve the feasibility of the FSL. Our third and final aim was to provide evidence-based recommendations on the type and duration of the observational period of SAD-exposed mother-infant dyads.

To provide an overview of the existing literature on PNA after exposure to psychotropic medication a review was performed, as described in chapter 2.

We explored if the neonatal serotonergic system and fetal cortisol levels play a role in the etiology of PNA by measuring neonatal urinary 5-hydroxyindoleacetic acid (5-HIAA) levels, chapter 3, and neonatal hair cortisol levels, chapter 4. 5-HIAA is the main serotonin metabolite and reflects the degree of serotonergic activity. The hair cortisol level of infants, measured on the first day after delivery, represents the mean cortisol level during the last trimester of fetal life. In these two prospective controlled studies SAD-exposed infants who were admitted postpartum were included. 5-HIAA and neonatal hair cortisol levels were compared between infants who did and did not develop PNA.

Chapter 5 describes the exploration of risk factors for PNA in infants exposed to SADs in utero. In this cohort study, SAD-exposed infants who were admitted postpartum were included. Possible risk factors, including type of feeding, type and dosage of SAD, prematurity, maternal smoking and symptoms of maternal anxiety and depression were analyzed for an association with PNA.

The aim of the study described in chapter 6 was to shorten and simplify the FSL, while preserving its clinimetric properties. In this observational study, SAD-exposed infants who were admitted postpartum were examined. During the observational period of 72 hours, trained nurses completed the FSL three times a day. From these completed lists, the adapted FSL was created by selecting items through forward analysis. As a high sensitivity is essential for screening, we assessed the clinimetric properties of the original and adapted FSL. Internal validity was assessed by cross-validation.

In chapter 7, we describe an observational study of SAD-exposed mother-infant dyads, which were admitted postpartum for the observation of possible consequences of either the maternal psychiatric disorder or fetal exposure to SADs. These possible complications can lead to medical interventions, including
adjustment of psychotropic medication, admission to the psychiatric department, additional investigations due to indistinctness about the origin of neonatal symptoms, treatment of PNA and consultation of an external organization for additional family care. Our aim was to gain insight into the prevalence and time to these interventions, to be able to formulate evidence-based recommendations on the type and duration of the observational period.

In chapter 8, the general discussion, the methods and results described in the previous chapters are reflected on. Furthermore, implications for future research and clinical practice are discussed.

Finally, in chapter 9 and chapter 10 the results of this thesis are summarized in English and Dutch, respectively.

All studies were performed in the OLVG west hospital (formerly Sint Lucas Andreas hospital), Amsterdam, the Netherlands, between 2007 and 2013. The psychiatry obstetric pediatric (POP) expert center of this hospital is an expert center on psychiatry and pregnancy and advises women with a psychiatric disorder prior to, during and after pregnancy. Within eight hours postpartum, these women are admitted to the maternity ward together with their infants for an observational period of at least 72 hours.
REFERENCES


