Chapter 8

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

**Main findings**

Chapter 2 presents an overview of literature on poor neonatal adaptation (PNA) after exposure to psychotropic medication in utero. This review identified several unresolved issues concerning the unknown etiology of PNA, the absence of a feasible observational tool and the lack of a guideline with respect to the type and duration of the observational period. In this thesis, we tried to (partly) resolve these issues.

In chapter 3, the role of serotonin in the development of PNA after exposure to selective antidepressants (SADs) in utero was examined. We analyzed the course of neonatal urinary 5-hydroxyindoleacetic acid (5-HIAA) levels, the main serotonin metabolite, during the first three days postpartum in SAD-exposed infants. This course differed between infants with and without PNA (p=<0.001) with higher 5-HIAA levels in infants with PNA on day one (p=0.001). The presence of maternal psychological distress modified this relationship. We concluded that a transient disturbance of the neonatal serotonergic system might play a role in the development of PNA.

We continued our exploration of the etiology of PNA by examining cortisol levels in hair of SAD-exposed infants, as described in chapter 4. Hair cortisol levels of female infants with PNA were higher compared to female infants without PNA while hair cortisol levels of boys did not significantly differ between groups. This suggests that hypothalamic pituitary adrenal (HPA) axis activity might play a sex-specific role in the development of PNA.

Chapter 5 describes the search on risk factors for PNA after exposure to SADs in utero. Formula feeding was associated with an increased risk of PNA compared to breast feeding or mixed feeding. Furthermore, we demonstrated that selective serotonin reuptake inhibitors (SSRIs) were associated with a mild increased risk of PNA compared to serotonin noradrenaline reuptake inhibitors (SNRIs). Dosage of the SAD did not influence the risk of PNA.

In order to improve the diagnostic process of PNA, we aimed to shorten and simplify the Finnegan scoring list (FSL) while preserving its clinimetric properties, as described in chapter 6. This resulted in an adapted FSL of eight equally weighed items with an area under the curve (AUC) of 0.91. As a high sensitivity is essential for screening, we assessed the clinimetric properties of the original and adapted FSL. The original FSL had a sensitivity of 100% and specificity of 48% for PNA.
compared to the diagnosis of PNA by the pediatrician. The adapted FSL had a sensitivity of 98% and specificity 37% at a cut-off of one and a sensitivity of 42% and specificity of 86% at a cut-off of two. We concluded that the adapted FSL has acceptable clinimetric properties and can serve as an easy to apply observational tool in SAD-exposed infants. As the specificity of the adapted FSL is low, the list should not be used as a diagnostic tool.

Finally, we aimed to provide evidence-based recommendations on the type and duration of the observational period of SAD-exposed mother-infant dyads, as described in chapter 7. In this observational study the type, number and time to maternal or neonatal medical interventions related to the maternal psychiatric disorder or fetal exposure to SADs were examined. In 38% of mother-infant dyads one or more interventions were performed. Most prevalent interventions were adjustment of psychotropic mediation and treatment of PNA. In 39% of infants, the final intervention was performed within 24 hours postpartum. After an observational period of 48 hours, this percentage was 87%. We concluded that the high prevalence and type of medical interventions requires professional observation of all mother-infant dyads exposed to SADs during pregnancy by a multi-disciplinary team with a duration of at least 48 hours.

Pathogenesis and etiology

Pathogenesis

The pathogenesis, i.e. the exact mechanism in which exposure to SADs leads to PNA, is unclear. Possible mechanisms proposed in literature are withdrawal of antidepressants, drug toxicity or an overlap between both. As symptoms of toxicity and withdrawal are largely similar, such as jitteriness and agitation, it is difficult to make this distinction solely based on the neonatal symptoms. As described in chapter 7, most infants developed symptoms after a time lag of several hours, which is more typical for withdrawal. In drug toxicity, symptoms develop directly postpartum. As insight into the pathogenesis might lead to a prediction on the risk and moment of onset of PNA, further investigation would be of additional value. Thereby, the correlation between antidepressant levels and neonatal symptoms could be assessed. For instance, the concentration of antidepressant could be measured in maternal serum during pregnancy, in combination with measurement of the antidepressant concentration in amniotic fluid, umbilical cord blood, breast milk and neonatal serum (for example in combination with the heel prick). Up to this moment, this type of research is performed in a few case-reports and two small cohort studies, which show high as well as low antidepressant levels in combination with neonatal symptoms.
**Etiology**

In this thesis, we tried to gain insight into the etiology of PNA, i.e. the factors that play a role in its development. Poor neonatal adaptation seems to have a complex multifactorial origin whereby many interrelated factors play a role. This might explain the difference in the presence and severity of PNA symptoms in infants. Apart from exposure to the antidepressant itself, other factors are suggested to play a role in the development of PNA. This is supported by our findings, as described in chapter 5. We showed that the type of antidepressant was only weakly associated with PNA. The dosage of antidepressant did not influence the risk of PNA. Furthermore, this study demonstrated that formula feeding was associated with an increased risk of PNA compared to breast feeding or mixed feeding. This might be related to the excretion of antidepressant into breast milk. Another possible explanation is that there may be more skin to skin contact during breast feeding compared to formula feeding.

Etiological factors that seem to be involved in the development of PNA include the HPA axis and the serotonergic system, as we showed in chapter 3 and 4. In these studies, we also described that other factors, including characteristics of antidepressant usage, neonatal gender and maternal and neonatal stress are involved. However, the strength of the association between these factors and PNA was mostly mild. In combination with the fact that most of these factors are interrelated, such as the HPA axis and the serotonergic system, it is difficult to examine their individual effect on PNA and it is not possible to establish the risk of PNA beforehand. The etiological complexity is further increased by the fact that the functioning of systems in the mother, such as the HPA axis, influences programming and development of these systems in the fetus. It is reported that this process of fetal-programming, is influenced by several factors.

Apart from our findings that the serotonergic system, HPA axis, maternal and neonatal stress and characteristics of antidepressant usage might play a role in the development of PNA, other factors may contribute to the development of PNA as well. However, research into these factors is limited. Genetic factors, such as a deficiency of cytochrome CYP450 2D6 leading to elevated plasma concentrations of SSRIs might contribute. Other drug- and patient-related characteristics that influence the effect of SSRIs might also play a role, such as the duration and timing of SAD use, use of multiple psychotropic drugs and distribution characteristics of the placenta. Furthermore, other neurotransmitters or hormones apart from serotonin and cortisol may also contribute to the development of PNA.
Prevalence
In literature, the reported prevalence of PNA varies. Most studies describe a prevalence of 30%, however there is a broad range (20 to 69%).\textsuperscript{2,4,8,9,25,28-30,34-36} Although we did not focus on establishing the prevalence of PNA in this thesis, we did calculate the percentage of infants with PNA in all our studies. The prevalence depends on the outcome measure, as further discussed in the section 'reflections on methodology'. When we consider the diagnosis of PNA by the pediatrician as outcome measure, the prevalence in our studies was 55% (24 of 44 infants, chapter 3), 38% (25 of 65 infants, chapter 4), 24% (43 of 181 infants, chapter 6) and 22% (35 of 159 infants, chapter 7). The difference in prevalence between our studies might be attributable to the difference in precision of measurement, related to sample sizes. However, it is also plausible that persistent training of nurses and pediatricians during the years have led to a better systematic and objective measurement and increased awareness of PNA. This might have resulted in the higher, more accurate prevalence in the most recently performed studies (chapter 3 and 4).

Diagnosis and management
The nonspecific nature of PNA symptoms makes it difficult to distinguish PNA from other, more severe neonatal pathology.\textsuperscript{2,20,29,37-39} The differential diagnosis includes perinatal infection, metabolic or neurologic problems, hyper viscosity, excitement syndromes (such as small for gestational age) and neonatal abstinence due to intoxications during pregnancy.\textsuperscript{4,25,31-33,36}

Due to the nonspecific nature of symptoms and multifactorial origin of PNA, it is unlikely that a specific marker can be developed. Therefore, close observation of infants by specialized caregivers is required. These caregivers need to be aware of the type and course of PNA symptoms and consider PNA as a diagnose 'per-exclusionem'.\textsuperscript{2,29,34,35,38,39} This does not imply that invasive additional testing should be performed in every infant with symptoms of PNA. Caregivers should 'wait-and-see' in case of mild symptoms that suit PNA, such as mild tremors and sleeping difficulties. However, in case of more severe or atypical symptoms, such as convulsions and hypo- or hyperthermia, we argue that additional testing should be performed in order to exclude all other possible diagnoses.

To enhance the diagnostic process of PNA, an observational tool is of additional value in order to recognize, observe and objectify the development and progression of neonatal symptoms. The FSL is widely used for this purpose, although it is originally designed to assess symptoms of neonatal abstinence after exposure to opiates and is error-prone due to its length and differential weighing of items.\textsuperscript{6,7,37} The adapted FSL, as described in chapter 6, might serve as an easy to apply obser-
vational tool. Due to its high sensitivity, it is useful for screening. However, due to its low specificity, the list should not be used as a diagnostic tool.

Training of nurses and pediatricians in the observation and diagnosing of PNA enhances reliability and uniformity of PNA assessment. In our center trained nurses administer the FSL every eight hours. The trained pediatrician examines the infant on a daily basis, interprets the scores and excludes other neonatal pathology, leading to a conclusion with respect to the presence or absence of PNA. At this moment training is provided by experts, however tools are lacking. Furthermore, studies on the inter-rater reliability between nurses and between pediatricians are not available. As a high inter-rater reliability results in less variation and thereby improves the reliability of results, this would be of additional value.8,9,12,14,15

Observation of mother-infant dyads exposed to antidepressants
Both the maternal psychiatric disorder as well as the SAD-exposure can lead to complications postpartum. These include the development of PNA, psychiatric decompensation or impaired attachment between mother and child, as described in chapter 7.2,8,9,16-19,40 Therefore, both mother and infant should be taken into account when considering duration and type of observation.

Duration of the observational period
As guidelines on the observational period of SAD-exposed mother-infant dyads are not available, the duration of this period differs between hospitals. Based on the observational study described in chapter 7, we would advise an observational period of at least 48 hours postpartum, which is in line with the advice of several experts in this field.1,2,8,9,13,14,21,22,41 Our recommendation is based on the finding that an observational period of 24 hours entails the risk of missing complications. In this study, the final intervention was performed in only 39% of dyads within this time frame. After an observational period of 48 hours, this percentage was 87%. Interventions included treatment of PNA, additional testing due to indistinctness about the origin of neonatal symptoms and adjustment of psychotropic medication.

The moment of onset of PNA symptoms varies between infants. In chapter 7, we reported that only 15% of infants developed PNA within 12 hours postpartum. Most infants (80%) developed PNA between 13-48 hours postpartum. The moment of onset of PNA symptoms is likely to be influenced by the half-life of the antidepressant, whereby a longer half-life results in a later moment of onset.1,9,17,18,23-25,42 However, also in antidepressants with a relatively short or intermediate half-life, PNA symptoms can develop relatively late, as we illustrated in chapter 5 and in a
case report. It is unknown whether other factors, such as the duration and timing of antidepressant use have influence on the moment of onset of PNA.

**Observational setting**

As mentioned earlier, we argue that specialized caregivers should observe mother-infant dyads exposed to antidepressants. However, it is debatable who could and should provide this specialized care as well as where the observation should take place. An advantage of hospital admission is the continuous observation by nurses and evaluation by a pediatrician on a daily basis, who evaluates symptoms and examines the infant. In case of nonspecific or severe symptoms of PNA, additional testing can immediately be performed to exclude other, more severe neonatal pathology. However, as described in chapter 7, additional testing was performed in only 2% of infants. Furthermore, there are also several disadvantages of hospital observation such as the lack of privacy, increased risk of infection and risk of over diagnosis.

It may be beneficial for parents, infants and the healthcare costs, to perform home observation. Thereby, there are two essential conditions that need to be met: 1. a risk-assessment should be made during pregnancy 2. (maternity) nurses and midwives should be trained in observation of PNA and recognition of psychiatric symptoms.

The risk-assessment could be performed by a psychiatry obstetric pediatric (POP) expert center during the third trimester of pregnancy. Home observation should only be considered in case of absence of risk factors for neonatal effects, psychiatric decompensation postpartum or impaired attachment between mother and child. Factors that can cause neonatal effects include illicit drugs or alcohol use during pregnancy, which can result in neonatal abstinence. Furthermore, exposure to benzodiazepines and lithium in utero can result in the floppy infant syndrome after birth. As we mentioned earlier, it is not possible to establish the risk of PNA beforehand, as the etiology of PNA is complex whereby many interrelated factors seem to play a role. Factors that can lead to psychiatric decompensation postpartum or impaired attachment include a severe psychiatric diagnosis, current psychiatric symptoms, unplanned and unwanted pregnancy, single motherhood, absence of a social support system, low social-economic status and earlier involvement of child welfare. After birth, a new risk assessment should be made, as additional risk factors such as a traumatic delivery might alter the advice. Furthermore, it is important to evaluate whether a mother has a psychiatric caregiver, which will be in close contact with her during the postpartum period.
Maternity nurses and midwives, who provide maternal and neonatal care in the home setting during the first week postpartum, should be trained in the observation of PNA and recognition of psychiatric symptoms. In case of nonspecific neonatal symptoms, a pediatrician should be contacted. When there are psychiatric symptoms, impaired attachment or psychosocial problems, the psychiatric caregiver or general practitioner should be contacted. Another option would be to train parents in the observation of PNA in their infant. In order to train maternity nurses, midwives and parents, training tools should be developed and their effect should be evaluated. A cost-effectiveness analysis comparing both observation modalities would be of additional value.

**Reflections on methodology**

**Outcome measure**
In order to examine factors associated with PNA, infants have to be divided into infants with and without PNA. However, there is no marker or diagnostic tool for PNA, which makes research in this field challenging. Some researchers use the FSL as outcome measure for PNA. However, the cut-off for PNA differs between studies. As the FSL is designed as observational tool and lacks specificity, as we showed in chapter 6, use of the FSL as outcome measure most likely results in overestimation of PNA. Another possible outcome measure is diagnosis of PNA by a pediatrician based on the course of symptoms and exclusion of other neonatal pathology. This most likely gives less overestimation of PNA compared to use of the FSL. However, in infants with neonatal pathology and possible PNA, symptoms are largely overlapping. This might lead to underestimation of PNA. In our center, we tried to minimize this effect by training of pediatricians. As pediatricians were not yet satisfactory trained when we performed the study on risk factors, described in chapter 5, we used the FSL as outcome measure in this study. After training, we did regard the diagnosis of PNA by the pediatrician as outcome measure in our other (prospective) studies, as described in chapter 3 and 4. This difference in outcome measures between our studies might have contributed to difference in the strength and significance of associations between etiological factors and PNA.

**Study design**
As there are ethical restrictions with respect to randomization of pregnant women and infants, most studies in this field, including the studies described in this thesis, are of observational design. This design is suitable for explorative research as it does not interfere with the natural course of symptoms. However, it is important to realize that it is not possible to prove causality based on observa-
tional studies. This is mainly caused by the inability to fully control for known and especially unknown confounders.\textsuperscript{16,18,19,41}

An important known confounder is the maternal psychiatric disorder. As maternal symptoms of depression can influence both the fetal development as well as neonatal behavior,\textsuperscript{1,2,8,18,22,42} it is essential to take this factor into account. We included the level of maternal depressive and anxiety symptoms in several studies (chapter 3, 4 and 5). This level was measured by the hospital anxiety and depression scale (HADS) during the third trimester of pregnancy and on the first day postpartum.\textsuperscript{1,43} This instrument is validated in an antenatal population and consists of 14 questions, seven for anxiety and seven for depression, with a time frame of 1 week.\textsuperscript{26,44} A score of eight or higher on the anxiety or depression subscale indicates depression or anxiety and is indicative for elevated psychological distress.\textsuperscript{4,43-45} As the HADS is no golden standard for the establishment of psychiatric disorders, its use might have led to non-differential misclassification. In turn, this might have resulted in underestimation of the role of the maternal psychiatric disorder.\textsuperscript{1-3,46}

**Implications for future research**

Throughout the discussion several recommendations for future research were formulated:

- To investigate the pathogenesis of PNA by correlating antidepressant levels to neonatal symptoms.
- To examine which other factors play a role in the etiology of PNA such as genetic factors, hormones and monoamines.
- To externally validate the adapted FSL.
- To develop training tools for the observation of PNA by maternity ward nurses, maternity nurses (for home observation), midwifes, parents and pediatricians and evaluate their effect.
- To examine the inter-rater reliability of the (adapted) FSL between nurses and the inter-rater reliability of the diagnose PNA between pediatricians.
- To examine what factors influence the moment of onset of PNA.
- To perform a cost-effectiveness analysis comparing hospital- and home observation.

**Implications for clinical practice**

Throughout the discussion several implications for practice were formulated:

- The etiology of PNA is complex, whereby many interrelated connected factors seem to play a role. Therefore it is not possible to establish the risk of PNA beforehand.
- The nonspecific nature of symptoms and multifactorial origin of PNA makes it unlikely that a specific marker can be developed. Therefore, the diagnostic process is based on the expertise of trained caregivers who need to be aware of the type and course of PNA symptoms.

- Inform parents on the risk and mostly mild and self-limiting character of PNA after exposure to antidepressants in utero. This would include information on the dosage of antidepressant, which does not seem to have much influence on this risk while breast feeding seems to reduce the risk of PNA.

- The pediatrician, who establishes the diagnose of PNA, should ‘wait-and-see’ in case of mild symptoms which suit PNA, however exclude all other possible diagnoses in case of severe or atypical symptoms such as convulsions. The differential diagnosis includes perinatal infection, metabolic or neurologic problems, hyper viscosity and excitation syndromes (such as small for gestational age) and intoxications during pregnancy.

- Apart from observation of possible PNA, other indications for observation of mother-infant dyads exposed to antidepressants during pregnancy include psychiatric evaluation of mother and observation of the attachment between mother and child. Mother-infant dyads exposed to antidepressants during pregnancy should be observed for at least 48 hours postpartum by specialized caregivers as a shorter observational period entails the risk of missing maternal or neonatal complications. In the absence of specialized home care, hospital admission is indicated.

- An observational tool, completed by trained nurses, is of additional value in order to recognize, observe and objectify the development and progression of PNA. The adapted FSL may serve as an easy to apply observational tool.
REFERENCES


