Chapter 9

Summary
This thesis focuses on symptoms of poor neonatal adaptation (PNA) after exposure to selective antidepressants (SADs) in utero. Symptoms of PNA, such as sleeping- and feeding difficulties, are mostly mild and self-limiting. However, the nonspecific nature of PNA symptoms makes it difficult to distinguish PNA from other, more severe neonatal pathology, such as perinatal infection. When the origin of symptoms is unclear, invasive additional testing may be necessary which can be stressful and harmful to the infant and parents. Apart from exposure to SA, other factors seem to play a role in the development of PNA. As knowledge on these etiological factors is limited, it is impossible to predict which infant will develop PNA. Therefore, all SAD-exposed infants are clinically observed postpartum.

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. Secondly, we aimed to improve the feasibility of the Finnegan scoring list, an observational tool for PNA. Our third and final aim was to formulate evidence-based recommendations on the type and duration of the observational period of SAD-exposed mother-infant dyads.

In chapter 1, the general introduction, current knowledge on PNA after exposure to SADs in utero was described and knowledge gaps were identified. Apart from PNA, exposure to antidepressants can have other consequences including congenital malformations, perinatal effects and long-term effects, which were discussed in this chapter. In addition, we reflected on the high prevalence of psychiatric disorders during pregnancy and postpartum. In part, this is caused by the fact that women with a history of a psychiatric disorder are vulnerable for recurrence or worsening of psychiatric symptoms during this period. As these symptoms can have negative effects on both mother and child, prevention and treatment are important. Thereby, the possible negative effects of SAD use and the psychiatric symptoms have to be weighed.

Chapter 2 provides an overview of the existing literature on PNA after exposure to psychotropic medication. With this review we identified several unresolved issues concerning the etiology of PNA, the absence of a feasible observational tool and the lack of evidence with respect to observation of infants exposed to psychotropic medication in utero.

Chapter 3 reports a prospective controlled study, wherein the role of the fetal serotonin system in the etiology of PNA after exposure to SADs 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.

**Chapter 4** describes a prospective controlled study into the role of cortisol in the development of PNA in SAD-exposed infants. Neonatal hair cortisol levels on the first day postpartum represent the mean cortisol level during the last trimester of fetal life. We compared hair cortisol levels between infants not exposed to SADs, SAD-exposed infants who developed PNA and SAD-exposed infants who did not develop PNA. 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** reports a cohort study on risk factors for PNA in SAD-exposed infants. 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. 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 **chapter 6**, we describe an observational study wherein we aimed to shorten and simplify the Finnegan scoring list (FSL) while preserving its clinimetric properties. The FSL has never been validated, however is widely used as an observational tool for symptoms of PNA and can support the pediatrician in the diagnostic process. However, the large amount of items and the differential weighing of items makes it time-consuming and error-prone. During the postpartum observation of SAD-exposed infants, trained nurses completed the FSL three times a day for 72 hours. From these completed lists, the adapted FSL was created by selecting items through forward analysis. 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, the clinimetric properties of the original and adapted FSL were assessed. The original FSL had a sensitivity of 100% and specificity of 48% 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 infants exposed to SADs in utero. As the specificity of the adapted FSL is low, the list should not be used as diagnostic tool.

Chapter 7 reports an observational study among mother-infant dyads, which were admitted directly postpartum for 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 of SAD-exposed mother-infant dyads. In 38% of mother-infant dyads one or more interventions were performed. The 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.

In chapter 8 we reflected on the results from the previous chapters. We concluded that PNA seems to have a multifactorial origin. Apart from the SAD-exposure, other factors including the HPA axis, serotonergic system, neonatal gender, maternal and neonatal stress seem to play a role. As most of these factors are interrelated, it is not possible to establish the risk of PNA beforehand. Due to this multifactorial origin and the nonspecific nature of symptoms, it is 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. Thereby, the adapted FSL might serve as an easy to apply screening tool. We would advise an observational period of at least 48 hours postpartum 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.

Furthermore, methodological issues were discussed in this chapter, including the lack of a validated diagnostic tool for PNA and the implications of observational studies. Lastly, implications for future research and future practice were discussed.