Perinatal Depression and Psychiatric Considerations

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Trailer

Perinatal depression (PND) is one of the most common complications of pregnancy. Estimates of prevalence range from 10% to 20%. The perinatal period is associated with complex and unique biological, socio-environmental, and psychological changes for each woman. PND is a burdensome disorder with a profound intrusive impact on the (expectant) mother (to be), her (unborn) child, but also the supporting system. PND is heterogeneous in presentation with likely multifactorial etiologies for each woman. Apart from psychosocial factors, researchers investigated potential underlying endocrinological, immunological, and (epi)genetic factors associated with PND. The Edinburgh Postnatal Depression Scale (EPDS) is the gold standard for detection. The main goals of treating PND are to reduce maternal psychiatric symptoms and to support maternal–child attachment. A stepped-care approach is advocated, in which mild to moderate symptoms should be treated with psychotherapeutic interventions, whereas women with severe symptoms or women who do not respond to nonpharmacological treatment, pharmacological treatment can be suggested. A weighted decision should be made.

Definitions

Perinatal period = period starting from conception to 12 months after birth

PND = perinatal depression

EPDS = Edinburgh Postnatal Depression Scale

DSM-5 definition of a MDD with postpartum onset = major depressive episode (MDD) with symptoms start during pregnancy or in the 4 weeks following delivery

Suicidality = broad concept that can range from suicidal thoughts to suicidal attempts as well as completed suicides themselves

Learning Objectives

After reading this chapter, the readers should be able to define PND and recognize the associated symptoms. The risk factors and underlying pathophysiology of a PND must be understood. The reader must gain insight into the treatment options, both therapeutic and medicinal.

25.1 Introduction

The perinatal period (pregnancy and the first postnatal year) is a period of important changes and great adjustment. It is a period of emotional ambivalence, where high intense positive affect go hand in hand with difficult negative emotions and, consequently, vulnerability to emotional problems such as depression [1].

"Life" is programmed in the early beginning. The first 1000 days (from conception until age two) can be considered as the most intense period of life, in which every human being is formed. In no other period of life, so many biological and as socio-emotional developmental milestones have to be reached. Therefore, the environment in which these developments take place is crucial, since organ structures and functions are formed under the influence of the environment and need to last a lifetime. Spending these 1000 days (even partially) in circumstances of parental depression places a burden on the child's development [2, 3]. Perinatal depression (PND) can have a significant adverse impact on the mother, her child, and the supporting environment (e.g., partner and family). PND is heterogeneous in presentation and most likely has multifactorial etiologies for each woman. Hence, the precise mechanisms that guide these intergenerational transmissions are largely unknown.

Since the use of assisted reproduction techniques, the rates of twins and triplets have significantly increased. After a debilitating

period of subfertility, couples may idealize a twin pregnancy. On the other hand, the news of a twin pregnancy may also cause anxiety because of the increased perinatal risks. Multiple pregnancy often causes more discomfort and requires greater psychosocial adaptation from parents than a singleton pregnancy. Furthermore, the physical changes that accompany pregnancy can strongly influence body image and self-confidence, which are important risk factors for PND. Obviously, sleep deprivation and increased workload are associated with the postpartum and these are even more common in twin or triplet pregnancies [4, 5]

25.2 Prevalence

Perinatal depression – comprising minor and major depressive episodes – is one of the most common complications of pregnancy [6, 7]. The estimated point prevalence of major depressive disorder is estimated in the 3·1–4·9% range during pregnancy and around 5% the first 3 months postpartum. Similarly, estimated point prevalence for minor depression is around 11% in pregnancy and 13% in the first 3 months postpartum. In addition, the period prevalence of depression during pregnancy and the first 3 months after delivery are estimated at 18.4% (12.7% having major depression) and 19.2% (7.1% having major depression), respectively [8–10]. According to a systematic review by Woody et al. (2017) [11], the overall pooled prevalence for PND is 11.9%. There were insufficient data to calculate the pooled incidence. There was a clear discrepancy between the low- and medium-income countries and the high-income countries on the other hand. It is suggested that 33% of postnatal depression has its onset during pregnancy and 27% already pre-pregnancy [12]. Moreover, PND is a burdensome disorder with a profound intrusive impact on the expectant mother, her (unborn) child, but also the supporting system [13].

The question arises whether the prevalence of PND is higher in twin and higher-order pregnancies. Most studies focus on the postpartum period, and only limited data are available on the prenatal period. Furthermore, most studies did not control for the baseline presence of depression before conception.

In a systematic review, the overall prevalence of PND in twin and higher-order pregnancies was estimated between 12.2% and 19% [14]. Ross et al. (2011) concluded that there is an association between multiple births and postpartum depression during the first postpartum year. Some smaller studies have demonstrated an increased prevalence of depression as well as anxiety in multiple pregnancies [4]. If further studies would confirm these data, this may warrant targeted interventions for this population.

Ross et al. (2011) indicated little or no increased risk for postpartum depression among women who use assisted reproductive technology (ART) to conceive versus women with naturally conceived multiple pregnancies. They pointed out that the women using ART differ from other childbearing women, because their pregnancy is planned, they are more likely to have a stable relationship and have a higher economic status [14]. Additionally, the meta-analysis by Van den akker et al. (2016) concluded that mothers of ART multiple births were significantly more likely to have depression and stress than mothers of ART singletons, but were no different from mothers of naturally conceived multiples [15].

Determining the prevalence of PND is associated with several methodological issues. First of all, the screening tools to assess depression as well as the time point of assessment within the studies vary greatly. Furthermore, different definitions of PND are applied. As a consequence, it is often not possible to differentiate between transient maternal distress and clinically significant postpartum depression. Third, the sample sizes of the study populations are often small and appropriate comparison groups lack. Additionally, most studies lack control of maternal psychiatric history and other important sociodemographic predictors of depression. The latter is of course a serious limitation. On the other hand, some studies

specifically exclude women with a known psychiatric history. Finally, most of the studies do not control for the use of ART, whereas this is crucial information, since ART and the occurrence of multiple births are correlated and subfertility as well as the associated reproductive treatments can cause stress, anxiety, and depression [14].

25.3 Diagnosis and Presentation

Currently DSM and International Classification of Diseases (ICD) do not categorize PND as a separate diagnosis. DSM-IV defined PND as an episode of major depressive disorder with onset within 4 weeks of delivery [16]. According to DSM-5 a specifier "with peripartum onset" can be added to a major depressive episode (MDD) if the symptoms start during pregnancy or in the 4 weeks following delivery [17]. The ICD, 11th Edition (ICD-11), uses a time frame of 6 weeks postpartum to identify "mental and behavioral disorders associated with the puerperium," without psychotic symptoms. A distinction can be made between mild and severe depression [18].

One of the main issues is the short timeframe used in these definitions. It is debated to further extend this timeframe to 6 months unto 1 year postpartum given the numerous, unique biological, psychological, and social traits and factors that extend beyond 4 weeks after delivery [19, 20].

The presentation of PND largely resembles the presentation of MDD outside the perinatal period. Depressed mood and/or loss of interest or pleasure must be present, together with five or more additional symptoms: changes in weight or appetite, psychomotor retardation or agitation, fatigue or loss of energy, concentration difficulties, sleep disturbances (insomnia or hypersomnia), feelings of worthlessness or excessive or inappropriate guilt, and recurrent thoughts of death and/or suicidal ideation. The symptoms must have been present for 2 weeks and must cause significant distress or functional impairment. When at least two but less than five symptoms are present in the depressive episode, this is defined as minor depression. On the other hand, the presentation and content of PND might differ from MDD outside the perinatal period. PND might be accompanied by a reduction in mother–child bonding, as well as important feelings of guilt and insufficiency towards/concerning motherhood. Furthermore, isolation on an emotional and social level might occur more often, since women are ashamed of having these negative feelings and thoughts during a period, which is supposed to be a joyful period according to societal perception.

Diagnosing PND is challenging. Often PND is under-recognized because some symptoms (fatigue, sleep disturbance, changes in weight or appetite) are perceived to be normal during the perinatal period [17].

When the depression is severe, suicidality may be present. This is a broad concept that can range from suicidal thoughts to suicidal attempts as well as completed suicides themselves. Suicide is one of the leading causes of maternal and perinatal mortality. Therefore, early detection and intervention may prevent self and infant harm [9]. The exact incidence is difficult to determine, because of the stigma associated with suicidality during the perinatal period [21]. Roughly one in 50 suicides in women aged 16–50 years and one in 25 suicides in women aged 20–35 years take place in the perinatal period [22].

PND is the largest risk factor for maternal suicide and infanticide [23]. Furthermore, a prospective longitudinal research by Martini et al. (2019) revealed that a history of suicide attempt is associated with suicidality and therefore an additional important risk factor. On the other hand, living with a partner and social support significantly reduced the odds. Other risk and protective factors associated with PND are discussed below [21]. Khalifeh et al. showed that suicide during the perinatal period is often violent and more likely to occur in women with a depression diagnosis and recent illness onset, whereas this depression was less likely to be actively treated, particularly with medication [22].

A large retrospective trial by Gressier et al. (2017) studied women admitted with their

child to a mother-baby unit (MBU) during the first year after birth. They concluded that more than 11% attempted suicide during the perinatal period, with two thirds of these attempts taking place in the postpartum period. Women attempting to commit suicide during pregnancy have different psychopathological and environmental profiles compared to those, attempting suicide during the postnatal period. Pregnancy suicide attempts are mostly linked to addictive behaviors and a history of miscarriage, which suggests pregnancy-related stress and/or difficulties which interfere with the pregnancy, whereas post-partum suicide attempts are more associated with mood regulation and younger age [24].

25.4 Subtypes and Course of Perinatal Depression

Recently, there has been increasing evidence that depressed mothers cannot be considered a homogeneous group [25–27]. Different subtypes of PND have been defined. Three different dimensions measured by the Edinburgh Postnatal Depression Scale (see below) were taken into account: depressed mood, anxiety, and anhedonia. On the basis of these dimensions, five distinct subtypes of PND were identified: severe anxious depression, moderate anxious depression, anxious anhedonia, pure anhedonia, and resolved depression. There are clear differences between these subtypes in terms of time of onset and symptom characteristics. Women with the subtype anxious anhedonia for example were more likely to have onset of symptoms in the postpartum period, and this subtype was associated with more severe depression [26]. On the other hand, the most depressed group in the study of the international postpartum depression: action towards causes and treatment (PACT) consortium was characterized by an onset of symptoms during pregnancy and more obstetric complications [25]. Furthermore, poor partner involvement is shown to be associated with increasing depressive symptoms during pregnancy [28].

With regard to the course of PND, further differences are observed. Although the majority of women recover from a PND, the depression can become chronic in a relatively large subgroup [27, 29]. Approximately 30% of postpartum-depressed mothers from community samples, and 50% of mothers with PND from clinical samples remained depressed beyond the first postnatal year [27]. These women also have an increased risk of approximately 40% for subsequent postnatal and non-postnatal relapse [10, 30, 31]. These findings are supported by the data from Torres et al. (2019). In their prospective study, only 66.3% of the mothers with a PND achieved full remission at 12 months postpartum, and for 9.7% of women, depressive symptoms persisted after 2 years of follow-up [29]. A perceived lower quality of partner relationship, a history of depression, sexual abuse, lower-quality maternal care, higher parental stress, contextual risk factors, and personality-related vulnerability have been consistently found to predict a chronic course of postpartum depression [27].

Furthermore, there is evidence for an increase of depressive symptomatology during pregnancy over the past decades, despite improvement of protective factors. Potential explanations may be greater awareness, high social expectations, and the influence of social media [32].

25.5 Postpartum Blues

Up to 80% of the women experience postpartum or baby blues. The onset is typically day two or three after delivery and last less than 10 days. The symptoms peak between 3 and 5 days after birth. It is important to mention that the postpartum blues is not considered to be pathological, but part of normal hormonal changes during the postpartum period. The syndrome is characterized by emotional liability (euphoria versus misery), anxiety, irritability, restlessness, insomnia, poor concentration, tearfulness, and hypersensitivity. The relationship between postpartum blues and postpar-

tum depression remains unclear. There is limited evidence that the intensity of the blues may predict the later development of depression, but no systematic research has confirmed this. Also, the impact of multiple births on the incidence of postpartum blues remains unknown. But it is highly probable that caring for more than one baby would cause more psychological stress for a mother [5, 33].

25.6 Risk Factors

In their recent review, Kimmel et al. (2019) state that the perinatal period is associated with complex and unique biological, socio-environmental, and psychological changes for each woman. Whether or not a PND is present depends on a complex combination of risk and protective factors. As a consequence, every woman has a unique mix of factors that are dysregulated or imbalanced [9, 19, 34, 35].

The most important risk factors are a personal history of depression, anxiety or trauma, as well as a family history of (perinatal) depression. Furthermore, the lack of social support is a common risk factor. Pregnant women and women in postpartum need both emotional and practical support. Support from their partner is essential, but a wider network they can rely on is needed. If this is missing, feelings of loneliness and hopelessness may arise. With regard to personality characteristics, it is known that neuroticism, low self-esteem, and perfectionism are more frequently associated with PND. Other risk factors that may play a role are ambivalence toward pregnancy, obstetrical stressors, and socio-economic status [5, 9, 36, 37].

The abovementioned risk factors apply to singleton as well as multiple pregnancies. Twin and higher-order pregnancies entail more specific risk factors such as prematurity, obstetric complications, use of ART, and operative delivery. These risk factors are more common among multiple birth mothers [38].

After birth, the prevalence of PND is also associated with child factors. The risk of prematurity is greater with twin and higher-order pregnancies and requires a larger adjustment of the parents, both practically and emotionally. Premature newborns may be more difficult to feed and need more vigilant care. Difficult temperament, low adaptability, and unsettled behavior can further implicate care. Separation of mother and infants is common with prematurity and can be a contributing factor to PND.

Taking care of two or more infants at the same time is exhausting, especially when it is impossible to meet the needs of the infants at the same time. This can lead to a sense of guilt and hopelessness [5].

25.7 Screening

Even though PND is highly prevalent (10–20%), it is estimated that only around 40% of the cases are detected, around 20% receive any form of treatment, and 3–5% achieve remission (Milgrom & Gemill 2015; Cox, Sowa, Meltzer-Brody, & Gaynes, 2016; Flynn, Davis, Marcus, Cunningham, & Blow, 2004; Kimmel et al. 2019). Factors that might influence under-identification and treatment seem to be the heterogeneity of PND clinical presentation, stigma associated with PND, lack of transportation, difficulty obtaining child care to attend appointments, complex decision-making around whether to take medication during the perinatal period, and lack of adequate availability of perinatal mental health care providers (Goodman, 2009; Hansotte, Payne, & Babich, 2017; Kimmel et al. 2019).

A positive screening indicates that the likelihood of a possible depression is increased. Therefore, it is very important that a proper diagnosis is made, based on clinical judgment. Furthermore, a thorough psychiatric history, medication history, as well as the impact on functioning must be assessed. Ideally, this should take place during preconception counseling [39].

The purpose of screening tools in PND is its rapid detection and treatment in order to reduce the associated morbidity and mortality. During the prenatal and postnatal period, there is an increased contact with care provid-

ers, but nevertheless, still too little attention is paid to potential PND. Over the past years, there has been an ongoing debate about the benefits of depression screening during the perinatal period as a routine component of adequate maternity care. Screening programs seem to have positive results. However, there is an important need for appropriate, longitudinal, "real world" evaluations of the effectiveness of PND screening and broader psychosocial assessment programs (Reilly et al. 2019). It is important to also offer a follow-up procedure and treatment if indicated [11, 37, 40].

Currently, The Edinburgh Postnatal Depression Scale (EPDS) is the gold standard to detect PND [41]. This scale was initially developed for the postpartum period, but it has also been validated for assessment during pregnancy [42]. It contains a 10-item list regarding depression, including the presence of suicidal thoughts, and anxiety symptoms during the past 7 days. Every item has four possible answers, scored zero to three. The total score ranges from 0 to 30. Different threshold values have been suggested, with a value of 10 or more suggesting possible depression and a value of 13 or more indicating probable depression. In the systematic review by Woody et al. the EPDS cut-off for PND used in the included studies ranged from 10 to 15 [9, 11].

25.8 Pathophysiology

Until present, the pathophysiological mechanisms of PND remain unrevealed. Apart from psychosocial factors, researchers investigated potential underlying endocrinological, immunological, and (epi)genetic factors associated with PND [9, 43, 44].

A possible hypothesis regarding the pathophysiology of PND is based on the extensive fluctuations of reproductive hormones during the perinatal period. The postpartum is characterized by a rapid decline in estrogen, progesterone, and allopregnanolone levels, which may affect neurotransmission and neuroplasticity in the central nervous system. Brain-derived neurotrophic factor (BDNF) is probably associated with this process [43, 45]. Oxytocin has also been studied in connection to PND [43]. Furthermore, endocrinological changes seem to be associated with PND, such as hypothalamic–pituitary–adrenal (HPA) axis dysfunction and thyroid hormone alterations [43, 45]. Neuroimmune pathways might also be connected to PND, for example decreased levels of ω3-polyunsaturated fatty acids (PUFAs), IL-6, and leptin [43, 45].

Furthermore, the systematic review by Figueiredo et al. explored the potential influence of genetic factors on the symptoms of PND [44]. They account for potential genetic–environmental interactions. Specifically, during late pregnancy and the early postpartum period women appear to be more susceptible to genetic factors or epigenetic modifications. Since this period is characterized by strong changes in estrogen levels, there is speculation about a possible role of estrogen as a neuromodulator with possible effects on neuroplasticity [44].

However, certain forms of PND likely have stronger biologic underpinnings, whereas other forms may be more strongly influenced by the contribution of psychosocial factors [9, 43]. Further research is needed.

25.9 Perinatal Bereavement

Twin and higher-order pregnancies are associated with increased risk of complications, including prematurity, congenital fetal anomalies, and perinatal mortality. Depending on the chorionicity, these complications may either affect one twin with a healthy co-twin or have consequences for both. Prematurity and congenital abnormalities require major adjustments from (future) parents and may entail heartbreaking ethical dilemmas. These may involve grief for the loss of an imagined child and the gradual adjustment to the reality of the actual infant. Loss of an infant during pregnancy, stillbirth, or neonatal death may encompass a complex psychological paradox with mourning and detachment on the one hand and attachment on the other hand [5, 46].

25.10 Treatment

25.10.1 General Recommendations

Efficient treatment of PND is imperative [9]. The main goals of treating PND are to reduce maternal psychiatric symptoms and to support maternal–child bonding [43]. Untreated PND is associated with increased risk for negative outcomes in mother and child during the perinatal period [47–49].

Women with PND are more likely to misuse alcohol, nicotine, and other substances during pregnancy, which could negatively impact pregnancy outcomes. Untreated PND may be associated with low birthweight, increased risk of preterm delivery, gestational hypertension, and perinatal death [39, 50].

Antenatal maternal depression and anxiety have been associated with a range of adverse outcomes for the child such as preterm birth, impaired mother–infant bonding, and impaired cognitive and socio-emotional development of the child (emotional problems, symptoms of ADHD, conduct disorders, impaired cognitive function, schizophrenia, and possibly autism) [39].

All women should receive information about PND and the potential treatment options, including the potential benefits and harms of each treatment. The psychiatric symptoms, severity of the depression, psychiatric history, and preferences of the woman must be taken into account. Social support and adequate sleep should be optimized [43].

A stepped-care approach is advocated, in which the intensity of the intervention matches the severity and acuity of the clinical presentation. Mild to moderate symptoms should be treated with psychotherapeutic interventions, whereas pharmacological treatment should be suggested for women with severe symptoms or women who do not respond to nonpharmacological treatment [43].

Obviously, not only the treatment, but also the prevention of PND is mandatory. In a large review by O'Connor et al., there was evidence for the effectiveness of counseling-based interventions like depression-focused cognitive behavior therapy (CBT) and interpersonal psychotherapy (IPT) in the prevention of PND [51].

25.10.2 Nonpharmacological Therapy

A recent review, on the effect of PND treatment for mothers on parenting and child development, found promising findings exist for IPT, CBT, maternal–child interaction guidance, and other interventions including massage and psychotherapeutic group support; it is difficult to draw any definitive conclusions regarding any one treatment that shows the most potential to influence maternal and infant outcomes. Letourneau et al. (2017) concluded that there is insufficient evidence available to make policy or practice recommendations. Further research in this area is recommended [52].

25.10.2.1 Interpersonal Therapy (IPT)

IPT is a validated form of psychotherapy with a focus on the interpersonal context and the changes and stressors that can lead to depressive symptoms. It is not surprising that this form of psychotherapy is helpful for PND, since the theme of role change during pregnancy and postpartum plays an important role. This form of therapy can also be useful if there are problems in the interpersonal context, such as relationship problems or little social support, because these are known risk factors for PND [53, 54].

A systematic review by Sockol et al. (2018) and a meta-analysis by van Ravensteyn et al. (2017) assessed the efficacy of IPT during pregnancy. In prevention studies, IPT was effective for reducing depressive symptoms and the prevalence of depressive episodes. In treatment studies, IPT reduced symptoms of depression and anxiety and improved relationship quality, social adjustment, and social support [53, 54].

25.10.2.2 Cognitive Behavioral Therapy (CBT)

The principle idea of CBT is the assumption that thoughts (dysfunctional patterns of cognition) have an influence on our behavior and on how we feel, and vice versa. The techniques used in CBT focus on changing the content of these irrational cognitions [54, 55].

Results of the meta-analysis by Sockol et al. (2015) and van Ravensteyn et al. (2017) provide evidence of CBT being effective in the treatment and prevention of PND, with small to moderate effects as a result [54, 55].

25.10.2.3 Mindfulness-Based Interventions (MBI)

Mindfulness can be defined as a mental state that is characterized by focusing on the present moment and awareness of present feelings, thoughts, and bodily sensations. MBI are relatively new and are effective in the prevention and treatment of depression and anxiety, especially by reducing the levels of rumination. Despite promising results in the general population, between-group analyses failed to find any significant post-intervention benefits of MBI for depression, anxiety, or stress in comparison to control conditions in a recent meta-analysis by Taylor et al. [56]

25.10.3 Pharmacologic Treatment

25.10.3.1 General Recommendations

As previously reported, the current guidelines agree on psychotherapy (especially cognitive behavioral therapy) as initial treatment for mild to moderate new depressive episodes versus antidepressants for severe depression.

The start or modification of antidepressant therapy during pregnancy or postpartum should be based on an individual assessment of the risks and benefits in each particular case. This must be properly discussed with the future parents and all care providers involved. Clear information about the risks of the medication, as well as the risks of untreated disease must be discussed extensively. It is advised to avoid switching medication during pregnancy unless the benefits outweigh the risks. Equally, suddenly stopping medication should be avoided to prevent withdrawal symptoms. Monotherapy is preferred, with the lowest effective dose. In women with severe PND, it is recommended that delivery should take place in hospital [39]. For ongoing depression, there is an ongoing debate on whether or not antidepressants can and should be discontinued [50].

In the past, much of the data regarding the risks of medication in the perinatal period have been retrospective. Fortunately, during recent years, there have been larger prospective cohort studies. Molenaar et al. (2018) reviewed 16 Clinical Practice Guidelines (CPG), half of which were exclusively on perinatal management, the other half were general guidelines with a section on perinatal recommendations. Most of the guidelines recommend sertraline and citalopram during pregnancy. Breastfeeding is encouraged with sertraline as preferred medication. Most of the guidelines agree on avoiding paroxetine during pregnancy, because of increased risk of congenital cardiovascular malformations in the newborn. Therefore, paroxetine is not the preferred treatment for new episodes, but on the other hand switching antidepressants for ongoing treatment is discouraged [50]. Fluoxetine was marked "unfavorable" by five guidelines due to its long half-life and its presence in breast milk.

A recent study analyzed prescribing patterns during pregnancy for antipsychotics (APs), antidepressants (ADs), and mood-stabilizing antiepileptics (AEDs) in Denmark from 2000 to 2016. A marked increase in the prevalence of the use of ADs during pregnancy was seen from 2000 to 2011 (from 6 to 41 per 1000 pregnancies ending in a delivery), but currently they appear slightly in decline. Age, smoking, obesity, and social status were generally associated with increased use of psychotropic drugs [57].

25.10.3.2 Congenital Malformation

Serotonin is essential for healthy fetal development during embryogenesis. SSRIs cross the placental barrier and block serotonin reuptake transporter (SERT) sites, disturbing the free movement of serotonin during this

critical phase of development, which can impact morphogenesis and organogenesis [58, 59].

Despite the available research, there is no general consensus regarding the risk of in utero antidepressant exposure and congenital malformations. The association between antidepressant use during pregnancy and congenital malformations could be explained by the underlying maternal depression, unaccounted potential confounders, lack of statistical power, etc. The available literature is limited on singleton pregnancies and multiple pregnancies are mostly excluded, due to the known increased risk of adverse pregnancy outcomes. Furthermore, miscarriage is usually excluded, although this can be an indicator of severe malformations [59].

According to the 2018 NICE guideline, there was some evidence for a statistically significant association between all SSRIs and congenital malformations ($p = 0.04$) with an absolute risk difference of 9 more per 1000 [60]. Regarding the risk of cardiac malformations, the cohort-study by Huybrechts et al. (2014) suggested no increase in the risk of cardiac malformations attributable to antidepressant use during the first trimester [61]. A Nordic population-based study by Furu et al. (2015) confirms these findings. Although the prevalence of septal defects and right ventricular outflow tract defects was higher in exposed infants, the lack of an association in the sibling-controlled analyses points against a teratogenic effect of these drugs [62].

Regarding the specific SSRIs, paroxetine was statistically associated with congenital ($p = 0.05$), major congenital ($p = 0.04$), and cardiac ($p = 0.006$) malformations, and fluoxetine with major congenital ($p = 0.008$) and cardiac ($p = 0.02$) malformations with absolute risk differences ranging from 3 to 8 more per 1000. There was some evidence for a statistically significant association between citalopram and escitalopram and ventricular septal defects with absolute risk difference of 4 and 9 more per 1000, respectively [60].

25.10.3.3 Pregnancy Outcome

The effect of antidepressant use and pregnancy outcome was extensively studied by Ross et al. (2014) in their systematic review and meta-analysis. They concluded that there was no significant association between antidepressant medication exposure and miscarriage. Gestational age and preterm delivery were statistically significantly associated with antidepressant exposure (mean difference [MD] [weeks], 0.45; 95% CI, 0.64–0.25; $P < 0.001$; and OR, 1.55; 95% CI, 1.38–1.74; $P < 0.001$, respectively). Also, antidepressant exposure during pregnancy was significantly associated with lower birth weight (MD [grams], −74; 95% CI, 117–31; $P = 0.001$). When this comparison group was limited to depressed mothers without antidepressant exposure, there no longer was a significant association. Antidepressant exposure was significantly associated with lower Apgar scores at 1 and 5 minutes (Ross 2014). SSRIs are also known for their increased risk of bleeding [14].

25.10.3.4 Poor Neonatal Adaptation Syndrome (PNAS) and Persistent Pulmonary Hypertension of the Newborn (PPHN)

Multiple studies support the existence of a poor neonatal adaptation syndrome (PNAS) after in utero exposure to SSRIs. The most common symptoms are irritability, constant crying, sleep disturbances, respiratory problems, tremors, hypotonia, vomiting, and feeding difficulties. Most symptoms develop within 2 days after birth, are usually mild, and disappear spontaneously.

Due to the absence of validated questionnaires for neonatal withdrawal based on SSRI use of the mother, the Finnegan questionnaire is frequently used. The Finnegan score assesses withdrawal symptoms based on addiction of the mother, but this has not been validated for withdrawal based on SSRI use in the mother [39, 63, 64]. Klinger et al. (2011) showed that infants who developed PNAS

had normal cognitive ability, but were at an increased risk for social–behavioral abnormalities. Therefore, they concluded that follow-up evaluation of symptomatic neonates should be considered [63].

Another risk associated with SSRI use during pregnancy is persistent pulmonary hypertension of the newborn (PPHN). Serotonin has a role in the development and modulation of the lungs, and this could be a factor in the development of PPHN [10]. The findings of a large network meta-analysis by Masarwa et al. (2019) suggest that exposure to SSRIs during pregnancy is associated with a twofold increased risk for PPHN. Sertraline is most likely to have the lowest risk for PPHN compared to other SSRIs [65].

25.10.4 Review Questions

1. Define a PND.
2. Which symptoms are associated with a PND?
3. How to screen for a PND?
4. Which factors play a role in the pathophysiology of PND
5. What are the treatment options of PND?

25.10.5 Multiple-Choice Questions

1. What is the prevalence of major and minor PND?
   (a) 10–20%
   (b) <5%
   (c) 5–10%
   (d) >20%

Answer: (a)

2. Which of the following symptoms are not mentioned in the definition of a MDD according to the DSM 5?
   (a) Suicidality
   (b) Sleep disturbances
   (c) Loss of interest
   (d) Panic attacks

Answer: (d)

3. What is the percentage of women who suffer from postpartum blues?
   (a) 50%
   (b) 80%
   (c) 20%
   (d) 40%

Answer: (b)

4. Which SSRI should be avoided during pregnancy because of increased risk of congenital cardiovascular malformations in the newborn?
   (a) Sertraline
   (b) Escitalopram
   (c) Paroxetine
   (d) Fluoxetine

Answer: (c)

5. Which questionnaire is currently considered the gold standard for PND screening?
   (a) EPDS
   (b) STAI
   (c) HAMD
   (d) MINI

Answer: (a)

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