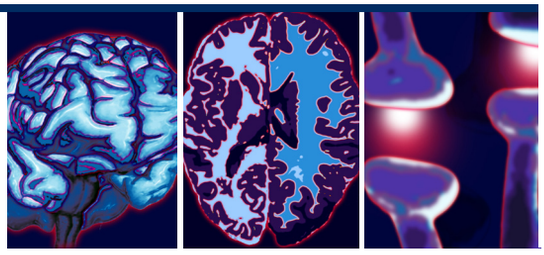
REVIEW



Perinatal depression: detection and treatment

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Practice points

- Perinatal depression is common, yet often unrecognized and undertreated.
- Failing to detect and treat perinatal depression has negative consequences, not only for the mother but also for the developing fetus, the infant and child development.
- Psychotherapy should be considered first choice for less severe maternal illness.
- Pharmacologic treatment of maternal perinatal depression needs careful risk–benefit analysis, weighing fetal exposure to the medicine against the effects of maternal illness itself.
- To date, alternative and complimentary treatments, while showing promising preliminary results, have not undergone well-powered rigorous investigations and cannot be generally recommended as an alternative treatment for perinatal depression.

SUMMARY Depression in women during their childbearing years is common. Routine depression screening coupled with multidisciplinary collaborative care models integrating case management is paramount. Risk factors for perinatal depression include previous history of depression, interpersonal conflict and limited social support. Antenatal depression may lead to poor pregnancy outcomes, such as pre-eclampsia, insufficient weight gain, decreased compliance with prenatal care and premature labor, and continue into postpartum depression, which in turn pose a risk for mother–infant bonding and subsequent child socioemotional development. Currently available literature suggests that overall, the risks of antidepressant use in pregnancy/lactation are small relative to the risks due to maternal untreated illness itself; however, for decision-making, careful individualized risk–benefit analysis and informed consent from the affected patient are crucial. Current guidelines suggest nonpharmacological treatments as first-line interventions for mild-to-moderate perinatal illness, while reserving pharmacological treatment for moderate-to-severe illness. Antidepressants, psychotherapies, alternative or complimentary approaches, and involving family in the supportive care of perinatal women are all effective strategies. More research is needed to determine the long-term and developmental effects in children exposed to antidepressants or untreated illness during pregnancy and lactation.

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Background & prevalence

Across the USA, prevalence studies show that one in five women experience an episode of major depressive disorder (MDD) during their lifetime [1] and illness onset is most commonly seen between the ages of 20 and 40 years, the prime age range for childbearing [2]. Studies have shown that 10–16% of pregnant or postpartum women are depressed, and even more women experience subsyndromal depressive symptoms, which are frequently overlooked [3,4]. A more recent meta-analysis, using stringent diagnostic criteria and not self-report measures, found slightly lower estimates of point prevalence for combined major and minor depression: 8.5–11% during pregnancy and 6.5–13% during the first year postpartum [5]. Finally, as many as 7.5% of pregnant women have a new onset episode of major depression during this time period [5]. Yet, most affected women do not present for treatment [6]; in fact, one study found that of the pregnant women who screened positive for depression in an obstetrics setting, 86% did not receive any form of treatment [7]. This study also showed that while most women seek some prenatal care over the course of their pregnancy, many women do not seek mental health services because of stigma [7]; thus, antenatal visits to an obstetrician or primary care provider may provide an opportunity for screening and intervention for depression in this high-risk group. Unfortunately, screening procedures alone have not been found to impact depression outcomes [8]. Since management of a depressed, pregnant or postpartum woman also includes care of her growing fetus or her breastfeeding infant, treatment may be complicated and requires an informed, multidisciplinary approach; including input from an obstetrician, psychiatrist and pediatrician to provide optimal care.

Antenatal depression

■ Clinical features & risk factors

Perinatal depression presents with similar symptoms as at any other time point in a woman's life. Existence of depressed or irritable mood or inability to experience pleasure, feelings of guilt, hopelessness and worthlessness, sleep disturbance (insomnia or hypersomnia), appetite or weight changes, attentional difficulties, decreased energy or unexplainable fatigue, and psychomotor agitation or retardation are all hallmarks of depressive illness. In severe cases, thoughts of suicide and distorted reality testing and paranoia (psychotic depression) may be present as well [9]. Anxiety and obsessive worries centering on pregnancy outcomes and fetal safety are a very common comorbidity of perinatal depression [10]. Generalized anxiety disorder, characterized by the presence of at least 6 months of excessive worry with additional unique somatic symptoms, occurs with a rate of 8.5% during the last trimester of pregnancy. This rate exceeds the prevalence rate in nonpregnant samples (~3%), suggesting that peripartum is a vulnerable period for generalized anxiety disorder. Prevalence of panic disorder during pregnancy is 1–2%, which is consistent with prevalence outside of childbearing. Current studies reveal conflicting data regarding the course of illness across peripartum, with several studies suggesting that panic symptoms improve during pregnancy and exacerbate postpartum [11,12], and others noting no change in the course of illness during the puerperium [13,14]. Co-occurring anxiety and depressive systems are common, with 50% of women with panic disorder reporting major depression. Obsessive worries centering on pregnancy outcomes are very common in pregnancy as well. However, the prevalence of obsessive–compulsive disorder is lower during pregnancy (0.2%) relative to both postpartum prevalence (2.7–3.9%) and lifetime prevalence in the general population (2.5%). One of the most common obsessional themes during pregnancy is the fear of intentionally or accidentally harming the fetus, or that the fetus may have some undetected medical condition. Obsessive thoughts about harming the fetus (e.g., falling down stairs and hurting the unborn) must be differentiated from psychotic delusions present in psychotic depression or bipolar illness (e.g., delusion that fetus is 'eating her up from the inside'). In general, women with obsessive–compulsive disorder-like thoughts about hurting their child are very distressed, identifying these thoughts as unwanted and unreasonable. By contrast, women with psychotic harmful thoughts towards their child lack insight into their delusions and may be at risk to act on their delusion (e.g., stabbing the fetus causing major abdominal injuries to herself). In such cases, imminent safety measures for the mother and child are warranted and necessitate emergency treatment of the mother. Finally, post-traumatic stress disorder can be present during peripartum with prevalence rates as high as 8%. Post-traumatic stress disorder symptoms

have been described in women who have experienced prior miscarriages or perinatal losses, those who have had traumatic prior deliveries, or have histories of childhood maltreatment, particularly sexual abuse, with symptoms sometimes precipitated by the intrusive procedures inherent in the management of pregnancy and delivery.

In general, risk factors for new onset or recurrence of perinatal depression are personal history (particularly during pregnancy or postpartum) or family history of unipolar or bipolar depression [15], limited social support and presence of interpersonal conflict [16]. Additional risk factors include history of physical, emotional or sexual abuse; history of (or current) cigarette smoking, alcohol consumption or substance use; life stressors, such as financial or occupational obligations; stressful health concerns or relationships [10]; living alone; and ambivalence regarding the pregnancy [17].

Screening

Several sensitive brief screening tools are available for practitioners and researchers for screening depression in pregnancy or postpartum. The measure used most commonly to screen for perinatal depression is the Edinburgh Postnatal Depression Scale (EPDS), a 10-item self-report questionnaire particularly sensitive to cognitive and affective symptoms of depression during this time period [18]. If a woman scores higher than 15 during pregnancy or 13 in the postpartum period, then further diagnostic assessment is indicated [19]. The anxiety subscale (items 5 and 6) on the EPDS has been validated for screening perinatal anxiety using a cut-off score above 4 [20]. Maternal depression can be quickly assessed in the clinic by also using the two-question Patient Health Questionnaire (PHQ)-2 or the nine-question PHQ-9 [21–24]. All three scales, EPDS and PHQ-2 and -9 are free of charge and easily found on the internet **(Table 1)** [201–203]. The Postpartum Depression Screening Scale and the Beck Depression Inventory–Second Edition are also viable screening options for maternal perinatal depression [25]. Several screening instruments can be used to assess symptom severity and general functioning. One of these is the Behavior And Symptom Identification Scale (BASIS)-24, a 24-item scale that measures symptoms and general functioning in six major areas: depression/functioning, relationships, self-harm, emotional lability, psychosis and substance abuse [26]. Screening tools do not address the duration of symptoms, degree of impairment or comorbid psychiatric disorders including anxiety disorders [27], thus, if a patient scores beyond the cutoff range for any of these tools, *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) diagnostic criteria should be assessed through further interview.

Regardless of the screening method used, it is important to further question patients who manifest depressive symptoms upon screening. Screening in conjunction with follow-up interviews by case managers in person improves the quality of care and leads to enhanced follow through with mental health recommendations, including greater adherence to medications and psychotherapy [28]. Current best practice uses collaborative care models with a psychiatric consultant who co-manages difficult cases with the primary and antenatal care clinicians during the acute phase of their illness. A recent meta-analysis found that there was a twofold increase in medication compliance over 6 months with the collaborative care approach compared with patients followed only with primary care, and enhanced functional outcomes were noted in

Table 1. Screening toolkit for primary care.

Toolkit	Sensitivity and specificity	Characteristics	Ref.
EPDS	Sensitivity = 0.86 Specificity = 0.78 For positive screen >10	5–10 min, self-administered, could be self-scored	[201]
PHQ-2	Sensitivity = 0.83 Specificity = 0.92 For positive screen >3	<1 min, self-administered or can be asked	[202]†
PHQ-9	Sensitivity = 0.88 Specificity = 0.88 For positive screen >10	5–10 min, self-administered and self-scored	[203]

†The two questions from the PHQ-9 for mood and anhedonia are used.
EPDS: Edinburgh Postnatal Depression Scale; PHQ: Patient Health Questionnaire.

these patients 2–5 years later [29]. However, it is important to note that most women do not follow through with a mental health referral [30] and that each woman appears to face unique logistical and psychological barriers to engaging in treatment [31]. Therefore, in order to provide optimal and effective personalized care and enhance treatment utilization, it is crucial for clinicians to ask women about their treatment preferences and individual specific barriers for follow through.

■ Consequences of antenatal depression

Unidentified and untreated depression can lead to detrimental effects on the mother and child. Suicide is the most catastrophic possible outcome of undertreated depression. In addition, depressed women are more likely to participate in unhealthy practices during pregnancy, such as smoking and illicit substance abuse. These women have higher rates of poor nutrition, in part because of lack of appetite, leading to poor weight gain during pregnancy and risking intrauterine growth retardation. Depressed women may be less compliant with prenatal care and feel less invested in the care toward their pregnancy. Women who have depression have increased pain and discomfort during their pregnancies, reporting worse nausea, stomach pain, shortness of breath, gastrointestinal symptoms, heart pounding and dizziness, compared with nondepressed women [32]. Untreated maternal depression in pregnancy has been associated with poor pregnancy and birth outcomes, such as inadequate maternal weight gain and risk for pre-eclampsia [33], higher likelihood for preterm birth and low birth weight [34,35], smaller head circumferences, increased risk for premature delivery, increased surgical delivery interventions causing extended hospital admissions postdelivery [36,37], as well as lower Apgar scores with more admissions to neonatal intensive care units (ICUs) for the newborns [38]. Finally, depression during pregnancy is a risk factor for postpartum depression [36].

Depression is not a benign psychological syndrome, but is associated with various neurobiological disturbances that can have direct and indirect physiological effects on the course and outcome of pregnancy. Research suggests that maternal depression leads to alteration in a mother's neuroendocrine axis and uterine blood flow, which may contribute to premature delivery, low birth weight and pre-eclampsia [39,40]. Negative birth outcomes are associated most highly with depression symptoms in the second and third trimesters [41]. Babies of mothers who suffered from depression and/or anxiety during their pregnancy have alterations in their hypothalamic–pituitary–adrenal cortisol stress response functioning (fetal programming) [42,43]. These infants cry more often and are more difficult to console than babies born to nondepressed mothers [38]. Infants of women at high risk for depression are shown to have disturbed sleep compared with low-risk infants, and this effect is evident at 2 weeks postpartum and persists at 24 weeks postpartum [44,45].

If depression continues into the postpartum period, there are risks for long-term effects on a child, such as poor mother–infant attachment, delayed cognitive and linguistic skills, impaired emotional development, and behavioral issues [46–49]. Studies show these babies are fussier, vocalize their needs less, and make fewer positive facial expressions than infants of nondepressed mothers [50]. If a baby is exposed to a depressed maternal environment during early infancy, and the mother has recurrent depressive episodes, the child shows changes in neuroendocrine functioning and more behavior problems at school entry [51]. Persistent maternal depression during pregnancy was associated with a 50% increase in the likelihood of developmental delays among exposed children when they reached 18 months of age [52], independent of whether or not their mothers suffered postpartum depression as well, indicating that the adverse effect was attributable to gestational depression. As these children grow, perhaps because of early exposure or the continued stressful home environment, they are more likely to have emotional instability and conduct disorders, attempt suicide and require mental health services themselves [53,54]. It is yet unknown whether effective treatment of gestational depression can ameliorate adverse reproductive or child outcomes.

■ Treatment of antenatal depression

Pharmacological treatment

There are few current medical standards for treatment of women who have depression during pregnancy, in part because ethical constraints preclude experimental studies (i.e., randomized controlled trials) using pharmacotherapy during gestation. Current available reproductive outcomes information is based

on observational studies, including single case reports or case series, registry data, and retrospective case–control or prospective cohort studies, all of which have limitations. Data derived from these sources are summarized in meta-analyses and serve as the basis for practice recommendations [55]. However, it is important to consider that in real-world clinical decision-making the relevance of these population-level obtained data regarding the risks of drug exposure in pregnancy must be individualized to the pregnant woman's own evaluation of her acceptable degree of risk compared with the anticipated benefit of drug treatment. Mutually, the patient and her physician must decide whether treatment with antidepressants yields a more favorable outcome than not treating with medication. So far, studies comparing treatment with antidepressants versus other evidence-based treatments during pregnancy are lacking, and only a little is known regarding treatment response to antidepressants during pregnancy [56]. Finally, often pregnant women are excluded from clinical research, which prevents systematic data on treatment response, adverse effects and reproductive outcomes from being collected. Subsequently, in real practice, women are exposed to these drugs without them having undergone the rigorous efficacy investigation and mandated surveillance; thus, some experts in the area of reproductive psychiatry suggest considerations of policy changes for pre- and postmarketing studies to also include pregnant women [57]. In the USA, the US FDA has proposed labeling changes for drug use in pregnancy and lactation [204] that require regular updating of reproductive outcome data, which is likely to enhance the comfort with decision-making in the patient and her doctor.

Most women do not seek treatment, but for those who do, many physicians are unsure of how to balance maternal medication needs with risk of exposure to the growing fetus [58]. In a recent publication, both the American Psychiatric Association and American College of Obstetrics and Gynecology suggested treatment algorithms for management of a depressed woman who is contemplating pregnancy and is already taking antidepressant medication, pregnant and not receiving treatment for depression yet, or pregnant but already undergoing pharmacological treatment for depression [59]. It is of interest that these guidelines favor the use of psychotherapy prior to considering medications for women who have mild depressive symptoms without major loss of functionality, suicidality or psychotic experiences; whereas those with a moderate-to-severe impact on functionality, recurrent depressive symptoms or suicidal thinking should engage in pharmacotherapy during pregnancy [59]. Finally, women with treatment-resistant, or life-threatening or psychotic depression may benefit from electroconvulsive therapy [59].

There are a few important guiding principles for the practitioner when considering prescribing medications during pregnancy. First, often women with a history of depression who have been asymptomatic for over a year may wish to attempt to reduce or discontinue their antidepressants a few months before conception and throughout the pregnancy [60]. While common practice, the clinician should be aware of the risk of relapse; of women who discontinue their antidepressants during pregnancy, 68% experience relapse symptoms compared with 26% of women who continue their medication regimen [61]. If a woman's depression history contains multiple relapses or severe symptoms, including suicide attempts and multiple inpatient psychiatric admissions, it is recommended that she remain on antidepressants for her own safety, regardless of pregnancy status [60].

Second, the physiological changes that occur during pregnancy (e.g., increased maternal plasma volume, increased cardiac output, reduced gastrointestinal motility and increased glomerular filtration rate) are all associated with significant changes in the pharmacokinetics of medications and generally drug doses have to be increased as the pregnancy unfolds in order to be effective [62]; however, this also poses risk for postpartum toxicity if dosing is not adjusted. In addition, the activity of certain hepatic enzymes responsible for drug metabolism is either up- or downregulated during pregnancy and leads to changes in drug levels and drug efficacy. For example, enzyme activity of CYP2D6 is known to be induced during pregnancy and all medications inactivated by this enzyme (e.g., fluoxetine [63]) show lowered levels across gestation. In future, personalized medicine will allow the identification of genetically determined functionality levels of these enzymes leading to more optimal drug dosing. There is ongoing debate about the safety of selective serotonin reuptake inhibitors (SSRIs) and other serotonergic/noradrenergic antidepressants when used during pregnancy [64,65]. All psychotropic medications cross the placenta and enter the amniotic fluid [66].

General guidelines include some straightforward principles: keep the medication regimen simple, use monotherapy and avoid medication changes during the pregnancy. Use of multiple medications in sequence and medication augmentation strategies will all increase the exposure of the fetus [67]. A woman's prior history to pharmacotherapy should be considered when choosing a medication [67]. Although many factors influence pharmacotherapy during pregnancy, drugs with fewer metabolites, drug–drug interactions, more protein binding (preventing placental passage) and lesser teratogenic risk, if known, should be prioritized when possible [67].

Third, when considering treatment of gestational depression with psychotropic medications, a physician must compare population-based data on reproductive risk with the unique woman's risk for disease exacerbation with its consequences for pregnancy and neonatal outcomes, and openly elicit the woman's input regarding the value she assigns to reproductive risk versus disease benefit. The developing fetus will be exposed either to the effects of the mother's depression or the medication [68]. A recent study comparing the birth and neonatal outcomes among women with untreated MDD versus SSRI-treated women show similar adverse outcomes for both conditions. Specifically, infants exposed to either SSRIs or continuous depression across gestation were more likely to be born preterm than infants with partial or no exposure [56]. Neither SSRI nor depression exposure increased the risk of minor physical anomalies or reduced maternal weight gain. Mean infant birth weights were equivalent [56]. However, this study also demonstrates that potential third variables may confound the findings (e.g., untreated MDD women are more likely to use substances, smoke and have preconception obesity), which may, in part, explain their negative reproductive outcomes [56]. Decision-making regarding specific drug use in a particular patient is based on state-of-the-art evidence on drug safety given available data, the patient's prior treatment response to specific medication and the patient's preference after considering all available information. Adverse pregnancy and child outcomes secondary to antenatal medication exposure are potential risks for fetal malformations (teratogenity), poor neonatal adaptation (NNA) following birth, increased risk for spontaneous abortions, or preterm birth, low birth weight and neurodevelopmental toxicity.

Teratogenity

Over the past years multiple research groups have investigated the teratogenic potential of SSRIs, and to date they converge that the absolute risk for any of these malformations in association with the use of SSRIs is likely to be small [69,70]. Two large case–control studies confirmed that gestational SSRI exposure does not increase the risk for major malformation above the population-level risk of 3% [71,72]. All currently used antidepressants (SSRIs, serotonin–norepinephrine reuptake inhibitors and tricyclic antidepressants [TCAs]) can also be used for the treatment of depression in pregnancy; however, often the limiting factor for prenatal use is the comfort level with the currently available and often controversial data on safety and efficacy for each specific drug. In recent years, one specific SSRI drug (paroxetine) was under much scrutiny after its developer, GlaxoSmithKline (London, UK), published a report based on a claims database study of 815 infants that showed babies born to mothers who were taking paroxetine during their first trimester had a 1.5- to 2.0-fold increased risk for congenital heart defects, in particular, atrial and ventricular septal defects [205]. A recent meta-analysis pooling all recent studies on the malformation risk of prenatal exposure to paroxetine [64] concluded that overall the methodological rigor across the studies was very heterogeneous (e.g., some studies had no data on the length of exposure, dosing or on other confounders), the study results were partially contradictory, and, ultimately, conclusive evidence is difficult to derive. While some studies suggest that gestational paroxetine exposure leads to increased risk of unspecific [73,74] or specific [73–77] cardiac malformations, other studies report no such connection [75,78,79]. For example, Einarson and colleagues recently demonstrated that the rate of cardiac defects for babies exposed to paroxetine in the first trimester and nonexposed infants was the same (0.7%, not statistically significant) and within the expected cardiac malformation risk range for all pregnancies [79], but the limitation of their study was the low levels of paroxetine used. Berard *et al.* suggest that the teratogenic paroxetine effect may be dose and timing dependent, for example >25 mg daily intake during the first trimester is associated with cardiac malformations [73]. At the time of writing, the use of paroxetine remains controversial. Most practitioners

avoid its use during pregnancy except for those women who have demonstrated a preferential positive response to this agent in the past. When paroxetine is used, monitoring the fetus with fetal echocardiography is recommended [67].

To date, the bulk of the literature does not reveal increased risk for congenital malformations associated with pregnant women taking TCAs, which historically were the medications of choice for the treatment of depression, but currently are not used extensively [80]. Doses of TCAs may need to be increased by as much as 1.6-times the prepregnancy dose in the second half of pregnancy to establish therapeutic levels as a result of increased plasma volumes and metabolism [81].

NNA syndrome

Studies show that up to 30% of infants exposed to SSRIs *in utero* during the third trimester are likely to have symptoms of poor NNA [82–85]. These symptoms include short-term self-limited jitteriness, tachycardia, hyperthermia, vomiting, hypoglycemia, irritability, inconsolable crying, abnormal muscle tone, eating difficulties, sleep disturbances, seizures and respiratory distress [82], which leads to an overall increased rate of neonatal ICU admissions for these newborns. The NNA symptoms cluster based on three proposed underlying pathophysiological mechanisms: serotonergic toxicity (e.g., tremor, tachypnea, diaphoresis and irritability/agitation), antidepressant discontinuation syndrome (e.g., hyperthermia, vomiting, increased muscle tonus and convulsions), and symptoms caused by the immaturity of the newborns' CNS (e.g., decreased suckling reflex and eating difficulties) [86]. Case reports have presented babies with TCA exposure experiencing temporary withdrawal symptoms within the first 12 h of life, including jitteriness, irritability, urinary retention, bowel obstruction and occasionally seizures [80,86].

Some international literature suggest tapering antidepressants in the third trimester to avoid late gestation exposure and prevent poor NNA or neonatal respiratory distress. Some studies have reported a 1% increased risk of persistent pulmonary hypertension of the newborn with maternal use of an SSRI after 20 weeks gestation [87–89]; however, another recent study refuted this increased risk [90]. The neonatal respiratory complications, ranging from mild tachypnea to a need for respiratory support, could either be explained by the neonate's late pregnancy exposure to antidepressants (i.e., consistent with underlying persistent pulmonary hypertension), or by postnatal antidepressant discontinuation syndrome, mainly reported in infants whose mothers' had near term exposure to venlafaxine [91]. However, recently Warburton and colleagues reported that neonates of mothers who had discontinued SSRIs 14 days prior to delivery had similar rates of respiratory distress and NNA problems compared with offspring of mothers with continued SSRI exposure until delivery, when controlling for other maternal and neonatal confounders [92]. The same research group also found that the length of gestational SSRI exposure, rather than timing, increased the risk for neonatal respiratory distress, lower birth weight and reduced gestational age, even when controlling for maternal illness and medication dose [93], thus, complicating the decision-making process for clinicians when contemplating fetal SSRI exposure. Therefore, most practitioners in the USA avoid tapering of SSRIs in late pregnancy, as it predisposes women to a substantially heightened risk of late pregnancy and postpartum morbidity secondary to depression [94]. As with any decision regarding pharmacotherapy during pregnancy, a decision regarding tapering should be considered on an individual basis, considering the risks for maternal illness versus the risk for neonatal withdrawal symptoms [26].

Spontaneous abortions & preterm birth

Wisner and colleagues demonstrated that the rates of preterm birth are over 20% both for women with untreated gestational MDD and continuous SSRI exposure [56]. However, socioeconomic characteristics among the untreated MDD group known to influence preterm birth rates independent of depression may have confounded the results [95]. Others have also found associations between gestational SSRI exposure and preterm birth [96,97]. Exposure to SSRIs during pregnancy was also associated with an increased risk of preterm delivery, a low 5-min Apgar score and neonatal ICU admission, which was not explained by lower Apgar scores or gestational age [98]. Research results are mixed when examining rates of antidepressant use and its relationship to spontaneous abortion, and may be confounded by the effect of the illness itself [99]. One study suggests that women taking antidepressants during pregnancy have a

statistically significant higher rate of spontaneous abortion (3.9%) regardless of the type of antidepressant [99]; whereas, other studies show spontaneous abortion rates are elevated for exposure to several different antidepressant classes, but only exposure to bupropion is statistically significant [100,101].

Neurobehavioral toxicity

The long-term outcomes associated with the apparently transient symptoms of the NNA syndrome have only just begun to be studied. The few empirical studies have shown SSRIs to be related to increased active sleep [102] and decreased facial and behavioral responses to acute pain in the first week postnatally and at 2 months of age, suggesting a blunting of pain reactivity [83,103]. In a recent review of studies on the long-term development of children with prenatal SSRI exposure, 11 studies (306 children) suggested no impairment with exposure, and two studies (81 children) suggested mild adverse effects [104]. Nulman *et al.* found there were no associations between the mother's use of TCAs and fluoxetine during pregnancy and long-term effects on global IQ, language or behavioral development in preschool children [105]. Some groups report less favorable motor (not mental or emotional) development in toddlers who were exposed to SSRIs *in utero* compared with controls [106]. Further research is needed to examine long-term outcomes for these children, and most likely gene–environment interactions will play a role. For example, Oberlander's group reported that the association between prenatal SSRI exposure, maternal depression and adverse child outcomes at 3 years of age were moderated by a specific child genotype in the serotonin transporter promoter region (*SLC6A4*) [107]. While prenatal exposure to SSRIs and maternal depression were related to internalizing behavior problems, the impact of maternal anxiety during late pregnancy on child behavior problem patterns was moderated by the child's genotype [107]. These findings suggest complex interactions of infant gene polymorphisms with maternal prenatal medication or untreated illness in explaining potential risk for the offspring.

Nonpharmacological treatment

Psychotherapy also has been studied in the treatment of depression and is considered to be an evidence-based treatment of mood disorders [108]. Interpersonal psychotherapy (IPT) or cognitive behavioral therapy (CBT) in particular, are commonly recommended psychotherapeutic treatments for unipolar depression [109]. IPT is useful in addressing interpersonal conflicts, role transitions and unresolved grief. In addition to improving symptoms, IPT has been demonstrated to also improve social functioning outcomes [108]. CBT specifically targets negative thinking and behaviors that maintain depression [109]. Couples counseling may also be recommended in women who have significant marital strain. Overall, there is evidence that evidence-based psychotherapies, such as IPT or CBT, can also be utilized safely during the peripartum period [110]. These interventions are tolerated and effective in treating postpartum depression, and are less effective in treating depression in pregnancy. There is failed evidence that they are effective as preventive strategies for perinatal depression [110]. Psychotherapeutic modalities, however, offer the potential of beneficial outcomes without substantial risk profiles and are, thus, suggested in recently published guidelines as first choice for women with mild perinatal depression [59].

Several alternative treatments for depression are becoming better utilized, including SAMe, folate, omega-3 fatty acids [111], bright light therapy, exercise [112], St John's Wort and acupuncture [26,113]. Certain types of acupuncture have reduced depressive symptoms in pregnant women, with a response rate similar to that of other standard treatments and yielded relatively few side effects, making it a possible treatment for depression during pregnancy [114]. Many providers advise pregnant women who take herbal supplements for their depression to cease during pregnancy, because limited safety data in pregnancy exist. There has also been interest in research on mind–body modalities as treatment options for depression in pregnancy, some of which have been practiced over thousands of years, such as progressive muscle relaxation, yoga or awareness-enhancing meditation [115,116]. While much of this research has methodological limitations (e.g., lack of randomized controlled trials), there seems to be emerging evidence for the efficacy of mind–body modalities for the treatment of depression [117]. Finally, studies have demonstrated that it is safe and effective for pregnant women who have severe depression to participate in electroconvulsive therapy if they and their provider see this as the best therapy option [118,119].

Postpartum depression

■ Prevalence, clinical features & screening

Postpartum depression develops in approximately 10–20% of women who give birth [120], with higher percentages in women in high-risk contexts [121–124]. Postpartum depression is often undetected and commonly underdiagnosed, as many women expect an adjustment period after having a baby and, therefore, may not recognize that the symptoms of depression are out of the ordinary [125], or because they believe that seeking treatment will result in immediate removal of their child by child protective services. Many women do not seek treatment because of the combination of demanding newborn care and the lack of energy and motivation that comes with the disease process [108]. Furthermore, after the 6 weeks postpartum obstetrics visit, women may have no further routine healthcare scheduled, thus losing connection to healthcare providers [125]. If postpartum depression is left untreated, the symptoms last an average of 7 months but can extend into the second year after delivery [108,125]. Depression has a wide impact, influencing all members of the family, and can lead to marital distress, family conflict, impaired quality in mother–infant bonding, and subsequently more hostile and coercive mother–child interactions [126].

The DSM-IV defines postpartum depression with the same symptom criteria as used for depression before or during pregnancy but specifies that it begin within the first 4 weeks after the baby is born [9], evidence, however, suggests that onset can occur anywhere between 24 h after giving birth and several months later [125]. Many epidemiologic studies define postpartum depression as depressive symptom onset within 3 months postpartum and others as within the first year after delivery [127]. Depression symptoms are often accompanied by comorbid anxiety and commonly women have many concerns regarding their efficacy as a mother or are preoccupied with the health, feeding and sleeping behaviors of their infants. As in pregnancy, MDD with postpartum onset must have the requisite clinical symptoms present for at least 2 weeks [9]. The same screening tools as those used in pregnancy can also be utilized in the postpartum period, and are valid, user-friendly and time efficient; the most commonly used screening tools are the EPDS, the Postpartum Depression Screening Scale and the Beck Depression Inventory–Second Edition, all of which were described earlier in the pregnancy section.

■ From baby blues to postpartum psychosis

Postpartum depression must be differentiated from the baby blues and postpartum psychosis. Approximately 70% of women experience symptoms of baby blues after delivery [128]. These women feel sad, weepy, irritable, anxious and confused, with increased sensitivity, fatigue, sleep disturbances and appetite changes [9]. The symptoms usually peak approximately 4 days postpartum and abate by day 10 [55,125]. Although these symptoms may only last a few hours to days, women who experience the baby blues are at a higher risk for developing postpartum depression. In women who were diagnosed with postpartum depression 6 weeks after delivery, two thirds had experienced baby blues symptoms [129]. Typically, baby blues symptoms resolve within 2 weeks.

Postpartum psychosis occurs less commonly, having an impact on 0.2% of women of childbearing age [130]. Women may experience hallucinations, delusions, unusual behavior, agitation, disorganized thought and inability to sleep for several nights [9,55]. Often the hallucinations and delusions center on the baby and immediate intervention is vital to protect the lives of mother and child [9]. Typically this disorder presents within 2 weeks postpartum or sooner [9]. Most often, postpartum psychosis is the result of an underlying bipolar affective disorder [9]. Any woman who has had an episode of postpartum psychosis in a prior pregnancy should be screened carefully for bipolar disorder. Women who have had a prior episode of postpartum psychosis are at a high risk for a subsequent episode, and specific treatment guidelines have been suggested [131,132]. Some clinicians suggest reintroduction of lithium or other mood stabilizers in late pregnancy or immediately postpartum (within the first 24–48 h of labor) to attenuate the risk for postpartum psychotic relapse. In females who decide against peripartum prophylactic treatment, treating obstetricians and midwives should be highly vigilant for early signs of postpartum psychotic decompensation and should have a low threshold to consult with psychiatry. Postpartum psychosis is considered a psychiatric emergency because of the potential for catastrophic suicide or infanticide [55].

Risk factors & epidemiology

Many women who develop postpartum depression have had antenatal symptoms of depression [133]. Once a woman experiences postpartum depression, she is at risk for depression relapses with or without additional pregnancies [134]. Research shows that women who have had previous episodes of postpartum depression have a 25% risk of recurrence [135]. Experts debate whether or not the rapid decline in reproductive hormone levels after delivery contributes to depression development. Bloch and coworkers found that when a decline of estradriol and progesterone was simulated in nonpregnant women, 63% of the women who had a history of postpartum depression experienced some changes in mood, whereas the women who did not have a history of postpartum depression did not experience any emotional changes. Thus, women who have a history of postpartum depression may be more sensitive to the systemic decrease in gonadal steroids postdelivery [136]. Other risk factors for postpartum depression include past depressive symptoms not related to pregnancy, a family history of depression, personal or family history of bipolar illness, and factors that influence depression at any time point, including poor social support, social conflict and life stressors [137].

Treatment of postpartum depression

Pharmacological treatment

Antidepressant medication and psychotherapy are both important treatment modalities for postpartum depression. SSRIs are medications prescribed most commonly but other agents should be considered with a patient's prior positive treatment response. Because of the high risk of recurrence in women who have a previous history of postpartum depression, one study suggests providing prophylactic sertraline to prevent onset of symptoms [135]. Some literature suggests that women who have postpartum depression may be likely to have a more positive response to serotonergic agents, such as SSRIs and venlafaxine, than to TCAs [138,139]. Increased anxious symptoms at initiation of medications is a common concern [140], thus some patients benefit from a slow titration to reduce initial side effects. Once a steady, effective dose is reached, then pharmacotherapy should continue for at least 6 months to prevent a relapse of symptoms [9]. If there is no improvement with antidepressants after 6 weeks of therapy, a psychiatric consultation is appropriate [55].

Many women are hesitant to take antidepressants while breastfeeding a child, as some research suggests that SSRIs interfere with secretion in the mammary glands causing problems in initiating breastfeeding [141]. All antidepressants are secreted to some degree into the breast milk, yet often the levels in the breast milk and the infant serum are low to undetectable [104,142–144]. For example, paroxetine and sertraline have been widely studied in lactating women and show very low to undetectable infant serum levels. By contrast, fluoxetine and its metabolite, norfluoxetine, have extremely long half-lives, they can accumulate in an infant's blood, reaching detectable levels [145]. Case reports link maternal fluoxetine use to colic, prolonged crying and vomiting, so it is not considered the first-line SSRI for breastfeeding women [146]. However, if a mother has a positive history responding to fluoxetine, the benefit outweighs the risk and it should be continued while monitoring the child for side effects. Ethical concerns prevent large randomized controlled trials in lactating mothers to determine efficacy and safety [60].

Mothers taking any antidepressant should be mindful of their infant's temperament and behavior, especially premature and sick newborns who may be predisposed to dehydration [55], and should notify their physician if they notice irritability, difficulty feeding or disturbed sleep patterns [60]. In general, no adverse effects are noted in infants when breastfeeding mothers take TCAs [147]. Small case reports of atypical antidepressants have found no negative effects on infants with maternal use of mirtazapine or trazodone [148,149], but have found increased risk for drowsiness and lethargy with nefazodone (only one case) [150] and increased seizure risk with exposure to bupropion if a baby has a history of seizures [151,152]. Larger studies are needed to explore these effects further. Research on long-term effects of SSRI and TCA exposure through breast milk on children shows no alteration in IQ, language development or behavior [152].

For postpartum women who have sleep difficulties, diphenhydramine may be helpful [153]. Lorazepam can be used in women who have profound sleep disruption; it has fewer active metabolites, reduces nighttime anxiety and enhances sleep. Lorazepam, however, is excreted into breast milk in low concentrations [154,155]. Several studies have observed that in lactating mothers taking lorazepam, there are no adverse effects on infants and no change in the amount of milk

consumed. Caution should be taken when prescribing lorazepam during an infant's first few weeks of life because of the relative immaturity of the hepatic metabolism [155].

Nonpharmacological treatment

Interpersonal psychotherapy is ideally suited to postpartum mothers, as almost all women have some concerns regarding role transitions and social support that occur during this important life milestone. IPT specifically targets effective elicitation of social support, adjustment to role changes, as well as unresolved grief that may contribute to distress around motherhood. A randomized controlled trial found that women who attended an IPT group reported improvement in their relationships with their partners and their bonds with their infants, even after therapy was completed [156]. Similarly, CBT has been shown to reduce depressive symptoms [157] by targeting unrealistic expectations that some women may have, such as the need to be a 'perfect' mother or a sense of shame by not being overjoyed with their infant during the immediate postpartum period. In addition, CBT encourages engagement in activities that are pleasurable and rewarding for the woman. Both psychotherapies have been shown to reduce or eliminate depression during an acute phase of treatment (up to ~16 weeks) [108]. Many women, especially those who have lactation concerns with pharmacotherapy, may be more comfortable beginning with IPT or CBT [108]. Additionally, behavioral strategies, such as adjusting the sleep schedule and using the support of other family members to assist with nighttime feedings, may enhance a woman's ability to sleep at night [158]. Overall, the evidence for psychotherapies such as IPT and CBT to improve depression during the postpartum period is more convincing than results for these interventions in pregnancy [110].

More recent work suggests that treating postpartum depression alone may not be sufficient in protecting children against long-term poor outcomes, and that dyadically based postpartum therapy interventions may be more beneficial for improving outcomes for infants of depressed mothers [47]. These relationship-based treatments may be short or long term, rooted in psychodynamic and attachment theories [159,160], and are sometimes combined with skill-based techniques targeting relaxation and coping [161,162]. These dyadic relationship-based psychotherapies appear to positively impact parenting and child outcomes despite mixed improvement of depression in the mothers [163,164].

Debate exists over the prospect of hormone therapy for postpartum depression. Estradiol has been recommended for its quick response, few side effects and minimal passage to the infant through breastfeeding [165]. One study evaluated the effects of transdermal 17β-estradiol versus placebo and found a significant decrease in depression scores in the estradiol group [166]. Half of the women receiving estradiol, however, were also taking antidepressants, so the effect of hormone therapy alone is unclear. Additionally, the hypercoagulable state of postpartum women may limit the clinical usefulness of estrogen treatments. Prophylactic progesterone (norethisterone enanthate) postpartum demonstrated an increased risk for depressive symptoms in the treatment group compared with placebo [167]. More research is needed to explore hormonal treatment possibilities further.

Conclusion & future perspective

Treatment of depression during the perinatal period is complex, requiring a collaborative approach across the broad range of providers who may work with the woman during this period, including obstetrics, pediatrics, psychiatry and nursing/midwifery. Treatment may be multimodal, and while there is evidence to support the use of specific therapeutic interventions during the perinatal period, the relative merits and associated risks of particular modalities (e.g., psychotherapy, complementary approaches and pharmacologic agents) or combinations of these modalities requires further investigation. Moreover, because ethics constrain the study of medication in pregnancy or early postpartum and limit the potential for randomized controlled trials, the specific contributions of pharmacotherapy versus illness to maternal and fetal risk has been difficult to quantify. Furthermore, novel treatment strategies such as vagal nerve stimulation and transcranial magnetic stimulation are as yet largely untested in pregnancy or postpartum [168,169].

Burgeoning current research is focused on epigenetic influences on infants during gestation and the neonatal period, specifically the interaction between infant genetic predisposition and maternal illness and treatment factors. Future studies investigating the impact of *in utero* drug exposure or untreated maternal

illness on infant development will have to take maternal and infant genetics into account as a potential moderating factor.

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