28 Psychiatric disorders in pregnancy

Robin Kopelman and Scott Stuart

Pregnancy and childbirth are naturally occurring life events accompanied by momentous neuroendocrine and psychosocial changes. These transitions are often accompanied by changes in mood and psychological functioning, and these changes in turn may have an impact on the developing fetus and/or infant.

One of the most unique aspects of perinatal medicine is its subject matter: it addresses the life and well-being of both the mother and her offspring. Likewise, perinatal psychiatry must address the suffering of the individual pregnant woman and her safety while being mindful of the significant potential effects of maternal mental illness on early child development (1,2).

Pregnancy and childbirth has historically been described—incorrectly—as a time of well-being, calm, and inner peace for women. Elevated gonadotropin levels, the sense of fulfillment, and the responsibility of caring for the young were believed to confer protection from mental disorders (3,4). Carefully designed studies, however, found no such decrease in the incidence of perinatal mental disorders (5,6). The current empirically based position is that events in women's reproductive cycles such as menstruation, pregnancy, childbirth, and menopause can be understood as biological (7) and psychological risk factors (8) for mood disorders.

Psychiatric disorders in the obstetric setting are frequent, with up to 40% of women having an identifiable mental disorder, most commonly depression (9,10). In the first several months postpartum, there is an increased risk for psychiatric admission or outpatient contact (4,11,12). It appears that the perinatal period places a subset of women at increased risk, and the overall prevalence and impact of the perinatal psychiatric disorders, as well as the unique treatment considerations for this population, make these disorders a topic of great significance for perinatal health-care providers. This chapter provides a current overview of the most common psychiatric disorders during pregnancy and the postpartum period.

MOOD DISORDERS IN PREGNANCY AND THE PUERPERIUM

An occasional low mood is a normal reaction to the disappointments, setbacks, and losses inherent in everyday life. It is usually transient and not associated with significant functional impairment. A depressed mood, however, may be a part of a serious, potentially disabling disorder such as major depressive disorder (MDD), bipolar disorder (depressive episodes alternate with periods of abnormally elevated or irritable mood), or dysthymic disorder (characterized by low-grade, more persistent depressive mood that has been present for at least 2 years). Epidemiologic data from around the world show that MDD is twice as common in women as in men (13).

Because low mood can be a normal experience, it is important for the clinician to be familiar with the diagnostic criteria for clinical depression. The *Diagnostic and Statistical Manual of Mental Disorders* (14) (DSM-IV) requires the presence of depressed mood or loss of interest and at least four of the following symptoms over the same 2-week period to diagnose major depression: weight loss or gain, insomnia or hypersomnia nearly every day, psychomotor agitation or retardation, fatigue or loss of energy, difficulties with concentration and memory, and guilt or suicidal thoughts.

Despite the serious consequences, detection rates for perinatal depression remain low, with only a small proportion of depressed women identified by health professionals (10,15). Depression in pregnant and recently delivered women may be underdiagnosed because of the common presence of symptoms that are also associated with normal perinatal changes, such as fatigue, insomnia, weight or appetite changes, and changes in libido (16,17).

Ultimately, less than one-third of depressed perinatal women receive treatment (10,15). Financial issues and concerns about safety of medications during pregnancy may play a significant role (18). Often, women discontinue medication on their own once they become aware that they are pregnant (19). Relapse rates for those women who discontinue antidepressants during pregnancy are high, with higher relapse rates in women with depression for more than 5 years, more than four episodes, and of younger age (20).

Rates of treatment can be improved by accurately identifying women with perinatal depression. A self-report questionnaire to screen for depression should be used with a standard interview in the obstetric setting to facilitate this (21). The Edinburgh Postnatal Depression Scale (22) is a commonly used screening measure, which is both sensitive and specific for perinatal depression. It focuses on psychologic symptoms, rather than the somatic symptoms associated with new parenthood, and has been validated for use in pregnancy (23). Additionally, it is brief (10 items) and is an easy-to-use score.

The treatment and therapeutic responses for depression during pregnancy and the postpartum period are similar to those outside of the perinatal period (24). The treatments of choice are psychotherapy and antidepressant medications (25–29).

DEPRESSION IN PREGNANCY

The incidence of major and minor depression during pregnancy is approximately 10% (30), which is similar to the nonpregnant female population (5). However, it may be as high as 27.6% among women in poor urban communities (31). Risk factors for perinatal depression are similar to those for depression at other times and consist primarily of a

personal or family history of depression and poor social support, particularly from the partner (8,32).

The risks of untreated depression during pregnancy are significant. Antenatal depression has been associated with an increased risk for pre-eclampsia (33), preterm delivery (34), and fetal growth retardation (35). Depressed pregnant women obtain less adequate prenatal care (36) and have more negative health behaviors (e.g., tobacco use) (37), both of which also negatively impact birth outcomes.

POSTPARTUM MOOD DISORDERS

The spectrum of postpartum mood disorders includes postpartum blues, postpartum depression (PPD), and postpartum psychosis.

Postpartum Blues

Postpartum blues is a transient experience characterized by insomnia, anxiety, mood lability, irritability, and tearfulness, occurring exclusively within the first 2 weeks after delivery. It occurs in up to 75% of postpartum women (38), making it so common that most practitioners believe that it should not be considered a disorder. It has a minor functional impact and usually resolves spontaneously. Management is limited to reassurance and support without medications. However, close follow-up is indicated; women experiencing severe blues symptoms are at higher risk to develop a postpartum depressive episode (39).

PPD

Prevalence estimates for PPD range from 6.8% to 13% (8,17,40–42) and up to 26% among adolescent mothers (43).

Risk factors for PPD include the following:

1. Personal or family history of depression (17,44).
2. Presence of depression during pregnancy (45).
3. Psychosocial factors such as marital conflict, being a single mother, lack of social/family support, the stress of caring for the infant (disrupted sleep and sleep deprivation), multiple births, complications during pregnancy (especially if necessitating prolonged bed rest), and other stressful life events during the year preceding the birth (30,44,46).

The onset of PPD occurs in up to 70% of patients within the first 3 months postpartum (41,47). The depressive episode may last from 3 months to 14 months (48), though women may have significant depression lasting much longer (49). The clinical picture of PPD is similar to that of major depression occurring in the nonpuerperal period (50,51).

Unrecognized or untreated depression may impair function and adversely affect the new mother's ability to care for her infant. Depression may also interfere with the new mother's ability to respond optimally to the infant and consequently may have adverse effects on early child development (1,2,52). Women with PPD are also less likely to engage in positive and healthy parenting practices (53).

Suicide and infanticide are the most serious complications of PPD. While approximately 15% of depressed individuals in the general population end their lives by suicide (54,55), having living children may offer some protection from suicide in the postpartum period (3). Women with perinatal

depression may nonetheless have thoughts of harming themselves or the infant (56) and the risk for suicide is a particular concern for these women (55). In the United Kingdom, suicide related to psychiatric disorder was found to be the leading cause of maternal death over the year following delivery (57).

Risk factors for suicide include a history of depression, prior suicide attempts, psychosis, and several psychosocial risk factors such as living alone, lack of family or social support, and feelings of guilt and hopelessness. Obstetricians should be aware of the risk and ask women about suicide and self-harm, as well as infanticide, with such questions as "Have you been feeling like life is not worthwhile?," "Have you had thoughts of harming yourself (or your baby), wanting to die or wanting to end your life?," "Have you thought about how you might harm yourself (or your baby) or end your life?," and "How likely is it that you might actually do something like that?" When suicidal or infanticidal ideation is present, emergency psychiatric consultation is warranted.

The pathogenesis of PPD remains undetermined. The belief that hormonal factors are the greatest contributors to PPD persists even though the empirical support that serum levels of gonadal hormones account for postpartum mood symptoms is equivocal at best (7). Likewise, there has not been clear evidence to support the hypothesis that a rapid decline of gonadal hormones and cortisol and/or the effect of their withdrawal on neurotransmitter activity trigger PPD (46,58,59).

There is, however, some recent research that suggests that there may be a subset of women who are susceptible to the abrupt hormonal withdrawal in the postpartum (60,61). Epidemiologic data demonstrating a high degree of overlap between the diagnosis of premenstrual dysphoric disorder and PPD have supported this theory (62,63). Several investigators have suggested that serotonin dysregulation in particular might play in PPD due to its role in depression at other times and its interaction with gonadal steroids (especially estradiol) (17,64–66). To date, treatment with selective serotonin reuptake inhibitors (SSRIs) have mixed results in preventing the onset of PPD (67). There are small amount of data suggesting prophylactic effects (58) and possible treatment benefit in PPD patients being treated with estradiol (68,69).

Postpartum Psychosis

The incidence of postpartum psychosis is 0.1% to 0.2% or 1 to 2 per 1000 births (70). In most cases, the onset occurs during the first 2 weeks postpartum. It is frequently heralded by one to two nights of insomnia and irritability (7). The most characteristic clinical presentation consists of confusion and delirium-like psychosis with disorganized behavior, mood lability, and hallucinations and delusions that are often focused on childbirth themes. While infanticide is quite rare, women with postpartum psychosis are more likely to experience thoughts of harming their infants than women with nonpsychotic PPD and are at risk for neglecting their infant (71,72).

Differential diagnoses for postpartum psychosis include bipolar disorder presenting as a manic episode, schizoaffective disorder, and major depression with psychotic features. The cognitive disturbance associated with postpartum psychosis

also makes thorough evaluation for delirium essential, with possible causes including cerebrovascular incidents (e.g., due to eclampsia), medications used in delivery, and metabolic or infectious etiologies (73). Research data suggest, however, that postpartum psychosis is most often a manifestation of bipolar disorder (74,75).

A personal or family history of postpartum psychosis as well as bipolar disorder (70,76) increases a woman's risk. The risk of recurrence in subsequent pregnancies is estimated to be 40% to 60% (77–79).

In addition to postpartum psychosis, psychotic illnesses in the puerperium also include schizophrenia. The lifetime prevalence of schizophrenia is about 1.5% spread equally across both genders, and women with schizophrenia get pregnant and give birth. Given that its peak age of onset is between 15 and 35 years of age, it is of particular clinical importance during women's reproductive years. However, the incidence of schizophrenia does not appear to be impacted by pregnancy and childbirth (70,80).

Schizophrenia and other psychotic disorders manifest a variable course ranging from acute episodes to a protracted disturbance of thought and behavior with gradual decline. Clinical course and prognosis are significantly improved by the availability of family and social support and psychiatric care. Patients may show negative symptoms (such as apathy or flat affect), disorganization, eccentric thinking and behavior, or acute psychotic manifestations, such as hallucinations or delusions. These symptoms may have a devastating impact on the mother and fetus or infant; women with schizophrenia have increased rates of a number of adverse pregnancy outcomes (81,82) and are at risk for suicide and other self-destructive behaviors, as well as infanticide (83).

As noted, any new-onset psychosis during pregnancy or the postpartum should be promptly evaluated for an identifiable medical (e.g., drug-induced psychosis, temporal lobe epilepsy, stroke, systemic lupus erythematosus, acute intermittent porphyria) or psychiatric (e.g., brief reactive psychosis, manic or depressive phase of bipolar disorder) cause. Treatment in the perinatal period includes control of the symptoms of disorganized thought and behavior through the administration of the lowest effective dose of antipsychotic medication (preferably from the high potency subgroup, such as haloperidol) and addressing psychosocial needs.

ANXIETY DISORDERS IN THE PERINATAL PERIOD

The course of anxiety disorders in the perinatal period, including obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), panic disorder, and generalized anxiety disorder, is variable. The relationship between the perinatal period and both obsessive compulsive disorder and PTSD makes additional discussion of these important.

Clinically, OCD presents with obsessions (intrusive thoughts or images) and/or compulsions (actions and rituals that the individual feels compelled to perform to reduce intense anxiety). Perinatal patients often report a fear of accidentally or intentionally harming the fetus or baby (84,85). The clinician should keep in mind that some patients may feel guilty because of their strange and frightening thoughts and may not report them spontaneously. It is helpful, therefore, for the clinician to inquire in a tactful and nonjudgmental way

whether the mother has any of these fears. These thoughts are not seen exclusively in OCD, as over 40% of women with PPD (86,87) and over 20% of new parents without a mental disorder (88) report these types of thoughts.

The prevalence of OCD during the perinatal period ranges from 0.2% to 3.9% and may be more common in the postpartum (89). Some women may be asymptomatic during one pregnancy, yet develop OCD in subsequent pregnancies (90). Pregnancy is believed to be a potential trigger for the onset of OCD (91) and the postpartum is considered to be a period for worsening of OCD (92). The onset of OCD may in fact be neurohormonally modulated. The possible role of estrogen, progesterone, oxytocin, and the serotonergic system has been investigated (93,94), but none of these hormones has been definitively linked to perinatal OCD.

PTSD develops subsequent to exposure to a traumatic event involving actual or threatened death or serious injury or a threat to the physical integrity of self or others. The response to the perceived threat is usually fear, helplessness, or horror. A typical triad of symptoms include reexperiencing of the event (e.g., nightmares, flashbacks), avoidance of stimuli associated with the event, and signs of hyperarousal such as insomnia or irritability (14). The prevalence of PTSD symptoms in perinatal women varies widely (0–7.7%) (95,96), with PTSD being most prevalent in a group of economically disadvantaged pregnant women.

In contrast to OCD, it is the events associated with the perinatal period rather than the hormonal changes associated with pregnancy and childbirth that are speculated to act as triggers for the development or exacerbation of PTSD symptoms. For example, deliveries that women appraise as traumatic, particularly those involving difficulties with pain control, powerlessness, or lack of control, are associated with PTSD (89). For women with a history of sexual abuse, procedures such as internal examination and delivery may trigger memories of the abuse (95,97).

Untreated anxiety disorders have been associated with negative outcomes such as preterm delivery (98). Anxiety in pregnancy, like perinatal depression, may have adverse effects on the emotional and behavioral well-being of children (99). More research is needed in this area as it is increasingly recognized that untreated anxiety and depression are likely to have a deleterious effect on fetal development.

Women with a history of anxiety disorders who plan to conceive should be informed of the variable course and the potential treatments. Treatment options for anxiety include psychotherapy and medication. Anxiety disorders are frequently associated with interpersonal difficulties such as fears of expressing anger, isolation, and excessive concern of being judged by others. Psychotherapy may be effective for both the anxiety and the interpersonal difficulties these patients have.

Medication may be necessary if symptoms interfere significantly with daily functions and/or psychotherapy is not accessible. As with other mental disorders, the use of medication should be assessed within a framework that balances the risks associated with nontreatment of the illness and the contextual and clinical factors that impact the woman's preferences, including her ability to access treatment, the risks to her personally from the illness, and the risks to the fetus or breast-feeding infant (100,101).

SSRI antidepressants, or the tricyclic antidepressants (TCAs), such as nortriptyline, may be helpful. Benzodiazepines have a role in the treatment of anxiety in the general population, but use of antidepressants is preferred in the perinatal period because they have better safety profiles in pregnancy and lactation (102).

TREATMENT: PSYCHOTHERAPY AND MEDICATIONS

Depression during pregnancy, PPD, and psychosis are potentially severe and disabling. Untreated, they may carry a significant risk to both the mother and to her offspring. The clinician needs to carefully weigh both the maternal benefits from the medications and the potential fetal risks (26,29,100,103). Medications during the first trimester, pregnancy, or the postpartum might be avoided if the depression is not severe and psychotherapy could be undertaken (26,27). This decision should be made in partnership with the patient. Again, careful assessment of the patient's experiences and clinical history, as well as the acceptability and accessibility of treatments is essential (18,100,101).

Psychotherapy can be an effective option for some women with perinatal depression. For women with milder symptoms who prefer psychosocial treatment, it should be considered first line. Psychologic treatments like interpersonal psychotherapy (IPT) are efficacious for antenatal depression (104). At present, there are not efficacy studies demonstrating the benefit of cognitive behavioral therapy (CBT) for antenatal depression. For postpartum women with milder symptoms, various psychosocial treatments delivered by nonmental health or mental health professionals have been shown to improve depressive symptoms (27). For more severe depression, benefit has only been shown in studies with well-defined treatments, such as IPT or CBT, delivered by highly trained professionals (27).

Psychotropic medication will be the first treatment choice for many women, particularly those with more severe illness or for whom other treatments are inaccessible. All psychotropic medications cross the placenta and their potential effects on the developing fetus must be considered (29). Three areas of potential impact of medications given during pregnancy are teratogenicity, if the medication is administered during the period of organogenesis; neonatal toxicity or withdrawal if the medication is given close to the time of birth; and later behavioral sequelae (103). There are few longitudinal studies examining behavioral changes in children exposed to antidepressants or depression during pregnancy (105), so subsequent discussion is focused on teratogenicity and withdrawal effects.

Antidepressants

TCAs have been available in the United States since 1963. Extensive cumulative experience has revealed no increased risk of major congenital malformations with their use in the first trimester (17,106). Use of TCAs in pregnancy has been associated with perinatal complications such as jitteriness and irritability in the newborn (103,107). Most investigators recommend the use of the secondary amine TCAs (e.g., nortriptyline) over the tertiary amines (amitriptyline).

While the SSRI antidepressants have been used for a shorter period of time, they have significant advantages over

the TCAs and are undoubtedly the most commonly prescribed (108). They have a more benign side effect profile, lacking cardiac toxicity or anticholinergic side effects, and have a much better safety profile compared with the tricyclics in cases of overdose (109).

The majority of studies have not found an increased rate of major malformations with the use of SSRIs in pregnancy (110–112). Some studies have demonstrated an increased, but small, risk of select anomalies (e.g., omphalocele, septal defects) with exposure to certain SSRIs (111–113). Concern has been raised about paroxetine, in particular, as two studies suggest that it confers an increased risk of cardiac defects with first-trimester exposure. The manufacturer subsequently changed product warning labels (114). Findings remain controversial (115), but at present, one should avoid initiating new treatment with paroxetine in women of childbearing age and consider fetal echocardiography in women exposed during early pregnancy. Third-trimester exposure to SSRIs has also been associated with a possible increased risk for persistent pulmonary hypertension of the newborn (116).

Peripartum effects of exposure include an association between SSRIs and premature delivery and low birth weight (34), though most studies have been unable to control for the possible impact of depression itself on pregnancy outcome. Furthermore, the slight decrease in birth weight and gestational age is not considered by most experts to be clinically significant. Both SSRIs and TCAs have been associated with symptoms secondary to discontinuation of medication exposure in the neonate (103,107,117). To minimize the risk of neonatal toxicity and withdrawal after delivery, the maternal dose of medication could be reduced during the 2 weeks prior to delivery (17).

Given the risk for recurrence of depression, psychiatric follow-up and maintenance treatment is considered the standard of care for perinatal disorders (118). Overall, a reasonable therapeutic goal for treating depression during pregnancy or PPD is to control symptoms and to recover function at a minimum effective dose of medication (17). When making a decision to reduce or temporarily discontinue medication, a discussion of the potential for relapse during pregnancy or postpartum is essential.

Other antidepressants are less commonly used, but may be encountered in perinatal women. The studies examining mirtazapine (119), bupropion (120,121), venlafaxine (122), trazodone, and nefazodone (123) do not suggest an increased risk of fetal anomalies. Monoamine oxidase inhibitors are generally not recommended for use in the perinatal period due to the lack of data and potential for hypertensive crisis (124).

In the immediate time period surrounding delivery, several additional issues should be considered. First, hepatic immaturity in the newborn may affect the metabolism of psychotropic medications, thus leading to potentially higher blood levels in the newborn (17). The infant's pediatrician should be informed of maternal medications to prevent possible adverse drug interactions with other medications that may be prescribed for the infant. Second, women who are not symptomatic in pregnancy or the postpartum, but who have a history of depression, especially PPD, may benefit from a preventive intervention with psychotherapy or antidepressant medication, though research data are limited at this time.

A woman might elect to initiate prophylactic treatment approximately 48 hours after delivery with an SSRI or start a preventive counseling intervention spanning pregnancy and postpartum (67,125).

All psychotropic medications are found in the breast milk at various concentrations. Infants' absorption rates vary and significant drug levels are rarely detected in infants' serum. These medications are not found in quantifiable amounts in breast milk and have not caused any adverse neonatal effect (126). In a pooled analysis, levels were particularly low for sertraline, paroxetine, and nortriptyline, making these medications preferred. Elevated infant levels occurred with fluoxetine and citalopram (127).

There are case reports of adverse events with breast-feeding exposure to all types of antidepressants. Most reports involve fluoxetine (105), probably due to its long half-life and resultant increased blood levels, making it generally not recommended for use in nursing mothers (126). Few long-term studies exist and clear evidence of developmental problems has not been described in infants exposed to antidepressant medications in breast milk (128). Prescription of an antidepressant for a breast-feeding woman is a case-specific, risk-benefit decision (101).

Mood Stabilizers

The mainstay of treatment and prevention of recurrence of bipolar disorder, including that during the perinatal period, is a mood stabilizer such as lithium carbonate, valproic acid, carbamazepine, or lamotrigine (129). Women who discontinue mood stabilizer treatment in the perinatal period have high rates of relapse (130). During an acute depressive or manic episode, an antidepressant or an antipsychotic medication may be necessary. Sleep hygiene in bipolar patients has been shown to be very important, and sleep deprivation itself may trigger relapse (131).

The association of cardiac malformations with lithium exposure in the first trimester is widely documented by the Lithium Baby Register. The risks of major congenital anomalies, cardiovascular abnormalities, and Ebstein's anomaly in fetuses who were exposed to lithium during the first trimester have been reported as 8% (15/183) and 3%, respectively (132,133). The relative risk seems to be smaller than initially reported and is estimated to be 1.5 to 3.5. Women who are on lithium maintenance and contemplate pregnancy should have preconception counseling.

Patients who have had a single episode of mood disorder could taper their lithium before conception and restart it if necessary after the first trimester. Lithium levels should be monitored closely during pregnancy. Current guidelines recommend taper 48 hours before delivery to avoid toxicity in the newborn (17) and restarting after delivery at prepregnancy dosing (134).

Patients with bipolar disorder who have had multiple episodes run a high risk of relapse without the medication. The maternal risk from recurrence may outweigh the fetal risk from exposure to lithium (17,135). Lithium is generally considered to be contraindicated during breast-feeding because its concentration in breast milk is about 40% of maternal serum (136-140). Both valproic acid and carbamazepine are considered compatible with breast-feeding

(17,140). Both should be avoided during pregnancy if possible because of their association with neural tube defects (17,141,142). An ultrasound examination of the fetal anatomy at 18 to 20 weeks is advisable. Lamotrigine may be another option for treatment during pregnancy and breast-feeding as it appears to have a more favorable safety profile than the other anticonvulsant mood stabilizers (143).

Antipsychotics

All antipsychotic medications (neuroleptics) cross the placenta and are secreted in breast milk. The atypical antipsychotics (clozapine, olanzapine, and risperidone) lack sufficient data with respect to potential teratogenic effects. Though they are increasingly used for psychosis and bipolar disorder due to improved medication tolerance and effectiveness in treating negative symptoms in schizophrenia, caution in use should be exercised.

Typical antipsychotic drugs have a larger amount of reproductive safety data available, especially haloperidol. The high-potency antipsychotics (e.g., haloperidol) are preferable to the low-potency drugs. Several of the typical antipsychotics (chlorpromazine, haloperidol) have been previously prescribed during pregnancy for hyperemesis with safety data in pregnancy obtained in these studies (144,145).

CONCLUSION

Psychiatric disorders are very common during pregnancy and the postpartum, and have a great deal of morbidity for both mother and infant. Many women are not recognized as having a psychiatric disorder, leading to a strong recommendation that screening instruments be used routinely in all obstetric settings. Both medications and psychotherapy are effective treatments, and all decisions regarding treatment must be made with a careful risk-benefit analysis that enlists the woman collaboratively in her care.

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