Diagnosing and Treating Depression During Pregnancy

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LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss diagnosis and management of hospitalized patients with complex medical or surgical problems who also demonstrate psychiatric symptoms or conditions. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Treatment of depression in pregnancy is a topic identified by many providers as difficult given the lack of randomized, double-blind, placebo-controlled studies in this population and often conflicting evidence regarding risks to the fetus and unborn child. Further complicating matters, women who choose to take psychiatric medications in pregnancy are thought to be more likely to have more severe depressive or anxiety symptoms, therefore contributing to their choice to continue psychotropic agents in pregnancy rather than to discontinue them. This makes it even more difficult to discern if any complications are due to the underlying psychiatric disorder or the psychotropic agents. This article will review several clinical questions that often arise in the treatment of depression during pregnancy and provide the reader a framework with how to utilize and provide the best care to the patient based on the current evidence base.

CASE VIGNETTE

Ms A, a 27-year-old single woman, complained of depression during the 25th week of her pregnancy. She described having a history of recurrent depression (with 1 psychiatric admission following a suicide attempt in her late teens). Her Edinburgh Postpartum Depression Scale[1] score of 23/30 was consistent with major depression, which she suspected was due to the stressful relationship with the father of her child. She endorsed having several weeks of depressed mood, poor sleep, fatigue, impaired concentration, and diminished appetite, but no thoughts of suicide.

HOW IS DEPRESSION DURING PREGNANCY DIAGNOSED?

Criteria for the diagnosis of depression are the same regardless of pregnancy status; however, depression is often overlooked in pregnancy, as the symptoms of depression are often similar to the somatic experiences associated with pregnancy. For example, it is common for pregnant women without an affective illness to experience disturbances of sleep and appetite, diminished energy, and decreased libido during pregnancy. Therefore, utilizing nonsomatic symptoms (eg, a lack of interest in the pregnancy, guilty ruminations, anhedonia, a passive death wish, or suicidal ideation) to help guide a diagnosis of depression in pregnancy may be more telling.

Risk factors for the development of depression in pregnancy include insufficient social support, living alone, marital discord, having an unwanted pregnancy, or having multiple children.[2] Age is a risk factor for depression during pregnancy; up to 26% of pregnant adolescents develop major depression.[3] In addition, a personal or family history of affective illness also predisposes to depression during pregnancy.[4] Further, if a woman discontinues her antidepressant medication at the time of conception, she has a much higher chance of redeveloping depressive symptoms during her pregnancy than if she were to remain on an antidepressant throughout her pregnancy.[5]

HOW COMMON IS DEPRESSION DURING PREGNANCY?

Contrary to the popular belief that pregnancy protects women from affective illness, the prevalence of mood disorders is similar for pregnant and nonpregnant women. Between 12% and 15% of women meet criteria for depression at some point during their pregnancy or the postpartum

Clinical Points

- Depression is often overlooked in pregnancy, as the symptoms of depression are often similar to the somatic experiences associated with pregnancy.
- Antidepressant medications can be safely utilized in the treatment of depression in pregnant women.
- Electroconvulsive therapy is a viable alternative for the treatment of severe, treatment-resistant depression in pregnancy.

period.[6,7] It is unclear why the second and third trimester of pregnancy seem to be linked with an increased risk of depression (as compared to the first trimester).

WHAT ARE THE RISKS OF UNTREATED DEPRESSION TO THE MOTHER AND TO THE FETUS?

Untreated depression during pregnancy may have a myriad of downstream consequences (to both the mother and the neonate). Some studies note that women who are depressed during pregnancy are more likely to use alcohol, illicit substances, and tobacco throughout pregnancy and to have worse nutrition and are less likely to be adherent with optimal prenatal care and to recognize or report the signs of labor.[8] Neonates whose mothers are depressed are more likely to have lower birth weights and preterm deliveries, as well as lower Apgar scores and a smaller head circumference.[2] Additionally, infants of depressed mothers may experience dysregulation of their hypothalamic-pituitary-adrenal axis and higher admission rates to neonatal intensive care units.[2] As they develop, these neonates may have more difficulty in engaging in social interactions, show less positive and more negative affect, and have worse developmental and emotional outcomes.[9,10]

HOW CAN DEPRESSION BE TREATED DURING PREGNANCY?

As with nonpregnant depressed individuals, treatment of depression involves both pharmacologic and nonpharmacologic approaches. Importantly, nonpharmacologic treatment of depression in pregnancy avoids any known or unknown risks associated with fetal pharmacologic exposure. Providing a patient with education on the topic of depression and the postpartum period is paramount. Psychotherapy (eg, psychodynamic, cognitive-behavioral) should be offered if the patient is able to engage in a psychotherapeutic relationship. Cognitive-behavioral therapy, supportive psychotherapy, and conjoint therapy (with the partner) are excellent options in this population. Other nonmedicinal interventions include improvement in nutrition and diet; elimination of caffeine, nicotine, and alcohol; and facilitation of proper sleep hygiene. Reduction of stressors, as well as provision of information on relaxation techniques, can also be useful. Some will benefit from referral to local support groups for women who struggle with depression during pregnancy and the postpartum period. Additionally, bright light therapy may be beneficial to those women who have a seasonal component to their affective illness.[11]

Pharmacologic treatment options should be seriously considered in women who are struggling with moderate to severe symptoms of depression, especially if the patient's ability to function and care for herself is compromised. Patient preference plays a role. Some women adamantly refuse to take any psychotropic medications during pregnancy despite the severity of their symptoms, whereas others feel more comfortable using psychotropics during pregnancy. Prior benefit from a psychotropic medication also plays a role in determining if a patient should return to pharmacologic management.

WHAT ARE THE RISKS OF USING SSRIs DURING PREGNANCY?

Selective serotonin reuptake inhibitors (SSRIs) are currently the most widely used class of antidepressants in pregnancy.[12] Unfortunately, they have been linked with poor pregnancy-related outcomes (typically denoted as decreased birth weight, decreased length of gestation, and lower Apgar scores).[2] Nevertheless, a recent meta-analysis failed to find any statistically significant and/or clinically relevant differences in SSRI-exposed and nonexposed infants in regard to these measures.[13] Unfortunately, approximately one-third of neonates exposed to SSRIs late in pregnancy experienced poor neonatal adaptation postdelivery, making it the most common adverse effect associated with SSRI use in pregnancy.[14] Other symptoms in neonates associated with maternal use of SSRIs during pregnancy include jitteriness, constant crying, and disruption of feeding and sleeping (typically beginning hours after birth and persisting up to 4 days postdelivery).[14] This constellation of symptoms may arise with any antidepressant at any dosage. Most neonates who experience these symptoms require only supportive care. A smaller percentage of neonates who experience neonatal abstinence syndrome have autonomic instability, tachypnea, hyperreflexia, hypertonia, and/or seizures.[14]

While several studies have sought to establish the prevalence and pattern of congenital anomalies linked with exposure to first-trimester use of SSRIs, the data remain controversial. No congenital anomalies were noted in prospective, controlled studies or in the meta-analyses of those studies.[15] While some retrospective, case-controlled studies demonstrated an increased risk of specific anomalies (including anencephaly, craniosynostosis, and omphalocele),[16,17] others did not.[16] While retrospective reviews demonstrated an increased risk of septal heart defects (which led the US Food and Drug Administration to classify paroxetine as a class D medication in pregnancy),[18] these data have been unconvincing. In fact, several studies have implicated SSRIs other than paroxetine as having an association with septal defects, while others demonstrated no increased risk.[15] A recent cohort study was able to take into account several confounding factors (eg, exposure to tobacco, alcohol, or other drugs and poor prenatal care) that are common in depression and to evaluate the risk of cardiac defects in fetuses exposed to SSRIs in the

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first trimester; several authors concluded that there was no substantial increase in the risk of cardiac malformations attributable to antidepressant use during the first trimester of pregnancy.[19]

A study by Chambers et al[20] raised concerns about the risk of persistent pulmonary hypertension of the newborn with exposure to SSRIs after 20 weeks of gestation; however, this issue remains controversial.[20] A relatively recent meta-analysis demonstrated that the late-term use of SSRIs in pregnancy led to an increased risk of persistent pulmonary hypertension in the newborn (odds ratio [OR] = 2.5); however, individual studies failed to control for known risk factors of persistent pulmonary hypertension (including smoking tobacco, obesity, prematurity, or cesarean section), all of which are more common in depressed women.[21] If SSRI exposure is associated with persistent pulmonary hypertension, the absolute risk should be quite low (0.3%).[21]

SHOULD SSRIs BE DISCONTINUED DURING THE COURSE OF PREGNANCY?

The question, "Should my patient be advised to discontinue her SSRIs late in pregnancy secondary to concerns of neonatal abstinence syndrome and persistent pulmonary hypertension?" is often asked. While studies demonstrate that newborns who are exposed to SSRIs during the last 2 weeks of pregnancy have an increased risk of respiratory distress and seizures, the prevalence of this complication in these 2 groups is similar when the severity of maternal mental illness is accounted for.[22] Given the concerns for relapse of depression and anxiety in the postpartum period, several experts recommend that SSRIs be continued throughout pregnancy and the postpartum period.[5,22]

WHAT ARE THE NEURODEVELOPMENTAL RISKS ASSOCIATED WITH USE OF SSRIs DURING PREGNANCY?

Evidence on the adverse neurodevelopmental outcomes in children who were exposed to SSRIs in utero is limited. One case-controlled, prospective study (40 children followed to 15–71 months old who had exposure to fluoxetine) found that exposure to fluoxetine did not adversely affect the children's global IQ, language development, or behavior[23]; however, IQ was significantly and negatively associated with the duration of the mother's depression, while language was negatively associated with the number of depressive episodes at time of delivery.[23] In another small study, children of depressed mothers treated with SSRIs were compared with children of depressed mothers who elected not to take any antidepressant medications during their pregnancy.[24] This study reviewed birth outcomes and postnatal neurodevelopmental functioning (between the ages of 6 and 40 months) and noted subtle effects on motor development in those exposed to SSRIs.[24] Overall, there are few data regarding long-term effects of in utero SSRI exposure; however, maternal depression may have a greater impact on the infant's developmental outcomes than psychotropic medication exposure itself.[9]

IS THERE AN ASSOCIATION BETWEEN SSRI USE AND AUTISM SPECTRUM DISORDERS?

Three studies have examined the relationship between autism spectrum disorders and in utero SSRI exposure.[25–27] None of these studies were able to control for the confounders thought to play a role in the development of autism spectrum disorders. These studies demonstrated a slightly increased risk of autism spectrum disorders with exposure to SSRIs; however, the increased risk may be all, or least in part, due to these confounding variables.[25–27]

WHAT ARE THE RISKS OF USING NON-SSRIs DURING PREGNANCY?

Although the SSRIs have the largest evidence base in terms of use in pregnancy, other psychotropics, serotonin-norepinephrine reuptake inhibitors (SNRIs) or other antidepressants, are also used. Two studies have looked specifically at the use of venlafaxine in pregnancy[28,29]; neither found an increased risk of congenital anomalies, although an increased risk of preterm birth was identified. Due to the risk of dose-related hypertension with the use of venlafaxine, blood pressure should be closely monitored. If a woman develops preeclampsia during pregnancy, venlafaxine should be tapered and/or discontinued. Only 1 study has specifically looked at the use of duloxetine in pregnancy; this multicenter cohort study did not demonstrate any increased risks of major malformations with exposure to duloxetine.[30]

Bupropion has been relatively well-studied in pregnancy, in part, thanks to the manufacturer's pregnancy registry.[31] An increased risk of major malformations has not been identified; however, a recent study demonstrated a slightly increased risk of cardiac defects (OR = 1.6; 95% CI, 1.0–2.8) when bupropion was used during pregnancy.[32] An increased risk of spontaneous abortion (miscarriage) has also been identified, as has decreased birth weight in association with use of higher dosages.[33]

A study of mirtazapine use in pregnancy demonstrated no increased risk of major malformations, although a higher rate of preterm birth was noted.[34] The same study demonstrated a nonstatistically significant and increased risk of spontaneous abortion (miscarriage).[34]

Mirtazapine may be a viable option for use in pregnancy given its side effect profile; nausea is experienced less often than with the SSRIs, and it may be beneficial in some patients with hyperemesis gravidarum.[35] Unfortunately, weight gain with mirtazapine can increase obstetrical complications, including gestational diabetes.[36] Additionally, mirtazapine's propensity to induce sedation may be more difficult to tolerate in pregnancy.

Prior to the widespread use of SSRIs, tricyclic antidepressants were widely utilized in pregnancy. Initial studies suggesting that limb anomalies arose have not been confirmed.[2] Neurobehavioral effects from fetal exposure have not been reported. Similar to neonatal abstinence syndrome, acute effects (eg, tachypnea, tachycardia, cyanosis, irritability, hypertonia, clonus) have been reported in infants exposed

to tricyclic antidepressants during pregnancy.[2] Other transient withdrawal symptoms have also been identified. Desipramine and nortriptyline are the preferred tricyclic antidepressants for use in pregnancy, as they are the least anticholinergic and least likely to exacerbate orthostatic hypertension and constipation, which are commonplace issues in pregnancy.

IS ELECTROCONVULSIVE THERAPY OR TRANSCRANIAL MAGNETIC STIMULATION AN OPTION IN TREATMENT OF SEVERE DEPRESSION IN PREGNANCY?

Electroconvulsive therapy (ECT) is effective in pregnancy and the postpartum period and should be considered for women suffering from severe depression, affective psychosis, or catatonia. ECT is often underutilized in this population; however, it should be considered in emergent settings, especially when the safety of the mother, fetus, or child is jeopardized, to avoid first-trimester exposure to psychotropic medications or in women who have had previous successful treatment with ECT. ECT is thought to be well-tolerated for both the patient and fetus; however, thoughtful consideration about potential risks to the fetus and patient is necessary.[37] Premature labor, uterine contractions, and vaginal bleeding have all been reported[38]; however, it should be noted that uterine smooth muscle typically does not contract during a seizure. The few cases of uterine contractions reported do not appear to lead to premature labor. Because pregnancy increases the risk of gastric regurgitation and pulmonary aspiration during ECT, some anesthesiologists prefer to intubate the patient after the first trimester in order to maintain a clear airway. Pretreatment assessment in pregnancy should include fetal heart tones, and, if the fetus is deemed to be viable, an obstetrician should be readily available during the procedure. Occasional congenital abnormalities have been reported in infants exposed to in utero ECT; however, neither the numbers nor the pattern of findings have implicated ECT as a causal factor.

To date, there has been only 1 study reviewing the use of transcranial magnetic stimulation in pregnancy.[39] This study indicates that transcranial magnetic stimulation may be a useful treatment option for women with depression during pregnancy; however, more study is required in order to determine which women are likely to benefit from this treatment. Given the preliminary nature of these data, ECT may be a better option for women with more severe or treatment-refractory depressive symptoms and women with suicidality and/or psychotic symptoms.

SHOULD ANTIDEPRESSANTS BE CONTINUED POSTPARTUM?

If a woman has chosen to utilize an antidepressant medication throughout pregnancy, it is typically recommended that she continue it postpartum. The postpartum period is a time of increased risk of affective illness; therefore, continuation of an antidepressant medication may be beneficial in maintenance of euthymia.

Many providers are concerned about the risk of postpartum psychosis and recommend continuation of antidepressants to prevent its onset. Postpartum psychosis is a rare, severe psychiatric illness occurring at a rate of 1–2 per thousand births[2]; onset is typically within the first 1–2 weeks postdelivery. Postpartum psychosis has a strong bidirectional link with bipolar disorder; major depressive disorder is not thought to increase the risk of postpartum psychosis. Patients may experience psychotic symptoms in the context of a major depressive episode; however, this is vastly different than the rapid onset of psychotic symptoms that are seen in an episode of postpartum psychosis.

WHAT ARE THE RISKS TO THE NEONATE FROM EXPOSURE TO AN ANTIDEPRESSANT THROUGH BREAST MILK?

Since psychotropic medications are secreted into breast milk, risks to the infant must be considered. Tolerability may vary considerably based on several different factors: the amount of exposure (which is dependent on maternal dosages, frequency of dosing, and rate of maternal metabolism, as well as the frequency and timing of feedings), the infant's rate of metabolism, and the amount of sedation induced (this may reduce the mother's energy to parent, as well as make the mother sleep too soundly to care for the infant overnight). In addition, weight gain and sexual dysfunction may be less tolerable in the postpartum period.

The American Academy of Pediatrics has deemed that a "safe" breast-feeding ratio of infant dose exposure to maternal dose is < 10%. The exception to this rule is fluoxetine (3%–12%).[40] However, if a woman is taking a medication during pregnancy, the recommendation is to leave the postpartum antidepressant dose unchanged. Continuation of the same medication postpartum limits the number of medication trials to the infant.

WHAT IS THE ROLE OF THE PRIMARY CARE PROVIDER IN CARING FOR WOMEN WITH PERINATAL DEPRESSION?

Given that 50% of pregnancies in the United States are unplanned,[41] preconception planning is a necessity, even if a woman does not identify that she is planning for conception in the near future. Documentation of birth control planning should be completed during each visit with a reproductive-aged woman. Additionally, the risks of medication to the pregnancy and fetus should be reviewed with the initial prescription of an antidepressant, rather than at time of conception. For women who are actively trying to conceive, establishing an appropriate psychotropic medication regimen, or tapering and discontinuing of medications if appropriate, is a vital role of the provider.

Once a patient is identified as having perinatal depression, the primary care provider has the opportunity to closely monitor the patient, especially if involved in obstetrical and/or pediatric care, and work with the patient and mental health professional to provide the care the patient deserves in order to have the best outcome possible.

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CASE DISCUSSION

Ms A's symptoms were consistent with a major depressive episode, utilizing both *DSM-IV* and *DSM-5* criteria. She had a good prior response to SSRIs and was willing to take an antidepressant medication during her pregnancy. She was counseled about the known risks of depression in pregnancy, as well as the known risks of antidepressants to the fetus and to the neonate. Unfortunately, specific data on all SSRIs are lacking. However, Ms A's physician would be well served by choosing a medication to which she had a good response in the past, rather than choosing a different medication based on a greater evidence base. Exposure to a single agent rather than to multiple agents is always preferred.

CONCLUSIONS

Unfortunately, randomized, double-blind, placebo-controlled studies (to look at the risks of antidepressants in pregnancy in comparison to women who have the same severity of depressive symptoms but are not receiving pharmacologic treatment) will not be conducted. Women who choose to use psychiatric medications in pregnancy are thought to most likely have more severe depressive or anxiety symptoms, therefore causing them to choose to continue psychotropic agents in pregnancy rather than to discontinue them. We tend to take the information that we have and consider individual patients' wishes, as well as a patient's clinical history, to provide the best treatment plan. In addition to pharmacologic management, patients should be counseled on the benefit of psychotherapy and educated on the effects of depression to herself and her fetus and neonate.

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