TREATMENT IN PSYCHIATRY

Choosing and Discussing SSRIs for Depression in Pregnancy: A Basic Guide for Residents

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There are many challenging aspects in treating women with a history of depression in the peripartum period, including the importance of preconception counseling, decisions regarding tapering off and restarting medication during pregnancy, and choice of medication. It is common during pregnancy and in the postpartum period to have low energy, poor sleep, and fatigue (1). Consequently, it is important to not attribute depression to normal pregnancy symptoms or to misinterpret normal pregnancy symptoms as depressive symptoms. Accurate diagnosis can be facilitated by the use of the Edinburgh Postnatal Depression Scale (1, 2). Important to diagnosis is the recognition that peripartum depression can be characterized by anxiety and intrusive, violent thoughts (3) in the absence of obsessive-compulsive disorder.

CASE

A trial of sertraline (25 mg) was begun for severe anxiety in a pregnant woman in the third trimester.

"Ms. A" is a 34-year-old, 3-months postpartum woman with a psychiatric history of depression and anxiety but no history of psychiatric hospitalizations, suicidality, or substance use and no history of medical illness. The patient was referred for outpatient medication management of postpartum depression and anxiety following a month-long partial hospitalization after the birth of her first child. She reported that she first became depressed during college and since then has experienced intermittent weeks-long depressive episodes associated with anhedonia and difficulty functioning. These episodes improved with a combination of therapy and medication. The patient denied any specific phobias, obsessions, compulsions, or panic symptoms. Her prior medication history included trials of multiple selective serotonin reuptake inhibitors (SSRIs), including sertraline, with limited efficacy and sexual side effects. She did not recall the daily dose of the prescribed SSRIs but said she had been on each for at least a couple of months. After many medication trials, she became euthymic on duloxetine (60 mg daily).

The patient discovered that she was pregnant at 6 weeks gestation. At that time, she tapered her medications at the recommendation of her former psychiatrist. She maintained euthymia up until her third trimester, at which time she began to experience significant anxiety and was prescribed sertraline (25 mg daily) by her former psychiatrist, who reportedly had heard that this was the "best medication for depression during pregnancy." She gave birth without complications, and there were no adverse outcomes to the newborn at the time of birth. Postpartum, her sertraline dosage was increased to 50 mg daily. However, she continued to report a subjective increase in anxiety postpartum, feeling overwhelmed with caretaking, and she experienced an increase in depression severity, including no longer enjoying spending time with her newborn, guilt, low self-worth, and insomnia. During the next few weeks, her sertraline daily dose was increased to 200 mg without good effect. The patient then began to have suicidal thoughts for the first time in her life and entered a partial hospitalization program. In the hospital program, she was tapered off sertraline and prescribed duloxetine, which resulted in a return to euthymia. At the time of presentation to the clinic, she continued to be euthymic and without suicidal thoughts.

TO MEDICATE OR NOT TO MEDICATE

Decisions regarding medication in the peripartum period must be made on a case-by-case basis. Treatment should focus on minimizing the number of harmful exposures (including risk of developing maternal psychiatric illness and risk of medication exposure to the fetus) and maximizing the number of beneficial nonpharmacological interventions (4). Nonpharmacological interventions include psychotherapy, exercise, nutrition, adequate sleep, family and social support, and assessing partner wellness. Among women who are taking an antidepressant, 68% with recurrent depression relapse during pregnancy when their antidepressant is discontinued proximate to conception (5). Despite this, conducting a trial off an antidepressant prior to conception for women with a history of mild depression is reasonable if nonpharmacological methods are also used (4). Factors to consider in the decision making regarding starting, continuing, or discontinuing a medication include the patient's individual psychiatric history, medication history, and history of nonpharmacologic treatment and effectiveness as well as current symptom severity, stage of pregnancy, treatment preference, and risks and benefits to the mother and fetus.

PRINCIPLES OF TREATMENT WITH MEDICATION

There is no one "best" medication for women during pregnancy or in the postpartum period. Decisions regarding medication choice are made on an individual basis and should take into account which medication has shown prior effi-

cacy with the patient (4). All SSRIs, with the exception of paroxetine, have a similar safety profile and thus have similar risks of harm to the developing fetus. If a patient is already taking a medication that has led to clinical stability, switching exposes the mother and infant to both increased risk of illness relapse with associated negative effects as well as risks associated with the medication. This creates a double exposure (4). The timing of exposure in pregnancy as well as the type of exposure are considerations to take into account (4). Prescribing a lower dose than what is needed to achieve remission of symptoms also leads to a double exposure to illness and medication. Therefore, the lowest effective dose should be prescribed. Maximizing the dose of one medication rather than exposing the patient to multiple medications is also preferred.

KEY POINTS/CLINICAL PEARLS

- Discontinuing a selective serotonin reuptake inhibitor (SSRI) proximate to conception in a patient with a history of moderate to severe major depression will likely lead to fetal exposure to a depressive relapse as well as exposure to an SSRI to treat the depressive relapse.
- Use of a subtherapeutic dose of an SSRI leads to exposure of the fetus to the negative effects of both the SSRI and depressive symptoms; the dose will likely need to be increased during pregnancy as the blood volume increases.
- With the exception of paroxetine, SSRIs have similar risks to the developing fetus; the two major risks are neonatal adaptation syndrome and persistent pulmonary hypertension of the newborn.
- Use of nonpharmacological interventions in a patient with a history of mild depression may be sufficient to prevent relapse of depressive symptoms during pregnancy.

FIRST-LINE TREATMENT

When medication is indicated, SSRIs are the first line for perinatal depression. This medication should be maintained throughout the duration of the pregnancy, because tapering in the third trimester increases the risk of relapse antenatally and in the postpartum period (6) but does not increase the risk of neonatal adaptation syndrome (7). Dose adjustments should correlate with clinical symptoms (4), and dose increase over the course of the pregnancy, as blood volume increases, is often required.

RISKS OF PERIPARTUM DEPRESSION FOR THE MOTHER AND INFANT

It may be helpful to explain to women that the risk of harm from clinically significant depression and anxiety to the fetus may be due to dysregulation of the hypothalamic-pituitary-adrenal axis, with resultant increased corticosteroid production, and therefore has a biological basis (8). The risk of harm to the mother and infant includes suicidal (19.3%) and infanticidal (41%) thoughts in the mother (2, 3), increased rates of C-section, longer hospital stays following delivery, increased rates of neonatal intensive care unit admission and preterm birth <32 weeks (8), nonadherence with postnatal care, poor self-care (including use of tobacco, alcohol, and illicit substances), and high use of other medications (1). There is also disrupted maternal-infant bonding (9) and the potential for behavioral problems and psychiatric illness in the offspring (10). Furthermore, prenatal depression is a major risk factor for postpartum depression, which creates other risks for the offspring, including risk of negative effects both on cognition (11) and mental health (9).

RISKS OF SSRIs

Two major risks of SSRI exposure during pregnancy include neonatal adaptation syndrome and persistent pulmonary hypertension of the newborn. Neonatal adaptation syndrome occurs postpartum and is characterized by difficulty feeding, irritability, low muscle tone, high-pitched cry, respiratory distress, jitteriness, tachypnea, and, rarely, convulsions. It is usually mild, spontaneously remits with supportive treatment in a few days, and occurs in about 25%–30% of infants who have been exposed to an SSRI. There is also risk of a lower 5-minute Apgar score. However, this may be due to the symptoms of neonatal adaptation syndrome (4). The second major risk is persistent pulmonary hypertension of the newborn. This occurs when the pulmonary vessels fail to relax and ranges in clinical severity from transient to fatal, with a 10%–20% risk of mortality. It is characterized by respiratory distress and cyanosis, is diagnosed with echocardiography, and is mostly treated with supportive care or inhaled nitrous oxide. In more severe cases, extracorporeal membrane oxygenation is used. With controls for confounding by indication, the risk of persistent pulmonary hypertension of the newborn following exposure to SSRIs is approximately 1.2–3.5 times the baseline risk of 1.9 in 1,000 live births (12).

Among the more controversial risks of SSRI exposure during pregnancy that obstetricians/gynecologists and patients may cite as a concern is the risk of malformations. In 2005, the Food and Drug Administration made an advisory warning stating that there was an increased risk of cardiac malformations with the use of paroxetine (13). This was found for doses >25 mg daily (13), and there was no evidence for other SSRIs (14). Another concern is the potential for negative developmental effects in the offspring. However, data have not shown any major risks for externalizing problems or for problems in language or with cognitive or motor development. There are conflicting data regarding an association with autism spectrum disorders. However, positive associations are likely from confounding factors (4).

APPLYING THE DATA TO THE CASE PRESENTATION

In the above case, Ms. A's fetus was exposed to two different medications, in-

cluding sertraline, which was previously shown to be an ineffective treatment for her. The mother and fetus were also exposed to clinically significant mood symptoms. The decision regarding the use of medication would have been better informed if the patient had had a trial off medication prior to conception. For duloxetine, other than an increased risk of spontaneous abortion, evidence, although limited, shows no increased risk of malformation to the fetus above baseline and no increased risk of adverse outcomes (15). Therefore, Ms. A's depressive relapse may have been prevented if duloxetine had been continued throughout her pregnancy.

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