Psychopharmacologic Management of Depression in Pregnant Women and Breastfeeding Mothers

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Major depression is common among women of childbearing age,[1] and depressive episodes frequently occur during pregnancy and/or lactation. In a study of young women seen in gynecologic settings, 21.5% had major depression.[2] An estimated 6.5% to 12.9% of women will experience major depression with postpartum onset,[3] and rates as high as 19.6% have been reported.[4] O'Hara et al[5] found that 9% of pregnant women suffer from depression, and a study of 4332 women who recently gave birth revealed that 12% met criteria for depression.[6]

Approximately 50% of all depressive episodes are treated in a primary care setting rather than by a psychiatrist.[7] Thus, physicians who treat women of childbearing age must be familiar with diagnostic criteria for major depression and both nonpharmacologic and pharmacologic options available to pregnant women and lactating mothers who meet these criteria. Physicians must be sure to offer explicit information regarding the risks and benefits of pharmacotherapy during pregnancy and lactation prior to starting treatment in women of childbearing age.

This article focuses on the use of selective serotonin reuptake inhibitors (SSRIs) in pregnancy and during lactation. In clinical practice, serotonin/norepinephrine reuptake inhibitors (eg, duloxetine, venlafaxine) and other atypical antidepressants (eg, bupropion, mirtazapine) are commonly used in the treatment of depression in women of childbearing age. A detailed discussion of their use in pregnant and lactating mothers, however, is outside the scope of this review and information regarding their use can be found elsewhere.[8,9]

DIAGNOSTIC EVALUATION

Major depressive disorder is characterized by depressed mood and/or decreased interest or pleasure in usual activities (anhedonia) accompanied by at least 4 of the following symptoms: sleep disturbance, appetite

TAKE HOME POINTS

- The diagnostic evaluation for major depression should determine whether diagnostic criteria are met and rule out other conditions that may be causing depressive symptoms, particularly bipolar disorder. In postpartum mothers, transient depression (ie, "postpartum blues") that resolves within 10 days of delivery must also be excluded.
- Referral to a psychiatrist is indicated if depression is complicated by a comorbid psychiatric illness, a high risk of obstetric complications, or a history of multiple episodes of depression or treatment-refractory depression or if the patient requires an agent other than a selective serotonin reuptake inhibitor (SSRI).
- Patients with current suicidal ideation, homicidal ideation, or psychotic symptoms constitute a psychiatric emergency and should be immediately evaluated in the emergency department or by a mental health professional.
- Psychotherapy alone is first-line treatment for mild depression in pregnant women and breastfeeding mothers. For moderate depression, psychotherapy or pharmacotherapy (usually with an SSRI) alone may be initiated. Depending on patient response, combination therapy with both an SSRI and psychotherapy may be required. Severe depression always requires immediate initiation of antidepressant therapy.

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disturbance, psychomotor agitation or slowing, decreased energy, impaired concentration or decision making, feelings of worthlessness or inappropriate guilt, and suicidal ideation.[10] A major depressive episode is defined as having the above symptom constellation for 14 consecutive days. Major depression is considered to have postpartum onset if the depressive symptoms develop within the first 4 weeks after delivery,[10] although some consider symptom onset within 3 months of delivery a determination of postpartum major depression.[11]

Once it is determined that a pregnant or lactating woman may have depression, a comprehensive evaluation, including medical, psychiatric, obstetric, and social history, is necessary to confirm the diagnosis. Up to 80% of women will develop "postpartum blues," a condition of transient depressive symptoms that resolve within 10 days of delivery and that does not require treatment.[12] Clinicians should be aware that normal symptoms experienced in pregnancy (eg, decreased energy, appetite changes, sleep disturbance) can mimic depressive symptoms. Finally, it is necessary to further determine if the patient has complex depression (**Table**), defined for the purposes of this review as a presentation in which referral to a psychiatrist for treatment should be considered. The assessment must determine whether suicidal ideation, homicidal ideation, or psychotic symptoms are present. Postpartum psychosis is rare (0.1%) and generally indicates the presence of underlying bipolar disorder.[11] Postpartum psychosis, suicidal ideation, and homicidal ideation (which can be directed toward the newborn infant) represent psychiatric emergencies, and immediate referral to a mental health professional or emergency department is indicated.

Patients with major depression frequently have medical, substance-related, and psychiatric comorbidities.[13–17] Comorbidities may have a significant impact on treatment decisions and, if present, the patient should be considered to have complex depression (Table). During the evaluation, it is especially important to rule out bipolar disorder, a condition that results in episodes of mania or hypomania as well as depression.[10] Manic episodes are defined as periods of elevated mood lasting 1 week or longer.[10] Other symptoms of mania include inflated self-esteem, decreased need for sleep, talkativeness, racing thoughts, distractibility, increased activity, and excessive involvement in pleasurable activities. Episodes of mania cause marked impairment in functioning and frequently require hospitalization. Although the symptoms of mania and hypomania are the same, symptoms are milder in hypomania and do not result in marked impairment or hospitalization.[10] Approximately one half to two thirds of women with bipolar disorder will experience a significant mood episode in the postpartum period, and these episodes are much more frequently depressed than manic.[18,19] In a naturalistic family practice study, 25.9% of patients with a mood disorder were found to have bipolar spectrum illness.[20] Primary care physicians should screen for bipolar disorder by inquiring about previous manic or hypomanic episodes. A convenient and practical tool to screen for symptoms of mania is the Mood Disorder Questionnaire (MDQ; available at www.psycheducation.org).[21] If a history of mania or hypomania is present (either by patient report and/or MDQ score ≥ 7), referral to a psychiatrist is indicated.

Table. Complex Depression

Suicidal ideation*
Homicidal ideation*
Psychosis*
Bipolar depression
Comorbid psychiatric disorders or substance abuse
High risk of obstetric complications
History of treatment-refractory depression
History of ≥ 2 prior depressive episodes
Failure of adequate therapeutic trials of ≥ 2 different antidepressants
Clinical indication for use of an agent other than a selective serotonin reuptake inhibitor

NOTE: Any of the above should result in consideration of referral to a psychiatrist for treatment.

*Psychiatric emergency that requires immediate referral to a mental health professional or emergency department.

In addition to evaluating for potential comorbidities, it is also important to inquire if pharmacologic treatment has been provided for depressed episodes, specifically the agent used, dose, duration of treatment, and response. Similarly, if the patient has a psychiatric history, the number and severity of previous depressive episodes and treatment history must be elicited. If a woman has had 1 episode of postpartum-onset depression, the risk of recurrence is high. In a recent study of 50 women with a history of postpartum-onset major depression, 13 (26%) experienced recurrence of major depression in the first 20 weeks postpartum, with a total of 20 (40%) experiencing recurrence in the first year.[22]

Social history should focus on both current psychosocial stressors and the level of available psychosocial support as well as risk factors for depression. The significant risk factors for postpartum depression include an annual income of less than $20,000, less than a college education, low occupational prestige, young age, single marital status, and multiple offspring.[6] Once the evaluation is

complete, the information gathered provides the basis for determining whether the patient is suffering from complex depression (Table), thereby warranting psychiatric referral, or if management by the primary care provider is appropriate. For interested readers, a detailed discussion regarding the use of data gathered for treatment planning can be found in the *Textbook of Psychopharmacology* by Newport and colleagues.[8]

RISK-BENEFIT DECISION MAKING

For primary care physicians, treatment options for major depression can be broadly grouped into 4 categories: (1) pharmacotherapy, (2) referral for psychotherapy, (3) referral to a psychiatrist, and (4) no treatment. A goal of the diagnostic evaluation is to gather the necessary information to discuss in detail the relative risks and benefits of each of these options with the patient. Risk-benefit decision making for treating depression in pregnant or breastfeeding women is complex.[8,23] In addition to considering possible risks to the fetus or infant from pharmacologic interventions, the risks of inadequate treatment or no treatment to both the mother and child must be taken into account. For ethical reasons, adequate controlled trials of antidepressants in pregnant or lactating women have not been performed.[8] Thus, safety data on the use of antidepressants in this population are based on case reports, case series, birth registries, retrospective surveys, and reports from teratology centers.[8] The result is an already complex clinical decision-making process further complicated by a lack of definitive studies. Nonetheless, it is possible to provide information so that pregnant and nursing mothers can make informed treatment decisions in consultation with their physician.

The risk to the mother from treatment with SSRIs is low. However, possible side effects include sexual dysfunction, weight change, sleep disturbance, anxiety, agitation, and nausea. In most cases, side effects are mild and resolve quickly; however, 10% to 20% of patients may discontinue treatment due to adverse events. A potentially life-threatening side effect is central serotonin syndrome, which can occur if an SSRI is administered with another agent that enhances serotonin function. Thus, a careful history is required before initiating treatment with an SSRI.[24] Although there is controversy in regard to whether antidepressants increase the risk of suicide in a minority of cases, this should not prevent physicians from initiating appropriate treatment. All depressed patients should be monitored carefully for suicide risk and side effects, especially early in treatment.

All antidepressants are believed to cross the placenta.[8,9] Therefore, treatment with antidepressants results in some degree of fetal exposure. Medication exposure may cause 3 general types of adverse events: (1) embryotoxicity, defined as deleterious effects that occur due to in utero exposure but that do not result in physical birth defects (eg, long-term neurobehavioral effects, neonatal withdrawal syndromes);[9] (2) teratogenicity, malformation of fetal organs or skeletal structures;[25] and (3) miscarriage. All antidepressants are excreted into breast milk; thus, there is a potential risk of adverse effects in breastfed infants of mothers taking these medications. A more detailed discussion of specific SSRIs used in pregnancy and lactation and the associated safety data can be found in subsequent sections.

Although there are risks associated with treatment, there is compelling evidence that lack of treatment carries its own set of risks. In women with depression during pregnancy, obstetric and neonatal complications occur more frequently, including operative deliveries (eg, cesarean sections, instrumental vaginal deliveries) and admission to the neonatal care unit.[26] Neonatal complications such as placental abnormalities, antepartum hemorrhages, and fetal distress have been observed more often in women with depression during pregnancy.[27] A recent study found that during both the second and third trimesters, depressed pregnant women had more sleep disturbances and higher anxiety and anger scores as compared with women without depression.[28] The same study found that newborns of the depressed mothers also had more sleep disturbances, were more active, and cried/fussed more.[28] O'Connor et al[29] found decreased time spent sleeping and increased frequency of awakenings in infants as old as 30 months whose mothers had mood disturbances during pregnancy. Further, prenatal maternal depression may slow fetal growth[30] and increase the risk of preterm delivery and other obstetric complications.[31,32]

There is considerable evidence that poorly controlled depression adversely affects infants and children of mothers with postpartum depression. Postpartum depression has been associated with delays in both cognitive and language development.[33] Several studies have shown that infants and children of depressed mothers are more to likely to exhibit attachment dysfunction, depressive symptoms, anxiety symptoms, and conduct disorder behaviors.[34–37] In a recent study, 76% of mothers with major depression reported that their mental health symptoms made it difficult to care for their children.[38] Weissman and colleagues[39] recently found that treatment of maternal depression results in a reduction of psychopathology in children of depressed mothers.

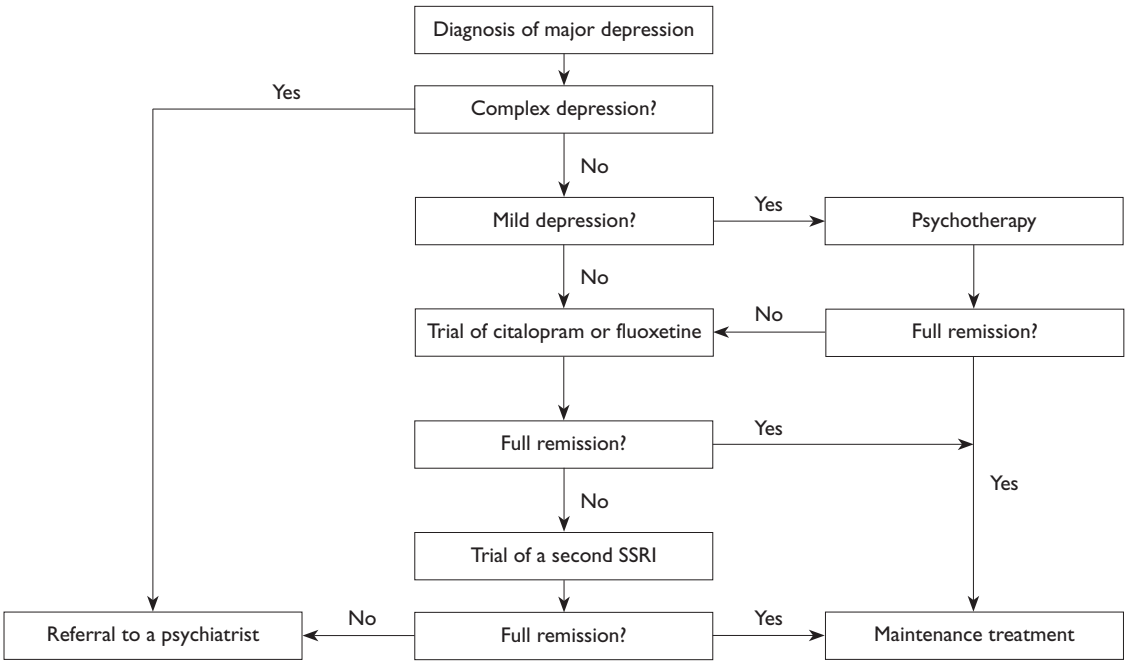

Figure 1. Algorithm for acute treatment of major depression during pregnancy. SSRI = selective serotonin reuptake inhibitor.

APPROACH TO THERAPY

Primary care physicians can use existing data to determine the best therapeutic option for the patient. **Figure 1** and **Figure 2** can be used to help guide treatment of major depression during pregnancy and lactation. In cases of mild depression, treatment with psychotherapy alone should be considered the first-line option (Figure 1). For the treatment of major depression in general, cognitive behavioral therapy (CBT) and interpersonal therapy have the best-documented efficacy.[40] Reports of psychotherapeutic treatment during pregnancy[41–44] and a recent controlled trial demonstrated that psychotherapy is an effective method for treating depression during pregnancy.[45] Similarly, CBT,[46,47] psychodynamic psychotherapy,[48] and interpersonal psychotherapy[49] have been shown to be effective in the treatment of postpartum depression. For moderate depression, psychotherapy or pharmacotherapy alone can be considered first-line treatment options;[40] however, the combination of psychotherapy and pharmacotherapy may be necessary if treatment response is inadequate. Severe depression always warrants initiation of an antidepressant as first-line treatment.[40] Pharmacotherapy may be used in combination with psychotherapy, particularly if interpersonal issues exist. "No treatment" is not recommended if the patient meets diagnostic criteria for major depression. Nonetheless, some patients may decline treatment. In these cases, close follow-up should be maintained along with continued discussions regarding the risks and benefits of treatment.

The minimum effective dose of medication should be used during pregnancy and lactation.[8] However, the dose should not be decreased to a point in which effectiveness is lost. The goal of treatment should be full remission of symptoms.[50] During pregnancy, dose adjustments may be necessary to maintain therapeutic effectiveness. For example, tricyclic antidepressants require an increase of approximately 1.6 times the preconception dose due to the effects of physiologic changes of pregnancy on pharmacokinetics.[51] One small study suggests a similar increase may be necessary during the third trimester for SSRIs as well.[52]

PHARMACOLOGIC TREATMENT OF DEPRESSION DURING PREGNANCY

Although no randomized, double-blind trials have been performed, emerging evidence from controlled trials indicates that antidepressants are effective during pregnancy. At least 1 study suggests that reassurance and continuous antidepressant pharmacotherapy during gestation can provide pregnant women with effective symptom control for depression.[53] Further, stopping antidepressant treatment during pregnancy may result in relapse of illness.[50,54,55] Among the classes

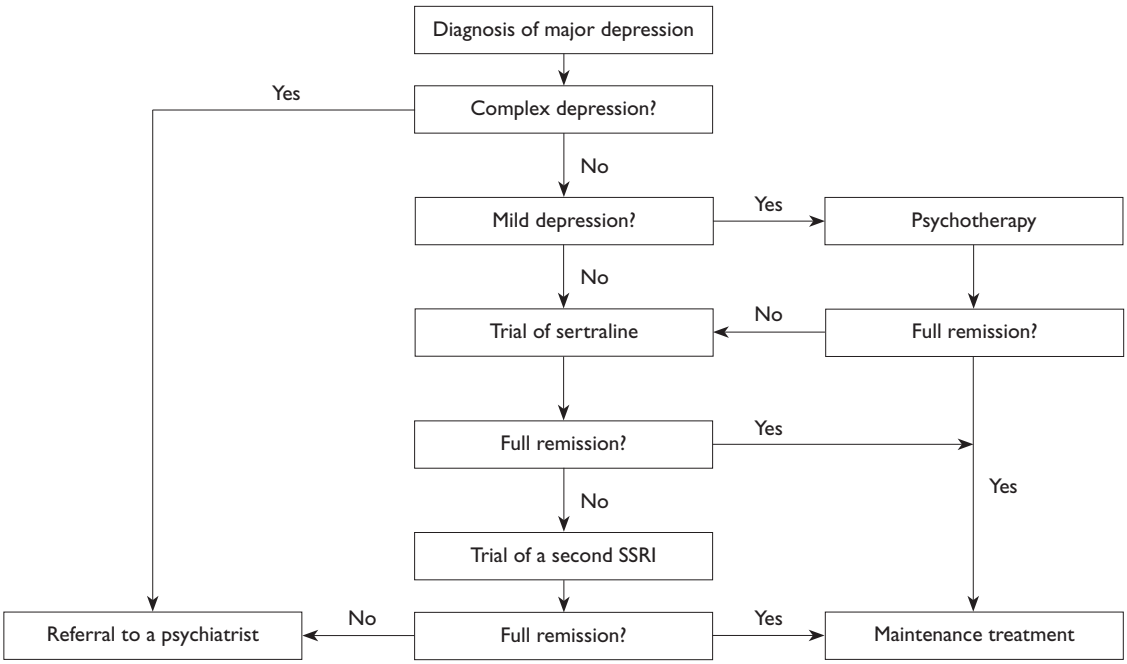

Figure 2. Algorithm for acute treatment of major depression during lactation. SSRI = selective serotonin reuptake inhibitor.

of antidepressants, SSRIs are considered the first-line agents for the treatment of depression during pregnancy,[8] both because of the general favorable tolerability profile and the availability of reproductive safety data.

Most available reproductive safety data are related to fluoxetine, including 10 studies of over 1700 fetal exposures.[56–65] Results of a meta-analysis revealed no increased risk of birth defects as a result of fetal exposure to fluoxetine.[66] However, 1 study found an elevated risk of spontaneous abortions in women exposed to fluoxetine as compared with unexposed women (13.5% versus 6.8%, respectively).[57] Another study that evaluated various SSRIs reported increased rates of low birth weight among the group treated with high-dose (40–80 mg/day) fluoxetine.[61] Chambers et al[58] found that pregnant women taking fluoxetine had an increased incidence of perinatal complications, including low birth weight, preterm delivery, and withdrawal-like symptoms. The potential for long-term neurodevelopmental complications has only been studied for fluoxetine, with 2 studies finding no evidence of long-term developmental delays.[67,68]

Louik et al[69] recently found no increased risk of birth defects in 9849 women who took fluoxetine, citalopram, escitalopram, or fluvoxamine during the first trimester. However, there was a small but statistically significant increased risk of omphalocele and septal defects in women taking sertraline as well as a small but statistically significant increased risk of right ventricular outflow tract obstruction defects in women taking paroxetine.[69] Another large study (N = 9622) evaluating fluoxetine, sertraline, paroxetine, and citalopram showed a small increased rate of anencephaly, omphalocele, and craniosyntosis in women taking SSRIs during the first trimester.[70]

Excluding the studies by Louik et al[69] and Alwan et al,[70] few studies have evaluated the effects of SSRIs such as fluvoxamine, sertraline, paroxetine, and citalopram in pregnancy. Data regarding fluvoxamine and sertraline are very limited, assessing only 92 and 181 total exposures, respectively.[56,63,71] Therefore, there is not enough evidence to draw conclusions about the safety of either agent during pregnancy. In 3 studies on the reproductive safety of citalopram involving 518 exposures,[63,72,73] increased preterm delivery was the only reported adverse effect; this increase was thought to be due to the underlying depression.[63] Of note, sertraline has been found to cross the placenta to a lesser degree than most other SSRIs, whereas citalopram crosses the placenta to a greater degree as compared with the other SSRIs.[74]

In 2005, the US Food and Drug Administration recommended that the manufacturer of paroxetine change the drug to pregnancy category D after learning

of preliminary unpublished epidemiologic data that suggested an increased risk of cardiovascular malformations in children born to mothers exposed to the drug during pregnancy.[75] However, in reports of 305 fetal exposures to paroxetine,[56,63,71,76] the only adverse event was transient neonatal withdrawal in 1 study.[76]

In summary, there is a fairly large but limited and somewhat conflicting body of literature on the safety of SSRIs during pregnancy. Limited evidence suggests that SSRIs may increase the risk of physical birth defects. Due to small sample sizes in some cases, firm conclusions must await further studies. The risk of spontaneous abortion and perinatal complications is thought to be somewhat greater for paroxetine and fluoxetine as compared with the other SSRIs (9.53% and 8.7% versus 5.57%).[9] Chambers et al[77] suggested that newborns are at higher risk for persistent pulmonary hypertension if their mothers used SSRIs during the final 20 weeks of gestation. Based on the currently available evidence, first-line use of fluoxetine or citalopram should be considered. A suggested algorithm is provided to assist with treatment planning in women who have no prior history of treatment (Figure 1). Expert consensus guidelines developed in 2001 recommend using any SSRI during pregnancy if it has established effectiveness in an individual.[78] Given the recent change of paroxetine to pregnancy category D and recent data that suggest an increased risk of omphalocele and septal defects in children born to women taking sertraline, these agents should be used with more caution in pregnant women.

Clinicians may be faced with clinical scenarios other than those discussed in this review, including preconception decisions about continuing ongoing antidepressant treatment, unplanned pregnancy when taking an antidepressant, and relapse during pregnancy when antidepressant treatment was stopped at conception. A detailed discussion of management decisions based on these scenarios is beyond the scope of this article. However, the information contained herein may provide a framework that can assist clinicians facing these situations. In more complex situations, referral to or consultation with a psychiatrist colleague should be considered. The reader is referred elsewhere for additional guidance.[8]

PHARMACOLOGIC TREATMENT OF DEPRESSION DURING LACTATION

The evidence base for using antidepressants specifically in postpartum depression is limited. Sertraline was shown to be more efficacious than placebo in a small sample of 21 women with postpartum depression and was as efficacious as nortriptyline in a sample of 95 women with postpartum depression.[79,80] Fluoxetine was more efficacious than placebo and as efficacious as CBT in 61 women with postpartum depression.[47] Paroxetine was shown to be as efficacious as CBT in a small sample of 35 women with postpartum depression.[46] Other antidepressants have either been shown to be no better than placebo or their effectiveness has only been tested in open-label studies. However, there is an expanding body of evidence examining the use of all major antidepressants in women who are breastfeeding.

As breastfeeding is almost universally encouraged given the benefits to infant health, careful consideration should be given to using any medications in mothers of breastfed infants. Expert consensus guidelines recommend the use of any antidepressant in the postpartum period if it has been used to effectively treat prior depressive episodes in the patient.[78] If no such treatment history exists, certain antidepressants could arguably be more appropriate than others given emerging evidence regarding the use of these medications in mother-infant pairs.

Because there is a substantial body of evidence showing that sertraline can be used with minimal risk to the infant, it has been recommended as a first-line agent in expert consensus guidelines.[78] Several independent studies have shown that the concentration of sertraline in breast milk is generally low and is not detectable in the serum of breastfed infants of mothers taking the drug.[81–83] Furthermore, no adverse effects were observed in infants participating in these studies.[81–83] Platelet serotonin levels (a proxy measure of brain SSRI activity) have been found to be minimally altered in breastfed infants of mothers taking sertraline, suggesting that sertraline is likely safe in this patient population.[84] Antidepressants with pharmacodynamic, pharmacokinetic, and infant safety profiles similar to sertraline (and thus represent reasonable alternatives to sertraline) include paroxetine,[85–88] fluvoxamine,[85] mirtazapine,[89] and most tricyclic antidepressants.[90]

When compared with sertraline and medications pharmacodynamically and pharmacokinetically similar to sertraline, fluoxetine,[91–93] venlafaxine,[94,95] and citalopram[96] have higher concentrations in breast milk and are more likely to be detected in the serum of breastfed infants of mothers taking these medications. Furthermore, adverse effects such as colic and poor sleep have been reported in infants of mothers taking fluoxetine and citalopram, respectively.[92,97] Fluoxetine, citalopram, and venlafaxine are best used during lactation if the patient has exhibited a prior response, with the caveat that a switch in medication may be necessary if the breastfed infant has adverse effects as a result of their use.

Little is known about the long-term effects of exposing infants to SSRIs or selective serotonin/norepinephrine reuptake inhibitors during breastfeeding. Buist et al[98] showed that children (age, 3–5 yr) exposed to tricyclic antidepressants from breast milk in infancy were developmentally indistinguishable from similarly aged children who had not been exposed. A suggested algorithm is provided for treatment planning in women who have had no prior history of treatment (Figure 2).

CONCLUSION

Primary care physicians frequently manage depression in pregnant and breastfeeding mothers. Although the literature is somewhat limited, physicians can rely on existing evidence for general treatment guidelines (Figure 1 and Figure 2). A thorough assessment is necessary to ensure that the patient meets diagnostic criteria for major depression and to differentiate between major depression and comorbid disorders; consideration should be given to a psychiatric referral in more complex cases (Table). Psychotherapy alone should be considered first-line treatment in all cases of mild depression. In moderate or severe depression, the patient and physician must have an in-depth discussion of treatment risks and benefits and develop a treatment plan together. Consultation with the patient's obstetrician should be considered as well. Antidepressant use during pregnancy and lactation is relatively safe, and physicians and patients should not be hesitant to initiate treatment when indicated. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 46.

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