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Treating depression in pregnancy: Practical suggestions

ABSTRACT

Failure to treat depression during pregnancy can lead to problems for the mother and the baby. However, given the lack of convincing evidence of the safety of antidepressant drugs to the fetus during pregnancy and lactation, any antidepressive treatment plan must be embarked on with caution. The authors offer practical guidelines for managing depression during pregnancy and lactation.

KEY POINTS

Neither bupropion nor paroxetine is recommended, especially during the first trimester, as data suggest adverse outcomes when they are used early in pregnancy.

The evidence suggests an increased risk of spontaneous abortion with antidepressant use, so any antidepressant should be prescribed and used with caution.

Decisions about using antidepressants during pregnancy are best made before a woman conceives. Treat all women of reproductive years as if they are pregnant.

All psychotropic drugs cross the placenta and enter into breast milk, so the fetus or neonate is always exposed. Pregnancy and lactation complicate treatment but do not preclude it.

CONTRARY TO CLINICAL LORE, pregnancy is not always a time of emotional well-being. In the real world, pregnant and nonpregnant women have similar rates of depression.[1]

Risks of not treating or undertreating depression in pregnancy include preterm delivery,[2] poor prenatal care and self-care,[3] and infants with smaller head circumference[4] and lower Apgar scores.[5] Clearly, depression should be treated. But antidepressant treatment in pregnancy requires striking a balance between relieving the mother's depression and minimizing exposure of the fetus and the breastfeeding neonate to drugs that have conflicting fetal and neonatal safety profiles.

The incidence of congenital malformations in newborns in the United States is 3% to 4%,[6] and no clinical decision is risk-free. Risks such as organ malformation or teratogenesis, neonatal toxicity, and long-term neurobehavioral sequelae must be taken into account (**TABLE 1**). We will address here the particular risks and benefits of antidepressant treatment throughout pregnancy and during breastfeeding, and we will offer guidelines for the practicing internist.

FIRST TRIMESTER

Organogenesis occurs during the first trimester, so the risk of congenital malformations needs to be weighed against the potential benefits of any medication given at this time. These risks should also be considered in treating any woman of childbearing age, as pregnancies often are unplanned and are not detected for some time.

TABLE 1

Treating depression in and around pregnancy: key considerations

First trimester	Because of the lack of data on the safety of antidepressants in pregnancy, treat every woman of reproductive age as if she is pregnant
	Discuss with the patient the risks of antidepressant drugs for the fetus and the newborn, especially during the first trimester, the time of fetal organogenesis
	Start antidepressant treatment if the patient is unable to care for herself, has insomnia, or shows signs of risk-taking behavior or suicidal ideation
	Preexisting antidepressant therapy may be stopped if the depression has been asymptomatic for longer than a year
	May use tricyclic antidepressants, fluoxetine, sertraline; avoid paroxetine or bupropion
Second trimester	If antidepressant therapy has been stopped, it may be restarted at this time; there is evidence that most relapses of depression occur during this trimester
	May use tricyclic antidepressants, fluoxetine, sertraline; advise patients that selective serotonin reuptake inhibitors (SSRIs) may be associated with an increased risk of persistent pulmonary hypertension in the neonate
Third trimester and after	If patient is taking antidepressants and the decision is made to stop the medications, taper very gradually to avoid causing withdrawal (eg, anticholinergic withdrawal, serotonin withdrawal) in the neonate
	For patients who are breastfeeding, nortriptyline is the preferred tricyclic, and sertraline and paroxetine are the preferred SSRIs; always use the lowest effective dose to minimize risks to the infant

General recommendations

Women with depression that has been asymptomatic for greater than 1 year may reduce or even discontinue their antidepressants a few months before attempting to conceive. These women should be monitored for relapse and should be weaned off antidepressants slowly. However, women with a long history of recurrent severe major depression should not discontinue their medications.

Antidepressant therapy is recommended for any pregnant woman with symptoms such as the inability to care for herself, suicidal ideation, insomnia, and risk-taking behaviors.

The treatment plan should be based on the patient's preferences and on her depression history (eg, number and severity of depressive episodes, suicide attempts, psychiatric admissions).

Evidence of safety

As yet, there has been no randomized, placebo-controlled study of antidepressant use in pregnancy, but we do have data from small prospective studies and from national registries and pharmaceutical companies.

No study has shown any antidepressant to be absolutely safe during any stage of pregnancy. However, studies have shown no increased risk of major malformations from taking antidepressants. These include four studies with tricyclic antidepressants.[7] While no controlled study has found an increased risk of congenital malformations with the use of selective serotonin reuptake inhibitors (SSRIs),[7] unpublished data from the Swedish national registry found that children of women who took paroxetine (Paxil) during the first trimester had a rate of congenital malformations twice that of the general population. Specifically, ventricular septal defects and atrial septal defects were found, ranging in severity from completely asymptomatic to requiring surgical correction. This led GlaxoSmithKline to change the prescribing information for paroxetine in 2005, currently recommending its use in the first trimester

First trimester: minimize fetal exposure to drugs during organogenesis

only after consideration of other treatment options.[8] We should keep in mind that these are unpublished data and can at best only establish a correlation. Good evidence-based data are lacking in this area, and therefore these findings deserve some consideration.

A small study found that children of women who took fluoxetine (Prozac) in the first trimester had an increased risk of minor anomalies, including syndactyly,[9] but that fluoxetine appears to be safe to use in the first trimester.

Evidence of spontaneous abortion

Studies[10,11] have shown slightly higher but not statistically significant rates of spontaneous abortion with antidepressant use during pregnancy. The drugs used included trazodone (Desyrel), nefazodone (Serzone), tricyclic antidepressants, venlafaxine (Effexor), bupropion (Wellbutrin), fluoxetine, sertraline (Zoloft), fluvoxamine (Luvox), and paroxetine (Paxil). Rates of spontaneous abortion found with specific antidepressants are as follows: fluoxetine 13.5%, tricyclics 12%, trazodone and nefazodone 13.5%, newer SSRIs (fluoxetine, fluvoxamine, sertraline, paroxetine) 10.7%, venlafaxine 12%, and bupropion 15.4%.[10] Controls in these studies were women not exposed to teratogens and who had rates of spontaneous abortion from 6.7% to 8%.

Clearly document the rationale for treatment, as fetal safety cannot be guaranteed

Interestingly, although these studies showed a slightly higher rate of spontaneous abortion in women taking antidepressants, only the bupropion study[10] showed an increase that was statistically significant. None of these studies found an increased risk in major malformations.

In a prospective case series of 21 women using newer antidepressants (nefazodone, mirtazapine [Remeron], and venlafaxine) during the first trimester of pregnancy,[11] no congenital abnormality was found. Some of the women were taking more than one antidepressant, which is common in everyday practice but has not been studied in pregnancy.

These studies show no evidence that antidepressant use in pregnancy increases the risk of congenital abnormalities, but seem to indicate that women taking antidepressants during the first trimester may have an increased risk of spontaneous abortion.

SECOND TRIMESTER

Little is known about depression or its treatment in the second trimester of pregnancy. However, a recent study[12] found that among women who stopped taking their antidepressant drugs, 68% had a relapse during pregnancy, whereas only 26% of those who did not stop their medications had a relapse; and 90% of those who had a relapse did so by the second trimester.[12]

Since organogenesis is generally complete by the second trimester, many psychiatrists restart antidepressants at this time, especially if the patient develops symptoms or if she is at high risk of recurrence.

In one study, the point prevalence of major depression was found to be 3.3% and that of minor depression to be 6.9% in women in their second trimester.[13] Unfortunately, only very few of the women identified as having a mental illness had already been identified and had been receiving treatment.

A study of eight women found that tricyclic antidepressant doses needed to be increased substantially during the second half of pregnancy to achieve therapeutic levels and response.[14]

Two case reports[15,16] described women being treated in the second trimester. One was of a woman with depression and anxiety successfully treated with repetitive transcranial magnetic stimulation during her second trimester.[15] The other was of a woman without major depression, carrying twins, with hyperemesis gravidarum in her 15th week, which resolved with 2 weeks of treatment with mirtazapine.[16] Neither twin showed any adverse effects at follow-up.

In addition, a recent retrospective case-control study found a slightly increased risk of persistent pulmonary hypertension in newborns exposed to SSRIs after the 20th week of gestation.[17]

THIRD TRIMESTER AND AFTER

During the third trimester, several issues arise in the management of depression:

- Should antidepressant therapy be tapered to minimize perinatal syndromes or neonatal toxicity?

- How should we adjust therapy in women who want to breastfeed?
- What are the long-term effects on children of mothers who took antidepressants during pregnancy?
- Should we treat women prophylactically to prevent relapse?

Perinatal and neonatal concerns

Various case reports have described perinatal syndromes in infants exposed to antidepressants nearer the time of delivery.[18] Tricyclic withdrawal syndromes include jitteriness, irritability, urinary retention, bowel obstruction, and occasionally seizures.[19] Withdrawal symptoms generally occur in the first 12 hours after birth and are usually transient.

One prospective study in which mothers were taking fluoxetine during the third trimester noted perinatal complications in their infants, including jitteriness, respiratory distress, and poor neonatal adaptation.[9] Other prospective studies have not observed perinatal distress in infants exposed to fluoxetine or other SSRIs.[20,21]

Also, as mentioned above, it is worth informing patients about the slightly increased risk of persistent pulmonary hypertension in newborns exposed to SSRIs after the 20th week of gestation.[17]

Breastfeeding concerns

Treating breastfeeding women with antidepressants is another clinical dilemma, as all antidepressants are excreted in breast milk. Also, half of new mothers breastfeed,[22] and because of the benefits of nursing, some women are reluctant to wean their infants when medication is prescribed. According to currently available data, breastfeeding infants exposed to nortriptyline (Pamelor) seem unlikely to develop detectable or elevated plasma levels.[23]

Respiratory depression due to elevated concentrations of the metabolite *N*-desmethyldoxepin has been reported in one case in a nursing infant whose mother was taking doxepin (Sinequan).[24]

For the SSRIs, substantial levels of fluoxetine were detected in a 6-week-old infant.[25] Also, fluoxetine and norfluoxetine have very long half-lives, and so they carry a greater potential for detectable serum levels in newborns. Studies on infants exposed to paroxetine or sertraline from breastfeeding noted infant serum levels that were negligible or undetectable.[26] Fluoxetine and citalopram produced elevated levels (ie, > 10% of the average maternal level) in 22% and 17% of infants, respectively, in a pooled analysis of antidepressant levels in lactating mothers and nursing infants.[23]

Using the minimum effective dose of antidepressant medication for a nursing mother keeps the dose received by the infant through breast milk as low as possible.

Given the lack of large, randomized controlled studies, we cannot assure women that an antidepressant is absolutely safe to take during nursing. Discussions with mothers should cover the risks and the benefits, and all such discussions should be documented in the medical record.

Once the child is born, both the clinician and the nursing mother should be alert to worrisome infant behaviors, such as irritability, poor feeding, or disturbed sleep, which may indicate adverse infant effects from maternal antidepressant use. Alternatives such as weaning or attempting nondrug treatments alone, if clinically appropriate, should be discussed.

Use the minimum effective dose of antidepressant for nursing mothers to keep breast milk levels low

Long-term effects on children

Mothers who take antidepressants often ask about long-term neurobehavioral sequelae in their children. Unfortunately, we have too few data to answer this question.

Data from animal studies show changes in neurotransmitter function and behavior after prenatal exposure to psychotropic medications. In one landmark prospective study, Nulman and Koren[27] found no neurobehavioral differences in children exposed to fluoxetine or tricyclics during pregnancy compared with a control group of children whose mothers were not exposed to antidepressants. These children were followed up to age 48 months and were tested for IQ, temperament, and cognitive function. No significant differences were found in the three groups.[27]

Clearly, larger studies are needed to establish a causal link between antidepressant use in pregnancy and lactation and long-term neurobehavioral effects in children.

Preventing recurrence

How should we manage women who have a history of recurrent depression or postpartum depression?

An epidemiologic study by Kendell and colleagues[28] noted a dramatic increase in rates of new psychiatric episodes for women within 3 months of giving birth. Major depression was the most common diagnosis, with 80% of these episodes being affective in nature.

Since the risk of a recurrent postpartum depression is 50%, tapering or discontinuing antidepressant medication in the third trimester must be done carefully and on a case-by-case basis, paying attention to factors such as personal history of affective illness, family history of depression, marital discord, psychosocial supports, recent adverse life events, and unwanted pregnancy.[29]

An earlier study showed no difference between nortriptyline and placebo in preventing recurrence of postpartum depression.[30] In a recent pilot randomized clinical trial,[31] sertraline prevented recurrence of postpartum depression better than placebo, and the time to recurrence was significantly greater with sertraline than with placebo. The number of patients in this study was very small, however.

Given the high rate of relapse, it is prudent to monitor for relapse of postpartum depression and to start antidepressant therapy immediately after delivery. A reasonable choice of drug would be either an SSRI or an antidepressant that the patient had responded to previously. Of course, one would also need to take into consideration whether the patient will be breastfeeding.

We are still far from having clear evidence that these drugs are *absolutely* safe in pregnancy

NONDRUG TREATMENTS

In any discussion of treatment for depression in pregnancy, nonpharmacologic options should be considered, and in some cases, nondrug treatments should be tried first.

Patients with severe depression may require electroconvulsive therapy. In the past, this was considered contraindicated in pregnancy, but it has since been found to be safe and effective as long as steps are taken to reduce the risk of potential side effects, such as memory loss, confusion, and headache. A review[32] that included 300 case reports of electroconvulsive therapy in pregnant women found complications in 28 cases, including the following serious complications: 4 cases of premature labor, 5 cases of spontaneous abortion, 3 cases of stillbirth and neonatal death, 1 case of respiratory distress in the newborn, and 5 cases of congenital anomalies.[32]

Unfortunately, only a few randomized controlled studies have examined the effect of psychotherapy in these patients. One study[33] evaluated the effect of interpersonal psychotherapy vs a parenting education program and found that there was significant improvement in mood for the women who received interpersonal therapy. This type of therapy may be well suited to pregnant women since it focuses on role transitions.

A study of interpersonal psychotherapy in women with postpartum depression[34] found it to be effective: up to 43.8% of women treated recovered from their depressive episode compared with 13.7% of the control group. In another study,[35] light therapy improved depression in pregnant women if there was a seasonal component.

HERBALS, ALTERNATIVE DRUGS NOT STUDIED IN PREGNANCY

Currently, we advise against the use of over-the-counter herbal products and supplements for the treatment of depression during pregnancy. These medicines are not regulated by the US Food and Drug Administration, and patients could be taking pills that contain either no or insufficient active ingredient. Also, no studies have specifically examined their use during human pregnancy.

SOME GUIDELINES FOR TREATING DEPRESSION IN PREGNANCY

- Decisions about using antidepressants during pregnancy are best made before a woman conceives. Treat all women of reproductive years as if they are pregnant.
- Knowing the patient's depression history and the severity of her symptoms is key to tailoring the antidepressant regimen.
- All psychotropic drugs cross the placenta and enter into breast milk, so the fetus or breastfeeding neonate is always exposed.

Pregnancy and lactation complicate treatment but do not preclude it. Always consider the fetal safety profile of any antidepressant drug before prescribing it, choose drugs with the best evidence of safety during pregnancy and lactation, and use the lowest effective dose. In breastfeeding women, nortriptyline, paroxetine, and sertraline are preferred.

- Maternal mental illness can adversely affect obstetrical outcome and infant development. Especially in women with a history of major depression, treatment should continue during pregnancy whenever possible. The decision to discontinue treatment is on a case-by-case basis. If you decide to discontinue treatment, taper gradually over 2 weeks.
- Simplify the regimen by using one drug, if possible. Data support the relative reproductive safety of tricyclics, fluoxetine, and sertraline.
- Monitor the severity of symptoms throughout pregnancy; higher doses of drugs may be necessary later in the pregnancy.
- The safety of antidepressant therapy during pregnancy and lactation cannot be guaranteed. Inform the patient of the risks of drug therapy and of the availability of nondrug therapies. Always clearly document the rationale behind the treatment and your discussions with the patient about safety.
- Whenever depression puts a pregnant woman at risk of harm to herself or to others, including her fetus, inpatient psychiatric admission is strongly recommended.
- For women with recurrent major depression, the treatment team should discuss risks and benefits with the patient before making any changes to her drug regimen. If depression in a pregnant patient does not respond well to drug therapy, refer her to a psychiatrist who specializes in treating pregnant women.
- We do not recommend using bupropion or paroxetine in pregnancy, especially during the first trimester; data suggest adverse outcomes from using these drugs early in pregnancy.
- Data suggest an increased risk of spontaneous abortion with antidepressant use, and any of these medications should be used cautiously. Further research is necessary in this area; we are still far from having clear evidence that these medicines are *absolutely* safe during pregnancy.

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