Severe antenatal unipolar major depression: Choosing treatment

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INTRODUCTION

Unipolar major depression is common in pregnant women and is often not treated [1]. In a nationally representative survey in the United States that identified pregnant and nonpregnant women with major depression, pregnant women were less likely to receive mental health treatment than nonpregnant women (49 versus 57 percent) [2]. Untreated disease causes maternal suffering and is associated with poor nutrition, comorbid substance use disorders, poor adherence with prenatal care, postpartum depression, impaired relationships between the mother and her infant and other family members, and an increased risk of suicide [3,4].

Barriers to treatment of antenatal depression include cost, opposition to treatment (eg, fear of exposing the fetus to antidepressant medication or lack of interest in psychotherapy), unavailability of psychotherapy, and stigma [3,4]. In addition, many clinicians are reluctant to use pharmacotherapy because they lack sufficient expertise [5], and the large literature is often inconsistent [6].

This topic reviews choosing a specific treatment for severe antenatal unipolar major depression. Other topics discuss treatment of mild to moderate episodes of antenatal unipolar major depression; general principles of treatment; risks of antidepressants during pregnancy; and the epidemiology, clinical features, assessment, and diagnosis of antenatal depression.

- (See "Mild to moderate episodes of antenatal unipolar major depression: Choosing treatment".)
- (See "Unipolar major depression in pregnant women: General principles of treatment".)
- (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors".)
- (See "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors".)
- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)
- (See "Unipolar major depression during pregnancy: Epidemiology, clinical features, assessment, and diagnosis".)

DEFINITIONS

Unipolar major depression — Unipolar major depression (major depressive disorder) is diagnosed in patients who have suffered at least one major depressive episode and have no history of mania or hypomania [7]. An episode of unipolar major depression is a period lasting at least two weeks, with five or more of the following nine symptoms: depressed mood, loss of interest or pleasure in most or all activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, guilt or thoughts of worthlessness, and recurrent thoughts about death or suicide (table 1). Additional information about the clinical presentation and diagnosis of unipolar major depression is discussed separately. (See "Unipolar depression in adults: Clinical features" and "Unipolar depression in adults: Assessment and diagnosis".)

Severity of illness — Selecting a treatment for antenatal major depression often depends upon the severity of illness:

- **Mild to moderate** – Mild to moderate episodes of unipolar major depression are generally characterized by five or six depressive symptoms (table 1), as indicated by a score <20 points on the self-report Patient Health Questionnaire – Nine Item (PHQ-9) (table 2). However, the instrument includes items about changes in appetite, energy, and sleep, which may reflect the physical effects of pregnancy rather than depression. Additional information about the PHQ-9 is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

  Patients with mild to moderate illness do not manifest suicidal behavior or obvious impairment of functioning, and are less likely to develop complications such as psychotic

features and catatonia, compared with patients who are severely ill. Mild to moderate depression can typically be managed in outpatient or partial hospital settings. Additional information about treating mild to moderate antenatal depression is discussed separately. (See "Mild to moderate episodes of antenatal unipolar major depression: Choosing treatment".)

- **Severe** – Severe unipolar major depression is characterized by seven to nine depressive symptoms (table 1), as indicated by a score ≥20 points on the PHQ-9 (table 2).

  Severely ill patients often report suicidal ideation and behavior, typically demonstrate obvious impairment of functioning, and often manifest poor judgement that places the patient and others (including children) at risk for imminent harm. In addition, patients with severe depression can develop complications such as psychotic features and catatonia, and often have a history of severe or recurrent depressive episodes [7]. Patients with severe major depression should be referred to a psychiatrist for management and often require hospitalization [8,9]. Treating major depression with psychotic features or catatonia is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment" and "Catatonia: Treatment and prognosis".)

Difficulties may arise in determining the number of depressive symptoms that are present during pregnancy because changes in appetite, energy, and sleep may due to depression, or may represent normal pregnancy-related changes. The presence of these somatic symptoms should be evaluated in the context of normal expectations for pregnancy. As an example, although food aversions can occur during pregnancy, patients with anorexia who fail to gain weight may have mild to moderate depression, and pregnant patients with anorexia who lose weight may have severe depression. In the same vein, pregnancy can cause fatigue. However, lack of energy to the point that patients need to make a significant effort to initiate or maintain usual daily activities can be a mild to moderate depressive symptom, and anergia to the point that patients cannot get out of bed for hours is probably a symptom of severe depression. Persistent uncertainty as to whether an episode of major depression is mild to moderate or severe can be resolved by referral to a psychiatrist (preferably one specializing in perinatal disorders).

GENERAL PRINCIPLES

The general principles and issues that are involved in treating unipolar major depression during pregnancy include:

- Setting
- History of prior treatment
- Educating patients and families
- Adherence
- Monitoring symptoms
- Prescribing antidepressants
- Managing nonresponse
- Making referrals

These general principles are discussed in detail separately. (See "Unipolar major depression in pregnant women: General principles of treatment".)

CHOOSING TREATMENT

Approach to treatment — We suggest that acute treatment of pregnant patients with severe unipolar major depression proceed according to the sequence described in the subsections below. Patients start with initial therapy and progress through each step until they respond. The primary treatments are antidepressant medications. In addition, psychotherapy is nearly always indicated as an adjuvant to pharmacotherapy, unless symptoms render the patient incapable of participating.

The duration of an adequate trial with antidepressant medications is discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Duration of an adequate trial'.)

Electroconvulsive therapy (ECT) is frequently indicated for patients with psychotic features, catatonia, high risk of suicide, and fluid and food refusal leading to dehydration and malnutrition. In addition, severe, antenatal unipolar major depression that does not respond to multiple antidepressant trials is often treated with ECT. (See 'Electroconvulsive therapy' below.)

Continuation treatment is generally indicated for patients who respond to acute treatment of unipolar major depression, and additional maintenance treatment is indicated for patients with an increased risk of recurrence. (See "Unipolar depression in adults: Continuation and maintenance treatment".)

Initial treatment — For pregnant women with severe unipolar major depression, we suggest antidepressant medications as initial treatment [1,4,10-13]. Using antidepressants is consistent with several practice guidelines, including those from the American Psychiatric Association, American College of Obstetricians and Gynecologists, and the United Kingdom National

Institute for Health and Care Excellence; the general consensus is that the benefits of antidepressants outweigh the potential risks [8-10,14-19]. Antidepressants are frequently used to treat prenatal unipolar major depression; in a nationally representative survey of pregnant women with major depression in the United States (n = 375), treatment with pharmacotherapy was reported by 40 percent, more than any other treatment modality [20]. The choice of antidepressant depends primarily upon the prior treatment history. (See 'Choosing an antidepressant' below.)

Nevertheless, psychotherapy is a reasonable alternative to antidepressants for severe antenatal depression in patients with a prior history of poor response to multiple antidepressants, or if patients decline pharmacotherapy after weighing the risks (see 'Weighing the risks' below). Psychotherapy is appropriate provided that the depressive syndrome does not include suicidal ideation or obvious impairment of function. If patients do not respond to psychotherapy after several sessions (eg, eight), we switch patients to antidepressants. In addition, psychotherapy can be administered as an adjunct to pharmacotherapy [13].

Although no randomized trials have evaluated the efficacy or safety of antidepressants during pregnancy, numerous trials that excluded pregnant patients have demonstrated the efficacy of antidepressants for treating the general population of patients with major depression [10]. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants'.)

Patients receiving pharmacotherapy for prenatal unipolar major depression typically receive psychotherapy as an adjuvant, provided that patients are not too ill to participate in therapy [21]. If depressive symptoms do not respond adequately to treatment, the frequency and/or intensity of psychotherapy is increased by scheduling more frequent outpatient visits or referring patients to a partial hospitalization program. Choosing adjunctive psychotherapy for patients with prenatal depression is discussed separately. (See "Mild to moderate episodes of antenatal unipolar major depression: Choosing treatment", section on 'Initial treatment'.)

Evidence supporting the use of pharmacotherapy plus psychotherapy includes randomized trials that indicate combined therapy is more efficacious than pharmacotherapy alone for treating the general population of patients with unipolar major depression [4,10,21]. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants plus psychotherapy'.)

Weighing the risks — Pregnant patients with severe depression, along with their partners, need to weigh various risks when deciding whether to use an antidepressant [1,5,11,14,17,22]:

- Risks to the mother and fetus posed by untreated depression, such as suicidal behavior; anorexia leading to poor nutrition and poor weight gain or to weight loss; and cognitive impairment, anhedonia, or anergia leading to poor self-care as well as nonadherence with prenatal care. Complications may arise, including psychotic features, catatonia, and comorbid substance use disorders (eg, alcohol and tobacco). In addition, antenatal depression is associated with:

  - Adverse pregnancy and neonatal outcomes (see "Antenatal depression: Pregnancy and neonatal outcomes")

  - Abnormal infant and child development (see "Antenatal depression: Risks of abnormal infant and child development")

  - Cognitive impairment and psychopathology in the offspring (see "Antenatal depression: Risks of cognitive impairment and psychopathology in the offspring")

  In addition, antenatal depression is a risk factor for postnatal depression. (See "Postpartum unipolar major depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Risk factors'.)

- Risks to the fetus and mother of using antidepressants; the fetus is exposed to all psychotropic medications primarily through umbilical circulation and amniotic fluid. Potential risks include:

  - Teratogenesis and pregnancy complications (see "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors" and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors")

  - Adverse neonatal and longer-term effects in children (see "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes")

  - Maternal adverse effects (table 3)

It appears that in the absence of medical information from clinicians, pregnant women frequently overestimate the risks of using antidepressants because of misleading reports in the media [5,23].

It is important to document the discussion of the risks of untreated depression and the risks and benefits of antidepressants [24].

Choosing an antidepressant — Factors to consider when selecting an antidepressant for pregnant patients include the following [1,19,23,25]:

- Prior efficacy and tolerability of antidepressants.
- Potential fetal adverse effects. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors" and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors".)
- If a medication was taken during conception, then the fetus has already been exposed and the medication should remain the same unless otherwise indicated by patient preference or by relapse of depression while on the medication.
- Potential maternal adverse effects (table 3).
- Plans regarding breastfeeding.
- Concurrent medications and potential drug-drug interactions.
- Family history of response to specific antidepressants.

Patients who were successfully treated with antidepressants prior to pregnancy and then stopped the antidepressant should generally receive the same drug during pregnancy [1,11,15,19,23]. There is no compelling evidence that the safety of fetal exposure differs among antidepressants. The one exception is monoamine oxidase inhibitors (MAOIs), which are not used during pregnancy. Animal studies have implicated them in congenital anomalies and there is the potential for hypertensive crisis when MAOIs are combined with tocolytic agents to delay labor [6].

Clinicians choosing a medication for pregnant patients with no prior treatment history should consider the safety of the drug during breastfeeding even if patients are not planning to breastfeed, because the decision may change. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding".)

We typically avoid recently marketed medications until more information is available regarding their effects in human pregnancy [15,17,23]. However, some clinical situations may warrant using newly developed drugs. As an example, euthymic patients with unintended pregnancies

while taking such drugs may face a high risk of relapse if they switch medications, and the fetus has already been exposed.

For patients with severe unipolar major depression during pregnancy who have not been treated with antidepressants in the past, we suggest selective serotonin reuptake inhibitors (SSRIs) as initial treatment, based upon their efficacy and tolerability in randomized trials that excluded pregnant patients [1]. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar major depression in adults: Choosing initial treatment", section on 'Selecting a specific antidepressant'.)

In addition, SSRIs have been used and studied more often in depressed, pregnant patients than other types of antidepressants [19,21,24,26]. Multiple studies have consistently observed that among pregnant women who were treated with antidepressants during the first trimester (total n approximately 25,000), SSRIs were prescribed for roughly 80 percent of patients [27-30]. One prospective observational study of pregnant women (n >4000) found that among the 20 medications prescribed most often during the first trimester, three were SSRIs (sertraline, fluoxetine, and escitalopram) [30].

Furthermore, SSRIs are not associated with specific patterns of congenital anomalies across studies, which is reassuring in so far as teratogenicity is usually established by a consistent risk and pattern of malformations [25]. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors", section on 'Teratogenicity'.)

Among the SSRIs, we typically select sertraline if the patient has not previously used antidepressants; however, citalopram and escitalopram are reasonable alternatives [15]. Evidence supporting the use of sertraline, citalopram, or escitalopram include observational studies, which found that first trimester exposure to sertraline, citalopram, or escitalopram was associated with little to no risk of teratogenicity [25]. In addition, other observational studies have found that sertraline is a reasonable choice during lactation [15]. The general principles of prescribing antidepressants during pregnancy are discussed separately, as are the risks of using sertraline, citalopram, or escitalopram during pregnancy, their safety during breastfeeding, and their dose (table 4) and side effects (table 3). (See "Unipolar major depression in pregnant women: General principles of treatment", section on 'Prescribing antidepressants' and "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors" and "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Selective serotonin reuptake inhibitors' and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

Although fluoxetine is efficacious for the general treatment of major depression [31], and observational studies suggest that first-trimester exposure is associated with little to no risk of teratogenicity [25], fluoxetine is often not a first-line choice for patients not previously treated with antidepressants [15]. The drug has a long half-life which predisposes to accumulation in breastfeeding infants. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Selective serotonin reuptake inhibitors'.)

Paroxetine is often avoided as initial treatment for pregnant patients with severe depression who have not been previously treated with antidepressants; multiple observational studies suggest paroxetine may be associated with a small absolute risk of congenital cardiac anomalies [3,15,17]. However, several other studies have found that paroxetine is not associated with cardiac anomalies. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors", section on 'Paroxetine'.)

We typically do not use fluvoxamine as initial treatment of prenatal depression for patients not previously treated with antidepressants because fluvoxamine has been studied less often than other SSRIs [15,27-30,32].

Treatment-resistant patients — Many pregnant patients with unipolar major depression do not respond to initial treatment with an SSRI. For these treatment-resistant patients, we suggest that clinicians reconfirm the patient's diagnosis and optimize the dose. As an example, if the patient is receiving and tolerating sertraline 150 mg/day, the dose should be increased to 200 mg/day. (See "Unipolar major depression in pregnant women: General principles of treatment".)

If patients remain nonresponsive to treatment, we suggest switching to a different SSRI. The process of switching from one SSRI to another is discussed separately. (See "Switching antidepressant medications in adults", section on 'Between SSRIs'.)

Indirect evidence from randomized trials supports using a different SSRI in treatment-resistant pregnant patients; these trials, which excluded pregnant patients, found that patients with major depression who did not respond to initial treatment with an SSRI can benefit from treatment with a different SSRI. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Choosing a drug'.)

Treatment-refractory patients — Patients with severe antenatal major depression may not respond to multiple trials of SSRIs. For these treatment-refractory patients, we suggest switching to a serotonin-norepinephrine reuptake inhibitor [19]. The serotonin-norepinephrine reuptake inhibitors are the second most frequently prescribed antidepressants in pregnant women [21]. We typically use venlafaxine because there is more experience using venlafaxine in

pregnant patients than other serotonin-norepinephrine reuptake inhibitors [27]. However, it is reasonable to use the serotonin-norepinephrine reuptake inhibitor duloxetine. The process of switching from an SSRI to a serotonin-norepinephrine reuptake inhibitor is discussed separately. (See "Switching antidepressant medications in adults", section on 'SSRI to SNRI'.)

Indirect evidence from randomized trials supports switching to venlafaxine in treatment-refractory pregnant patients; these trials, which excluded pregnant patients, found that venlafaxine can benefit depressed patients who did not respond to initial treatment with an SSRI. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Antidepressants'.)

Other randomized trials (which excluded pregnant patients) have demonstrated that serotonin-norepinephrine reuptake inhibitors are efficacious as initial treatment of unipolar major depression. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants' and "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar major depression in adults: Choosing initial treatment", section on 'Selecting a specific antidepressant'.)

In addition, the risk of congenital anomalies with venlafaxine is regarded as low [10,25], and the drug is a reasonable choice for lactating women. (See "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors", section on 'Venlafaxine' and "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Venlafaxine and desvenlafaxine'.)

General information about the pharmacology, administration (table 4), and side effects (table 3) of venlafaxine and other SNRIs in adults is discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

Other options — Severe, antenatal unipolar major depression may not respond to sequential trials of SSRIs and venlafaxine. Other treatment options for these patients include duloxetine, bupropion, mirtazapine, tricyclic antidepressants, repetitive transcranial magnetic stimulation, and electroconvulsive therapy. Disabling depression is often treated with electroconvulsive therapy in lieu of multiple antidepressant trials.

- **Duloxetine** – Randomized trials that excluded pregnant patients indicate duloxetine is efficacious for major depression [33]; observational studies suggest that duloxetine does not appear to be associated with congenital malformations, and that the drug may be compatible with breastfeeding. The general efficacy, risks of teratogenicity and pregnancy complications, dose (table 4), and side effects (table 3) of duloxetine are discussed separately, as is its safety during breastfeeding. (See "Unipolar depression in adults:

Choosing treatment for resistant depression" and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors", section on 'Duloxetine' and "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Duloxetine' and "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Duloxetine'.)

- **Bupropion** – Bupropion is also a reasonable choice [10], especially for prenatal patients who have comorbid attention deficit hyperactivity disorder (ADHD) or nicotine dependence [19]; however, bupropion is contraindicated in patients with eating disorders or epilepsy. Evidence supporting the use of bupropion includes randomized trials that excluded pregnant patients [34]. In addition, the risk of congenital anomalies with bupropion is regarded as low [10,25], and other studies suggest that bupropion is a reasonable choice for lactating women. The general efficacy, risks of teratogenicity and pregnancy complications, dose (table 4), and side effects (table 3) of bupropion are discussed separately, as is its safety during breastfeeding. (See "Unipolar depression in adults: Choosing treatment for resistant depression" and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors", section on 'Bupropion' and "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Bupropion' and "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Bupropion'.)

- **Mirtazapine** – Randomized trials that excluded pregnant patients indicate mirtazapine is efficacious for major depression [35]. In addition, observational studies suggest that the drug may be helpful for women with hyperemesis gravidarum due to its antinausea properties [36,37]. Other observational studies suggest that the risk of teratogenicity with mirtazapine is low, and that the drug may be compatible with breastfeeding. The general efficacy, risks of teratogenicity and pregnancy complications, dose (table 4), and side effects (table 3) of mirtazapine are discussed separately, as is its safety during breastfeeding. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Antidepressants' and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors", section on 'Mirtazapine' and "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Mirtazapine' and "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Mirtazapine'.)

- **Tricyclic antidepressants** – Tricyclics are reasonable to use during pregnancy [10], based upon randomized trials that excluded pregnant patients [38]. In addition, most observational studies have not found an association between tricyclics and congenital anomalies, with the exception of clomipramine [27]; other studies suggest that tricyclics (eg, nortriptyline) are excreted into human breast milk in low concentrations. When prescribing tricyclics, we prefer nortriptyline because it is less likely to cause orthostatic hypotension and anticholinergic side effects. However, tricyclics are not first- or second-line drugs because they are often poorly tolerated and lethal in overdose [10]. The general efficacy, teratogenic risks, dose (table 4), and side effects (table 3) of tricyclics are discussed separately, as is their safety during breastfeeding. (See "Unipolar depression in adults: Choosing treatment for resistant depression" and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors", section on 'Teratogenicity' and "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects" and "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Tricyclics'.)

- **Transcranial magnetic stimulation –** Repetitive transcranial magnetic stimulation (TMS) is also reasonable for pregnant patients with severe prenatal depression that does not respond to initial and next step treatments [19,39]. Left sided high frequency TMS or right sided low frequency TMS, targeting the dorsolateral prefrontal cortex, have each been used during pregnancy [40]. Antidepressants initiated prior to TMS are frequently continued during TMS. Using TMS for antenatal major depression is consistent with practice guidelines, including those from the Canadian Network for Mood and Anxiety Treatments [18,19].

  Evidence supporting the use of TMS for depression during pregnancy includes randomized trials in the general population of depressed patients. (See "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)", section on 'Efficacy'.)

  In addition, small studies in pregnant women with unipolar major depression suggest that TMS is beneficial:

  - A one-month randomized trial compared active TMS with sham TMS in pregnant women with unipolar major depression [41]. Active treatment included 20 daily sessions administered five days per week to the right dorsolateral prefrontal cortex, at 1 Hz as a single train of 900 pulses per session at 100 percent motor threshold. Among the 22 patients who completed the study protocol, improvement was greater with

active TMS than sham. However, three cases of preterm birth occurred in week 35 or 36, all within the active treatment group.

- Small observational studies in pregnant patients suggest that TMS is efficacious and safe for both the mother and fetus [42-44]. As an example, a prospective observational study found that among pregnant patients (n = 30) with major depression who had not responded to antidepressants and were then treated with TMS (18 sessions over three weeks), response (reduction of baseline symptoms ≥50 percent) occurred in 41 percent and remission in 21 percent [45]. This rate of remission is comparable to that seen in patients who are not pregnant. In addition, across multiple studies in pregnant patients (total n = 41), significant maternal and fetal adverse effects were not observed [40,44].

The administration, efficacy, and safety of TMS in the general population of patients with major depression is discussed separately. (See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)" and "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)".)

Electroconvulsive therapy — For severely depressed, pregnant patients who do not respond to multiple (eg, three to five) trials of antidepressants, or who decline pharmacotherapy, we suggest electroconvulsive therapy (ECT) [19,21,39,40]. In addition, ECT is frequently preferred over multiple medication trials for patients who require a fast response, including patients with a high risk of suicide (eg, suicidal behavior or suicidal plan with intent), fluid and food refusal leading to dehydration and malnutrition, severe psychotic features, or catatonia [46,47]. If available, a second opinion from a perinatal psychiatrist can help resolve questions about indications. Using ECT for depression during pregnancy is consistent with multiple practice guidelines [8,10,14].

ECT is typically well tolerated and there are no absolute contraindications to ECT, including pregnancy or compromised general medical status [40,48]. Nevertheless, safety concerns regarding ECT necessitate preprocedure obstetric consultation (consistent with guideline recommendation), with emphasis upon assessing risk factors for vaginal bleeding, spontaneous abortion, preterm labor, abruption, and uteroplacental insufficiency due to the association of ECT with transient increases or decreases in blood pressure and uterine contractions. The patient's general medical status is also evaluated. Medical consultation prior to ECT is discussed separately, as is the use of ECT for patients with general medical conditions. (See "Medical evaluation for electroconvulsive therapy" and "Overview of electroconvulsive therapy (ECT) for adults", section on 'Patients with comorbid general medical illness'.)

ECT is generally given three times per week on alternate days. Most patients regardless of indication remit with 6 to 12 treatments, but some patients require 20 or more. Reviews of prenatal ECT have found that the mean number of treatments per ECT course was approximately 10 [49,50]. The number and frequency of treatments in the general use of ECT is discussed separately, as are the adjustments in ECT technique for pregnant patients. (See "Overview of electroconvulsive therapy (ECT) for adults", section on 'Treatment course' and "Technique for performing electroconvulsive therapy (ECT) in adults", section on 'Pregnancy'.)

Following an acute course of ECT, clinicians usually prescribe continuation and maintenance pharmacotherapy. (See "Unipolar depression in adults: Continuation and maintenance treatment".)

ECT is generally regarded as effective and rapid for major depression during pregnancy [4,10,47,48]. Evidence supporting the use of ECT includes randomized trials that excluded pregnant patients, and observational studies of pregnant patients [50-53]. Multiple reviews of ECT and antenatal depression have concluded that ECT is beneficial in all trimesters [40,54]. The efficacy of ECT in the general population of patients with unipolar major depression is discussed separately. (See "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)", section on 'Efficacy'.)

In addition, ECT during pregnancy is generally regarded as safe for the mother and fetus [40,47,48,50,54-56]. The electric current administered to the mother does not pass through the uterus [47]. ECT may pose fewer risks than severe, untreated episodes of major depression [47,57] and may be preferable for patients who want to avoid fetal exposure to pharmacotherapy [54].

However, ECT may cause adverse maternal effects; reviews have found that the most common side effects related to pregnancy include vaginal bleeding, uterine contractions, and preterm labor [40,49]. As an example, a review of observational studies included 339 pregnant patients who were treated with ECT, and found that there were there were 20 maternal complications, of which 18 were thought to be related to ECT [50]:

- Uterine contractions or preterm labor – 12 cases
- Vaginal bleeding – 2 cases
- Hematuria – 1 case
- Abdominal pain – 1 case
- Placental abruption – 1 case (possibly related to acute hypertension)
- Status epilepticus – 1 case

The general adverse effects of ECT include cardiopulmonary events, aspiration pneumonia, fractures, dental and tongue injuries, headache, nausea, and cognitive impairment. (See "Overview of electroconvulsive therapy (ECT) for adults", section on 'Adverse effects'.)

In pregnant patients who are treated with ECT, the common general adverse effects after each ECT treatment are usually managed as follows [48]:

- Headache and/or myalgia – Acetaminophen (nonsteroidal anti-inflammatory drugs may alter maternal and fetal hemostasis, and lead to early constriction or closure of the fetal ductus arteriosus).
- Nausea – Meclizine, metoclopramide, or prochlorperazine.

ECT may also cause fetal complications; the most commonly observed complication is transient bradyarrhythmia [40,49]. As an example, a review of observational studies included 339 pregnant patients who were treated with ECT, and found that there were 25 fetal or neonatal adverse events, of which 11 were thought to be related to ECT [50]:

- Transient fetal arrhythmias (typically bradycardia, thought to be the result of hypoxia) – 8 cases
- Fetal death due to maternal status epilepticus – 1 case
- Miscarriage 24 hours post-ECT – 1 case
- Multiple brain infarctions after multiple ECT courses during pregnancy – 1 case

The possibility of teratogenicity due to ECT is discussed separately. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Electroconvulsive therapy'.)

Psychotic depression — Treatment of unipolar psychotic depression is similar for pregnant and nonpregnant patients. Psychotic depression is generally treated with an antidepressant plus an antipsychotic; however, ECT is a reasonable alternative [19,58]. The specific choice depends upon several factors that are discussed separately, as is the administration of treatment and evidence of efficacy (in randomized trials that excluded pregnant patients). (See "Unipolar major depression with psychotic features: Acute treatment", section on 'First line'.)

Observational studies suggest that first trimester exposure to SSRIs, venlafaxine, and tricyclics is associated with little to no risk of teratogenicity [10,25]. In addition, most observational studies have found that prenatal exposure to first- and second-generation antipsychotics does not appear to increase the risk of major physical malformations above rates observed in the general population. (See "Antenatal use of antidepressants and the potential risk of

teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors", section on 'Teratogenicity' and "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors" and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Antipsychotics'.)

ECT is generally regarded as safe during pregnancy, especially if the technique for performing ECT is modified for pregnant patients. (See 'Electroconvulsive therapy' above and "Technique for performing electroconvulsive therapy (ECT) in adults", section on 'Pregnancy'.)

Pregnant patients with psychotic depression frequently require hospitalization. Although perinatal psychiatric inpatient units are preferable, these facilities are typically not available [58].

Anxiety — For major depressive episodes that include high levels of anxiety, monotherapy with an antidepressant drug is usually preferred over the combination of an antidepressant and a benzodiazepine [4,21]. However, an antidepressant plus a benzodiazepine at initiation of treatment may be necessary for severe anxiety. Benzodiazepines are often added at the beginning of pharmacotherapy, using standard doses, and then gradually discontinued once the antidepressant begins to take effect. Given the risk of dependence and possibly increased risks of neonatal complications, we suggest not using benzodiazepines for more than two weeks, especially near term. However, longer use may be necessary to achieve remission of symptoms. The general efficacy and use of adjunctive benzodiazepines for the general treatment of anxious depression are discussed separately. (See "Unipolar depression in adults: Treatment with anxiolytics", section on 'Benzodiazepines'.)

Clonazepam and lorazepam are generally preferred for anxious depression; benzodiazepines with shorter half-lives (eg, alprazolam) can result in rebound anxiety. However, the intermediate length half-lives of clonazepam and lorazepam may predispose to accumulation in the infant, and benzodiazepines can cause a withdrawal syndrome. We typically use lorazepam because it has a shorter half-life than clonazepam.

We generally avoid diazepam in pregnant patients unless they are uniquely responsive to it. Diazepam can be sedating and its long half-life makes it more likely to persist in breastfed infants than drugs with shorter half-lives [59].

The risks of congenital malformations and postnatal risks (including neonatal withdrawal or toxicity) due to antenatal exposure to benzodiazepines are discussed separately. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Benzodiazepines' and

"Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors", section on 'Selective serotonin reuptake inhibitors plus benzodiazepines'.)

UNPLANNED PREGNANCIES AND DISCONTINUING ANTIDEPRESSANTS DURING PREGNANCY

Women who currently suffer unipolar major depression and are treated with pharmacotherapy may present with an unplanned pregnancy, in which case the fetus has been exposed to the antidepressant [21]. For these patients, we suggest that they continue their antidepressant, especially if the depressive episode has been severe (eg, marked by suicide attempts, psychotic features, or functional incapacitation) [10].

However, if the depressive syndrome has been mild to moderate and the patient feels strongly about avoiding further exposure, pharmacotherapy can be discontinued for the first trimester (during organogenesis), and subsequently restarted. In addition, it is reasonable to switch the patient from pharmacotherapy to psychotherapy (eg, cognitive-behavioral therapy or interpersonal psychotherapy), while monitoring for deterioration [4,14]. A gradual (eg, at least over one to two weeks) taper of antidepressants is preferred to avoid worsening of the depressive syndrome [4,10,21]; patients may nevertheless insist upon abruptly stopping the drug due to concerns about teratogenicity.

Unplanned pregnancy may also arise in women who are currently euthymic and treated with antidepressants; these patients need to decide whether to continue treatment [10]. The factors involved include the risks of recurrence and maternal depression, as well as the risks of using antidepressants during pregnancy.

Discontinuing antidepressant drugs in pregnant women who are euthymic can lead to recurrence of depression, based upon randomized trials that were conducted in the general population of patients with major depression (who were not pregnant). (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Antidepressant medications'.)

In addition, multiple observational studies suggest that stopping antidepressants may cause depressive relapses [60-62]. As an example, one prospective observational study in a perinatal psychiatry program enrolled euthymic, pregnant women with a prepregnancy history of major depression, who were either currently taking antidepressants (primarily selective serotonin reuptake inhibitors) or had recently (<12 weeks prior to last menstrual period) discontinued

them for at least one week [63]. Among patients who maintained antidepressants throughout the pregnancy (n = 82) or who discontinued antidepressants (n = 65), relapse occurred in fewer patients who continued treatment (26 versus 68 percent). The investigators also found that among patients who stopped treatment, reintroducing antidepressants attenuated the risk of relapse, but not entirely.

The increased risk of recurrence associated with discontinuation of antidepressants may be especially high in pregnant women with a lifetime history of several (eg, four) depressive episodes before pregnancy [64]. This finding is consistent with observations in the general population of patients with major depression that with each recurrence of major depression, the risk of a subsequent episode increases. (See "Unipolar depression in adults: Course of illness", section on 'Recurrence'.)

Many women who learn that they are pregnant while taking antidepressants decide to stop treatment during the first trimester [62,65]. Retrospective studies of health insurance databases have found that among women (total n >25,000) who used antidepressants during the three to six months immediately preceding their pregnancy, 50 to 80 percent discontinued treatment during pregnancy [28,66-68].

For women who conceive while taking antidepressants but wish to discontinue them, a slow taper is preferred rather than abrupt discontinuation [10,21]. As an example, the drug can be tapered over one to two months by decreasing the dose approximately 25 percent every one to two weeks. This can diminish the risk of drug withdrawal symptoms and increase the probability of detecting incipient depressive symptoms before a full-blown depressive episode recurs.

If a woman becomes pregnant while on paroxetine and is stable, we suggest that she continue the medication, especially if response to paroxetine occurred after several other failed antidepressant trials. Although findings from multiple observational studies suggest that paroxetine may be associated with a small absolute risk of congenital cardiac anomalies, several other studies have found that paroxetine is not associated with cardiac anomalies [15,17]. In addition, switching increases the risk of relapse and number of drug exposures. Nevertheless, patients may prefer to switch to another drug (eg, sertraline), especially if paroxetine is the only drug they have used [10]. The evidence that paroxetine may possibly be associated with an increased risk of congenital heart anomalies is discussed separately. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors", section on 'Paroxetine'.)

MILD TO MODERATE EPISODES

Treatment of mild to moderate episodes of antenatal unipolar major depression is discussed separately. (See "Mild to moderate episodes of antenatal unipolar major depression: Choosing treatment".)

MINOR DEPRESSION

Unipolar minor depression is diagnosed in patients with two to four depressive symptoms lasting for a period of at least two weeks, and no history of mania or hypomania. (See "Unipolar minor depression in adults: Epidemiology, clinical presentation, and diagnosis", section on 'Diagnosis'.)

Management of minor depression is discussed separately. (See "Unipolar minor depression in adults: Management".)

BIPOLAR DEPRESSION

Depression can occur in the context of bipolar disorder, which is marked by episodes of hypomania (table 5) or mania (table 6). Distinguishing bipolar depression from unipolar depression is discussed separately, as is treatment of bipolar major depression during pregnancy. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Unipolar major depression' and "Bipolar disorder in pregnant women: Treatment of major depression".)

ANTIDEPRESSANTS AND BREASTFEEDING

The safety of antidepressants in lactating women is discussed separately. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Antidepressants'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Depression in adults (The Basics)" and "Patient education: Coping with high drug prices (The Basics)")
- Beyond the Basics topics (see "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definition of major depression** – An episode of unipolar major depression is a period lasting at least two weeks, with five or more of the following nine symptoms: depressed mood, loss of interest or pleasure in most or all activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, guilt or thoughts of worthlessness, and recurrent thoughts about death or suicide (table 1). In addition, there has never been an episode of mania or hypomania. (See 'Unipolar major depression' above.)
  - **Mild to moderate episodes** – Mild to moderate episodes of unipolar major depression are generally characterized by five or six depressive symptoms. Patients with mild to moderate illness do not manifest suicidal behavior or obvious impairment of functioning, are less likely to develop complications such as psychotic features, and can typically be managed in outpatient or partial hospital settings.
  - **Severe episodes** – Severe unipolar major depression is characterized by seven to nine depressive symptoms. Severely ill patients often report suicidal ideation and behavior, typically demonstrate obvious impairment of functioning, and often manifest poor

judgement that places the patient and others at risk for imminent harm. In addition, patients with severe depression can develop complications such as psychotic features, and often have a history of severe or recurrent depressive episodes. Patients with severe major depression should be referred to a psychiatrist for management and often require hospitalization. (See 'Severity of illness' above.)

- **General principles of treatment** – The general principles and issues involved in treating unipolar major depression during pregnancy include setting, history of prior treatment, educating patients and families, adherence, monitoring symptoms, prescribing antidepressants, managing nonresponse, and making referrals. (See "Unipolar major depression in pregnant women: General principles of treatment".)

- **Initial treatment** – For pregnant women with severe unipolar major depression, we suggest antidepressant medications as initial treatment rather than psychotherapy (**Grade 2B**). However, psychotherapy is a reasonable alternative in patients with a prior history of poor response to multiple antidepressants, or if patients decline pharmacotherapy after weighing the risks. Using psychotherapy is appropriate provided that the depressive syndrome does not include suicidal ideation or obvious impairment of function. Patients receiving pharmacotherapy typically receive psychotherapy as an adjuvant. (See 'Initial treatment' above and 'Weighing the risks' above.)

  Pregnant patients with severe unipolar major depression who were successfully treated with antidepressants prior to pregnancy should generally receive the same drug during pregnancy. For patients who have not been treated with antidepressants in the past, we suggest selective serotonin reuptake inhibitors (SSRIs) as initial treatment, rather than other antidepressants (**Grade 2B**). We typically select sertraline if the patient has not previously used antidepressants; however, citalopram and escitalopram are reasonable alternatives. (See 'Choosing an antidepressant' above.)

- **Treatment-resistant patients** – Many pregnant patients with unipolar major depression do not respond to initial treatment with an SSRI. For these treatment-resistant patients, we suggest switching to a different SSRI, rather than other antidepressants (**Grade 2C**). (See 'Treatment-resistant patients' above.)

- **Treatment-refractory patients** – Patients with severe antenatal major depression who do not respond to multiple trials of SSRIs are generally switched to a serotonin-norepinephrine reuptake inhibitor (eg, venlafaxine). (See 'Treatment-refractory patients' above.)

- **Other treatment options** – Severe, antenatal unipolar major depression may not respond to sequential trials of SSRIs and venlafaxine. Other treatment options for these patients include duloxetine, bupropion, mirtazapine, a tricyclic antidepressant, repetitive transcranial magnetic stimulation, and electroconvulsive therapy. (See 'Other options' above.)

- **Unplanned pregnancy** – Women who currently suffer unipolar major depression and are treated with pharmacotherapy may present with an unplanned pregnancy; we encourage these patients to continue their antidepressant, especially if the depressive episode has been severe and is remitted with the current medication regiment. However, if the depressive syndrome has been mild to moderate and the patient feels strongly about avoiding further exposure, pharmacotherapy can be discontinued for the first trimester (during organogenesis), and subsequently restarted. In addition, it is reasonable to switch the patient from pharmacotherapy to psychotherapy, while monitoring for deterioration. However, discontinuing antidepressant medications may cause recurrence of depression. (See 'Unplanned pregnancies and discontinuing antidepressants during pregnancy' above.)

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