Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors

AUTHORS: Donna Stewart, CM, MD, FRCPC, Simone Vigod, MD, MSc, FRCPC
SECTION EDITORS: Jennifer Payne, MD, Charles J Lockwood, MD, MHCM
DEPUTY EDITOR: David Solomon, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Apr 07, 2023.**

INTRODUCTION

Pregnant patients with psychiatric illnesses are often treated with antidepressant medications. As an example, studies of pregnant patients in Europe have found that antidepressants were used by approximately 3 percent [1-5], and in the United States by 8 percent [6-9]. The most commonly used and studied drugs are selective serotonin reuptake inhibitors (SSRIs) [7,9-14].

SSRIs and other antidepressants cross the placenta and fetal blood brain barrier. Prenatal exposure thus involves potential risks of teratogenesis, adverse pregnancy outcomes, and postnatal effects.

This topic reviews the potential adverse consequences that may be associated with using SSRIs during pregnancy, including teratogenicity, pregnancy complications, and other adverse outcomes. The potential adverse antenatal effects of antidepressants other than SSRIs, postnatal outcomes among infants exposed in utero to antidepressants, principles of teratology, choice of treatment for depressed pregnant patients, safety of antidepressants in lactating patients, and treatment of postpartum depression are discussed separately:

- (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 "Congenital anomalies: Approach to evaluation".)
- (See "Severe antenatal unipolar major depression: Choosing treatment".)
- (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding".)
- (See "Severe postpartum unipolar major depression: Choosing treatment".)

QUALITY OF EVIDENCE

Information about the risks of antidepressant medications during pregnancy comes from low- to moderate-quality studies. In the absence of randomized trials, the evidence is based upon observational studies that can yield associations confounded by measured and residual (unmeasured) factors [10,13,15]. Observational studies include retrospective case-control studies, which carry the risk of recall bias. In addition, population-based registry studies typically rely upon prescription databases that may misclassify exposure, given that patients may not take a prescribed drug. Some studies do not precisely define outcomes, or group together different types of malformations across a range of severity from mild to severe. Other studies do not specify the antidepressant dose or timing of use during the antenatal period. Some observed associations between exposure and outcome are based upon a small number of exposed and affected infants, and some associations may occur by chance due to an excessive number of comparisons.

Specific confounding factors that can lead to spurious associations between fetal exposure to antidepressants and adverse outcomes include the following [10,11,13,16-18]:

- Confounding by indication – Anxiety, depressive, and other disorders are indications for using antidepressants. Pregnant patients who are psychiatrically ill and take antidepressants are often compared with pregnant patients who are healthy and do not take antidepressants; thus, observed associations between prenatal exposure to antidepressants and pregnancy outcomes may be confounded by exposure to maternal psychiatric illness. The association between the antidepressant and outcome may be spurious because it is the illness that is associated with the outcome.

- Severity of illness – Among pregnant patients with depression or anxiety, the mental disorder is typically more severe in patients who are prescribed antidepressants than in patients not prescribed antidepressants.

- Other potential confounds in patients prescribed antidepressants for a particular disorder include sociodemographic factors such as age and socioeconomic status, comorbid general medical and psychiatric illnesses, and use of other medications (eg, benzodiazepines and antipsychotics).

- Ascertainment (surveillance) bias may exist such that congenital defects, which might have otherwise gone undetected, are discovered in offspring of patients using antidepressants because they are more likely to undergo prenatal and postnatal ultrasonography, echocardiography, and thorough postnatal physical examination. Thus, there may be a greater likelihood that malformations are detected, especially mild defects, such as small ventricular septal defects that often close during childhood.

Teratogenicity — Observed associations that are inconsistent across studies are less likely to represent a true effect. Teratogens are thought to consistently cause similar types of malformations across studies [10]. However, studies of antidepressant exposure and adverse pregnancy outcomes often yield conflicting results and fail to show a pattern.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The selective serotonin reuptake inhibitors (SSRIs) include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. The adverse pregnancy risks of antidepressants have been more widely studied in SSRIs than other antidepressant medications because SSRIs are used more often [13,19-22]. Across multiple studies of patients who used antidepressants during the first trimester (total n approximately 110,000), SSRIs were prescribed for approximately 70 to 80 percent [1,6,8,11,14,23]. One prospective observational study of pregnant patients (n >4000) found that among the 20 medications prescribed most often during the first trimester, three were SSRIs (sertraline, fluoxetine, and escitalopram) [6].

Although SSRIs differ in their pharmacologic properties, the pregnancy outcomes observed for each drug (usually from underpowered analyses) are comparable, suggesting that the impact of SSRIs is likely a class effect of the SSRI drugs. Thus, studies that examine the antenatal risks of SSRIs primarily evaluate the drugs collectively rather than individually.

The pharmacology, administration, and side effects of SSRIs are discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

Teratogenicity — In studies that analyzed birth defects collectively across different organ systems, most studies found that SSRIs as a drug class were not associated with congenital anomalies, indicating that SSRIs are not major teratogens [5,10-12,16-18,24-32].

Evidence that suggests SSRIs are not teratogenic includes the following observational studies [33,34]:

- A meta-analysis of 12 observational studies compared infants of mothers who used antidepressants during pregnancy (n >50,000; largely SSRIs) with unexposed infants (n >1,200,000) [35]. The risk of congenital malformations was comparable in the two groups.

- A subsequent national registry study (nearly 1,300,000 births) compared infants who were exposed to SSRIs in early pregnancy (n >10,000) with infants not exposed [29]. After adjusting for potential confounds (eg, maternal age, smoking, and body mass index [BMI]), the analyses found that the risk of severe congenital malformations was comparable in the two groups.

- A study of three national registries included pregnancies that were exposed to SSRIs (n >12,000) or not exposed (n >500,000) [33]. The incidence of major congenital anomalies in the exposed and unexposed offspring was comparable (3.1 and 2.7 percent).

In studies that have observed an association between SSRI exposure and congenital anomalies, the magnitude of the increased risk was small, and the analyses did not account for relevant confounding factors, such as depression or other indications for the SSRI [36]:

- A study of national registries from multiple countries identified infants who were exposed to SSRIs or venlafaxine during the first trimester (n >36,000) and infants who were not exposed (n >2,100,000); the analysis controlled for several potential confounding factors, such as maternal age, smoking, diabetes, and use of other medications (eg, antiepileptics) [31]. The incidence of major birth defects was modestly greater for exposed infants than unexposed infants (odds ratio 1.13, 95% CI 1.06-1.20). However, this clinically small increase was not observed in analyses that adjusted further for potential family-related confounding factors by analyzing siblings (2288 infants) discordant for both exposure and birth defects. The sibling-controlled analysis found that exposure was not associated with an increased risk of major birth defects (odds ratio 1.06, 95% CI 0.91-1.24); this suggests that the increased risk observed in the initial analysis was the result of residual confounding due to other unmeasured factors that were not controlled for in the analysis.

- A meta-analysis of nine studies included pregnant patients who received SSRIs in the first trimester and pregnant patients in the general population [37]. The risk of major congenital anomalies was modestly greater in the offspring of patients treated with SSRIs (relative risk 1.11, 95% CI 1.03-1.19). However, some of the studies had limited control for potential confounders. In a second analysis that was restricted to the four studies that included only pregnant patients with psychiatric diagnoses, who either received SSRIs or

did not, the risk in the two groups was comparable (relative risk 1.04, 95% CI 0.95-1.13). By including only pregnant patients with psychiatric diagnoses in both exposed and unexposed groups, the second meta-analysis controlled for confounding by indication.

Cardiac defects — It is not known whether antenatal SSRIs are associated with congenital heart defects. Although multiple studies have reported that SSRIs are associated with a small increased risk of cardiovascular defects [35,38], several other studies have found no association between antenatal exposure to SSRIs and heart defects [11,12,16,23,29,36]. Also, in some studies that found antenatal SSRIs were associated with cardiac defects, the analyses failed to adjust for potential confounding factors [33,39].

Observational studies that have found an association between prenatal exposure to antidepressants and a small increased risk of cardiovascular defects include the following:

- A meta-analysis of 13 studies compared infants of mothers who used antidepressants (n >20,000; largely SSRIs) during pregnancy with infants who were not exposed (n >1,500,000) [35]. Adjustment for potential confounding factors varied across studies and included maternal age, smoking, and psychiatric disorders. The risk of congenital cardiac malformations was increased in the group that was exposed to antidepressants (relative risk 1.4, 95% CI 1.1-1.7). Given that the baseline risk for cardiovascular malformations in the general population of infants is approximately 1 percent or 10 in 1000 [40], a relative risk increase of 1.4 would result in an absolute risk of 14 in 1000 live births.

- A meta-analysis of 10 studies found that the risk of congenital cardiac malformations was greater in infants exposed to SSRIs in utero (n >22,000), compared with unexposed infants (n >2,300,000; odds ratio 1.32, 95% CI 1.01-1.73) [38]. For every 1000 children in each group, there were two more cases of cardiac defects in the exposed group (absolute risk difference). However, heterogeneity across studies was moderate to large.

- A subsequent, national registry study included infants who were either exposed in utero to SSRIs (n = 845) or not exposed (n >70,000) [41]. After adjusting for potential confounds (maternal age, year of conception, and use of antiepileptics or insulin), the analyses found an increased risk for “severe congenital heart defects” in the exposed group compared with unexposed infants (0.71 versus 0.17 percent). However, this result was based upon only six positive cases in the exposed group (limiting estimate precision), and adjustment for confounding was limited. More so, the overall risk for congenital heart defects was not elevated for SSRI exposure (1.30 versus 0.75 percent of infants), nor was there an elevated risk for ventricular septal defects, atrial septal defects, or pulmonary valve stenosis.

Observational studies that found antenatal SSRI exposure was not associated with an increased risk of cardiac defects include the following [29,37]:

- A meta-analysis of four studies included nearly 2 million pregnant patients who either used or did not use SSRIs; three studies relied upon electronic health records and one study used self-report questionnaires to assess SSRI use [42]. The mean duration of follow-up ranged from discharge after delivery to six years. Adjustment for potential confounding factors varied across studies and included maternal depression, risk factors for congenital heart disease, and use of other psychotropic drugs. The risk of congenital heart defects in the exposed and unexposed offspring was comparable.

- A subsequent study of national registries from multiple countries identified infants who were exposed to SSRIs or venlafaxine during the first trimester (n >36,000) and infants who were not exposed (n >2,100,000); the analysis controlled for several potential confounding factors, including family-related confounding factors by analyzing siblings (2288 infants) discordant for both exposure and birth defects [31]. The incidence of cardiac defects was not increased in babies exposed to antidepressants.

- A study of a national primary care database identified three groups of pregnant patients: those who were treated for depressive and anxiety disorders with SSRIs during the first trimester (exposed, n >2700), patients who were treated for depressive and anxiety disorders with SSRIs before but not during pregnancy (discontinued medication, n >5100), and those who were not treated with antidepressants before or during pregnancy (unexposed, n >200,000) [43]. After adjusting for potential confounding factors (eg, maternal age, alcohol and/or drug use, and use of antipsychotics), the analyses found that the risk of congenital heart anomalies within five years of birth was:

  - Comparable in the exposed offspring and unexposed offspring

  - Comparable in the exposed infants and discontinued medication group of infants (this analysis controlled for confounding by indication)

  The study also found that independent of antidepressant prescriptions, several covariates were associated with an increased risk for cardiac defects: increasing maternal age, diabetes in pregnancy, problematic alcohol and illicit drug use, and obesity. This suggests that the estimates of studies that fail to account for these variables may not be valid because of residual confounding.

The inconsistent results regarding the association between antenatal SSRI exposure and the risk of congenital heart defects may be explained at least in part by genetic factors that modify

the risk [44,45]. One study examined this hypothesis in mother-infant dyads that included 1180 infants with cardiac defects and 1644 control infants with no major cardiac defects [46]. The investigators focused upon genetic variants related to the folate, homocysteine, and glutathione/transsulfuration metabolic pathways, which are implicated in the risk of cardiac defects, and may also be affected by SSRIs because they are involved in the synthesis of neurotransmitters such as serotonin. Analysis of genetic samples found that in SSRI users, common maternal and infant genotypes associated with these metabolic pathways increased the risk of cardiac defects to varying degrees, depending upon the specific gene (relative risks ranging from 1.8 to 8.0). Among nonusers of SSRIs, the same genetic variants did not increase the risk. These results are preliminary and in-utero genetic testing of infants is not part of standard clinical practice.

Pregnancy complications

Spontaneous abortion — Most studies suggest that SSRIs appear to be associated with little to no risk for spontaneous abortion (miscarriage), especially in studies that control for potential confounding factors [47]:

- A national registry study identified pregnant patients with depression who were either treated with SSRIs or other antidepressants (n >22,000 pregnancies), or not treated with these drugs (n >1800 pregnancies) [48]. The analysis controlled for potential confounding factors (eg, maternal age, use of other medications, and drug abuse), and found that the risk of miscarriage in the two groups was comparable.

  In a second study using the same registry data, patients exposed to SSRIs in the first 35 days of pregnancy (n >22,000) were compared with patients who discontinued SSRI treatment 3 to 12 months prior to conception (n >14,000) [49]. The incidence of miscarriage was comparable in the exposed group and the control group (13 and 14 percent).

- A different national registry study identified three groups of pregnant patients: those who used SSRIs during pregnancy (exposed, n >20,000), those who used SSRIs but discontinued them prior to pregnancy (discontinued SSRIs, n >5000), and those who did not use SSRIs (unexposed, n >1 million) [50]. After controlling for potential confounding factors (eg, maternal age, alcohol and tobacco consumption, and prior miscarriages), the analyses found that the risk of first trimester spontaneous abortion was greater in the:

  - SSRI-exposed than unexposed pregnancies (hazard ratio 1.08, 95% CI 1.04-1.13)

- Pregnancies with discontinued use of SSRIs than unexposed pregnancies (hazard ratio 1.26, 95% CI 1.16-1.37)

- Pregnancies with discontinued use of SSRIs than exposed pregnancies

Hypertensive disorders of pregnancy — Multiple studies suggest that SSRIs are associated with a small increased risk of hypertensive disorders in pregnancy [51]. A meta-analysis included seven observational studies with more than 1 million pregnant patients; five of the studies were prospective, and all or most of the studies controlled for potential confounding factors such as maternal age, diabetes status, and cigarette smoking [52]. The risk of hypertensive disorders in pregnancy among patients who used SSRIs and patients who did not use antidepressants was as follows:

- Gestational hypertension or preeclampsia – Relative risk 1.21, 95% CI 1.05-1.40; heterogeneity across studies was moderate to large

- Gestational hypertension – Relative risk 1.14, 95% CI 1.00-1.30; heterogeneity was small

- Preeclampsia – Relative risk 1.32, 95% CI 0.99-1.78; heterogeneity was large

The risk of the combined outcome of gestational hypertension or preeclampsia was modestly elevated in patients using SSRIs. For each separate outcome, the risk was comparable for patients using SSRIs and patients not using antidepressants; nevertheless, the estimates for these separate outcomes were in the same direction as the combined outcome.

Gestational diabetes — Antenatal SSRIs do not appear to be associated with gestational diabetes mellitus. A study of administrative health care datasets included cases of gestational diabetes (nearly 21,000) and control pregnant patients without gestational diabetes (n >200,000) [53]. The cases and controls were matched for year of pregnancy. After adjusting for potential confounders (eg, sociodemographic variables, maternal chronic comorbidities, and medications other than antidepressants), the analyses found that use of SSRIs in cases and controls was comparable.

Postpartum hemorrhage — It is possible that SSRI exposure during the third trimester is associated with an increased risk for postpartum hemorrhage [54]. Some studies have found that SSRIs are associated with postpartum hemorrhage; however, these results may be confounded by indication (see 'Quality of evidence' above). Other evidence suggests that indications for SSRIs such as anxiety and depressive disorders, rather than SSRIs per se, are associated with an increased risk of postpartum hemorrhage. In addition, multiple studies failed to find an association between SSRI exposure and postpartum hemorrhage.

Observational studies that found third trimester exposure to SSRIs was associated with postpartum hemorrhage include the following [55,56]:

- A study of a nationwide insurance claims database identified pregnant patients with mood or anxiety disorders (primarily depression), who were either treated with SSRIs at the time of delivery (n >11,000) or were not treated with antidepressants in the five months before delivery (n >69,000) [57]. After controlling for potential confounding factors (eg, maternal age, coagulopathies, and use of other medications), the analyses found that postpartum hemorrhage occurred in more patients who were exposed to SSRIs than patients who were not (4 versus 3 percent).

- In a study that examined hospital records of pregnant patients who delivered live born babies vaginally, postpartum hemorrhage occurred in more patients who used SSRIs during pregnancy (n = 500), compared with patients who did not (n >39,000; 18 versus 9 percent) [58]. In addition, the average volume of blood loss was slightly greater in patients exposed to SSRIs than controls (484 versus 398 mL in nonusers).

- A study of administrative health care data for pregnant patients examined the incidence of postpartum hemorrhage in those with late gestation exposure to antidepressants (n = 558; primarily SSRIs or venlafaxine), and patients with psychiatric disorders who were not dispensed antidepressants (controls; n = 1292) [59]. Postpartum hemorrhage occurred in more patients who were exposed to antidepressants than controls (16 versus 11 percent).

One study that suggests SSRIs are not associated with postpartum hemorrhage, but that psychiatric diagnoses are associated with postpartum hemorrhage, used national registry data to identify three cohorts of pregnancies: SSRI exposure during the second and/or third trimester (n >8000), patients with psychiatric diagnoses related to SSRI use but no exposure to antidepressants (psychiatric controls, n >9000), and patients with no psychiatric diagnoses related SSRI use and no exposure to antidepressants (unexposed group, n >31,000) [5]. After adjusting for potential confounding factors (eg, maternal age at delivery, use of other medications, and chronic general medical illnesses), the analyses showed that:

- The risk of postpartum hemorrhage was marginally lower in patients with SSRI exposure than psychiatric controls (odds ratio 0.84, 95% CI 0.71-1.00).

- The likelihood of postpartum hemorrhage in patients with SSRI exposure and the unexposed group was comparable.

- Postpartum hemorrhage was more likely in psychiatric controls than the unexposed group (odds ratio 1.3, 95% CI 1.1-1.5).

In addition, the following observational studies found that SSRI exposure in the third trimester was not associated with postpartum hemorrhage:

- A study of administrative health care datasets identified pregnancies that included exposure to SSRIs during the last month before delivery (n >6000) and pregnancies with no exposure (n >300,000) [60]. After adjusting for potential confounding factors such as maternal age, diabetes, and mood disorder, the analyses found that the risk of postpartum hemorrhage was comparable in the two groups.

- In a national registry study that compared pregnant patients with SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) exposures after week 30 of gestation (n = 123), with nonexposed pregnant patients (n >55,000), the incidence of postpartum hemorrhage was similar [61].

- A prospective study included pregnant patients who either took SSRIs or SNRIs during the third trimester (n = 51) or did not (n = 212); the incidence of postpartum hemorrhage in the two groups was comparable [62].

Multiple studies suggest that antenatal antidepressants are not associated with postpartum hemorrhage if they are discontinued at least 30 days prior to delivery [5,56].

Preterm birth — Multiple observational studies of pregnant patients indicate that exposure to SSRIs is associated with an increased risk of preterm birth (eg, <37 weeks gestational age) [51,63]:

- A meta-analysis of 18 studies (n >1,200,000 pregnant patients) found that SSRI exposure was associated with preterm birth (relative risk 1.7, 95% CI 1.5-1.9) [64], consistent with a prior meta-analysis of 13 studies (odds ratio 1.6) [65].

- A meta-analysis of three studies included pregnant patients treated with SSRIs during the first trimester (n >16,000) and pregnant patients with depression but no exposure to SSRIs (n >97,000) [66]. SSRI exposure was associated with a small increased risk of preterm birth (odds ratio 1.2, 95% CI 1.1-1.3).

- Subsequently, a national registry study compared infants exposed to first trimester SSRIs (n >18,000) with nonexposed infants (n >1,500,000) [14]. After accounting for potential confounding variables such as parental age and history of psychiatric illness, the analyses found that the risk of preterm birth was modestly greater in the exposed group than the nonexposed group (odds ratio 1.3, 95% CI 1.2-1.4).

In addition, antenatal exposure is also associated with a small reduction in gestational age at birth that may not be clinically meaningful (eg, three days). A meta-analysis of 15 studies (number of pregnant patients not reported) found that exposure to antidepressants (mostly SSRIs) was associated with a decrease in gestational age at birth [65]. However, the mean difference in gestational age between exposed and unexposed infants was approximately three days, which is probably not clinically significant. A subsequent retrospective study also found that delivery occurred three days earlier in patients exposed to SSRIs [58], and a prospective study found that gestation was reduced by two days [51]. Also, a prospective study of 145 pregnant patients who received SSRIs (90 percent of sample) or venlafaxine in the first trimester failed to find a dose-response relationship between exposure and gestational age at birth [67].

The effect of SSRIs upon preterm delivery may be related to the timing of exposure. In a meta-analysis of 41 observational studies (n >5,000,000 pregnant patients) that controlled for potential confounding factors (eg, maternal age, smoking, and history of prematurity), first trimester exposure to antidepressants (mostly SSRIs) was not associated with preterm birth [68]. However, third trimester exposure was associated with premature delivery (odds ratio 2.0, 95% CI 1.6-2.4); controlling for depression did not eliminate the effect.

Although the weight of the evidence indicates that exposure to SSRIs is associated with preterm birth, some study results suggest that it is the underlying psychiatric diagnoses that are responsible for observed associations between antenatal SSRIs and preterm birth. A national registry study identified three cohorts of pregnancies: SSRI exposure (n >15,000), patients with psychiatric diagnoses related to SSRI use but no exposure to antidepressants (psychiatric controls, n >9000), and patients with no psychiatric diagnoses related to SSRI use and no exposure to antidepressants (unexposed group, n >31,000) [5]. After adjusting for potential confounding factors (eg, maternal age at delivery, use of other medications, and chronic general medical illnesses), the analyses showed that the risk of preterm birth was:

- Lower in patients with SSRI exposure than psychiatric controls (odds ratio 0.84, 95% CI 0.74-0.96).
- Comparable in patients with SSRI exposure and the unexposed group.
- More likely in psychiatric controls than the unexposed group (odds ratio 1.3, 95% CI 1.1-1.4).

Low birth weight — It is not clear if using SSRIs during pregnancy is associated with low birth weights, due to conflicting results across observational studies.

The following observational studies in pregnant patients who either received SSRIs or did not suggest that antenatal exposure to SSRIs may be associated with low birth weight:

- A meta-analysis of nine studies (n >1,200,000 pregnant patients) found that exposure to SSRIs was associated with low birth weight (<2500 g; relative risk 1.5, 95% CI 1.2-1.8) [64]. However, heterogeneity across studies was significant.

- A meta-analysis that included 15 studies with nearly 2 million pregnant patients found that SSRI use was associated with low birth weight (relative risk 1.4, 95% CI 1.1-1.7) and being small for gestational age (risk ratio 1.5, 95% CI 1.2-1.8). However, for both results, heterogeneity across studies was moderate to large [69]. In addition, it's not clear whether the underlying studies controlled for potential confounding factors such as maternal age or psychiatric history.

- In some studies, first trimester exposure to SSRIs appeared to be associated with a birth weight reduction ranging from approximately 120 to 190 g:

  - A meta-analysis of two studies included pregnant patients treated with SSRIs during the first trimester (n >15,000) and pregnant patients with depression but no exposure to SSRIs (n >92,000) [66]. Birth weight was lower in the offspring of patients treated with SSRIs that offspring of controls, such that the mean difference was 117 g less in the SSRI exposure group.

  - One prospective study of 145 pregnant patients who received SSRIs (90 percent of sample) or venlafaxine in the first trimester found that after controlling for potential confounding factors such as maternal age and anxiety and depressive symptoms, higher daily doses were associated with a mean birth weight reduction of 187 g [67]. However, the analyses failed to show a dose-response relationship between exposure and being small for gestational age.

Evidence that suggests antenatal exposure to antidepressants is not associated with low birth weight includes the following observational studies that controlled for confounding by indication [70]:

- A meta-analysis of 20 studies (number of pregnant patients not stated) found that birth weights were lower in babies of mothers who took antidepressants (mostly SSRIs) than babies of all mothers who did not [65]. However, the mean difference between exposed and unexposed babies was 74 g, a small difference that is unlikely to be clinically significant. More so, when depressed mothers who took antidepressants during pregnancy were compared with depressed mothers not exposed to antidepressants (six

studies), the association between antidepressant exposure and lower birth weight was no longer statistically significant.

- Subsequently, a national registry study identified pregnancies with SSRI exposure (n >15,000) and pregnancies in patients with psychiatric diagnoses related to SSRI use but no exposure to antidepressants (psychiatric controls, n >9000) [5]. After adjusting for potential confounding factors (eg, maternal age at delivery, use of other medications, and chronic general medical illnesses), the analyses showed that the risk of being born small for gestational age was comparable in the two groups.

- In another subsequent national registry study, infants exposed to first trimester SSRIs (n >18,000) were compared with nonexposed infants (total n >1,500,000) [14]. After accounting for potential confounding variables such as parental age and history of psychiatric illness, the analyses found that the risk of being born small for gestational age in the exposed and nonexposed infants was comparable.

Apgar score — It is not clear whether antenatal exposure to SSRIs is associated with low Apgar scores (<7 points) (calculator 1) because relatively little research has been conducted. Although observational studies have found that the risk of low Apgar scores is greater in neonates exposed in utero to SSRIs, compared with unexposed neonates, the studies typically accounted for a limited number (eg, two or three) of potential confounding factors. In addition, the absolute magnitude of the difference in scores between exposed and unexposed neonates does not seem clinically significant:

- A registry study identified pregnant patients with psychiatric disorders (primarily depressive disorders or anxiety disorders), and compared outcomes in offspring exposed to SSRIs during the second and/or third trimester with offspring who were not exposed [5]. After adjusting for potential confounding factors (parity and BMI), the risk of five-minute Apgar scores <7 was greater in the exposed neonates than unexposed neonates (odds ratio 2.2, 95% CI 1.7-2.7).

- A retrospective study utilized hospital birth registry data from nearly 25,000 births, including infants exposed in utero to SSRIs (n = 358) [71]. After adjusting for potential confounders (maternal age, smoking, and pregravid BMI), low Apgar (<7) scores at five minutes were more likely to occur in exposed infants than unexposed infants (odds ratio 2.3, 95% CI 1.5-3.5).

- A meta-analysis of 14 studies found that Apgar scores at five minutes were lower among infants exposed in utero to antidepressants (mostly SSRIs), compared with unexposed

infants [65]. However, the mean difference between the two groups was only 0.2 points, which is probably not clinically significant.

Perinatal death — Multiple studies suggest that SSRIs are not associated with an elevated risk of perinatal death [72]. For example:

- A study of national registries from five countries (n >1,600,000 births) included more than 29,000 mothers who filled an SSRI prescription during pregnancy; among the births, there were more than 6000 stillbirths, 3600 neonatal deaths, and 1500 postnatal deaths [73]. After controlling for potential confounding factors (eg, maternal age, smoking, diabetes, and psychiatric illness), analyses found that the risks of stillbirth, neonatal death, and postnatal death were each comparable for patients who used or did not use SSRIs.

- A retrospective study utilized hospital birth registry data from nearly 25,000 births, including infants exposed in utero to SSRIs (n = 358) [71]. After adjusting for potential confounders (maternal age, smoking, and pregravid BMI), perinatal mortality was comparable in the in the exposed and unexposed infants (odds ratio 2, 95% CI 0.6-6).

Postnatal effects — Potential neonatal problems such as the neonatal behavioral syndrome, neurodevelopmental effects, and persistent pulmonary hypertension of the newborn are discussed separately. (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)

Specific SSRIs — We do not consider one SSRI as "safer" or "less safe" to use during pregnancy than another, with the possible exception of paroxetine. Several studies have found that paroxetine was associated with a small increased risk for congenital cardiovascular malformations; however, other studies have found no such risk. (See 'Paroxetine' below.)

Few studies have had sufficient power to evaluate the risks associated with specific SSRIs, including the more widely studied medications, such as citalopram, fluoxetine, paroxetine, and sertraline. Newer (eg, escitalopram) and less frequently used SSRIs (eg, fluvoxamine) have been less well studied. In addition, across studies that have assessed individual SSRIs, there is substantial inconsistency in the type and magnitude of adverse events reported, which suggests that the observed associations are less likely to represent a true effect [10]. However, studies of specific SSRIs suggest that they are associated with postpartum hemorrhage, as do some studies that assessed SSRIs collectively. (See 'Postpartum hemorrhage' above.)

The following sections review studies of teratogenicity and pregnancy complications for specific SSRIs. For some specific SSRIs, there are negative findings that differ from results of studies that evaluated SSRIs collectively, which may be due in part to smaller sample sizes for specific

SSRIs. As an example, SSRIs as a class are associated with a small increased risk of hypertensive disorders in pregnancy (see 'Hypertensive disorders of pregnancy' above), whereas citalopram is not. (See 'Pregnancy complications' below.)

Citalopram

Teratogenicity — Exposure to citalopram appears to be associated with little to no risk of birth defects, based upon observational studies [10,12,23,26,27,31,41,74-76]. Multiple reassuring meta-analyses have been conducted, including the following:

- A meta-analysis of seven studies found that the incidence of congenital malformations in babies who were exposed (n >7000) or not exposed (n >2,300,000) in utero to citalopram was comparable [38]. In addition, the rate of major malformations and the rate of cardiac anomalies were each comparable for the two groups.

- A systematic review identified four studies that included nearly 2 million pregnant patients who either used or did not use SSRIs; the mean duration of follow-up ranged from discharge after delivery to six years, and adjustment for potential confounding factors varied across studies [42]. A meta-analysis of three of the studies found the risk of congenital heart defects in the exposed and unexposed offspring was comparable.

- A meta-analysis included two studies of pregnant patients with psychiatric disorders (which controlled for confounding by indication) who used or did not use citalopram during the first trimester [37]. Adjustment for other potential confounding factors included maternal age, diabetes, and hypertension, as well as other factors. The risk of major congenital anomalies collectively across different organ systems was comparable in the offspring of exposed and unexposed mothers, as was the specific risk of congenital heart defects.

In some observational studies that found an association between early pregnancy exposure to citalopram and birth defects [36,77,78], the type of defect varied across studies, which suggests the findings did not represent true effects [10,34,39], and that citalopram is not a major teratogen [79].

Pregnancy complications — Most studies have found that citalopram is not associated with major pregnancy complications, except for postpartum hemorrhage:

- **Spontaneous abortion** – Multiple studies suggest that citalopram is not associated with spontaneous abortion [49]. As an example, a national registry study identified pregnant patients with depression, and found that the risk of spontaneous abortion was

comparable in patients who were treated with citalopram and patients who were not exposed to antidepressants [48].

- **Hypertensive disorders of pregnancy** – Multiple studies suggest that citalopram is not associated with hypertensive disorders of pregnancy [80]. As an example, a study of an insurance claims database found that among pregnant patients with depression, the risk of preeclampsia was comparable for patients who were treated with citalopram during the second and third trimesters (n >1000) and patients who received no antidepressants (n >59,000) [81].

- **Postpartum hemorrhage** – A study of pregnant patients with mood or anxiety disorders in a nationwide insurance claims database found that use of citalopram at the time of delivery (n >800) was associated with postpartum hemorrhage (relative risk 1.5, 95% CI 1.1-2.0) [57].

Escitalopram

Teratogenicity — Several studies suggest that escitalopram is not associated with teratogenic effects [10,76]:

- A meta-analysis of three observational studies found that the incidence of congenital malformations in babies who were exposed (n >600) or not exposed (n >1,700,000) in utero to escitalopram was comparable [38]. In addition, the rate of major malformations and the rate of cardiac anomalies were each comparable for the two groups.

- A subsequent study using a nationally representative database found that the incidence of major congenital anomalies was comparable for children exposed to escitalopram during the first trimester (n = 333), and for children of mothers with unmedicated depression (n >23,000) [27]. In addition, the rate of major cardiac anomalies was comparable for the two groups.

- A meta-analysis included five studies of pregnant patients from the general population; adjustment for potential confounding factors varied across studies [37]. The risk of major congenital anomalies in the offspring of mothers who used or did not use escitalopram during pregnancy was comparable.

Pregnancy complications — Escitalopram does not appear to be associated with major pregnancy complications, except for postpartum hemorrhage:

- **Spontaneous abortion** – Multiple studies suggest that escitalopram is not associated with spontaneous abortion [49]. As an example, a national registry study identified pregnant

patients with depression, and found that the risk of spontaneous abortion was comparable in patients who were treated with escitalopram and patients who were not exposed to antidepressants [48].

- **Hypertensive disorders of pregnancy** – A study of an insurance claims database found that among pregnant patients with depression, the risk of preeclampsia was comparable for patients who were treated with escitalopram during the second and third trimesters (n >1000) and patients who received no antidepressants (n >59,000) [81].

- **Postpartum hemorrhage** – A study of pregnant patients with mood or anxiety disorders in a nationwide insurance claims database found that use of escitalopram at the time of delivery (n >1000) was associated with postpartum hemorrhage (relative risk 1.6, 95% CI 1.2-2.1) [57].

Fluoxetine

Teratogenicity — Most observational studies have not found an association between use of fluoxetine during pregnancy and an increased risk of birth defects [10,12,27,78,82,83]. As an example:

- A meta-analysis of four studies (n >1,200,000 births) compared infants of mothers who used fluoxetine during pregnancy (n >52,000) with infants who were not exposed, and found that the risk of congenital malformations overall was comparable for the two groups [35].

- A meta-analysis included two studies of pregnant patients with psychiatric disorders (which controlled for confounding by indication) who used or did not use fluoxetine during the first trimester [37]. Adjustment for other potential confounding factors included maternal age, diabetes, and hypertension, as well as other nonoverlapping factors. The risk of major congenital anomalies was comparable in the offspring of exposed and unexposed mothers.

In addition, multiple studies suggest that antenatal exposure to fluoxetine is not associated specifically with congenital cardiovascular malformations [27,36,78,84]:

- A meta-analysis of four studies (nearly 1,600,000 births) compared infants of mothers who used fluoxetine during pregnancy (n >17,000) with infants who were not exposed, and found that the risk of congenital heart malformations was comparable for the two groups [27].

- A systematic review identified four studies that included nearly 2 million pregnant patients who either used or did not use SSRIs; the mean duration of follow-up ranged from discharge after delivery to six years, and adjustment for potential confounding factors varied across studies [42]. A meta-analysis of three of the studies found that the risk of congenital heart defects in the offspring who were exposed or not exposed to fluoxetine was comparable.

- A meta-analysis included three studies of pregnant patients with psychiatric disorders who used or did not use fluoxetine during the first trimester [37]. Adjustment for other potential confounding factors included maternal age, diabetes, and hypertension, as well as other nonoverlapping factors. The risk of congenital heart defects was comparable in the offspring of exposed and unexposed mothers.

Nevertheless, some studies suggest that fluoxetine may be associated with a small increased risk of teratogenicity [84]:

- A meta-analysis of six observational studies found that the incidence of major congenital malformations was greater in babies who were exposed in utero to fluoxetine (n >3000), compared with unexposed babies (n >1,200,000; odds ratio 1.3, 95% CI 1.1-1.5) [38]. For every 1000 children in each group, there were 7 more cases of malformations in the exposed group (absolute risk difference). In addition, the rate of cardiac anomalies was greater in exposed offspring (odds ratio 1.6, 95% CI 1.1-2.3; absolute risk difference of 4 per 1000).

- A subsequent study of national registries from multiple countries identified infants who were exposed to fluoxetine during the first trimester (n >6200) and infants who were not exposed (n >2,100,000); the analysis controlled for several potential confounding factors (eg, country of residence, maternal diabetes, and antenatal maternal smoking) [31]. The risk of major birth defects was greater for exposed infants than unexposed infants (odds ratio 1.3, 95% CI 1.1-1.4), as was the risk of cardiac defects (odds ratio 1.3, 95% CI 1.1-1.6).

- A subsequent case-control study examined the antenatal use of fluoxetine in mothers of infants with birth defects (n >17,000 cases) and mothers of infants without birth defects (n >9000 controls) [76]. The analysis controlled for potential confounding factors (eg, maternal obesity and smoking), and found that exposure to fluoxetine during the first trimester was greater in babies with congenital anomalies than babies with no defects. As an example, exposure was greater among infants (n = 27 cases) with right ventricular outflow tract obstruction compared with controls (odds ratio 2.0, 95% CI 1.4-3.1).

Nevertheless, the authors concluded that the absolute risk was small; if the association is causal, the absolute risk would increase from 1 per 1000 children to 2 per 1000.

One problem in studying whether specific SSRIs such as fluoxetine are associated with teratogenicity is that most studies are underpowered to detect the effects of a particular SSRI. To mitigate this problem, investigators have developed Bayesian analyses that use a known pretest probability for the association, based upon previous studies. This enables one to estimate the effect of the drug more precisely. In a study of nearly 28,000 infants that used this approach and controlled for maternal race, education, smoking, and prepregnancy body weight, in-utero fluoxetine exposure was associated with a twofold increased risk of right ventricular outflow obstruction and craniosynostosis [76]. This supports the idea that there may be an increased risk for defects with fluoxetine, but that the absolute magnitude of such a risk is likely to be small since these defects are rare.

Pregnancy complications — Fluoxetine does not appear to be associated with major pregnancy complications, except for postpartum hemorrhage:

- **Spontaneous abortion** – Multiple studies suggest that fluoxetine is not associated with spontaneous abortion [49]. As an example, a national registry study identified pregnant patients with depression, and found that the risk of miscarriage was comparable in patients who were treated with fluoxetine and patients who were not exposed to antidepressants [48].

- **Hypertensive disorders of pregnancy** – Multiple studies suggest that fluoxetine is not associated with hypertensive disorders of pregnancy [80]. As an example, a study of an insurance claims database found that among pregnant patients with depression, the risk of preeclampsia was comparable for patients who were treated with fluoxetine during the second and third trimesters (n >5000) and patients who received no antidepressants (n >59,000) [81].

- **Postpartum hemorrhage** – A study of pregnant patients with mood or anxiety disorders in a nationwide insurance claims database found that use of fluoxetine at the time of delivery (n >3000) was associated with postpartum hemorrhage (relative risk 1.5, 95% CI 1.3-1.8) [57].

Fluvoxamine

Teratogenicity — No association between first trimester fluvoxamine exposure and teratogenicity has been found, but this drug has been studied less than other SSRIs [11,23]. Two meta-analyses of four observational studies each found that the incidence of congenital

malformations in babies who were exposed (n >400) or not exposed (n >1,600,000) in utero to fluvoxamine was comparable [37,38]. In addition, the rate of major malformations and the rate of cardiac anomalies were each comparable for the two groups.

Pregnancy complications — A case-control study of administrative health data found that fluvoxamine was not associated with pregnancy induced hypertension; however, the number of exposures to fluvoxamine for the entire sample of cases plus controls was small [80].

Paroxetine

Teratogenicity — Although some evidence suggests that paroxetine may be associated with a small absolute increase in congenital heart defects [25,85], results across different observational studies are inconsistent [10].

Studies that suggest first trimester use of paroxetine is not associated with an excess risk of congenital cardiac anomalies include the following [12,36,78,86,87]:

- A systematic review identified four studies that included nearly 2 million pregnant patients who either used or did not use SSRIs; the mean duration of follow-up ranged from discharge after delivery to six years, and adjustment for potential confounding factors varied across studies [42]. A meta-analysis of three of the studies found that the risk of congenital heart defects in the offspring who were exposed or not exposed to paroxetine was comparable (odds ratio 1.0, 95% CI 0.8-1.2).

- In a subsequent study of national registries from multiple countries (n >2,100,000 pregnancies) that controlled for several potential confounding factors, the risk of cardiac malformations among infants (n >2800) exposed to paroxetine during the first trimester and infants not exposed was comparable [31].

- A study used prospectively collected data to compare the incidence of cardiovascular birth defects following exposure to paroxetine (n = 1174) with the incidence following exposure to drugs that are considered safe in pregnancy (n = 1174); the rate of defects for both groups was 0.7 percent [88].

By contrast, several studies support an association between in-utero paroxetine exposure and cardiac defects [27,76,77,89]. However, the results suggest that the increased risk is marginal and the absolute risk is small. In a meta-analysis of 18 studies, first trimester exposure to paroxetine (n >20,000) was associated with a slightly elevated risk for cardiac defects (odds ratio 1.3, 95% CI 1.1-1.5) [90].

Pregnancy complications — Antenatal exposure to paroxetine does not appear to be associated with spontaneous abortion. However, two studies have yielded contradictory results regarding exposure to paroxetine and hypertensive disorders of pregnancy, and one study suggests that paroxetine is associated with an increased risk of postpartum hemorrhage.

- **Spontaneous abortion** – Multiple studies suggest that paroxetine is not associated with spontaneous abortion [49]. As an example, a national registry study identified pregnant patients with depression, and found that the risk of miscarriage was comparable in patients who were treated with paroxetine and patients who were not exposed to antidepressants [48].

- **Hypertensive disorders of pregnancy** – It is not clear if paroxetine is associated with hypertensive disorders of pregnancy due to conflicting findings across studies:

  - A study of an insurance claims database found that among pregnant patients with depression, the risk of preeclampsia was comparable for patients who were treated with paroxetine during the second and third trimesters (n >3000) and patients who received no antidepressants (n >59,000) [81].

  - An observational study of an administrative health care dataset examined use of paroxetine among pregnant patients with pregnancy induced hypertension (n >1200 cases) and pregnant patients without pregnancy induced hypertension (n >12,000 controls) [80]. After adjusting for potential confounding factors (eg, maternal age, depression, and use of other medications), the analyses found that exposure to paroxetine was greater in patients with hypertension than controls (odds ratio 1.81, 95% CI 1.02-3.23). However, there were only 18 cases of hypertension with exposure to paroxetine.

- **Postpartum hemorrhage** – A study of pregnant patients with mood or anxiety disorders in a nationwide insurance claims database found that use of paroxetine at the time of delivery (n >2000) was associated with postpartum hemorrhage (relative risk 1.4, 95% CI 1.1-1.7) [57].

Sertraline

Maternal and fetal concentrations — Concentrations of sertraline in fetal circulation appear to be relatively low, compared with maternal circulation. A prospective observational study assessed maternal serum and cord blood concentrations at delivery in six mother-infant pairs [91]. The median serum and cord blood concentrations were 15 and 6 ng/mL. In addition, there was no correlation between maternal serum concentrations and cord blood

concentrations of sertraline; this suggests a relatively low penetration of sertraline into fetal circulation, which supports the view that the drug is relatively safe during pregnancy.

Teratogenicity — Several reviews have found that in most studies, early pregnancy exposure to sertraline was not associated with major congenital abnormalities collectively across different organ systems, nor with cardiovascular malformations in particular [10,84,92]. Among the relatively few studies that found an increased risk for some birth defects, the absolute risk appeared to be low [36,93].

Observational studies that found sertraline was not associated with birth defects include the following [12,23,27,76]:

- A meta-analysis of six studies found that the incidence of congenital malformations in babies who were exposed (n >4000) or not exposed (n >2,300,000) in utero to sertraline was comparable [38]. In addition, the rate of major malformations collectively and the rate of cardiac anomalies were each comparable for the two groups.

- A systematic review identified four studies that included nearly 2 million pregnant patients who either used or did not use SSRIs; the mean duration of follow-up ranged from discharge after delivery to six years, and adjustment for potential confounding factors varied across studies [42]. A meta-analysis of three of the studies found that the risk of congenital heart defects in the offspring who were exposed or not exposed to sertraline was comparable (odds ratio 1.0, 95% CI 0.8-1.2).

- A subsequent study collected data from national registries from multiple countries (n >2,100,000 pregnancies) and controlled for several potential confounding factors; the risk of major birth defects among infants (n >7000) exposed to sertraline during the first trimester and infants not exposed was comparable, as was the risk of cardiac defects [31].

In studies that have observed an association between antenatal sertraline exposure and congenital anomalies, the analyses may not have controlled for relevant confounding factors, such as depression and other indications for the SSRI. As an example, a meta-analysis of 13 studies included pregnant patients who received sertraline in the first trimester and pregnant patients in the general population [37]. The risk of congenital heart defects was greater in the offspring of patients treated with sertraline (relative risk 1.4, 95% CI 1.1-1.8). However, some of the studies had limited control for potential confounders. More so, in a second analysis that was restricted to the three studies that included only pregnant patients with psychiatric diagnoses, who either received sertraline or did not, the risk in the two groups was comparable (relative risk 1.1, 95% CI 0.9-1.4). By including only pregnant patients with psychiatric diagnoses, the second meta-analysis controlled for confounding by indication.

Pregnancy complications — Sertraline does not appear to be associated with major pregnancy complications, except for postpartum hemorrhage:

- **Spontaneous abortion** – Multiple studies suggest that sertraline is not associated with spontaneous abortion [49]. As an example, a national registry study identified pregnant patients with depression, and found that the risk of spontaneous abortion was comparable in patients who were treated with sertraline and patients who were not exposed to antidepressants [48].

- **Hypertensive disorders of pregnancy** – Multiple studies suggest that sertraline is not associated with hypertensive disorders of pregnancy [80]. As an example, a study of an insurance claims database found that among pregnant patients with depression, the risk of preeclampsia was comparable for patients who were treated with sertraline during the second and third trimesters (n >7000) and patients who received no antidepressants (n >59,000) [81].

- **Postpartum hemorrhage** – A study of pregnant patients with mood or anxiety disorders in a nationwide insurance claims database found that use of sertraline at the time of delivery (n >4000) was associated with postpartum hemorrhage (relative risk 1.3, 95% CI 1.1-1.5) [57].

SELECTIVE SEROTONIN REUPTAKE INHIBITORS PLUS BENZODIAZEPINES

It is not clear if the combination of selective serotonin reuptake inhibitors (SSRIs) plus benzodiazepines is associated with major congenital malformations, due to limited data that are available and the conflicting results across studies.

Evidence that suggests antenatal SSRIs plus benzodiazepines may be associated with teratogenic effects includes a meta-analysis of three studies, which found that the risk of major congenital malformations was greater in the offspring of mothers treated with antidepressants plus benzodiazepines in the first trimester, compared with the offspring of unexposed mothers (sample sizes not reported) [94]. However, the meta-analysis included all antidepressants rather than focusing upon SSRIs.

In addition, other studies not included in the meta-analysis have found that concurrent treatment with SSRIs and benzodiazepines was not associated birth defects. As an example, a national registry study included pregnant patients with first trimester exposure to SSRIs plus benzodiazepines (exposed, n = 400) and the general population of pregnant patients (unexposed, n >1.2 million) [29]. After adjusting for potential confounding factors (eg, maternal

age, smoking, and body mass index), the analyses found that in the exposed and unexposed groups, the risk of relatively severe congenital malformations collectively across organ systems was comparable, as was the risk of cardiovascular defects. Another study, using national registry data from five countries and controlling for potential confounds, also found that the combination was not associated with major birth defects [31].

Additional information about the teratogenic and postnatal effects of benzodiazepines is discussed separately. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Benzodiazepines'.)

ANTIDEPRESSANTS OTHER THAN SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The potential adverse antenatal consequences that may be associated with antidepressants other than selective serotonin reuptake inhibitors are discussed separately. (See "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors".)

OTHER MEDICATIONS AND ELECTROCONVULSIVE THERAPY

The teratogenic and postnatal effects of anticonvulsants, antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy are discussed separately. (See "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Effects of ASMs on the fetus and child' and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy".)

BREASTFEEDING

The safety of antidepressants in lactating patients is discussed separately. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding".)

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".)

SUMMARY

- **Choosing treatment** – Options for treating depressed pregnant patients include psychotherapy and pharmacotherapy. Moderate to severe maternal major depression poses risks to both the mother and fetus that often outweigh the possible risks associated with antidepressants. (See "Severe antenatal unipolar major depression: Choosing treatment".)

- **Quality of evidence** – Information about the risks of antidepressants during pregnancy comes from observational studies. These low- to moderate-quality studies can yield associations confounded by indication, severity of illness, and unmeasured factors. (See 'Quality of evidence' above.)

- **Use of selective serotonin reuptake inhibitors (SSRIs)** – SSRIs are used more widely for antenatal depression than other antidepressants, and more is known about the antenatal risks of SSRIs. Studies that examine the risks of SSRIs primarily evaluate the drugs collectively rather than individually. (See 'Selective serotonin reuptake inhibitors' above.)

- **Teratogenicity** – First trimester exposure to SSRIs is associated with a low risk of teratogenicity, and individual SSRIs as well as SSRIs as a group are not considered major teratogens. Although some data suggest that SSRIs (particularly paroxetine) may be associated with a small absolute increase in congenital heart defects, several studies have found no such association. (See 'Teratogenicity' above and 'Teratogenicity' above.)

- **Pregnancy complications** – SSRIs are associated with little to no risk of miscarriage and gestational diabetes, and a small increased risk of hypertensive disorders of pregnancy. It is possible that SSRI exposure during the third trimester is associated with an increased risk for postpartum hemorrhage. (See 'Pregnancy complications' above.)

- **Preterm birth** – In-utero exposure to SSRIs is associated with preterm birth (eg, <37 weeks gestational age), and a small reduction in gestational age at birth that is probably not clinically significant. (See 'Preterm birth' above.)

- **Low birth weight** – It is not clear if SSRIs are associated with low birth weight. (See 'Low birth weight' above.)

- **Apgar scores** – It remains unknown whether antenatal exposure to SSRIs is associated with low Apgar scores. (See 'Apgar score' above.)

- **Perinatal death** – SSRIs do not appear to be associated with perinatal death. (See 'Perinatal death' above.)

- **Specific SSRIs** – We do not consider one SSRI to be safer or less safe than another to use during pregnancy, with the possible exception of paroxetine. Several studies have found that paroxetine was associated with a small increased risk for congenital cardiovascular malformations; however, other studies have found no such risk. (See 'Specific SSRIs' above and 'Paroxetine' above.)

Topic 89067 Version 25.0

→