Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors

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INTRODUCTION

Pregnant women with psychiatric illnesses are often treated with antidepressant drugs. As an example, studies of pregnant women in Europe have found that antidepressants were used by approximately 3 percent [1-4], in Quebec by 4 percent [5], and in the United States by 8 percent [6-9]. Compared with selective serotonin reuptake inhibitors (SSRIs), other antidepressants have been used and studied less frequently [1,2,6-13].

Antidepressants cross the placenta and fetal blood brain barrier. Prenatal exposure thus involves potential risks of teratogenesis, pregnancy complications (eg, spontaneous abortion and postpartum hemorrhage), preterm birth, and low birth weight, as well as postnatal effects (eg, poor neonatal adaptation syndrome and disrupted behavioral development).

This topic reviews the potential adverse consequences that may be associated with the antenatal use of antidepressant drugs other than SSRIs. The potential adverse effects of using SSRIs during pregnancy, postnatal outcomes among infants exposed in utero to SSRIs or serotonin-norepinephrine reuptake inhibitors, principles of teratology, choice of treatment for depressed pregnant patients, safety of antidepressants in lactating women, and treatment of postpartum depression are discussed separately:

- (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: 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 drugs during pregnancy comes from low to moderate quality studies. For some drugs (eg, duloxetine and venlafaxine), better information is available from larger studies that analyzed the effects of a drug class (eg, serotonin-norepinephrine reuptake inhibitors) in toto, rather than small studies of individual drugs. The quality of studies that have examined the risks of antidepressants during pregnancy is discussed separately. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors", section on 'Quality of evidence'.)

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)

Serotonin-norepinephrine reuptake inhibitors (SNRIs) include duloxetine and venlafaxine; the risks of using these drugs during pregnancy are discussed in the subsections below. There is little to no information about the antenatal risk of using other SNRIs, including desvenlafaxine, levomilnacipran, or milnacipran [5].

This section discusses the risks of antenatal SNRIs as a drug class. The risks specific to duloxetine and venlafaxine are discussed below. (See 'Duloxetine' below and 'Venlafaxine' below.)

The pharmacology, administration, and side effects of SNRIs are discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

Teratogenicity — The SNRIs duloxetine and venlafaxine do not appear to be associated with an increased risk of congenital malformations [10]. As an example, a study of an insurance claims

database compared infants born to depressed mothers who received duloxetine or venlafaxine during the first trimester (n >6,000) with infants whose depressed mothers were not treated with antidepressants (n >180,000) [11]. Propensity scoring was used to match the two groups for observed potential confounders (eg, maternal age, obesity, and substance use disorders; depression severity; chronic maternal illnesses; and use of other medications). The risk of congenital cardiac defects was comparable among infants exposed to duloxetine or venlafaxine compared with unexposed infants.

Pregnancy complications

- **Spontaneous abortion** – It is not clear if duloxetine or venlafaxine is associated with spontaneous abortion (miscarriage) due to conflicting results across studies, which are discussed below. (See 'Pregnancy complications' below and 'Pregnancy complications' below.)

- **Hypertensive disorders of pregnancy** – Although some observational studies suggest that duloxetine and venlafaxine may be associated with an increased risk for hypertensive disorders of pregnancy (eg, gestational hypertension and/or preeclampsia), the sample sizes of many studies are too small to firmly judge the risk:

  - A registry study identified pregnant women who either continued SNRIs during pregnancy (n = 21) or discontinued SNRIs prior to pregnancy (n = 17) [14]. After adjusting for potential confounding factors (eg, maternal age, prepregnancy body mass index, parity, prepregnancy medical complications, and smoking), the analyses found an increased risk for gestational hypertension in those who continued compared with those who discontinued SNRIs (14 versus 6 percent). However, the sample size was small, the analyses did not control for severity of depression, and the risk of preeclampsia was comparable among both groups (10 and 6 percent).

  - A systematic review found that in two studies, pregnant women who used SNRIs (total n >1600) were at a greater risk of preeclampsia, compared with unexposed pregnant women (adjusted relative risk of 1.5 and 2.0) [15]. However, an association between depression/anxiety and preeclampsia cannot be excluded (confounding by indication).

  - An observational study prospectively followed pregnant women (n = 686), most of whom were treated with at least one psychotropic medication, including an SNRI (n = 71; primarily venlafaxine) [16]. The incidence of hypertensive disorders of pregnancy was greater among patients who received an SNRI than patients who did not (23 versus 11 percent).

- **Postpartum hemorrhage** – Multiple observational studies suggest that administration of duloxetine or venlafaxine at the end of pregnancy is associated with postpartum hemorrhage:

  - A meta-analysis of two studies examined the rate of postpartum hemorrhage in pregnant women (sample size not reported) who were either treated with SNRIs or were not treated with antidepressants [17]. The risk of postpartum hemorrhage was greater in patients treated with SNRIs than women who did not receive antidepressants (odds ratio 1.6, 95% CI 1.4-1.9).

  - A study of claims data identified pregnant women who were treated with SNRIs (largely venlafaxine) in late pregnancy (during the last 30 days; n >1300) and in mid-pregnancy (the last five months but not in the last 30 days of pregnancy; n >200), as well as women who were not treated with antidepressants during pregnancy (n >300,000). The analyses adjusted for potential confounders including maternal sociodemographics, maternal general medical and psychiatric comorbidities, smoking, and use of medications (eg, blood thinners). Postpartum hemorrhage occurred in more women who were exposed to SNRIs in late pregnancy (11 percent), but not in women exposed in mid-pregnancy (10 percent), relative to unexposed women (7 percent) [18].

The association between administration of duloxetine or venlafaxine at the end of pregnancy and postpartum hemorrhage is consistent with the association between use of selective serotonin reuptake inhibitors (SSRIs) and bleeding. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Bleeding'.)

Postnatal effects — The postnatal effects of SNRIs are discussed separately.

- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)
- (See "Infants and children with antenatal exposure to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors: Risk of abnormalities in growth, motor skills, and cognition".)
- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of psychopathology in the offspring".)

Duloxetine — This section discusses the potential adverse consequences that may be associated with the antenatal use of duloxetine. The pharmacology, administration, and side effects of duloxetine are discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Duloxetine'.)

Teratogenicity — Duloxetine does not appear to be a major teratogen:

- A meta-analysis of four observational studies found that among infants who were exposed to duloxetine during the first trimester (n = 668), major congenital malformations occurred in 2.4 percent, which was comparable to the malformation rate in the background population [19].

- A subsequent study of an administrative health dataset included pregnant women who were either treated with duloxetine during the first trimester (n >2500) or were not treated (n >1,200,000) [20]. After adjusting for the propensity (probability) to receive duloxetine, based upon potential confounding factors (eg, age, comorbidities, and other medications), the analyses found that the risk of major congenital malformations was comparable for the two groups. In addition, the rate of malformations was comparable for infants exposed in utero to duloxetine and infants exposed to either venlafaxine or an SSRI.

Information about the teratogenicity of SNRIs as a class is discussed elsewhere in this topic. (See 'Teratogenicity' above.)

Pregnancy complications — The association between duloxetine and spontaneous abortion (miscarriage) is not clear because of conflicting results across studies. One study suggests that duloxetine is not associated with preeclampsia but is associated with postpartum hemorrhage.

- **Spontaneous abortion** – It is not clear if duloxetine is associated with spontaneous abortion, due to conflicting results across studies.

  - A retrospective national registry study identified pregnant women with depression who were either exposed to antidepressants (n = 210) or not (n = 105) [21]. The risk of spontaneous abortion was greater in women who were treated with duloxetine (sample size not reported), compared with women who were not exposed to antidepressants (relative risk 3, 95% CI 2-6). However, the analysis did not control for potential confounding factors because the number of exposed women was low.

  - The manufacturer's pharmacovigilance database included duloxetine-exposed pregnancies that were followed prospectively (n = 233) [22]. Spontaneous abortions occurred in 18 percent; this rate appeared to be generally consistent with historic rates in the general population.

  - Analyses of adverse events reported to the US Food and Drug Administration found that pregnancy complications (eg, spontaneous abortions) associated with duloxetine and complications associated with a group of other antidepressants were comparable

[22]. Likewise, complications associated with duloxetine and with all other drugs were comparable.

- **Preeclampsia** – It does not appear that duloxetine is associated with preeclampsia. A study of an administrative health dataset included pregnant women who were either treated with duloxetine during the first 20 weeks of gestation (n >3000) or were not treated (n >1,400,000) [20]. After adjusting for the propensity (probability) to receive duloxetine, based upon potential confounding factors (eg, age, comorbidities, and other medications), the analyses found that the risk of preeclampsia was comparable for the two groups. In a second analysis that examined the risk in women treated with duloxetine after the first 20 weeks of pregnancy, the risk of preeclampsia was again comparable in women exposed to duloxetine and unexposed women.

- **Postpartum hemorrhage** – Duloxetine is associated with postpartum hemorrhage. A study of an administrative health dataset included pregnant women who were either treated with duloxetine during the month prior to delivery (n >950) or were not treated (n >4,100,000) [20]. After adjusting for the propensity to receive duloxetine, based upon potential confounding factors, the analyses found that the risk of postpartum hemorrhage was greater in the exposed women than the unexposed women (relative risk 1.53, 95% CI 1.08-2.18). In addition, the rate of postpartum hemorrhage was greater in women exposed to duloxetine than women exposed to an SSRI (relative risk 1.48, 95% CI 1.03-2.12). The rates for women exposed to duloxetine and women exposed to venlafaxine were comparable.

Preterm birth — It is not clear if duloxetine is associated with preterm birth (delivery that occurs between 20 and 37 weeks of gestation). A study of an administrative health dataset included pregnant women who were either treated with duloxetine during the first 20 weeks of gestation (n >2900) or were not treated (n >1,300,000) [20]. After adjusting for the propensity (probability) to receive duloxetine, based upon potential confounding factors (eg, age, comorbidities, and other medications), the analyses found that the risk of preterm delivery was comparable for the two groups. However, in a second analysis that examined the risk in women treated with duloxetine after the first 20 weeks of pregnancy, the risk of preterm delivery was modestly greater in women exposed to duloxetine than unexposed women (relative risk 1.19, 95% CI 1.04-1.37).

Small for gestational age — It does not appear that duloxetine is associated with small for gestational age infants. A study of an administrative health dataset included pregnant women who were either treated with duloxetine during the first 20 weeks of gestation (n >2900) or were not treated (n >1,300,000) [20]. After adjusting for the propensity (probability) to receive

duloxetine, based upon potential confounding factors (eg, age, comorbidities, and other medications), the analyses found that the risk of small for gestational age was comparable for the two groups. In a second analysis that examined the risk in women treated with duloxetine after the first 20 weeks of pregnancy, the risk of small for gestational age was again comparable in women exposed to duloxetine and unexposed women.

Postnatal effects — The postnatal effects of SNRIs are discussed separately.

- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)
- (See "Infants and children with antenatal exposure to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors: Risk of abnormalities in growth, motor skills, and cognition".)
- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of psychopathology in the offspring".)

Venlafaxine — This section discusses the potential adverse consequences that may be associated with the antenatal use of venlafaxine. The pharmacology, administration, and side effects of venlafaxine are discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Venlafaxine'.)

Teratogenicity — The risk of congenital anomalies with venlafaxine is generally regarded as low [10,23,24], and most observational studies have found that in utero exposure to venlafaxine is not associated with an increased risk of congenital malformations [25]:

- A registry study identified pregnant women with a diagnosis of depression and/or anxiety who either used venlafaxine during the first trimester (n >700) or did not (n >14,000) [5]. After adjusting for potential confounding factors (eg, maternal age, diabetes, and use of other medications), the analyses showed that the frequency of major congenital malformations in the offspring was comparable in those with and without venlafaxine exposure (12 and 11 percent).

- A meta-analysis of four observational studies found that among infants who were exposed to venlafaxine during the first trimester (n = 3186), major congenital malformations occurred in 3.4 percent, which was comparable to the malformation rate in the background population [19].

  One of the studies drew upon national registries from multiple countries and identified infants who were exposed to venlafaxine during the first trimester (n >2700) and infants who were not exposed (n >2,100,000); the analyses controlled for several potential

confounding factors, such as maternal age, smoking, diabetes, and use of other medications (eg, antiepileptics) [26]. The risk of major birth defects was comparable for the two groups, as was the specific risk for cardiac defects in the sibling-controlled analyses.

- In a prior meta-analysis of two observational studies (n >400 infants exposed in utero to venlafaxine), the rate of major malformations and the rate of cardiac anomalies were each comparable for the exposed and unexposed groups [27].

Pregnancy complications — It is not clear if antenatal exposure to venlafaxine is associated with spontaneous abortion, due to inconsistent results across different studies. However, studies suggest that venlafaxine is associated with preeclampsia, and one study found that the drug is associated with postpartum hemorrhage.

- **Spontaneous abortion** – Different studies have yielded contradictory results regarding exposure to venlafaxine and spontaneous abortion:

  - A study of prospective pregnancy surveillance data identified women who were treated with venlafaxine at any stage of pregnancy (n = 281) or were not treated with antidepressants (n = 1405) [25]. After adjusting for potential confounding factors (eg, gestational age at enrollment), the analyses found that the risk of spontaneous abortion was comparable for the two groups.

  - A prospective observational study included pregnancies with first trimester exposure to venlafaxine, SSRIs, or nonteratogenic drugs; there were 150 women in each group [28]. The incidence of spontaneous abortion in each of the three groups was comparable.

  - A retrospective national registry study identified pregnant women with depression who were either exposed to antidepressants (n = 210) or not (n = 105) [21]. The risk of spontaneous abortion was greater in women who were treated with venlafaxine (sample size not reported), compared with women who were not exposed to antidepressants (relative risk 1.8, 95% CI 1.2-2.7). However, the analysis did not control for potential confounding factors because the number of women exposed to venlafaxine was low.

- **Hypertensive disorders of pregnancy** – There is concern that venlafaxine exposure may increase the risk for hypertensive disorders of pregnancy. Venlafaxine can cause hypertension in nonpregnant patients, and may contribute to preeclampsia:

- A study of a nationwide insurance claims database found that among pregnant women with depression, preeclampsia occurred in more women who were treated with venlafaxine during the second and third trimesters (n >1100), compared with women who received no antidepressants (n >59,000) (9 versus 5 percent) [29]. The incidence of preeclampsia also appeared to be greater with venlafaxine than SSRIs.

- A study using health care utilization databases identified pregnant women with depression who were either treated with venlafaxine between gestational weeks 10 and 20 (n >400), or who received no antidepressants (n >65,000) [30]. The analysis adjusted for potential confounders (eg, maternal age, depression, and use of other psychotropic drugs), and found that the incidence of preeclampsia was greater in women treated with venlafaxine, compared with controls (6 versus 2 percent of women).

- **Postpartum hemorrhage** – Venlafaxine may increase the risk of postpartum hemorrhage. A study of a nationwide insurance claims database included pregnant women with mood or anxiety disorders who were either treated with venlafaxine at the time of delivery (n >700) or were not treated with antidepressants in the five months before delivery; venlafaxine was associated with an increased risk of postpartum hemorrhage (relative risk 2.2, 95% CI 1.7-3.0) [31].

Preterm birth — It is not clear whether venlafaxine is associated with preterm birth (delivery that occurs between 20 and 37 weeks of gestation), due to conflicting results across studies:

- A study of prospective pregnancy surveillance data identified women who were treated with venlafaxine at any stage of pregnancy (n = 198) or were not treated with antidepressants (n = 1081) [25]. After adjusting for potential confounding factors (eg, gestational age at enrollment), the analyses found that the risk of preterm birth was comparable for the two groups.

- A national registry study compared women who took antidepressants during early pregnancy (n = 732) with the general population of pregnant women (n >860,000) [32]. The majority of women treated with antidepressants (68 percent) received venlafaxine. After controlling for potential confounds (eg, maternal age, smoking, and body mass index), the analysis found that antidepressants were associated with an increased risk of preterm birth (odds ratio 1.6, 95% CI 1.2-2.2).

Low birth weight — A study of prospective pregnancy surveillance data identified women who were treated with venlafaxine at any stage of pregnancy (n = 140) or were not treated with antidepressants (n = 815) [25]. After adjusting for potential confounding factors (eg, gestational

age at enrollment), the analyses found that the risk of low birth weight was comparable for the two groups.

Postnatal effects — The postnatal effects of SNRIs are discussed separately.

- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)
- (See "Infants and children with antenatal exposure to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors: Risk of abnormalities in growth, motor skills, and cognition".)
- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of psychopathology in the offspring".)

ATYPICAL ANTIDEPRESSANTS

Atypical antidepressants include bupropion and mirtazapine; the risks of using these drugs during pregnancy are discussed in the subsections below. There is little to no information about the antenatal risk of using other atypical antidepressants such as agomelatine.

Bupropion — This section discusses the potential adverse consequences that may be associated with the antenatal use of bupropion. The pharmacology, administration, and side effects of bupropion are discussed separately. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Bupropion'.)

Teratogenicity — The risk of teratogenicity with bupropion is generally regarded as low [10,23,33,34]. Although a few studies have described a link with cardiac anomalies, the absolute risk is thought to be small and the specific defect across studies is somewhat inconsistent [35-37].

Evidence that suggests bupropion is not associated with teratogenicity includes the following:

- A study of a public insurance claims database compared infants born to depressed mothers who received bupropion during the first trimester (n >6,000) with infants whose depressed mothers were not treated with antidepressants (n >180,000) [11]. Propensity scoring was used to match the two groups for observed potential confounders. The risk of congenital cardiac defects in exposed infants and controls was comparable.

- A prospective observational study enrolled pregnant women who took either bupropion (n = 136) or nonteratogenic drugs (n = 133) during the first trimester; the two groups were matched on age, smoking, and alcohol consumption [33]. The prevalence of major

malformations was comparable in the infants exposed to bupropion and controls (0 and 2 infants). In a second analysis that was limited to women taking bupropion for depression, the results were identical.

- Two studies sponsored by the manufacturer:

  - A retrospective study examined a private insurance claims database (United Healthcare) that included first trimester exposures to bupropion (n >1200), first trimester exposure to other antidepressants such as selective serotonin reuptake inhibitors (SSRIs; n >4700), and exposure to bupropion before pregnancy or during the second or third trimester [38]. The prevalence of congenital malformations was comparable in the three groups (2.2 to 2.3 percent). In addition, the rate of cardiovascular defects was comparable across the three groups (1.0 to 1.1 percent).

  - In addition, a prospective pregnancy registry (Bupropion Pregnancy Registry) study (n = 675 exposures) found that birth defects occurred in 3.6 percent of pregnancies, which is generally regarded as comparable with the rate in the general population [39].

Although the following three studies suggest that first trimester exposure to bupropion is associated with cardiac anomalies, the specific defect is somewhat inconsistent across studies. Two of the studies found that bupropion was associated with an increased risk of left ventricular outflow tract obstruction (but not ventral septal defects), whereas the third study found that bupropion was associated with ventral septal defects (but not left outflow tract defects). In addition, the absolute risk of left outflow tract defects appears to be small, on the order of 2.1 to 2.8 per 1000 births [37]. Further, analyses in the three studies did not control for confounding by indication (using bupropion for depression or smoking cessation), due to the small number of infants exposed to bupropion [35,36] or the small number of infants with cardiac defects [40]; maternal smoking may increase the risk congenital heart defects [41,42].

- A retrospective case-control study examined maternal use of bupropion among infants with major birth defects (n >12,000 cases) and infants with no defects (n >5000 controls), and controlled for potential confounding factors (eg, maternal smoking and obesity) [35]. Although the likelihood of first trimester exposure to bupropion was greater in babies with left ventricular outflow tract obstruction than controls (odds ratio 2.6, 95% CI 1.2-5.7), the absolute risk for this defect was considered low (2.1 per 1000 births). In addition, bupropion was not associated with other congenital heart defects, such as septal defects.

- A registry study identified infants with cardiac defects (n >7000 cases) and infants with no malformations (n >8000 controls) [36]. First trimester exposure to bupropion was greater in babies with ventral septal defects than babies with no malformations (0.6 versus 0.2

percent). However, bupropion was not associated with other congenital heart defects, such as left outflow tract defects.

- A study sponsored by the manufacturer reanalyzed data from the United Healthcare insurance claims database described above, using different case definitions of cardiovascular defects [40]. The prevalence of left ventricular outflow tract obstruction was greater among infants with first trimester exposure to bupropion, compared with infants with first trimester exposure to other antidepressants (2.8 versus 0.7 per 1000 births).

Pregnancy complications — Bupropion may be associated with spontaneous abortions (miscarriages), but does not appear to be associated with hypertensive disorders of pregnancy (eg, preeclampsia) or postpartum hemorrhage:

- A prospective observational study enrolled pregnant women who took either bupropion (n = 136) or drugs not considered teratogens (n = 133) during the first trimester; the two groups were matched on age, smoking, and alcohol consumption [33]. Spontaneous abortions occurred in more patients exposed to bupropion than controls (15 versus 5 percent).

- Studies of pregnant women with mood or anxiety disorders in a nationwide insurance claims database found that use of bupropion during the second and third trimesters (n >2000) was not associated with preeclampsia [29], and that use at the time of delivery (n >1000) was not associated with postpartum hemorrhage [31].

- An observational study prospectively followed pregnant women (n = 686), most of whom were treated with at least one psychotropic medication, including bupropion (n = 73) [16]. The incidence of hypertensive disorders of pregnancy was comparable for patients who received bupropion and patients who did not.

Preterm birth — Two small studies suggest that bupropion is not associated with preterm birth:

- A 12-week randomized trial compared bupropion sustained release (150 mg per day) with placebo for smoking cessation in pregnant women who were between 13 to 30 weeks gestation (n = 65) [43]. One preterm birth occurred in each group.

- A registry study identified pregnant women who smoked and were either treated with bupropion during pregnancy (n = 72) or were not (n >900); women with depression were excluded [44]. After adjusting for potential confounding factors (eg, maternal age, diabetes, and hypertension), the analyses showed that the likelihood of preterm delivery

was lower in women who received bupropion than women who did not (odds ratio 0.12, 95% CI 0.03-0.50).

Other neonatal outcomes — Based upon small, prospective studies, bupropion does not appear to be associated with adverse neonatal outcomes such as low birth weight:

- A 12-week randomized trial compared bupropion sustained release (150 mg per day) with placebo for smoking cessation in pregnant women who were between 13 to 30 weeks gestation (n = 65) [43]. Gestational age, birth weight, and Apgar scores at one and five minutes were each comparable for the two groups.

- A prospective observational study enrolled pregnant women who took either bupropion (n = 136) or nonteratogenic drugs (n = 133) during the first trimester; the two groups were matched on age, smoking, and alcohol consumption [33]. Gestational age and birth weight were comparable for the two groups.

Postnatal effects — One study found an association between fetal exposure to bupropion and risk of attention deficit hyperactivity disorder (ADHD) as a child, but the association may have been confounded by undiagnosed parental ADHD or other factors and has yet to be replicated. The study used a health care claims database to identify mothers who used bupropion during pregnancy (n = 114) or an SSRI during pregnancy (n = 916), as well as depressed mothers who did not use antidepressants during pregnancy (n = 3532) [45]. After controlling for potential confounding factors (eg, sex of the child, parental psychiatric diagnoses, and perinatal complications), the analyses found that ADHD occurred more often with in utero exposure to bupropion than exposure to an SSRI or no exposure (4.4 versus 2.5 and 2.5 percent of offspring).

Mirtazapine — This section discusses the potential adverse consequences that may be associated with the antenatal use of mirtazapine, based upon observational studies with small numbers of women exposed to the medication. The pharmacology, administration, and side effects of mirtazapine are discussed separately. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Mirtazapine'.)

Teratogenicity — Based upon limited data, there appears to be little risk of teratogenicity with mirtazapine [10,46,47]:

- In a systematic review of six observational studies, with a total of 334 infants who were exposed to mirtazapine during pregnancy, mirtazapine was not associated with an increased incidence of major congenital malformations, compared with other antidepressants or nonteratogenic medications [48]. Among the 334 infants, major

malformations occurred in 9 (2.7 percent), a rate that is comparable to what is observed in the general population. (See "Congenital anomalies: Epidemiology, types, and patterns", section on 'Major'.)

- A prospective study included infants who were exposed in utero during the first trimester to mirtazapine (n = 292) or an SSRI (n = 307), and a third group who were not exposed to an antidepressant or known teratogen (n = 309) [49]. The incidence of major birth defects with mirtazapine, SSRIs, or nonexposure was comparable (3, 4, and 2 percent of infants).

Pregnancy complications — It is not clear if mirtazapine during pregnancy is associated with spontaneous abortion due to conflicting results across two studies; however, the prospective study found that the drug was not associated with miscarriage. Mirtazapine exposure does not seem to be associated with preeclampsia or postpartum hemorrhage.

- **Spontaneous abortion** – Mirtazapine was not associated with spontaneous abortion in a prospective observational study, which found that the incidence of spontaneous abortion was comparable among depressed women who took mirtazapine (n = 104) and depressed women who took nonteratogenic drugs (n = 104) [50].

  By contrast, a retrospective national registry study identified pregnant women with depression who were either exposed to antidepressants (n = 210) or not (n = 105) [21]. The risk of spontaneous abortion was greater in women who were treated with mirtazapine (sample size not reported), compared with women who were not exposed to antidepressants (relative risk 2.2, 95% CI 1.3-3.7). However, the analysis did not control for potential confounding factors because the number of exposed women was low.

- **Hypertensive disorders of pregnancy** – A retrospective study of pregnant women with depression in a nationwide insurance claims database found that use of mirtazapine during the second and third trimesters (n >200) was not associated with preeclampsia [29].

- **Postpartum hemorrhage** – A study of pregnant women with mood or anxiety disorders in a nationwide insurance claims database found that use of mirtazapine at the time of delivery (n >100) was not associated with postpartum hemorrhage [31].

Preterm birth — It is not clear if mirtazapine is associated with preterm birth (delivery that occurs between 20 and 37 weeks of gestation) due to conflicting results across two prospective observational studies. However, the larger study suggests that the drug does not pose a risk:

- One study included three groups of infants who were exposed in utero to mirtazapine (n = 279) or to an SSRI (n = 302), or who were not exposed to an antidepressant or known

teratogen (n = 302) [49]. The incidence of preterm birth with mirtazapine, SSRIs, or nonexposure was comparable (11, 11, and 9 percent of infants).

- In a study of pregnant women, preterm birth occurred in more women who took mirtazapine (n = 104), compared with women who took substances considered nonteratogenic, such as acetaminophen or antacids (n = 104) (10 versus 2 percent) [50].

Low birth weight — Mirtazapine does not appear to be associated with low birth weight [47]. A prospective study included infants who were exposed in utero to mirtazapine (n = 274) or to an SSRI (n = 298), or who were not exposed to an antidepressant or known teratogen (n = 302) [49]. The median birth weight with mirtazapine, SSRIs, or nonexposure was comparable (approximately 3200 to 3300 grams).

Perinatal death — In a prospective observational study of pregnant women, the incidence of stillbirth among women who took mirtazapine (n = 104) and women who took nonteratogenic drugs (n = 104) was comparable [50].

Postnatal effects

- **Poor neonatal adaptation** – Use of mirtazapine late in pregnancy may be associated with the poor neonatal adaptation syndrome, but evidence is weak. An observational study of 54 neonates who were exposed to mirtazapine during the third trimester found that poor neonatal adaptation occurred in 26 percent, which the authors concluded was comparable to the incidence seen with other antidepressants [47]. In addition, the risk was lower among breastfed infants than infants who were fed only with formula (19 versus 55 percent). However, the study appeared to be retrospective. Additional information about antidepressants and the poor neonatal adaptation syndrome is discussed separately. (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes", section on 'Poor neonatal adaptation'.)

- **Autism** – Antenatal mirtazapine does not appear to be associated with autism. A national registry study included pregnant women with a lifetime diagnosis of depression or anxiety (n >18,000) who were either treated with mirtazapine during pregnancy (n = 36) or were not [51]. The risk of autism in the offspring was comparable for the exposed and unexposed groups.

In addition, a review of different studies with a total of 21 infants, who were studied for up to one year, found that intrauterine exposure to mirtazapine was not associated with adverse effects upon neurobehavioral development [48].

SEROTONIN MODULATORS

Serotonin modulators include trazodone.

Limited data suggest that the risk of teratogenicity and major pregnancy complications with trazodone appears to be low [10,52]:

- In one prospective observational study, first trimester exposure to trazodone or nefazodone (n = 147) or to drugs considered nonteratogenic (n = 147) resulted in a comparable number of major malformations, as well as miscarriages and stillbirths [53].
- Studies of pregnant women with mood or anxiety disorders in a nationwide insurance claims database found that use of trazodone during the second and third trimesters (n >300) was not associated with preeclampsia [29], and that use at the time of delivery (n >100) was not associated with postpartum hemorrhage [31].

There is little to no information about the antenatal risk of using other serotonin modulators, including vilazodone and vortioxetine. The pharmacology, administration, and side effects of the serotonin modulators are discussed separately. (See "Serotonin modulators: Pharmacology, administration, and side effects".)

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants include amitriptyline, desipramine, imipramine, and nortriptyline. This section discusses the potential adverse consequences that may be associated with the antenatal use of tricyclics. The pharmacology, administration, and side effects are discussed separately. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

Teratogenicity — The risk of teratogenicity with tricyclic antidepressants is generally regarded as low [23,54-60], and most studies have found that prenatal exposure to tricyclics was not associated with congenital anomalies:

- A registry study identified pregnant women with a diagnosis of depression and/or anxiety who either used a tricyclic antidepressant such as amitriptyline during the first trimester (n = 382) or did not (n >14,000) [5]. After adjusting for potential confounding factors (eg, maternal age, diabetes, and use of other medications), analyses showed the frequency of major congenital malformations was comparable with and without exposure (13 and 11 percent).

- A meta-analysis of two observational studies found that the incidence of congenital malformations in babies who were exposed (n >300) or not exposed (n >49,000) in utero to tricyclics was comparable [27]. In addition, the rate of cardiac anomalies was comparable for the two groups.

- A study of an insurance claims database compared infants born to depressed mothers treated with tricyclics during the first trimester (n >3000) with infants whose depressed mothers were not treated with antidepressants (n >180,000) [11]. Propensity scoring was used to match the two groups for observed potential confounders. The risk of congenital cardiac defects among exposed infants and controls was comparable.

- A study of a nationally representative sample of live births compared children exposed to tricyclics during the first trimester (n >2400) with children of mothers with unmedicated depression (n >23,000) [61]. In analyses that adjusted for potential confounding factors (eg, maternal age, smoking, and body mass index), the incidence of major congenital anomalies was comparable. In addition, the rate of major cardiac anomalies was comparable for the two groups.

Although as a group tricyclic agents are typically viewed as nonteratogenic, some data suggest that antenatal use of clomipramine may be associated with congenital anomalies [62]. In one national registry study that compared pregnant women exposed to tricyclics (n >1600; primarily clomipramine) with pregnant women not exposed to antidepressants (n >1,000,000), exposure was associated with a modestly elevated risk of severe malformations (odds ratio 1.4, 95% CI 1.1-1.7), including cardiovascular defects (odds ratio 1.6, 95% 1.1-2.4) [63].

Pregnancy complications

- **Spontaneous abortion** – In a national registry study that identified pregnant women with depression, the risk of spontaneous abortion in women who were treated with tricyclic agents (eg, clomipramine or nortriptyline) and women who were not exposed to antidepressants was comparable [21].

- **Hypertensive disorders of pregnancy** – Multiple studies have found that exposure to tricyclics is associated with preeclampsia:

  - A study of a nationwide insurance claims database found that among pregnant women with depression, preeclampsia occurred in more women who were treated with tricyclics during the second and third trimesters (n = 441), compared with women who received either selective serotonin reuptake inhibitors (n = 19,000) or no antidepressants (n = 59,219) (11 versus 5 and 5 percent) [29].

- A study using health care utilization databases identified pregnant women with depression who were either treated with tricyclics between gestational weeks 10 and 20 (n >100), or who received no antidepressants (n >65,000) [30]. The analysis adjusted for potential confounders (eg, maternal age, depression, and use of other psychotropic drugs), and found that the incidence of preeclampsia was greater in women exposed to tricyclics, compared with controls (10 versus 2 percent).

- **Postpartum hemorrhage** – Exposure to tricyclics during second or third trimester of pregnancy may be associated with postpartum hemorrhage. A study of a nationwide insurance claims database identified pregnant women with mood or anxiety disorders (primarily depression), who were either treated with tricyclics at the time of delivery (n = 175) or were not treated with antidepressants in the five months before delivery (n >69,000) [31]. There was a trend for an association between exposure and postpartum hemorrhage (relative risk 1.8, 95% CI 0.9-3.5), and the risk was comparable to the statistically significant risk observed between exposure to all antidepressants and bleeding (relative risk 1.4, 95% CI 1.3-1.6).

Preterm birth — A systematic review identified one observational study of antenatal tricyclic antidepressants and preterm birth (delivery that occurs between 20 and 37 weeks of gestation, total n = 418 pregnant patients); use of tricyclics during pregnancy was not associated with preterm birth [27].

Postnatal effects — Peripartum exposure to tricyclics may result in transient neonatal withdrawal symptoms [62,64-66], as well as hypoglycemia, respiratory diagnoses, central nervous system diagnoses, and jaundice [63]. Regarding longer term outcomes, studies of children exposed in utero to tricyclics have reported normal motor and behavioral development at three years of age and that global intelligence quotient, language development, temperament, mood, arousability, activity level, distractibility, and behavior problems were comparable in exposed and unexposed children [62,64,67,68]. In addition, antenatal tricyclics do not appear to be associated with an increased risk of attention-deficit hyperactivity disorder [69] or autism [51,70].

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors include phenelzine, selegiline, and tranylcypromine. Animal studies have shown that exposure to monoamine oxidase inhibitors in pregnancy is associated with fetal growth restriction; few human data are available [63,71-73]. The pharmacology, administration, and side effects of monoamine oxidase inhibitors are discussed separately. (See

"Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

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

OTHER MEDICATIONS AND ECT

The teratogenic and postnatal effects of anticonvulsants, antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy (ECT) 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 women 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

- **Treatment options for severe antenatal depression** – Options for treating depressed pregnant patients include psychotherapy and pharmacotherapy. The risks of untreated moderate to severe maternal major depression, to both the mother and fetus, often outweigh the risks associated with antidepressants. (See "Severe antenatal unipolar major depression: Choosing treatment".)

- **Quality of evidence** – Compared with selective serotonin reuptake inhibitors, other antidepressants have been used and studied less often in pregnant women. Information about the risks of antidepressants during pregnancy comes from low to moderate quality studies. (See 'Introduction' above and "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors", section on 'Quality of evidence'.)

- **Duloxetine and venlafaxine** – The evidence regarding the potential risks of antenatal duloxetine or venlafaxine suggests the following:

  - Teratogenicity – Duloxetine and venlafaxine exposure during pregnancy do not appear to be associated with congenital malformations. (See 'Teratogenicity' above and 'Teratogenicity' above and 'Teratogenicity' above.)

  - Spontaneous abortion (miscarriage) – It is not clear if duloxetine or venlafaxine are associated with spontaneous abortion, due to conflicting results across studies. (See 'Pregnancy complications' above and 'Pregnancy complications' above.)

  - Hypertensive disorders of pregnancy (eg, gestational hypertension and/or preeclampsia) – There is concern that venlafaxine exposure may increase the risk for hypertensive disorders of pregnancy, based upon observational studies that combined venlafaxine and duloxetine and other studies that evaluated venlafaxine alone. By contrast, one relatively rigorous study found that duloxetine is not associated with preeclampsia. (See 'Pregnancy complications' above and 'Pregnancy complications' above and 'Pregnancy complications' above.)

  - Postpartum hemorrhage – Administration of duloxetine or venlafaxine at the end of pregnancy appears to be associated with postpartum hemorrhage. (See 'Pregnancy complications' above and 'Pregnancy complications' above and 'Pregnancy complications' above.)

  - Preterm birth – It is not clear if duloxetine and venlafaxine are associated with preterm birth. (See 'Preterm birth' above and 'Preterm birth' above.)

  - Postnatal effects – Several studies have evaluated the postnatal effects of duloxetine and venlafaxine.

    - (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)

- (See "Infants and children with antenatal exposure to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors: Risk of abnormalities in growth, motor skills, and cognition".)
- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Risk of psychopathology in the offspring".)

- **Bupropion** – The risk of teratogenicity with bupropion is generally regarded as low. Bupropion may be associated with spontaneous abortion, but does not seem to be associated with hypertensive disorders of pregnancy, postpartum hemorrhage, preterm birth, or low birth weight. (See 'Bupropion' above.)

- **Mirtazapine** – Based upon limited data, there appears to be little risk of teratogenicity with mirtazapine. In addition, intrauterine exposure does not seem to be associated with spontaneous abortion, preeclampsia, postpartum hemorrhage, low birth weight, or stillbirth. It is not clear if antenatal mirtazapine is associated with preterm birth due to conflicting results across two studies, but the larger study suggests that the drug does not pose a risk. (See 'Mirtazapine' above.)

- **Trazodone** – Based upon limited data, the risk of teratogenicity and major pregnancy complications with trazodone appears to be low. (See 'Serotonin modulators' above.)

- **Tricyclics** – The risks of teratogenicity with tricyclic antidepressants as a group are generally regarded as low; however, one large study found that clomipramine was associated with an elevated rate of severe malformations, including cardiovascular defects. Antenatal exposure to tricyclic agents is not associated with spontaneous abortion but is associated with hypertensive disorders of pregnancy and may perhaps be associated with postpartum hemorrhage. In addition, exposure is not associated with preterm birth or abnormal motor and behavioral development. (See 'Tricyclic antidepressants' above.)

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