Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy

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Literature review current through: **Oct 2023.**
This topic last updated: **Feb 16, 2023.**

INTRODUCTION

Among women with an established pregnancy, surveys estimate that psychotropic drugs are taken by 21 to 33 percent [1,2]. Although these medications are often necessary to control a psychiatric illness that predates or emerges during pregnancy, pharmacotherapy entails risks of structural malformations, pregnancy complications, neonatal toxicity and withdrawal, and adverse developmental effects.

This topic reviews the risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy during pregnancy. The risks of antidepressants and antiepileptics during pregnancy and the principles of teratology are discussed separately. (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors" and "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Effects of ASMs on the fetus and child' and "Congenital anomalies: Approach to evaluation".)

DEFINITION OF A TERATOGEN

Teratogens are factors that can alter normal intrauterine development of fetal growth, anatomic structures, physical functioning, and postnatal development. This definition encompasses environmental exposures, maternal medical disorders, infectious agents, and genetic conditions.

Most discussions of teratogens usually center on drug exposures. In determining whether a drug is a teratogen, many authorities stipulate that the exposure causes a pattern of defects [3]. Thus, if exposure is associated with an increase in birth defects greater than that expected in the general population, but the defects vary and there is no discernible pattern, the drug is generally not considered teratogenic. An overview of teratology is discussed separately. (See "Congenital anomalies: Causes", section on 'Teratogens'.)

GENERAL PRINCIPLES

All psychotropic drugs presumably cross the placenta and are present in the amniotic fluid [4]. Embryonic and fetal exposure to maternal pharmacotherapy can cause [2,5-7]:

- Miscarriage
- Major and minor structural malformations
- Fetal growth restriction and low birth weight
- Preterm delivery
- Neonatal toxicity and withdrawal
- Postnatal developmental effects upon behavior, cognition, and emotional regulation

Medication effects upon the fetus vary according to gestational age [2,5,7]. As an example, the fetus is most vulnerable to major morphologic teratogenesis during organogenesis in the embryonic period of the first trimester, between the third and eighth week of gestation (weeks of gestation are counted from the first day of the last menstrual period) (figure 1 and figure 2). Organogenesis occurs 5 to 10 weeks from the first day of the last menstrual period, or 3 to 8 weeks from conception (conception occurs approximately two weeks after the first day of the last menstrual period). By contrast, neonatal toxicity and withdrawal are the result of third trimester exposure.

The estimated risk of major congenital malformations appears to vary among psychotropic medications; the rank order from greatest to least teratogenic risk is [8-13]:

- Valproate
- Carbamazepine
- Lithium

- Lamotrigine
- Antipsychotics
- Antidepressants

In discussing teratogenic effects, patients should be informed that the base rate for congenital defects in the general population is at least two to five percent [14-17]. The incidence of defects is two to three percent at birth but increases to five percent or higher after one year when hidden defects are discovered.

The estimated risks of congenital defects from pharmacotherapy are typically based upon birth registry and observational studies [6]. Although these studies probably provide the best evidence of the risks, the accuracy of these estimates is uncertain due to ascertainment bias. In addition, information about teratogenic effects is usually presented in terms of monotherapy, whereas many studies are confounded due to concomitant exposure to multiple psychotropic and nonpsychotropic medications [18], and acutely ill pregnant patients often require medication combinations [19-22]. Further, it is often not possible to separate the effects of drugs from the psychiatric illness itself, and studies often do not control for potential confounding factors, such as comorbid substance use disorder, maternal age, maternal body mass index, and prior miscarriages.

Although a drug may increase the risk of a congenital anomaly, the absolute risk may be low [23]. As an example, the estimated risk of Ebstein anomaly (abnormalities of the tricuspid valve and right ventricle) in the general population is 1 in 20,000 live births [24-26]. Following first-trimester exposure to lithium, the risk increases 20-fold to approximately 1 in 1000, which many authorities consider low [5,23,27].

Resources — Current information about the possible teratogenic effects of medications is available from several resources; these are discussed separately. (See "Congenital anomalies: Approach to evaluation".)

In addition, the possible teratogenic effects of drugs and suggestions for managing them can be found for all drugs included in the UpToDate drug database: search on the drug name, choose the drug information topic for that drug, and click on the “Pregnancy Implications” section of the topic outline. Clicking on the name of a drug cited within any UpToDate topic will also bring you to the drug information topic.

QUALITY OF EVIDENCE

The quality of evidence that informs us about the risks of psychotropic drugs 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'.)

ANTIPARKINSONIAN DRUGS USED FOR TREATING EXTRAPYRAMIDAL SYMPTOMS

Among the antiparkinsonian drugs that are used to treat extrapyramidal symptoms secondary to antipsychotics, reviews suggest that the risk of teratogenicity with antihistamines (eg, diphenhydramine) appears to be low [28], and that organ malformation appears to be less likely with diphenhydramine than amantadine, benztropine, and trihexyphenidyl [23,29]. As an example, a study used an administrative claims database to identify 270 infants exposed to diphenhydramine during the first trimester and found no association with congenital defects [30]. However, other studies have found that prenatal use of diphenhydramine was associated with congenital malformations [4], including a case-control study in which prenatal exposure to diphenhydramine was greater among children with oral clefts (n = 599) than controls (n = 500) [31].

ANTIDEPRESSANTS

Much of the evidence about the teratogenicity, pregnancy complications, and postnatal risks associated with antidepressants is based upon observational studies of pregnant patients with unipolar major depression.

- (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors".)
- (See "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors".)
- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)

ANTIEPILEPTICS

Most observational studies that have examined the association between antiepileptics and congenital malformations and postnatal risks have been conducted primarily in pregnant

patients with epilepsy. (See "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Effects of ASMs on the fetus and child'.)

ANTIPSYCHOTICS

First-generation antipsychotics have often been used and studied during pregnancy [2,32]. However, the risks of prenatal exposure to first-generation antipsychotics have been examined primarily in patients with hyperemesis gravidarum who received low doses of antipsychotics as antiemetics and were presumed to not have a psychiatric disorder, and secondarily in patients with psychotic disorders and mood disorders [23,32].

Second-generation antipsychotics are more widely used during pregnancy than first-generation drugs. A study of administrative claims data (n >580,000 pregnant women) found that antenatal exposure to second-generation antipsychotics (primarily quetiapine, olanzapine, or risperidone) occurred in 0.7 percent of the women, whereas first-generation antipsychotic (most commonly haloperidol, chlorpromazine, or perphenazine) exposure occurred in 0.1 percent [33].

Maternal weight gain — Postpartum maternal weight may be greater than prepregnancy weight due to the use of antipsychotics during pregnancy. A national birth registry of pregnancies (n >900,000) found that a body mass index ≥26 (overweight or obesity) following delivery was more probable in patients treated with antipsychotics than untreated women (odds ratio 2) [32].

Placental passage — Fetal exposure to antipsychotics may vary due to differences in placental permeability to these drugs. A prospective observational study of 50 pregnant patients examined the placental passage of antipsychotics, defined as the ratio of umbilical cord serum drug concentration to maternal serum drug concentration [21]. (Umbilical cord and maternal plasma concentrations were drawn at delivery; drugs cross the placenta more readily late in pregnancy.) The placental passage ratios were as follows:

- Olanzapine – 72 percent
- Haloperidol – 66
- Risperidone – 49
- Quetiapine – 24

The ratio for quetiapine was lower than that for olanzapine and haloperidol.

Teratogenicity — Most studies have generally found that prenatal exposure to first- and second-generation antipsychotics did not increase the risk of major physical malformations

above rates observed in the general population [3,32,34,35]. As an example, one study examined live births (n >1,300,000) that included infants with first trimester exposure to first- and second-generation antipsychotics (n >9000) [36]. After adjusting for potential confounding factors (eg, maternal age, indications for antipsychotics, and concomitant medications), the analyses found that rates of congenital and cardiovascular defects were comparable in the exposed and unexposed children, with the exception of risperidone, which was associated with a small increased risk in overall malformations (risk ratio 1.26, 95% CI 1.02-1.56).

Postnatal effects

Neonatal toxicity and withdrawal — Chronic administration of antipsychotics during the third trimester may cause symptoms of neonatal toxicity and withdrawal, including [1,5,23,34,37,38]:

- Abnormal movements (dyskinesia)
- Abnormally increased or decreased muscle tone
- Agitation
- Crying
- Hyperactivity
- Hyperreflexia
- Irritability
- Motor restlessness
- Sedation
- Tremor
- Hypotension
- Tachycardia
- Difficulty breathing
- Difficulty feeding
- Gastrointestinal dysfunction (eg, functional bowel obstruction)

Many of the symptoms of toxicity and withdrawal were described in a US Food and Drug Administration warning [38]. Although the incidence of these symptoms is not known, extrapyramidal symptoms (eg, abnormal movements, restlessness, and tremor) may be more likely to occur with first-generation antipsychotics and risperidone than with other second-generation antipsychotics [3]. Symptoms typically subside within hours to days, but may persist for weeks to months after birth [3]. Specific treatment is usually not necessary, but more severely affected newborns may require longer hospital stays [38].

Developmental effects — Intrauterine exposure to antipsychotics may adversely affect neuromotor functioning during infancy. A prospective observational study was conducted six months postpartum and controlled for maternal psychiatric status and other variables; neuromotor performance (eg, posture, muscle tone, and reflexes) was poorer in babies with prenatal antipsychotic exposure (n = 22) compared with babies with no prenatal psychotropic exposure (n = 85) [22]. However, assessment at six months may not predict long-term outcome. In addition, information processing and learning were comparable for the two groups.

However, prenatal exposure to antipsychotics does not appear to be associated with psychopathology in the offspring. A retrospective study of electronic medical records identified mother-child pairs (n >400,000), including children with gestational exposure to antipsychotics (n = 706) [39]. The analyses controlled for potential confounding factors observed at baseline, such as maternal age and general medical and psychiatric disorders, based upon the probability (propensity) of receiving treatment. The risk of attention-deficit hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) in the exposed and nonexposed children was comparable. In addition, an analysis of sibling pairs, one exposed in utero to antipsychotics and the other not, suggested that exposure to antipsychotics did not increase the risk of ADHD or ASD.

First-generation — The reproductive safety risks of first-generation antipsychotics are generally regarded as low, based upon a literature that extends back to the 1960s [2,4,21].

Perinatal mortality — Use of first-generation antipsychotics during pregnancy does not appear to increase perinatal mortality [40]. A prospective observational study found that the frequency of stillbirths and neonatal deaths were each similar in patients treated with typical antipsychotics (n >3000) and in untreated patients (n >38,000) [41]. Perinatal mortality is discussed separately. (See "Perinatal mortality".)

Teratogenicity — Most studies have not found an increased risk of birth defects following prenatal exposure to first-generation antipsychotics, including chlorpromazine, haloperidol, perphenazine, prochlorperazine, and trifluoperazine [1,3,4]. Although a 1996 meta-analysis of three prospective observational studies and one retrospective study (n >2500 live birth infants exposed to first-generation antipsychotics during pregnancy and n >71,000 unexposed infants) found a small increased risk of congenital malformations (odds ratio 1.2) [23], subsequent prospective studies have not [40]. As an example, a prospective observational study found that congenital malformations were comparable in newborns exposed in utero to haloperidol or penfluridol (n = 128) and in unexposed newborns (n = 581; 3 versus 4 percent) [37].

Preterm birth — Antenatal exposure to first-generation antipsychotics may be associated with spontaneous preterm birth. In a prospective observational study of pregnant women exposed

to either first-generation antipsychotics (n = 284) or nonteratogenic drugs (n = 1122), premature delivery occurred more often in the group with first-generation antipsychotic exposure (16 versus 9 percent) [40].

Birth weight — Although it is not clear if prenatal exposure to first-generation antipsychotics are associated with abnormal birth weight, larger studies have failed to find such an association. Two prospective observational studies found that birth weights were comparable for infants exposed to first-generation antipsychotics (n = 2860 and 229) and for unexposed infants (n = 35,353 and 1122) [40,41]. By contrast, two smaller prospective observational studies (n = 846 and 83) each found that birth weights were less (approximately 220 grams) in babies exposed to typical antipsychotics compared with unexposed babies [37,42].

Postnatal effects — Neonatal disorders may be associated with late term, in utero exposure to first-generation antipsychotics. A prospective observational study of pregnant women who received either first-generation antipsychotics (n = 284) or nonteratogenic drugs (n = 1122) found that disorders in the newborn occurred more often in the group with first-generation antipsychotic exposure (22 versus 4 percent of newborns) [40].

Reviews have concluded that prenatal exposure to first-generation antipsychotics does not appear to adversely affect behavioral, cognitive, or emotional development [2,43,44]. As an example, a prospective observational study of children exposed in utero to typical antipsychotics (n >2000) and children not exposed (n >26,000) found that intelligence quotient scores measured at four years of age were comparable [41].

Second-generation

Perinatal mortality and teratogenicity — Second-generation antipsychotics are usually not associated with fetal deaths (stillbirths) or teratogenic effects [1,3]:

- A prospective observational study compared outcomes in 151 pregnant patients treated during the first trimester with atypical antipsychotics (primarily olanzapine, risperidone, and quetiapine) and a comparison group of 151 unexposed pregnant women. The rate of spontaneous abortions, stillbirths, and major congenital malformations were each comparable for the two groups [19].

- A subsequent prospective observational study found that the rate of spontaneous abortions, stillbirths, and major congenital malformations were each comparable in 133 pregnant patients treated with atypical antipsychotics (usually throughout the entire pregnancy) and 133 unexposed pregnant women [45].

In addition, the reported rates of fetal death and congenital malformations for specific second-generation drugs generally do not exceed rates in the general population:

- **Aripiprazole** – A prospective observational study included 71 pregnant women who were exposed during the first trimester to aripiprazole (usually in conjunction with antidepressants, antiepileptics, other antipsychotics and/or benzodiazepines), and 161 pregnant women who were not exposed [46]. The incidence of major malformations was comparable for the exposed and unexposed groups (2.8 and 1.2 percent), as was the incidence of major plus minor malformations (8.5 and 4.3 percent).

  A second prospective observational study compared 163 infants exposed to aripiprazole in the first trimester with 690 infants of mothers with psychiatric diagnoses who did not use an atypical antipsychotic during pregnancy. After adjustment for potential confounding factors, the analyses found that the rate of major malformations in the two groups was comparable [47].

- **Clozapine** – The manufacturer has received 523 reports about use of clozapine during pregnancy; congenital anomalies occurred in 4 percent and there was no pattern of defects [3].

- **Olanzapine** – The manufacturer has received 610 prospective reports about use of olanzapine during pregnancy; the olanzapine exposure (mean dose 10 mg per day) was initially reported during pregnancy and the outcomes were prospectively ascertained following birth [48]. Stillbirth occurred in 5 cases (0.8 percent), including one in which a normal fetus died when the mother committed suicide at month eight of the pregnancy. In addition, congenital malformations occurred in 4 percent. The rate of stillbirth and congenital anomalies were consistent with general population rates.

- **Quetiapine** – The manufacturer has received 298 reports about prospective and retrospective use of quetiapine during pregnancy (most reports involved patients who took other medications); congenital anomalies occurred in 5 percent and there was no pattern of defects [3].

- **Risperidone** – The manufacturer has received 713 reports about use of risperidone during pregnancy. Among the 68 prospectively reported pregnancies with a known outcome, organ malformations occurred in 4 percent and spontaneous abortions in 17 percent [49]. However, one study found that risperidone was associated with a small increased risk in overall malformations. (See 'Teratogenicity' above.)

- **Ziprasidone** – The manufacturer has received 57 reports about use of ziprasidone during pregnancy; normal outcomes occurred in 50 cases, spontaneous abortions in 5, malformation in 1, and stillbirth in 1 [3].

Nevertheless, some studies have found an association between first trimester exposure and major malformations. In a prospective observational study of pregnant women exposed to either second-generation antipsychotics (n = 561, primarily women with psychotic disorders) or nonteratogenic drugs (n = 1122), major congenital malformations occurred more often in the group with second-generation antipsychotic exposure (5.2 versus 2.5 percent of babies) [40]. Specifically, cardiovascular defects (mostly atrial and ventricular septal defects) were more frequent with second-generation antipsychotic exposure than nonteratogenic drug exposure (odds ratio 3, 95% CI 1-8). In addition, elective termination of pregnancy occurred in more women taking second-generation antipsychotics. Spontaneous abortions and stillbirths were comparable for the two groups.

Birth weight — The association between exposure to second-generation antipsychotics during pregnancy and birth weight is not clear due to conflicting results across prospective observational studies. Two studies found that birth weight was comparable for babies who were exposed in utero to atypical antipsychotics and babies not exposed [40,45]. In other studies, prenatal exposure to second-generation antipsychotics was associated with large for gestational age births [42] and higher infant birth weights [50]. Yet other studies have found that prenatal exposure was associated with low birth weight [19,21].

Postnatal effects — Neonatal disorders may be associated with late term, in utero exposure to second-generation antipsychotics. A prospective observational study of pregnant women who received either second-generation antipsychotics (n = 561) or nonteratogenic drugs (n = 1122) found that disorders in the newborn occurred more often in the group with second-generation antipsychotic exposure (16 versus 4 percent of newborns) [40].

There is little information about the association between fetal exposure to second-generation antipsychotics and behavioral, cognitive, and emotional outcomes [3,44].

BENZODIAZEPINES

Benzodiazepines are often used during pregnancy to manage severe anxiety or agitation, and drugs with short half-lives (eg, lorazepam) are preferred. This approach is consistent with practice guidelines from the United Kingdom National Institute for Health and Care Excellence [51].

Teratogenicity — Due to conflicting results across studies, it is not known if exposure to either benzodiazepines or hypnotic benzodiazepine receptor agonists (eg, zaleplon, zolpidem, or zopiclone) during pregnancy is associated with an increased risk of congenital malformations. However, the best data, from a systematic review that included nine observational studies with more than one million subjects, suggest that benzodiazepines are not associated with an increased risk [51]. Meta-analyses from this systematic review and results from other observational studies not included in the review all indicate that benzodiazepines are not associated with birth defects [52-54]:

- The systematic review included the following meta-analyses of prospective observational studies [51]:
  - A meta-analysis of five studies (n >3000 exposed infants and >127,000 unexposed infants) found that the risk of major congenital malformations was nearly identical for the two groups.
  - A meta-analysis of five studies (n >6000 exposed infants and >1,000,000 unexposed infants) found that the risk of cardiac malformations was similar for the two groups (however, heterogeneity across studies was large).
  - A meta-analysis of two studies (n >3000 exposed infants and >893,000 unexposed infants) found that benzodiazepines were not associated with an increased risk of orofacial cleft.
- A birth registry study found that the incidence of congenital malformations was comparable for infants exposed in utero to hypnotic benzodiazepine receptor agonists (n >1000) and control infants (n >1,000,000; 4 and 5 percent) [55].
- A meta-analysis of seven cohort studies (n >1000 infants exposed during pregnancy to benzodiazepines and >70,000 infants not exposed) found that there was no relationship between fetal exposure to benzodiazepines and major malformations [18].

Nevertheless, some retrospective studies suggest that benzodiazepines or hypnotic benzodiazepine receptor agonists may be associated with congenital malformations [23,56]:

- A meta-analysis of four case-control studies (166 infants with fetal exposure to benzodiazepines and 5970 control infants not exposed) found that major malformations were associated with the use of benzodiazepines during pregnancy (odds ratio 3; 95% CI 1-7); however, heterogeneity across studies was significant [18].

- A meta-analysis of six case-control studies (285 infants with fetal exposure to benzodiazepines and 14,686 control infants not exposed) found that exposure was associated with an elevated risk of oral cleft (odds ratio 2; 95% CI 1-3); however, heterogeneity across studies was significant [18].

- A birth registry study found that congenital malformations were marginally increased in newborns exposed during pregnancy to benzodiazepines or hypnotic benzodiazepine receptor agonists (n >1900), compared with all newborns (n >873,000; odds ratio 1.2; 95% CI 1.0-1.6) [57]. In particular, the risk of pylorostenosis was nearly three times greater than expected and alimentary tract atresia nearly four times greater.

To the extent that benzodiazepines are associated with teratogenic effects, many authorities consider the absolute increase small [5,18,23]. As an example, retrospective case-control studies suggest that fetal exposure to benzodiazepines may increase the risk of oral cleft from the general population base rate of 6 in 10,000 births to 11 in 10,000 births [5]. It is also worth noting that case-control studies may be subject to recall bias [52]. In addition, compared with pregnant patients who do not use benzodiazepines or hypnotic benzodiazepine receptor agonists, patients using these drugs may be older and more likely to smoke and use other drugs (eg, antiepileptics, which are regarded as teratogens) [58]. (See "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Effects of ASMs on the fetus and child'.)

Spontaneous abortion — Benzodiazepines appear to be associated with spontaneous abortion (miscarriage). A meta-analysis of three prospective observational studies included approximately 600 pregnant women treated with benzodiazepines during the first trimester and approximately 600 unexposed pregnancies, and found that benzodiazepines were associated with an increased risk of spontaneous abortion (odds ratio 2, 95% CI 1-3) [51].

Preterm birth — Antenatal benzodiazepines may be associated with preterm birth (eg, <37 weeks gestational age). A national registry study identified pregnant women with preterm deliveries (n >42,000), including women treated with benzodiazepines or hypnotic benzodiazepine receptor agonists early in the pregnancy (typically first trimester; n = 161), and women treated later in the pregnancy (n = 50) [57]. Preterm birth occurred more often with early exposure compared with no exposure (odds ratio 1.5, 95% CI 1.3-1.8); preterm delivery was also associated with later exposure (odds ratio 2.6, 95% CI 1.9-3.4).

Birth weight — Based upon prospective observational studies, benzodiazepines do not appear to be associated with low birth weight (eg, <2500 g). A meta-analysis of three prospective observational studies included pregnant women treated with benzodiazepines (n = 478) and

pregnant women not treated with benzodiazepines (n = 559), and found that risk of low birth weight was nearly identical in the two groups [51].

However, one retrospective study found that use of benzodiazepines during pregnancy was associated with low birth weight. A national registry study identified low birth weight infants (n >27,000), including infants exposed to benzodiazepines or hypnotic benzodiazepine receptor agonists early in the pregnancy (typically first trimester; n = 103), and infants exposed later in the pregnancy (n = 28) [57]. Low birth weight occurred more often with early exposure compared with no exposure (odds ratio 1.3, 95% CI 1.1-1.6); low birth weight was also associated with later exposure (odds ratio 1.9, 95% CI 1.3-2.8).

Postnatal effects — Chronic administration of benzodiazepines proximal to delivery can cause neonatal toxicity and withdrawal, including [2,5,52,57]:

- Low Apgar scores
- Apnea
- Hypothermia
- Hyperreflexia
- Hypertonia or hypotonia
- Irritability
- Lethargy
- Restlessness
- Tremor
- Diarrhea
- Poor feeding
- Vomiting

This toxicity and withdrawal is widely reported [4], and may occur more often in preterm infants than term infants [59]. Symptoms may persist for up to three months [4].

It is not clear if using benzodiazepines during pregnancy adversely affects neurobehavioral development, due to conflicting results among studies [2,44]. However, in the largest prospective study, motor and cognitive functioning were comparable at age three years for children exposed in utero to benzodiazepines (n = 1870) and unexposed children (n = 48,412) [60].

LITHIUM

Placental passage — Lithium appears to completely equilibrate across the placenta. An observational study of 27 infant-mother pairs found that the ratio of lithium serum concentrations in umbilical cord blood to maternal blood was 1.1, across a wide range of maternal concentrations [61].

Serum concentrations — Lithium levels may drop as pregnancy progresses, and doses may need to be increased. (See "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section on 'Refractory patients'.)

Perinatal mortality — It is not clear if prenatal exposure to lithium increases perinatal mortality, due to conflicting results across prospective observational studies:

- One study found that the frequency of miscarriages and stillbirths were each similar in patients treated with lithium (n = 138) and controls (n = 148) [62].
- However, a second study found that miscarriages occurred in more patients exposed to lithium during the first trimester (n = 183) than women exposed to nonteratogenic substances (n = 748; 16 versus 6 percent) [63].

General information about perinatal mortality is discussed separately. (See "Perinatal mortality".)

Teratogenicity — Observational studies have found that fetal lithium exposure is associated with teratogenic effects. In a meta-analysis of four prospective and retrospective studies that compared exposed infants (n = 365) and unexposed infants (n >974,000), the risk of congenital malformations was twice as great in exposed infants (odds ratio 2, 95% CI 1-4) [51]. In addition, a subsequent prospective observational study of patients who received lithium during the first trimester (n = 123) found that anomalies occurred in 6.5 percent of infants [63]. By comparison, the rate in pregnant bipolar patients not exposed to lithium (n = 61) was 3.3 percent, and in pregnant women exposed to nonteratogenic substances (n = 711) was 2.7 percent. However, the increased absolute risk of congenital abnormalities (7 per 1000) is considered small [51].

Cardiac — Antenatal lithium exposure is generally thought to be associated with teratogenic effects that primarily involve the heart [2,5]. Cardiac malformations that have been observed include Ebstein anomaly (abnormalities of the tricuspid valve and right ventricle), right ventricular outflow tract obstruction defects, coarctation of the aorta, and mitral atresia [5,64-66]:

- A prospective observational study found that cardiovascular anomalies were more common among infants exposed to lithium during the first trimester (n = 123) than infants

exposed to nonteratogenic substances (n = 711; 4.1 versus 0.6 percent) [63].

- A retrospective study of an administrative claims database examined cardiac defects in infants with first trimester exposure to either lithium (n = 663) or lamotrigine (n = 1945). After adjusting for the probability (propensity) to receive lithium or lamotrigine, based upon potential confounding factors such as maternal age, general medical and psychiatric diagnoses, and use of concomitant medications, the analyses found that cardiac defects occurred in more infants exposed to lithium than lamotrigine (2.4 versus 1.4 percent) [67]. In addition, infants exposed to lithium were compared with infants who were not exposed to either lithium or lamotrigine (n >1,000,000); right ventricular outflow tract obstruction defects were more common in lithium exposed infants than controls (0.6 versus 0.2 percent).

  Other analyses suggested that the association between lithium exposure and cardiac defects may perhaps be dose-dependent. Among infants who were exposed to a maternal daily dose of 600 mg or less, the risk of cardiac malformations was 1.1 (95% CI 0.5-2.6), whereas the risk with a dose of more than 900 mg was 3.2 (95% CI 1.5-7.0).

However, other studies suggest that lithium is not associated with an increased risk of cardiac malformations, including a meta-analysis of two retrospective studies that found the risk in exposed (n = 120) and unexposed (n >973,000) infants was comparable [51].

Ebstein anomaly may be the most common fetal cardiac defect associated with prenatal lithium exposure. The estimated risk of the anomaly in the general population is 1 in 20,000 live births [24-26]; following first-trimester exposure to lithium, the risk appears to increase 20-fold to approximately 1 in 1000 [68], an absolute risk that many authorities consider low [2,5,23,27,69]. However, the evidence that lithium causes the anomaly is uncertain [35]. As an example, a meta-analysis of six observational studies (n = 264) found that antenatal exposure to lithium did not differ statistically between cases of Ebstein anomaly and controls without the defect [70]. While the odds ratio estimate was not statistically significant, the upper confidence level was consistent with an increased risk of the malformation, suggesting that there is uncertainty about the risk of harm. In addition, a retrospective study of an administrative claims database, which identified infants with first trimester exposure to lithium (n = 663), found that none of the infants were diagnosed with Ebstein anomaly [67].

Ebstein anomaly is discussed separately. (See "Ebstein anomaly: Clinical manifestations and diagnosis".)

Preterm birth — Use of lithium during pregnancy may be associated with preterm delivery. A prospective observational study found that preterm birth occurred in more patients treated

with lithium during the first trimester (n = 131) than patients treated with nonteratogenic substances (n = 683; 14 versus 6 percent) [63]. An overview of preterm delivery is discussed separately. (See "Preterm labor: Clinical findings, diagnostic evaluation, and initial treatment".)

Birth weight — Birth weight may be increased in babies exposed in utero to lithium, but the increase does not appear to be clinically significant. A prospective observational study found that birth weight was greater in lithium exposed babies (n = 138) than unexposed babies (n = 148; 3475 versus 3383 grams) [62]. Maternal lithium dose was not correlated with birth weight.

Postnatal effects — Use of lithium during the second and third trimester can result in neonatal complications, including [4,6,7,34,71-73]:

- Cardiomegaly
- Gastrointestinal bleeding
- Goiter and hypothyroidism
- Hepatomegaly
- Arginine vasopressin resistance (previously called nephrogenic diabetes insipidus)
- Polyhydramnios
- Premature labor
- Shock

Lithium toxicity can also occur in newborns with late pregnancy exposure; symptoms include [4,6,7,34,71-73]:

- Low Apgar scores
- Apnea, shallow respirations, and cyanosis
- Bradycardia or tachycardia
- Cardiac arrhythmias and abnormal electrocardiogram
- Feeding difficulties
- Lethargy or coma
- Muscle flaccidity and hypotonia
- Poor suck, grasp, and Moro reflexes
- Seizures
- Twitching

Neonatal lithium toxicity and complications are more common in newborns with higher serum lithium concentrations. In a study of 24 infants exposed in utero to lithium, lower Apgar scores, higher rates of central nervous system and neuromuscular complications, and longer hospital stays were observed in infants born with umbilical cord serum lithium concentrations >0.6

mEq/L (0.6 mmol/L), compared with infants with lower concentrations [61]. Lithium toxicity generally resolves in one to two weeks.

Available studies suggest that prenatal lithium exposure does not adversely affect developmental outcomes:

- A prospective study found that major developmental milestones (eg, smiling, lifting head, sitting, crawling, standing, talking, and walking) were achieved at comparable ages for lithium-exposed children (n = 22) and unexposed controls (n = 148) [62].
- A retrospective study found that behavioral measures of development were comparable for children exposed to lithium prenatally (n = 60) compared with their unexposed siblings (n = 57) [74].
- Another retrospective study found that intelligence quotient was comparable in children exposed to lithium prenatally (n = 20), compared with unexposed children (n = 19) [75].

ELECTROCONVULSIVE THERAPY

Neither the number nor pattern of congenital malformations in children exposed in utero to electroconvulsive therapy (ECT) implicates it as a causal factor in organ dysgenesis [5,76]. A review of 300 case reports of ECT during pregnancy found five reports of congenital anomalies, including hypertelorism, talipes equinovarus (clubfoot), optic atrophy, anencephaly, and pulmonary cysts [77]. The review concluded that these malformations were not the result of ECT, and that there was no evidence of postnatal developmental effects. In addition, there is little or no evidence that fetal exposure to ECT adversely affects intrauterine growth, or causes neonatal toxicity or adverse developmental effects [5]. The most common adverse effects of ECT in the mother are premature contractions and labor, and in the fetus bradyarrhythmias [78].

The risk of teratogenic effects and neonatal toxicity posed by ECT anesthetic drugs appears to be low [71,77-79]:

- **Glycopyrrolate** – The anticholinergic glycopyrrolate does not readily cross the placenta, and there do not appear to be any reports of teratogenesis with the injected solution.
- **Methohexital or propofol** – Although the general anesthetics methohexital and propofol cross the placenta, there do not appear to be any reports of teratogenesis with either drug.

- **Succinylcholine** – The muscle relaxant succinylcholine generally does not appear to significantly affect the fetus; typically, only a small amount at most crosses the placenta.

In addition, it is unlikely that these drugs cause congenital malformations and toxicity because of the infrequent and brief exposure that occurs during a course of ECT.

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: Bipolar disorder".)

SUMMARY

- **Definition of a teratogen** – Teratogens are factors that can alter normal intrauterine development of fetal growth, anatomic structures, physical functioning, and postnatal development. This definition encompasses environmental exposures (eg, drugs), maternal medical disorders, infectious agents, and genetic conditions. (See 'Definition of a teratogen' above and "Congenital anomalies: Causes", section on 'Teratogens'.)

- **Psychotropic drugs and teratogenicity** – The estimated risk of major congenital malformations appears to vary among psychotropic medications; the rank order from greatest to least teratogenic risk is (see 'General principles' above):

  - Valproate
  - Carbamazepine
  - Lithium
  - Lamotrigine
  - Antipsychotics
  - Antidepressants

- **Quality of evidence** – Much of the evidence about the teratogenicity, pregnancy complications, and postnatal risks associated with antidepressants is based upon observational studies of pregnant patients with unipolar major depression.

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

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

- **Antiparkinsonian drugs** – Among the antiparkinsonian drugs that are used to treat extrapyramidal symptoms secondary to antipsychotics, reviews suggest that organ malformation appears to be less likely with diphenhydramine than amantadine, benztropine, or trihexyphenidyl. (See 'Antiparkinsonian drugs used for treating extrapyramidal symptoms' above.)

- **Antiepileptics** – Most observational studies that have examined the association between antiepileptics and congenital malformations and postnatal risks have been conducted primarily in pregnant patients with epilepsy. (See "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Effects of ASMs on the fetus and child'.)

- **Antipsychotics** – Most studies have found that exposure during pregnancy to first- and second-generation antipsychotics does not appear to increase the risk of major physical malformations above rates observed in the general population. However, chronic administration of antipsychotics during the third trimester may cause symptoms of neonatal toxicity and withdrawal. (See 'Antipsychotics' above.)

- **Benzodiazepines** – The best evidence suggests that exposure to benzodiazepines or to hypnotic, benzodiazepine receptor agonists during pregnancy is not associated with an increased risk of congenital malformations. Benzodiazepines also do not appear to be associated with low birth weight. However, antenatal exposure to benzodiazepines appears to be associated with spontaneous abortion and preterm birth. Chronic administration of benzodiazepines proximal to delivery can cause neonatal toxicity and withdrawal. (See 'Benzodiazepines' above.)

- **Lithium** – Although observational studies have found that fetal lithium exposure is associated with teratogenic effects, the increased absolute risk of congenital abnormalities (7 per 1000) is considered small. The associated teratogenic effects may involve the heart (eg, Ebstein anomaly of the tricuspid valve), but the results from different studies are conflicting as to whether antenatal lithium exposure is associated with cardiac defects. Second and third trimester lithium exposure can lead to neonatal complications and lithium toxicity. (See 'Lithium' above.)

- **Electroconvulsive therapy** – Neither the number nor pattern of congenital malformations in children exposed in utero to electroconvulsive therapy (ECT) implicates it as a causal

factor in organ dysgenesis. The risk of neonatal toxicity and adverse developmental effects posed by ECT also appears to be low. (See 'Electroconvulsive therapy' above.)

Topic 17159 Version 24.0