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# Use of Psychiatric Medications During Pregnancy and Lactation

*It is estimated that more than 500,000 pregnancies in the United States each year involve women who have psychiatric illnesses that either predate or emerge during pregnancy, and an estimated one third of all pregnant women are exposed to a psychotropic medication at some point during pregnancy (1). The use of psychotropic medications is a cause of concern for physicians and their patients because of the potential teratogenic risk, the risk of perinatal syndromes or neonatal toxicity, and the risk for abnormal postnatal behavioral development. With the limited information available on the risks of the psychotropic medications, clinical management must incorporate an appraisal of the clinical consequences of offspring exposure, the potential effect of untreated maternal psychiatric illness, and the available alternative therapies. The purpose of this document is to present current evidence on the risks and benefits of treatment for certain psychiatric illnesses during pregnancy.*

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Obstetrics with the assistance of Zachary N. Stowe, MD and Kimberly Ragan, MSW. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

## Background

Advising a pregnant or breastfeeding woman to discontinue medication exchanges the fetal or neonatal risks of medication exposure for the risks of untreated maternal illness. Maternal psychiatric illness, if inadequately treated or untreated, may result in poor compliance with prenatal care, inadequate nutrition, exposure to additional medication or herbal remedies, increased alcohol and tobacco use, deficits in mother–infant bonding, and disruptions within the family environment (see Table 1). All psychotropic medications studied to date cross the placenta (1), are present in amniotic fluid (2), and can enter human breast milk (3). For known teratogens, knowledge of gestational age is

helpful in the decision about drug therapy because the major risk of teratogenesis is during embryogenesis (ie, during the third through the eighth week of gestation). The U.S. Food and Drug Administration (FDA) has provided a system for categorizing individual medications (see Table 2), although this system has considerable limitations. Categories of risk for neonates from drugs used while breastfeeding also are shown in Table 2. Electronic resources for information related to the fetal and neonatal effects of psychotropic drug therapy in pregnancy and with breastfeeding include Reprotox (www.reprotox.org) and TERIS (http://depts.washington.edu/terisweb). Providing women with patient resources for online information that are well referenced is a reasonable option.

**Table 1. Impact of Psychiatric Illness on Pregnancy Outcome**

| Illness | Teratogenic Effects | Impact on Outcome | | Treatment Options |
|---|---|---|---|---|
| | | Obstetric | Neonatal | |
| Anxiety disorders | N/A | Increased incidence of forceps deliveries, prolonged labor, precipitate labor, fetal distress, preterm delivery, and spontaneous abortion | Decreased developmental scores and inadaptability; slowed mental development at 2 years of age | Benzodiazepines<br>Antidepressants<br>Psychotherapy |
| Major depression | N/A | Increased incidence of low birth weight, decreased fetal growth, and postnatal complications | Increased newborn cortisol and catecholamine levels, infant crying, rates of admission to neonatal intensive care units | Antidepressants<br>Psychotherapy<br>ECT |
| Bipolar disorder | N/A | See major depression | See major depression | Lithium<br>Anticonvulsants<br>Antipsychotics<br>ECT |
| Schizophrenia | Congenital malformations, especially of cardiovascular system | Increased incidence of preterm delivery, low birth weight, small for gestational age, placental abnormalities, and antenatal hemorrhage | Increased rates of postnatal death | Antipsychotics |

Abbreviations: ECT, electroconvulsive therapy; N/A, not available (eg, no studies identified)

**Table 2. Psychiatric Medications in Pregnancy and Lactation***

| Generic Name | Trade Name | Pregnancy Risk Category† | American Academy of Pediatrics Rating‡ | Lactation Risk Category§ |
|---|---|---|---|---|
| **Anxiolytic Medications** | | | | |
| *Benzodiazepines* | | | | |
| Alprazolam | Xanax | $D_m$ | Unknown, of concern | L3 |
| Chlordiazepoxide | Librium | D | N/A | L3 |
| Clonazepam | Klonopin | $D_m$ | N/A | L3 |
| Clorazepate | Tranxene | D | N/A | L3 |
| Diazepam | Valium | D | Unknown, of concern | L3, L4 if used chronically |
| Lorazepam | Ativan | $D_m$ | Unknown, of concern | L3 |
| Oxazepam | Serax | D | N/A | L3 |
| *Benzodiazepines for Insomnia* | | | | |
| Estazolam | ProSom | $X_m$ | N/A | L3 |
| Flurazepam | Dalmane | $X_m$ | N/A | L3 |
| Quazepam | Doral | $X_m$ | Unknown, of concern | L2 |

*(continued)*

**Table 2.** Psychiatric Medications in Pregnancy and Lactation* *(continued)*

| Generic Name | Trade Name | Pregnancy Risk Category† | American Academy of Pediatrics Rating‡ | Lactation Risk Category§ |
|---|---|---|---|---|
| **Anxiolytic Medications *(continued)*** | | | | |
| *Benzodiazepines for Insomnia* (continued) | | | | |
| Temazepam | Restoril | $X_m$ | Unknown, of concern | L3 |
| Triazolam | Halcion | $X_m$ | N/A | L3 |
| *Nonbenzodiazepine Anxiolytics and Hypnotics* | | | | |
| Buspirone | BuSpar | $B_m$ | N/A | L3 |
| Chloral hydrate | Noctec | $C_m$ | Compatible | L3 |
| Eszoplicone | Lunesta | $C_m$ | N/A | N/A |
| Zaleplon | Sonata | $C_m$ | Unknown, of concern | L2 |
| Zolpidem | Ambien | $B_m$ | N/A | L3 |
| **Antiepileptic and Mood Stabilizing Medications** | | | | |
| Lithium carbonate | Eskalith, Lithobid, Lithonate | D | Contraindicated | L4 |
| Valproic acid | Depakote (divalproex sodium) | $D_m$ | Compatible | L2 |
| Carbamazepine | Tegretol | $D_m$ | Compatible | L2 |
| Lamotrigine | Lamictal | $C_m$ | Unknown | L3 |
| **Antidepressants** | | | | |
| *Tricyclic and Heterocyclic Antidepressants* | | | | |
| Amitriptyline | Elavil, Endep | $C_m$ | Unknown, of concern | L2 |
| Amoxapine | Asendin | $C_m$ | Unknown, of concern | L2 |
| Clomipramine | Anafranil | $C_m$ | Unknown, of concern‖ | L2 |
| Desipramine | Norpramin | C | Unknown, of concern | L2 |
| Doxepin | Sinequan, Adapin | C | Unknown, of concern | L5 |
| Imipramine | Tofranil | C | Unknown, of concern | L2 |
| Maprotiline | Ludiomil | $B_m$ | N/A | L3 |
| Nortriptyline | Pamelor, Aventyl | C | Unknown, of concern‖ | L2 |
| Protriptyline | Vivactil | C | N/A | N/A |
| *Selective Serotonin Reuptake Inhibitors* | | | | |
| Citalopram | Celexa | $C_m$ | N/A | L3 |
| Escitalopram | Lexapro | $C_m$ | N/A | L3 in older infants |
| Fluoxetine | Prozac | $C_m$ | Unknown, of concern | L2 in older infants, L3 if used in neonatal period |
| Fluvoxamine | Luvox | $C_m$ | Unknown, of concern | L2 |
| Paroxetine | Paxil | $D_m$ | Unknown, of concern | L2 |
| Sertraline | Zoloft | $C_m$ | Unknown, of concern | L2 |
| *Other Antidepressants* | | | | |
| Bupropion | Wellbutrin | $B_m$ | Unknown, of concern | L3 |
| Duloxetine | Cymbalta | $C_m$ | N/A | N/A |
| Mirtazapine | Remeron | $C_m$ | N/A | L3 |
| Nefazodone | Serzone | $C_m$ | N/A | L4 |

*(continued)*

**Table 2.** Psychiatric Medications in Pregnancy and Lactation* *(continued)*

| Generic Name | Trade Name | Pregnancy Risk Category† | American Academy of Pediatrics Rating‡ | Lactation Risk Category§ |
|---|---|---|---|---|
| | | **Antidepressants *(continued)*** | | |
| *Other Antidepressants* (continued) | | | | |
| Trazodone | Desyrel | $C_m$ | Unknown, of concern | L2 |
| Venlafaxine | Effexor | $C_m$ | N/A | L3 |
| | | **Antipsychotic Medications** | | |
| *Typical Antipsychotics* | | | | |
| Chlorpromazine | Thorazine | C | Unknown, of concern | L3 |
| Fluphenazine | Prolixin | C | N/A | L3 |
| Haloperidol | Haldol | $C_m$ | Unknown, of concern | L2 |
| Loxapine | Loxitane | C | N/A | L4 |
| Perphenazine | Trilafon | C | Unknown, of concern | N/A |
| Pimozide | Orap | $C_m$ | N/A | L4 |
| Thioridazine | Mellaril | C | N/A | L4 |
| Thiothixene | Navane | C | N/A | L4 |
| Trifluoperazine | Stelazine | C | Unknown, of concern | N/A |
| *Atypical Antipsychotics* | | | | |
| Aripiprazole | Abilify | $C_m$ | N/A | L3 |
| Clozapine | Clozaril | $B_m$ | Unknown, of concern | L3 |
| Olanzapine | Zyprexa | $C_m$ | N/A | L2 |
| Quetiapine | Seroquel | $C_m$ | Unknown, of concern | L4 |
| Risperidone | Risperdal | $C_m$ | N/A | L3 |
| Ziprasidone¶ | Geodon | C | Unknown, of concern | L4 |

Abbreviation: N/A, not available

*The average half-life of elimination is listed for major metabolites.

†The U.S. Food and Drug Administration classifies drug safety using the following categories: A, controlled studies show no risk; B, no evidence of risk in humans; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy. Risk category adapted from Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 7th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2005. The "m" subscript is for data taken from the manufacturer's package insert.

‡American Academy of Pediatrics 2001

§Lactation risk categories are listed as follows: L1, safest; L2, safer; L3, moderately safe; L4, possibly hazardous; L5, contraindicated. For more information, see Hale TW. Medications in Mother's Milk. Amaraillo (TX): Pharmasoft Publishing, 2004.

‖Original committee report 1994 listed as "compatible," and a correction was later published.

¶Not listed in Briggs. Risk category taken from Physicians' Desk Reference 1992, 1993, 1994, 1996, and 2004.

## General Treatment Concepts

Optimally, shared decision making among obstetric and mental health clinicians and the patient should occur before pregnancy. Whenever possible, multidisciplinary management involving the obstetrician, mental health clinician, primary health care provider, and pediatrician is recommended to facilitate care.

A single medication at a higher dose is favored over multiple medications for treatment of psychiatric illness during pregnancy. Changing medications increases the exposure to the offspring. The selection of medication to minimize the risk of illness should be based on history of efficacy, prior exposure during pregnancy, and available reproductive safety information (see Table 3). Medications with fewer metabolites, higher protein binding (decreases placental passage), and fewer interactions with other medications are preferred.

## Major Depression

Prevalence rates for depression are estimated at 17% for adults in the United States (4); women twice as often as men experience depression (5). The highest rates for

**Table 3.** Management Issues Associated With Medication Use During Pregnancy and Lactation

| Medication Class | Management Issues | | | | | Treatment Options |
|---|---|---|---|---|---|---|
| | Birth Defects | Pregnancy | Delivery | Neonatal | Lactation | |
| Benzodiazepines | Possible increased incidence of cleft lip or palate | Ultrasonography for facial morphology | Floppy infant syndrome | Withdrawal syndrome | Infant sedation reported | Clonazepam<br>Lorazepam<br>Alprazolam |
| Selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and tricyclic antidepressants | None confirmed | Decreased serum concentrations across pregnancy | None | Neonatal, withdrawal syndrome | None | Fluoxetine<br>Sertraline<br>Paroxetine<br>Citalopram<br>Nortriptyline |
| Lithium | Increased incidence of heart defects | Ultrasonography or fetal echocardiography for heart development or both<br>Decreased serum concentrations across pregnancy | Intravenous fluids<br>Increased risk for lithium toxicity in mother | Increased risk for lithium toxicity in infant | Monitor infant complete blood count, thyroid-stimulating hormone levels, and lithium levels | Sustained release lithium |
| Antiepileptic Drugs | Increased incidence of birth defects | Decreased serum concentrations across pregnancy<br>Folate supplementation, Vitamin K for some antiepileptic drugs | None | Neonatal symptoms, Vitamin K for some antiepileptic drugs | Monitor infant complete blood count, liver enzyme levels, antiepileptic drug levels | Lamotrigine<br>Carbemazepine |
| Antipsychotic Medications | None Confirmed | Avoid anticholinergic medications for side effects | None | Possible risk for neuroleptic malignant syndrome and intestinal obstruction | None | Haloperidol |

depression occur in women between the ages of 25 years and 44 years (6). Symptoms include depressed or irritable mood, anhedonia, weight loss or gain, appetite and sleep changes, loss of energy, feelings of excessive guilt or worthlessness, psychomotor agitation or retardation and, in more severe cases, suicidal ideation (7). Approximately 10–16% of pregnant women fulfill diagnostic criteria for depression, and up to 70% of pregnant women report symptoms of depression (6, 8–10). Many symptoms of depression overlap with the symptoms of pregnancy and often are overlooked (6, 11). Of women taking antidepressants at conception, more than 60% experienced symptoms of depression during the pregnancy (12). In a study of pregnant women taking antidepressants before conception, a 68% relapse of depression was documented in those who discontinued medications during pregnancy (13) compared with only a 25% relapse in those who continued antidepressant medications.

Postpartum depression is classified as a major episode of depression that occurs within the first 4 weeks postpartum (7) or within the first 6 weeks postpartum (14). Many women in whom postpartum depression was diagnosed reported having symptoms of depression during pregnancy (9, 15–17). These symptoms may be difficult to differentiate from normal postpartum adaptation. Survey tools (eg, Edinburgh Postnatal Depression Scale, Beck Depression Inventory, and the Postpartum Depression Screening Scale), are widely used to identify depression during the perinatal period (18). The detection rate is in the range of 68–100% (better for severe depression) with specificities in the range of 78–96% (19).

Untreated maternal depression is associated with an increase in adverse pregnancy outcomes, including premature birth, low birthweight infants, fetal growth restriction, and postnatal complications. This association is stronger when depression occurs in the late second to early third trimester (20). Newborns of women with untreated depression during pregnancy cry more and are more difficult to console (20–22). Maternal depression also is associated with increased life stress, decreased social support, poor maternal weight gain, smoking, and alcohol and drug use (23), all of which can adversely

affect infant outcome (24–26). Later in life, children of untreated depressed mothers are more prone to suicidal behavior, conduct problems, and emotional instability and more often require psychiatric care (27, 28).

### Bipolar Disorder

Bipolar disorder, historically called manic–depressive disorder, affects between 3.9% and 6.4% of Americans and affects men and women equally (4, 29–31). It commonly is characterized by distinct periods of abnormally and persistently elevated, expansive, or irritable mood and separate distinct periods of depressed mood or anhedonia (7). Women are more likely than men to experience depressive episodes of bipolar disorder (32), rapid cycling (33), and mixed episodes (34, 35). Typical onset of bipolar disorder for women is in the teens or early twenties.

Rates of postpartum relapse range from 32% (36) to 67% (37). In one study, it was reported that pregnancy had a protective effect for women with bipolar disorder (38), but the participants may have had milder illness. Perinatal episodes of bipolar disorder tend to be depressive (37, 39) and, when experienced with one pregnancy, are more likely to recur with subsequent pregnancies (37). There also is an increased risk of postpartum psychosis as high as 46% (40, 41).

### Anxiety Disorders

Anxiety disorders include panic disorder, obsessive–compulsive disorder (OCD), generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), social anxiety disorder, and specific phobias. Collectively, anxiety disorders are the most commonly occurring psychiatric disorders, with a prevalence of 18.1% among adults 18 years and older in the United States (42). Panic disorder, GAD, PTSD, agoraphobia, and specific phobias are two times more likely to be diagnosed in women than men. Anxiety and stress during pregnancy are documented as factors associated with poor obstetric outcomes, including spontaneous abortions (43), preterm delivery (44, 45), and delivery complications (46), such as prolonged labor, precipitate labor, clinical fetal distress, and forceps deliveries (47). A direct causal relationship has not been established.

Panic disorder is characterized by recurrent panic attacks that arise spontaneously in situations that are not expected to cause anxiety. Most investigators agree that women are at greatest risk for exacerbation of panic disorder during the postpartum period (48, 49). In a recent study PTSD was reported to be the third most common psychiatric diagnosis among economically disadvantaged pregnant women, with a prevalence of 7.7% (50). Women with PTSD were significantly more likely to have a comorbid condition, principally major depression or GAD. Many reports have documented traumatic obstetric experiences (eg, emergency delivery, miscarriage, and fetal demise) as precipitants to PTSD-related symptomatology. The incidence of OCD during pregnancy is unknown. Despite limited formal investigation, most clinicians and researchers agree that pregnancy seems to be a potential trigger of OCD symptom onset, with 39% of the women in a specialized OCD clinic experiencing symptom onset during pregnancy (51). It generally is accepted that OCD worsens during the postpartum period.

### Schizophrenia-Spectrum Disorders

Schizophrenia is a severe and persistent mental illness characterized by psychotic symptoms, negative symptoms, such as flat affect and lack of volition, and significant occupational and social dysfunction (7). Schizophrenia occurs in approximately 1–2% of women, with the most common age of onset during the childbearing years (52).

A variety of adverse pregnancy outcomes in women with schizophrenia have been reported, including preterm delivery, low birth weight infants, small for gestational age fetuses (53, 54), placental abnormalities and antenatal hemorrhage, increased rates of congenital malformations, especially of the cardiovascular system (55), and a higher incidence of postnatal death (53). However, in one study it was found that schizophrenic women were not at higher risk for specific obstetric complications but were at greater risk of requiring interventions during delivery, including labor induction and assisted or cesarean delivery (56). If left untreated during pregnancy, schizophrenia-spectrum disorders can have devastating effects on both mother and child, with rare reports of maternal self-mutilation (57, 58), denial of pregnancy resulting in refusal of prenatal care (59), and infanticide (60, 61).

## Clinical Considerations and Recommendations

▶ ***What is the evidence regarding the safety and efficacy of treatment for depression during pregnancy?***

Most data related to antidepressants in pregnancy are derived from the use of selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline, citalopram, and paroxetine). Overall, there is limited evidence of teratogenic effects from the use of antidepressants in pregnancy or adverse effects from exposure during breastfeeding (62–64). There are two reports from GlaxoSmithKline

based on a Swedish national registry and a U.S. insurance claims database that have raised concerns about a 1.5–2-fold increased risk of congenital cardiac malformations (atrial and ventricular septal defects) associated with first-trimester paroxetine exposure (www.gskus.com/news/paroxetine/paxil_letter_e3.pdf). The manufacturer subsequently changed paroxetine's pregnancy FDA category from C to D (www.fda.gov/cder/drug/advisory/paroxetine200512.htm).

More recently, the teratogenic effect of SSRI use during the first trimester of pregnancy was examined in two large case–control studies from multisite surveillance programs (65, 66). In the National Birth Defects Prevention Study, no significant associations were found between SSRI use overall and congenital heart defects (66). However, an association was found between SSRI use (particularly paroxetine) during early pregnancy and anencephaly, craniosynostosis, and omphalocele. Importantly, these risks were found only after more than 40 statistical tests were performed. Even if findings were not the result of chance, the absolute risks associated with SSRI use identified in this study were small. For example, a twofold to threefold increase in birth defects would occur for omphalocele (1 in 5,000 births), craniosynostosis (1 in 1,800 births) and anencephaly (1 in 1,000 births). In contrast, in the Slone Epidemiology Center Birth Defects Study no increased risk of craniosynostosis, omphalocele, or heart defects associated with SSRI use overall during early pregnancy was found (65). An association was seen between paroxetine and right ventricular outflow defects. Additionally, sertraline use was associated with omphalocele and atrial and ventricular septum defects. A limitation of this study is that the authors conducted 42 comparisons in their analyses for their main hypotheses. Both of these case–control studies were limited by the small number of exposed infants for each individual malformation. The current data on SSRI exposure during early pregnancy provide conflicting data on the risk for both overall and specific malformations. Some investigators have found a small increased risk of cardiac defects, specifically with paroxetine exposure. The absolute risk is small and generally not greater than two per 1,000 births; hence, these agents are not considered major teratogens.

Exposure to SSRIs late in pregnancy has been associated with transient neonatal complications, including jitteriness, mild respiratory distress, transient tachypnea of the newborn, weak cry, poor tone, and neonatal intensive care unit admission (67–71). A more recent FDA public health advisory highlighted concerns about the risk of an unconfirmed association of newborn persistent pulmonary hypertension with SSRI use (72) (www.fda.gov/cder/drug/advisory/SSRI_PPHN 200607. htm).

The potential risk of SSRI use in pregnancy must be considered in the context of the risk of relapse of depression if treatment is discontinued. Factors associated with relapse during pregnancy include a long history of depressive illness (more than 5 years) and a history of recurrent relapses (more than four episodes) (13). Therefore, treatment with all SSRIs or selective norepinephrine reuptake inhibitors or both during pregnancy should be individualized. At this time, paroxetine use in pregnant women and women planning pregnancy should be avoided, if possible. Fetal echocardiography should be considered for women exposed to paroxetine in early pregnancy. Because abrupt discontinuation of paroxetine has been associated with withdrawal symptoms, discontinuation of this agent should occur according to the product's prescribing information.

Tricyclic antidepressants (TCAs) have been available in the United States since 1963 and were widely used by women during pregnancy and lactation before the introduction of SSRIs. Results from initial studies, which suggested that TCA exposure might be associated with limb anomalies (73–75), have not been confirmed with subsequent studies (76, 77). Neonatal neurobehavioral effects from fetal exposure have not been reported (78).

Acute effects associated with TCA exposure include case reports of fetal tachycardia (79), neonatal symptoms such as tachypnea, tachycardia, cyanosis, irritability, hypertonia, clonus, and spasm (72–82), and transient withdrawal symptoms (83). In more recent studies, a significant link between prenatal exposure to TCAs and perinatal problems has not been documented (64, 84–86).

Atypical antidepressants are non-SSRI and non-TCA antidepressants that work by distinct pharmacodynamic mechanisms. The atypical antidepressants include bupropion, duloxetine, mirtazapine, nefazodone, and venlafaxine. The limited data of fetal exposure to these antidepressants (70, 85–89), do not suggest an increased risk of fetal anomalies or adverse pregnancy events. In the one published study of bupropion exposure in 136 patients, a significantly increased risk of spontaneous abortion, but not an increased risk of major malformations, was identified (90). In contrast, the bupropion registry maintained at GlaxoSmithKline has not identified any increased risk of spontaneous abortion, although these data have not undergone peer review.

Antidepressant medication is the mainstay of treatment for depression, although considerable data show that structured psychotherapy, such as interpersonal psychotherapy or cognitive behavioral therapy, are effective treatments for mild to moderate depression and are beneficial adjuncts to medication. In addition, electroconvulsive therapy is an effective treatment for major depression and is safe to use during pregnancy (91, 92).

### ▶ *What is the evidence regarding the safety and efficacy of lithium for the treatment of bipolar disorders during pregnancy?*

Use of lithium in pregnancy may be associated with a small increase in congenital cardiac malformations. The initial retrospective data suggested that fetal exposure to lithium was associated with a 400-fold increase in congenital heart disease, particularly Ebstein's anomaly (93, 94). A subsequent meta-analysis of the available data calculated the risk ratio for cardiac malformations to be 1.2–7.7 and the risk ratio for overall congenital malformations to be 1.5–3 (95). In more recent small studies, limited in their statistical power, the magnitude of early estimates of teratogenic potential of lithium could not be confirmed (96–98).

Fetal exposure to lithium later in gestation has been associated with fetal and neonatal cardiac arrhythmias (99), hypoglycemia, nephrogenic diabetes insipidus (100), polyhydramnios, reversible changes in thyroid function (101), premature delivery, and floppy infant syndrome similar to that seen with benzodiazepine exposure (102). Symptoms of neonatal lithium toxicity include flaccidity, lethargy, and poor suck reflexes, which may persist for more than 7 days (103). Neurobehavioral sequelae were not documented in a 5-year follow-up of 60 school-aged children exposed to lithium during gestation (104).

The physiologic alterations of pregnancy may affect the absorption, distribution, metabolism and elimination of lithium, and close monitoring of lithium levels during pregnancy and postpartum is recommended. The decision to discontinue lithium therapy in pregnancy because of fetal risks should be balanced against the maternal risks of exacerbation of illness. In a recent study, it was reported that abrupt discontinuation of lithium was associated with a high rate of bipolar relapse among pregnant women (39). The following treatment guidelines have been suggested for women with bipolar illness who are treated with lithium and plan to conceive: 1) in women who experience mild and infrequent episodes of illness, treatment with lithium should be gradually tapered before conception; 2) in women who have more severe episodes but are only at moderate risk for relapse in the short term, treatment with lithium should be tapered before conception but reinstituted after organogenesis; 3) in women who have especially severe and frequent episodes of illness, treatment with lithium should be continued throughout gestation and the patient counseled regarding reproductive risks (95). Fetal assessment with fetal echocardiography should be considered in pregnant women exposed to lithium in the first trimester. For women in whom an unplanned conception occurs while receiving lithium therapy, the decision to continue or discontinue the use of lithium should be in part based on disease severity, course of the patient's illness, and the point of gestation at the time of exposure.

### ▶ *What is the evidence regarding the safety and efficacy of the antiepileptic drugs valproate and carbamazepine for the treatment of bipolar disorders during pregnancy?*

Several anticonvulsants, including valproate, carbamazepine, and lamotrigine, currently are used in the treatment of bipolar disorder. Data regarding fetal effects of these drugs are derived primarily from studies of women with seizures. Whether the underlying pathology of epilepsy contributes to the teratogenic effect on the fetus is unclear. Epilepsy may not contribute to the teratogenic effects of antiepileptic drugs based on the results of a recent study that demonstrated similar rates of anomalies between infants of women without epilepsy and infants of women with epilepsy but who had not taken antiepileptic drugs during pregnancy (105).

Prenatal exposure to valproate is associated with a 1–3.8% risk of neural tube defects, with a corresponding dose–response relationship (106–113). Other congenital malformations associated with valproate use include craniofacial anomalies (114), limb abnormalities (115), and cardiovascular anomalies (116–118). A "fetal valproate syndrome" has been described with features of fetal growth restriction, facial dysmorphology, and limb and heart defects (119–121). Varying degrees of cognitive impairment, including mental development delay (122), autism (123–126), and Asperger's syndrome (124), have been reported with fetal valproate syndrome (124, 127, 128). Acute neonatal risks include hepatotoxicity (129), coagulopathies (130), neonatal hypoglycemia (131), and withdrawal symptoms (132).

Carbamazepine exposure in pregnancy is associated with a fetal carbamazepine syndrome manifest by facial dysmorphism and fingernail hypoplasia (124, 133–136). It is unclear whether carbamazepine use increases the risk of fetal neural tube defects or developmental delay (124, 127, 133–139). Fetal exposure to lamotrigine has not been documented to increase the risk of major fetal anomalies (140–145), although there may be an increased risk of midline facial clefts (0.89% of 564 exposures) as reported by one pregnancy registry (143), possibly related to higher daily maternal doses (greater than 200 mg/day) (145). The reproductive safety of lamotrigine appears to compare favorably with alternative treatments, but lacking are studies of the effectiveness of this antiepileptic drug as a mood stabilizer in pregnancy.

In managing bipolar disorders, the use of valproate and carbamazepine are superior to that of lithium for patients who experience mixed episodes or rapid cycling but exhibit limited efficacy in the treatment of bipolar depression. In contrast, lamotrigine is efficacious in the prevention of the depressed phase of illness (146, 147). Lamotrigine is a potential maintenance therapy option for pregnant women with bipolar disorder because of its protective effects against bipolar depression, general tolerability, and growing reproductive safety profile relative to alternative mood stabilizers. Because both valproate and carbamazepine are associated with adverse effects when used during pregnancy, their use, if possible should be avoided especially during the first trimester. The effectiveness of folate supplementation in the prevention of drug-associated neural tube defects has not been documented; however, folate supplementation of 4 mg/day should be offered preconceptionally and for the first trimester of pregnancy. Prenatal surveillance for congenital anomalies by maternal serum alpha-fetoprotein level testing, fetal echocardiography, or a detailed ultrasound examination of the fetal anatomy or a combination of these procedures should be considered. Whether the use of antiepileptic drugs such as carbamazepine increase the risk of neonatal hemorrhage and whether maternal vitamin K supplementation is effective remains unclear (148).

### ▶ *What is the evidence regarding the safety and efficacy of treatment for anxiety disorders during pregnancy?*

Use of benzodiazepines does not appear to carry a significant risk of somatic teratogenesis. In early studies of in utero exposure to diazepam, a benzodiazepine, an increased risk of oral clefts was reported (149–151). In a subsequent meta-analysis, it was demonstrated that prenatal benzodiazepine exposure increased the risk of oral cleft, although the absolute risk increased by 0.01%, from 6 in 10,000 to 7 in 10,000 (76). In a recent case–control study of 22,865 infants with congenital anomalies and 38,151 infants without congenital anomalies, an association of congenital anomalies, including oral clefts with exposure to five different benzodiazepines, was not found (152). Similar findings were documented in a case–control study of clonazepam (153). If discontinuation of benzodiazepine use is considered during pregnancy, benzodiazepines should not be abruptly withdrawn.

The data regarding neonatal toxicity and withdrawal syndromes are well documented, and neonates should be observed closely in the postpartum period. Floppy infant syndrome, characterized by hypothermia, lethargy, poor respiratory effort, and feeding difficulties, is associated with maternal use of benzodiazepines shortly before delivery (154–162). Neonatal withdrawal syndromes, characterized by restlessness, hypertonia, hyperreflexia, tremulousness, apnea, diarrhea, and vomiting, have been described in infants whose mothers were taking alprazolam (163), chlordiazepoxide (164–166), or diazepam (167, 168). These symptoms have been reported to persist for as long as 3 months postpartum (81).

The long-term neurobehavioral impact of prenatal benzodiazepine exposure is unclear. The existence of a "benzodiazepine-exposure syndrome," including growth restriction, dysmorphism, and both mental and psychomotor retardation, in infants exposed prenatally to benzodiazepines is disputed (169–171). In one study, no differences in the incidence of behavioral abnormalities at age 8 months or IQ scores at age 4 years were found among children exposed to chlordiazepoxide during gestation (172).

### ▶ *What is the evidence regarding the safety and efficacy of treatment for schizophrenia during pregnancy?*

The atypical antipsychotics (eg, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and aripiprazole) have replaced the typical agents as first-line medications for psychotic disorders (Table 2). The atypical antipsychotics generally are better tolerated and possibly are more effective in managing the negative symptoms of schizophrenia. They also are used increasingly for bipolar disorder, obsessive–compulsive disorder, and treatment-resistant depression. The reproductive safety data regarding the use of atypical antipsychotics remains extremely limited. In a prospective comparative study of pregnancy outcomes between groups exposed and unexposed to atypical antipsychotics, outcomes of 151 pregnancies with exposure to olanzapine, risperidone, quetiapine, and clozapine demonstrated a higher rate of low birth weight (10% in the exposed versus 2% in the nonexposed group) and therapeutic abortions (173).

The typical antipsychotic drugs have a larger reproductive safety profile and include haloperidol, thioridazine, fluphenazine, perphenazine, chlorpromazine, and trifluoperazine. No significant teratogenic effect has been documented with chlorpromazine, haloperidol, and perphenazine (174–176). In a study of 100 women treated with haloperidol (mean dose of 1.2 mg/day) for hyperemesis gravidarum, no differences in gestational duration, fetal viability, or birth weight were noted (177). In a large prospective study encompassing approximately 20,000 women treated primarily with phenothiazines for emesis (178), investigators found no significant associa-

tion with neonatal survival rates or severe anomalies. Similar results have been obtained in several retrospective studies of women treated with trifluoperazine for repeated abortions and emesis (179, 180). In contrast, other investigators reported a significant association of major anomalies with prenatal exposure to phenothiazines with an aliphatic side chain but not with piperazine or piperidine class agents (181). Reanalysis of previously reported data obtained also identified a significant risk of malformations associated with phenothiazine exposure in weeks 4–10 of gestation (182). In clinical neurobehavioral outcome studies encompassing 203 children exposed to typical antipsychotics during gestation, no considerable differences have been detected in IQ scores at 4 years of age (183, 184), although relatively low antipsychotic doses were used by many women in these studies.

Fetal and neonatal toxicity reported with exposure to the typical antipsychotics includes neuroleptic malignant syndrome (185), dyskinesia (186), extrapyramidal side effects manifested by heightened muscle tone and increased rooting and tendon reflexes persisting for several months (187), neonatal jaundice (188), and postnatal intestinal obstruction (189).

Fetuses and infants also may be exposed to drugs used to manage the extrapyramidal side effects (eg, diphenhydramine, benztropine, and amantadine). In a case–control study, oral clefts were associated with a significantly higher rate of prenatal exposure to diphenhydramine than controls (149). In contrast, in several other studies diphenhydramine use has not been found to be a significant risk factor for fetal malformations (190, 191). Clinical studies of the teratogenic potential of benztropine and amantadine use are lacking.

In summary, typical antipsychotics have been widely used for more than 40 years, and the available data suggest the risks of use of these agents are minimal with respect to teratogenic or toxic effects on the fetus. In particular, use of piperazine phenothiazines (eg, trifluoperazine and perphenazine) may have especially limited teratogenic potential (181). Doses of typical antipsychotics during the peripartum should be kept to a minimum to limit the necessity of utilizing medications to manage extrapyramidal side effects. There is likewise little evidence to suggest that the currently available atypical antipsychotics are associated with elevated risks for neonatal toxicity or somatic teratogenesis. No long-term neurobehavioral studies of exposed children have yet been conducted. Therefore, the routine use of atypical antipsychotics during pregnancy and lactation cannot be recommended. In a woman who is taking an atypical antipsychotic and inadvertently conceives, a comprehensive risk–benefit assessment may indicate that continuing therapy with the atypical antipsychotic (to which the fetus has already been exposed) during gestation is preferable to switching to therapy with a typical antipsychotic (to which the fetus has not yet been exposed).

### ▶ *What is the risk of using psychiatric drugs while breastfeeding?*

Breastfeeding has clear benefits for both mother and infant and, in making the decision to recommend breastfeeding, these benefits should be weighed against the risks to the neonate of medication exposure while breastfeeding (Table 2). Most medications are transferred through breast milk, although most are found at very low levels and likely are not clinically relevant for the neonate. For women who breastfeed, measuring serum levels in the neonate is not recommended. Most clinical laboratory tests lack the sensitivity to detect and measure the low levels present. However, breastfeeding should be stopped immediately if a nursing infant develops abnormal symptoms most likely associated with exposure to the medication. Evaluation of the literature on drug levels in breast milk can facilitate the decision to breastfeed (192).

In the treatment of depression, published reports regarding SSRI use and lactation now consist of 173 mother–infant nursing pairs with exposure to sertraline, fluoxetine, paroxetine, fluvoxamine, and citalopram (193, 194–215). In results from studies, it has been shown that, quantitatively, medication exposure during lactation is considerably lower than transplacental exposure to these same SSRIs during gestation (193, 201, 208, 216). Generally, very low levels of SSRIs are detected in breast milk. Only a few isolated cases of adverse effects have been reported, although infant follow-up data are limited. The package insert for citalopram does report a case of an infant who experienced a transient apneic episode. Long-term neurobehavioral studies of infants exposed to SSRI antidepressants during lactation have not been conducted.

The TCAs also have been widely used during lactation. The only adverse event reported to date is respiratory depression in a nursing infant exposed to doxepin, which led to the conclusion that doxepin use should be avoided but that most TCAs are safe for use during breastfeeding (217). Data regarding the use of atypical antidepressants during lactation are limited to the use of venlafaxine (218) and bupropion (219, 220).

The existing data regarding lithium use and lactation encompass 10 mother–infant nursing dyads (103, 221–225). Adverse events, including lethargy, hypotonia, hypothermia, cyanosis, and electrocardiogram changes,

were reported in two of the children in these studies (103, 223). The American Academy of Pediatrics consequently discourages the use of lithium during lactation (226). Because dehydration can increase the vulnerability to lithium toxicity, the hydration status of nursing infants of mothers taking lithium should be carefully monitored (102). There are no available reports regarding the long-term neurobehavioral sequelae of lithium exposure during lactation.

Only one adverse event, an infant with thrombocytopenia and anemia (227), has been reported in studies regarding valproate use and lactation, which includes 41 mother–infant nursing dyads (227–235). Studies of the neurobehavioral impact of valproate exposure during lactation have not been conducted. The American Academy of Pediatrics and the World Health Organization (WHO) Working Group on Drugs and Human Lactation have concluded that use of valproate is compatible with breastfeeding (226, 236). Reported adverse effects of carbamazepine in breast milk include transient cholestatic hepatitis (237, 238) and hyperbilirubinemia (239). The WHO Working Group on Drugs and Human Lactation has concluded that use of carbamazepine with breastfeeding is "probably safe" (236).

In the management of anxiety disorders, benzodiazepine use exhibits lower milk/plasma ratios than other classes of psychotropics (240, 241). Some investigators concluded that benzodiazepine use at relatively low doses does not present a contraindication to nursing (242). However, infants with an impaired capacity to metabolize benzodiazepines may exhibit sedation and poor feeding even with low maternal doses (243).

Of typical antipsychotic medications, chlorpromazine has been studied in seven breastfeeding infants, none of whom exhibited developmental deficits at 16-month and 5-year follow-up evaluations (244). However, three breastfeeding infants in another study, whose mothers were prescribed both chlorpromazine and haloperidol, exhibited evidence of developmental delay at 12–18 months of age (245).

# Resources

American Academy of Pediatrics
Web: www.aap.org

American Psychiatric Association
Web: www.psych.org

National Institutes of Health
Daily medication:
http://dailymed.nlm.nih.gov/dailymed/about.cfm
Lactation medication:
toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

# Summary of Recommendations and Conclusions

***The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):***

- Lithium exposure in pregnancy may be associated with a small increase in congenital cardiac malformations, with a risk ratio of 1.2–7.7.
- Valproate exposure in pregnancy is associated with an increased risk of fetal anomalies, including neural tube defects, fetal valproate syndrome, and long-term adverse neurocognitive effects. It should be avoided in pregnancy, if possible, especially during the first trimester.
- Carbamazepine exposure in pregnancy is associated with fetal carbamazepine syndrome. It should be avoided in pregnancy, if possible, especially during the first trimester.
- Maternal benzodiazepine use shortly before delivery is associated with floppy infant syndrome.

***The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):***

- Paroxetine use in pregnant women and women planning pregnancy should be avoided, if possible. Fetal echocardiography should be considered for women who are exposed to paroxetine in early pregnancy.
- Prenatal benzodiazepine exposure increased the risk of oral cleft, although the absolute risk increased by 0.01%.
- Lamotrigine is a potential maintenance therapy option for pregnant women with bipolar disorder because of its protective effects against bipolar depression, general tolerability, and a growing reproductive safety profile relative to alternative mood stabilizers.
- Maternal psychiatric illness, if inadequately treated or untreated, may result in poor compliance with prenatal care, inadequate nutrition, exposure to additional medication or herbal remedies, increased alcohol and tobacco use, deficits in mother–infant bonding, and disruptions within the family environment.

***The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):***

- Whenever possible, multidisciplinary management involving the patient's obstetrician, mental health clinician, primary health care provider, and pediatrician is recommended to facilitate care.
- Use of a single medication at a higher dose is favored over the use of multiple medications for the treatment of psychiatric illness during pregnancy.
- The physiologic alterations of pregnancy may affect the absorption, distribution, metabolism, and elimination of lithium, and close monitoring of lithium levels during pregnancy and postpartum is recommended.
- For women who breastfeed, measuring serum levels in the neonate is not recommended.
- Treatment with all SSRIs or selective norepinephrine reuptake inhibitors or both during pregnancy should be individualized.
- Fetal assessment with fetal echocardiogram should be considered in pregnant women exposed to lithium in the first trimester.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and June 2007. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.



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Use of psychiatric medications during pregnancy and lactation. ACOG Practice Bulletin No. 92. American College of Obstetricians and Gynecologists. Obstet Gynecol 2008;111:1001–20.