Psychotropic Drug Use During Pregnancy: Weighing the Risks

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Although psychotropic drugs have not been tested or approved by the Food and Drug Administration for use during pregnancy, some women continue to take these medications while they are pregnant, particularly since mood and anxiety disorders cluster in women during childbearing years. The relative risks and benefits of drug therapy for these women must be weighed with each patient and treatment limited to those situations in which the risks to mother and fetus from the disorder are presumed to exceed the risk of drug treatment. Risks of psychotropic drug use during pregnancy include teratogenic effects, direct neonatal toxicity, and the potential for longer term neurobehavioral sequelae. Of growing concern is the risk of untreated psychiatric disorder as it may potentially affect fetoplacental integrity and fetal central nervous system development. Coordination of care with the patient, her husband or partner, and the obstetrician is essential, as is careful medical record documentation when treating pregnant patients with psychiatric disorders.

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Over the last decade, reviews of the outcome of fetal exposure to antipsychotics, antidepressants, benzodiazepines, and mood stabilizers suggest relatively low teratogenic potential of many of these agents, although data are typically insufficient to determine absolute risk of organ dysgenesis. Even less is known about the possibility of subtle neurobehavioral sequelae associated with prenatal exposure to psychotropics.

ASSESSMENT OF WOMEN OF CHILDBEARING POTENTIAL

Some women present with psychiatric symptoms for the first time during pregnancy. Others who have a past psychiatric history and already take psychiatric medications request information about risks and benefits of maintaining medication versus risks of treatment discontinuation. Sophisticated patients may wonder about the impact of untreated mood or anxiety symptoms on fetal well-being. Many women have unplanned pregnancies while taking medications including psychotropics, and their requests for consultation are often urgent.

The relative risks and benefits of drug therapy must be weighed with the patient and treatment limited to those situations in which the risks to mother and fetus from the disorder are presumed to exceed the risk of drug treatment. At the same time, clinician and patient must both acknowledge that no clinical decision is ever risk free.

Risks of Pharmacotherapy

Prenatal exposure to psychotropics includes risks of (1) teratogenic effects, (2) direct neonatal toxicity, and (3)
the potential for longer-term neurobehavioral sequelae, so-called “behavioral teratogenesis.” Teratogenicity refers to gross organ malformation that occurs during the first 12 weeks of gestation.\textsuperscript{35} Fetal exposure to a teratogen results in increased risk of congenital malformations.\textsuperscript{36} The incidence of congenital malformations in the United States is about 3\% to 4\%.\textsuperscript{37} Exposure to a teratogen before 2 weeks gestation (corresponding to the time prior to the first missed menses) is not typically teratogenic and is more likely to result in a nonviable blighted ovum.\textsuperscript{38} The date of treatment interruption and the range of half-lives of prescribed medications is thus relevant. Early recognition of pregnancy permits discontinuation of medications without the risk of prenatal exposure during critical periods of development. Discontinuation of long half-life agents makes prenatal exposure more likely. Decisions regarding psychotropic drug use during pregnancy must be based on available reproductive safety data, irrespective of the half-life of the agent.

Behavioral teratogenesis, or long-term neurobehavioral sequelae associated with fetal exposure to a drug,\textsuperscript{39–41} has been demonstrated in animal studies with changes in behavior after prenatal exposure to psychotropics including antipsychotics, antidepressants, and benzodiazepines; these results, however, have not been consistent.\textsuperscript{39,42–44} Alterations in noradrenergic, dopaminergic, cholinergic, and serotonergic function have also been observed in animals after in utero exposure to psychoactive agents,\textsuperscript{39,42–47} but the relevance of these observations for humans has yet to be demonstrated.

Behavioral outcomes after prenatal exposure to psychotropics, including tricyclic antidepressants,\textsuperscript{48} benzodiazepines,\textsuperscript{49} lithium,\textsuperscript{50} and more recently fluoxetine,\textsuperscript{51} have been reported. Except for fluoxetine data, most data are extremely limited by retrospective design and by small sample size. Furthermore, relevant control groups with psychiatric disorders but no psychotropic exposure have been omitted.

Perinatal syndromes—physical and behavioral symptoms observed in the acute neonatal period—are frequently attributed to drug exposure at or near the time of birth. Symptoms of perinatal distress include a range of transient neonatal syndromes associated with exposure to antidepressants,\textsuperscript{52–55} antipsychotics,\textsuperscript{56–59} and benzodiazepines\textsuperscript{60–64}. The incidence of these adverse events, however, is low, and the significance of anecdotal reports that describe these syndromes must be critically assessed.

**Risks Associated With Psychiatric Illness**

Absolute risk from in utero exposure to psychotropics may be difficult to quantify, but so too, are risks of untreated psychiatric disorder. Consequences of untreated psychiatric disorder must be calculated against the risk of prenatal exposure to drug. Impaired self-care and failure to follow prenatal guidelines owing to psychiatric symptoms may adversely affect the outcome of pregnancy. Suicidality associated with depressive illness or impulsivity seen in bipolar disorder are other examples of clinical risks that may drive the decision to institute pharmacologic treatment during pregnancy. Risk for chronicity and treatment resistance,\textsuperscript{65,66} associated particularly with repeated relapse of psychiatric disorder,\textsuperscript{67} is also a factor in the potential use of psychotropic drugs during pregnancy. To date, the impact of neuroendocrinologic changes associated with psychiatric disorder or the impact of untreated psychiatric symptoms on the fetoplacental unit\textsuperscript{29,31,68} is unclear, but is of some concern because of data that suggest adverse effects of untreated depression and anxiety on neonatal outcome.\textsuperscript{28–31,33,34}

**PSYCHOTROPIC DRUGS IN PREGNANCY**

### Antipsychotics

While an early case report describing limb malformation raised concerns regarding first trimester exposure to haloperidol,\textsuperscript{69} several studies (but not all) have failed to demonstrate increased teratogenic risk with high-potency neuroleptics.\textsuperscript{70–72} A recent meta-analysis describing teratogenic risk associated with several psychotropics, including antipsychotics, notes a higher risk of congenital malformations after first trimester exposure to low-potency neuroleptics.\textsuperscript{9}

Little is known about the consequences of prenatal exposure to high-potency neuroleptics such as haloperidol, and even less is known about reproductive safety of atypical antipsychotics such as clozapine, risperidone, and olanzapine. Two small retrospective studies found no association between fetal exposure to haloperidol and congenital deformities.\textsuperscript{70,71} No adverse effects were described in one case report of clozapine use during pregnancy.\textsuperscript{72} No information is available yet regarding the reproductive safety of risperidone or olanzapine in pregnancy.

No systematic data are available regarding treatment-related adverse effects in neonates after neuroleptic exposure in utero. However, case reports of neonates who have demonstrated motor restlessness, tremor, difficulty with oral feedings, hypertonicity, dystonic movements, and parkinsonian-like effects have all been observed.\textsuperscript{45,59,73,74} These symptoms have typically been of short duration.\textsuperscript{75} Long-term neurobehavioral studies of prenatal exposure to neuroleptics are lacking. Animal data suggest the possibility of behavioral abnormalities after fetal exposure to high- and low-potency antipsychotics, although the implications of these findings for humans are unclear.\textsuperscript{42,76–79}

### Antidepressants

Although pregnancy has frequently been thought to offer protection against psychiatric disorder,\textsuperscript{80} one prospective study of pregnant and puerperal women described rates of major and minor depression (using RDC criteria)
at about 10%. In another recent prospective study, high rates of relapse were described during pregnancy in women with recurrent affective disorder who reduced or discontinued antidepressants. Another recent retrospective review also noted rates of reintroduction of antidepressant therapy across pregnancy of approximately 50% in women who had discontinued their treatment proximate to conception (Cohen LS, Alshuler LL, Stowe Z. 1997. Unpublished data). Given the high prevalence of mood disorder during childbearing years, women may present with new-onset or recurrent depression during pregnancy. Others may query treatment options in light of the well-established need for maintenance antidepressant therapy and concerns regarding relapse after potential antidepressant discontinuation.

**Tricyclic antidepressants.** In the 1970s, case reports suggested a possible association between first trimester exposure to tricyclic antidepressants (TCAs) and limb malformations, but later studies have failed to confirm these findings. Three prospective and more than 10 retrospective studies have examined the risk for organogenesis after first trimester exposure to TCAs. A combined 500,000 births have been evaluated, and over 400 cases of first trimester exposure to TCAs are documented. While the accumulated cases of TCA exposure are few and estimates of risk are based on tricyclics of a class versus a particular TCA, no single study or group of studies consistently support an increased risk of congenital malformations after first trimester exposure to TCAs.

Various case reports describe perinatal syndromes after exposure to TCAs. These reports have included TCA withdrawal syndromes with characteristic symptoms of jitteriness, irritability, and seizures after exposure to TCAs during labor and delivery. Symptoms of functional bowel obstruction and urinary retention—presumably secondary to anticholinergic effects of TCAs—have also been reported. While several animal studies describe a spectrum of behavioral abnormalities during the first 30 days of life after prenatal exposure to TCAs, no systematically derived data are available regarding long-term sequelae of such exposure in humans. The significance of changes at the receptor level—including decreased adrenergic receptor binding and decreased density of serotonin receptors—in animals exposed to tricyclics prenatally is unclear and remains to be studied.

**Serotonin selective reuptake inhibitors.** Although the history of TCA safety during pregnancy is reassuring, the majority of patients with a mood disorder receive a newer agent. Except for fluoxetine, the reproductive safety data of serotonin selective reuptake inhibitors (SSRIs) are limited. Four prospective studies have evaluated rates of malformations in approximately 1100 fluoxetine-exposed children. The postmarketing surveillance register established by the manufacturer of fluoxetine and one other retrospective study adds to this body of information. Approximately 1900 cases of first trimester exposure to fluoxetine have been reported to the manufacturer (Data on file. Eli Lilly and Co. 1996). Approximately 750 of these patients were prospectively assessed; the rest were retrospectively assessed. No increased risk of congenital malformations over that for the general population was observed for those either retrospectively or prospectively studied.

Chambers and colleagues recently noted no higher rates of major congenital malformations in 228 pregnant women who took fluoxetine during the first trimester than in the general population. Higher rates of minor malformations, however, were described, along with a greater frequency of admissions to special care nurseries in children of women who took fluoxetine during the latter stages of pregnancy. Interpretation of these latter findings is limited by methodological difficulties. Only half the sample of exposed children were examined for the presence of minor malformations, which raises the question of selection bias; also, some raters were not blind to maternal treatment status.

The safety of sertraline and paroxetine use during pregnancy is relatively unknown; postmarketing surveillance of exposure to these agents is lacking. Data are available from one study in which the safety of paroxetine was assessed in 63 infants exposed to the drug during the first trimester of pregnancy—none developed congenital malformations. However, prospective data on the use of paroxetine, sertraline, mirtazapine, fluvoxamine, venlafaxine, nefazodone, and trazodone are not available.

The risk of neonatal toxicity or long-term neurobehavioral consequences from SSRIs remains unclear. After exposure to fluoxetine, one neonate manifested agitation and tachycardia. In one recent study, higher rates of perinatal complications after late trimester exposure to fluoxetine were reported. This last study had several methodologic limitations and is inconsistent with three other studies that noted no perinatal distress in infants exposed to fluoxetine even late in pregnancy (references 105, 110, and Koren G, personal communication). In a study of longer term neurobehavioral function after prenatal exposure to fluoxetine, Nulman and colleagues noted no difference in children up to 4 years of age who were exposed to fluoxetine compared with a nonexposed control group.

**Other antidepressants.** Scant information is available regarding reproductive safety of monoamine oxidase inhibitors (MAOIs); thus, they are typically avoided during pregnancy. Psychostimulants such as amphetamine and methylphenidate are frequently used as adjuncts in the treatment of affective disorder. However, data regarding stimulant use during pregnancy are difficult to interpret, since populations sampled have frequently suffered substance abuse disorders as opposed to affective disorder.
Electroconvulsive Therapy

Electroconvulsive therapy (ECT) has been in use during pregnancy for over 50 years.112 The safe use of ECT during pregnancy has been claimed particularly in high-risk situations (i.e. mania and psychotic depression).113,114 Two recent reviews of ECT use during pregnancy note efficacy and safety of the procedure115,116 with one case of placental abruption described.117

Mood Stabilizers

Lithium. Concern regarding the extent to which prenatal exposure to lithium heightens the risk for congenital, and specifically cardiovascular, malformations dates back to the early 1970s and the first reports from the International Register of Lithium Babies.118,119 Initial and subsequent reports from the Register described increased rates of cardiovascular malformations, most notably Ebstein’s anomaly.118–120

Recent epidemiologic studies suggest a more modest teratogenic risk associated with first trimester exposure to lithium than proposed previously.26,121–125 A pooled review of two cohort studies and four case control studies—conducted after the sealing of the Register of Lithium Babies—supports the possibility that first trimester exposure to lithium is associated with an increased risk of cardiovascular malformations.27 However, the authors revised the risk estimate of Ebstein’s anomaly after first trimester exposure to lithium to range from 10 to 20 times that noted in the general population. With a baseline risk for Ebstein’s anomaly estimated at 1/20,000 in the absence of exposure, the revised risk for this congenital malformation after first trimester exposure lies between 1/2000 (0.05%) and 1/1000 (0.1%). Hence, while the relative risk for Ebstein’s anomaly may be increased, the absolute risk is small.

Perinatal toxicity in offspring exposed to lithium at the time of labor and delivery has also been reported, including a “floppy baby” syndrome characterized by cyanosis and hypotonicity.126–128 One case of neonatal hypothyroidism and nephrogenic diabetes insipidus has also been described. A naturalistic study of bipolar women maintained on lithium treatment during pregnancy and the puerperium found no direct evidence of neonatal toxicity in newborns whose mothers were taking lithium either during pregnancy or during labor and delivery.129 Limited data are available regarding behavioral outcome of older children exposed to lithium during pregnancy. A 5-year follow-up investigation of children exposed to lithium during the second and third trimester of pregnancy and born without physical malformations revealed no significant behavioral problems.30

Anticonvulsants. Studies of reproductive safety of anticonvulsants have focused on epileptic patients, not on pregnant women treated for psychiatric illness. While children of epileptic women appear to have greater numbers of congenital malformations regardless of perinatal anticonvulsant exposure compared with the general population, malformations in offspring exposed to anticonvulsants in utero remain higher than in nonexposed controls, even after controlling for the effects of epilepsy.130,131

Carbamazepine exposure during the first trimester is associated with spina bifida at a rate of 1%.132 Valproic acid has been associated with neural tube defects with estimates of risk ranging from 3% to 5%.133–135 Combining anticonvulsants makes the risk higher, perhaps due to higher maternal plasma drug levels.136–138 Although first trimester exposure to anticonvulsants was associated with orofacial clefts in one study,139 no specific anticonvulsant appeared to be responsible for the increased risk. In another study, a syndrome of minor malformations (i.e., rotated ears, flat nasal bridge, fingernail hypoplasia) that tend to disappear over time has been reported in infants exposed to anticonvulsants.24

Benzodiazepines

Concern about first trimester exposure to benzodiazepines dates back more than 20 years.140,141 Early reports describe an increased risk of oral clefts after first trimester exposure to drugs such as diazepam,141,142 but later studies do not support the association. To date, fourteen studies address the relationship between prenatal exposure to benzodiazepines and risk for congenital anomalies.20–22,85,140,141,143–151 Methodological differences in sampling and study design render comparisons challenging.

One meta-analysis suggests that first trimester exposure to benzodiazepines significantly increases risk of oral clefts as compared with the risk in the general population (6/10,000 [0.06%]). The authors note a risk for oral clefts of 0.7% after first trimester exposure to benzodiazepines, or approximately a tenfold increase in risk over the general population. Methodological limitations inherent in the analysis included pooling of studies of different benzodiazepines administered at different doses for varying amounts of time in dissimilar populations and ascertained in a noncontrolled fashion. For example, while a significant association appears between first trimester exposure to alprazolam and oral clefts (odds ratio = 11.5), the results are derived from a voluntary postmarketing surveillance register with its inherent ascertainment bias.151 More data in regard to reproductive safety are available for diazepam and alprazolam than for clonazepam; teratogenic risk after clonazepam exposure has not been assessed in any controlled human studies.

Perinatal benzodiazepine exposure, at or about the time of delivery, has been linked to impaired temperature regulation, apnea, depressed Apgar scores, muscular hypotonicity, and failure to feed. In one prospective study of 39 pregnant women with panic disorder, clonazepam (0.5–3.5 mg/day) was given alone for varying periods.152 No evidence of congenital malformations was noted al-
though the sample was quite small. The Apgar scores, however, were uniformly high, and no infants showed signs of neonatal withdrawal syndromes, hypotonia, temperature dysregulation, or other perinatal difficulties. Studies of neurobehavioral function after prenatal exposure to benzodiazepines include reports of developmental and motor delays, although data are limited by marked ascertainment bias.\textsuperscript{143,149} The balance of data, although limited, do not support a significant impact on neurobehavioral function.\textsuperscript{145}

**TREATMENT GUIDELINES**

Treatment guidelines for psychotropic use during pregnancy must factor in or derive from (1) severity of disorder (i.e., risk of relapse or threat to maternal and fetal well-being), (2) reproductive safety of the medication, and (3) capacity of patients to bear symptoms. Nonetheless, risk of intervention can only be relatively quantified and no decision is risk free. Patients and physicians must work collaboratively as they weigh risks and benefits using the best information available.

**Psychosis**

Psychotic symptoms may impair a woman’s ability to obtain prenatal care\textsuperscript{153,154} and increase the risk for impulsivity and dangerous behaviors.\textsuperscript{155} The first onset of psychosis during pregnancy calls for careful evaluation. To minimize exposure to a drug, mild or intermittent psychotic symptoms, especially in the first trimester, may respond to p.r.n., as opposed to daily use neuroleptics. However, patients suffering from severe new-onset or chronic psychosis, or patients with past decompensations when tapered from drugs, or those who are noncompliant with pharmacotherapy, may actually limit overall prenatal drug exposure, if they avoid the need for reintroduction of higher dose treatment after relapse by maintaining treatment throughout pregnancy with lower doses. These patients may then be better able to cooperate with prenatal care guidelines and improve their outcomes.

Despite reports of neonatal extrapyramidal symptoms associated with antipsychotic exposure at or around the time of delivery, abrupt neuroleptic discontinuation just prior to labor and delivery heightens the risk for maternal decompensation within weeks of delivery.\textsuperscript{156,157}

**Mood Disorders**

**Major depression.** The prevalence of depression during pregnancy appears comparable to rates in matched nongravid women.\textsuperscript{158,159} Since mood disorder predominantly clusters in women of reproductive age, and with growing numbers of these women receiving treatment for depression, many will confront the challenge of considering pharmacologic treatment during pregnancy. Heightening the dilemma is an awareness that maternal mood and anxiety disorders have an impact on child development\textsuperscript{29,34,160,161} and may obviously affect fetal well-being and obstetrical outcome.

Making the diagnosis of depression during pregnancy can be difficult. Disturbances in sleep and appetite, fatigue, and change in libido frequently accompany pregnancy in nondepressed women. Better markers of mood disorder in pregnant women include a lack of interest in the pregnancy, guilty ruminations, and profound anhedonia. Antidepressants during pregnancy are best reserved for those patients who have neurovegetative symptoms that interfere with maternal well-being, or for those who experience the symptoms as intolerable.

Management of major depression during pregnancy depends on the severity of the disorder. Mild depressive symptoms during pregnancy may improve with nonpharmacologic treatments. Cognitive therapy\textsuperscript{162} or interpersonal therapy\textsuperscript{163} in particular may be helpful. These psychotherapies may also be the first choice for patients with mild-to-moderate past episodes who become pregnant or wish to discontinue antidepressants while planning a pregnancy. Taper, followed by discontinuation of antidepressant, may be appropriate for these patients when performed in conjunction with cognitive behavioral strategies and may help to eliminate the need for medication. However, it should be underscored that patients with histories of recurrent major depression who discontinue antidepressant treatment proximate to conception appear to be at high risk for relapse early in pregnancy.\textsuperscript{164}

Pharmacotherapeutic intervention is clearly appropriate for pregnant patients with symptoms of severe depression, including diminished oral intake, suicidality, or psychosis. Patients with recurrent major depression who have previously tried and failed to discontinue antidepressants may choose to continue treatment during attempts to conceive and during pregnancy. Among TCAs, desipramine and nortriptyline are preferred since they are less anticholinergic and the least likely to exacerbate orthostatic hypotension. With the most extensive literature supporting its reproductive safety, compared with other antidepressants, fluoxetine is a good choice during pregnancy. Severely depressed patients with suicidality or psychosis are treated best in a hospital setting, and ECT is frequently the treatment of first choice.

Data are not sufficient regarding teratogenic risk associated with sertraline or paroxetine. However, these agents may be appropriate in certain situations for women with mild-to-moderate depression who are trying to conceive. Sertraline or paroxetine might be tapered after early documentation of pregnancy. Discontinuation of short half-life SSRIs after documentation of pregnancy (and prior to the first missed period) would permit washout of drug and metabolite prior to the establishment of fetoplacental circulation—allowing for continued treatment prior to pregnancy with drug discontinuation after documentation of
pregnancy. Unfortunately, many women present for advice well into their first trimester, and to minimize patient distress and the possible need for reinstitution of treatment, discontinuation requires a gradual taper. Even with a rapid washout, the use of short-acting agents proximate to conception means possible fetal exposure to drugs lacking sufficient data regarding reproductive safety.

The safety of MAOIs during pregnancy is unknown; hence, these antidepressants should be avoided if possible. Unfortunately, reproductive safety information is also inadequate for buproprion, trazodone, venlafaxine, mirtazapine, and nefazodone. Thus, their use during pregnancy is also best avoided, if possible, until reassuring data are forthcoming.

A past history of depression or depression during pregnancy is associated with puerperal worsening of mood. Patients with past episodes of depression who discontinue medications during pregnancy need to anticipate the possibility of reemergent symptoms during the postpartum period. Those patients who have had severe major depression may benefit from prophylactic reintroduction of antidepressants either during the latter portion of the third trimester or immediately after delivery, even though no abundant systematically derived data support the practice. Based on anecdotal reports of neonatal irritability and other symptoms in infants born to mothers who were treated with antidepressants at or around the time of delivery, some early reports have recommended discontinuation of antidepressants prior to delivery to avoid these rare perinatal syndromes. The drawbacks of this plan are evident since it withdraws treatment from patients precisely as they enter a period of heightened risk for affective worsening.

Bipolar disorder. The association of bipolar disorder and puerperal worsening of mood is evident, with reported rates of relapse as high as 30% to 50%. The impact of pregnancy on bipolar disorder is less clear, although one recent study of pregnant bipolar women describes relapse rates of approximately 50% within 6 months of lithium discontinuation. High rates of relapse are apparent in bipolar patients who abrupty discontinue lithium, which makes the possibility of abrupt discontinuation of lithium a tenuous alternative when pregnancy is documented. Lastly, recurrence of illness after lithium discontinuation may itself promote the progression of the disorder, with an associated decrease in well intervals and a possibility of increased risk for chronicity or treatment resistance.

Bipolar women who are maintained on lithium treatment deserve family planning, as planned pregnancy increases available options. Reproductive risk counseling also involves the patient in the process of weighing the relative risks of treatment options. The decision to use lithium during pregnancy depends on illness severity and cycling. Those patients with a single past episode of mania or long periods of interepisode affective well-being may be able to gradually taper and discontinue lithium prior to an attempt at conception. Gradual taper of lithium may minimize relapse.

Bipolar women with more than one past episode of mania and depression offer a greater clinical challenge. Lithium discontinuation (if pursued) should await early documentation of pregnancy. This strategy minimizes exposure and affords antimanic prophylaxis for the longest period of time while women try to conceive. Maintenance of lithium therapy until early documentation of pregnancy is particularly prudent for older patients since the time required for them to conceive may be longer than for younger patients. This strategy, however, involves a more abrupt discontinuation of lithium if fetal exposure is to be minimized and may actually provoke or at least hasten relapse.

For women who have severe bipolar disorder, maintenance of lithium treatment before and during pregnancy is advisable. These patients are at the highest risk for clinical deterioration in the absence of treatment. Accepting the relatively small absolute increase in teratogenic risk with first trimester exposure to lithium seems particularly justified in this high-risk group. Consider, for example, that a full relapse of bipolar disorder in these patients will require aggressive treatment, including hospitalization, neuroleptics, clonazepam, or ECT. For these patients who previously discontinued lithium, the drug should be reintroduced, regardless of the trimester.

Some early reports recommended switching pregnancy prophylaxis with lithium to alternative mood stabilizers such as carbamazepine or valproic acid. These recommendations reflected concerns about first trimester exposure to lithium. More recent studies, however, describe the rates of malformations after prenatal exposure to carbamazepine that approximate 1%. Rates of neural tube defects after in utero exposure to valproic acid have been estimated to be as high as 5%. Compared with the revised risk for first trimester exposure to lithium, these risks are relatively high. Moreover, lithium response may not predict comparable benefit from an anticonvulsant. For rapid cycling bipolar patients or nonresponders to lithium, valproic acid or carbamazepine treatment should be accompanied by administration of folate to reduce the risk of neural tube defects in offspring.

Women who use lithium during the first trimester of pregnancy should be counseled about the increased relative risk of congenital malformations. They should be reassured as well, however, that there is a low absolute risk, and that fetal cardiac ultrasonography can be performed at 16 to 18 weeks gestation. For those patients who are maintained on lithium therapy during pregnancy, the drug may be tapered by 25% to 30% just prior to delivery, i.e., from 900 mg/day to 600 mg/day, to minimize risk for lithium toxicity during periods of rapid shifts in plasma volume characteristic of the puerperium. However, lithi-
um should not be discontinued entirely as the postpartum period is a time of heightened risk for bipolar women. The risk for puerperal decompensation in bipolar women is estimated at 30% to 50%. Several investigators have evaluated the extent to which postpartum prophylaxis with lithium attenuates this impressive risk. Significant reduction in rates of relapse are observed in women who receive lithium during the first 48 hours postpartum compared with women who do not. Anecdotal reports of neonatal lithium toxicity including lethargy and hypotonia notwithstanding, follow-up studies of children whose mothers have received prophylactic lithium are somewhat reassuring.

Anxiety Disorders

Panic disorder. Panic disorder typically has a chronic and recurrent course, although some patients can successfully taper and discontinue antipanic medication for periods of time during the course of their illness. While a past report suggested a protective effect of pregnancy on the symptoms of panic disorder, recent studies describe persistence or worsening of panic symptoms during pregnancy. Pregnancy may ameliorate symptoms of panic in some patients, but other patients appear to experience persistence or exacerbation of symptoms. Predictors of the relapse of panic disorder during pregnancy are not yet established, although at least one study has suggested quick relapse of panic disorder in remitted patients who either tapered or discontinued antipanic drugs during pregnancy.

The preferred approach to treatment with antipanic medications for patients who wish to conceive is to taper these drugs slowly. Adjunctive cognitive-behavioral therapy may help these patients to discontinue medications or increase the well interval prior to relapse. If taper is unsuccessful, reinstitution of pharmacotherapy may be indicated. Given the reported increase in the risk of oral clefts reported in one recent meta-analysis of first trimester benzodiazepine exposure, TCAs or fluoxetine are alternatives of choice. If patients do not respond to these antidepressants, the use of benzodiazepines is reasonable. Although patients may inadvertently conceive on antipanic drugs, abrupt discontinuation of antipanic medication is not recommended. Taper of antipanic medications with adjunctive cognitive-behavioral therapy may, however, be pursued to minimize or eliminate fetal exposure.

Obsessive-compulsive disorder. Pregnancy has been associated with the onset of obsessive-compulsive disorder (OCD). In one study, 52% of women experienced the onset of OCD during their first pregnancy; other studies have failed to confirm this finding. No known biological mechanism explains the high rates of OCD in pregnancy, and no systematic data are available that prospectively describe the course of OCD during pregnancy. Behavioral techniques (cognitive-behavioral therapy) for OCD are an alternative to medication for some patients. For patients who suffer from OCD, TCAs and fluoxetine represent a reasonable pharmacologic approach during, or particularly after, the first trimester. The TCA, clomipramine, may be used but while not considered teratogenic, it may aggravate orthostatic hypotension. In anecdotal reports, clomipramine has been linked with neonatal seizures. The medication is not, however, absolutely contraindicated for pregnant women who suffer from severe OCD. Its use is also not absolutely contraindicated during labor and delivery, since withdrawal of clomipramine in women with active illness may increase risk for puerperal worsening of the disorder.

CONCLUSION

Psychotropic medications may be used during pregnancy when the potential risk to the fetus from drug exposure is outweighed by the risk of untreated maternal psychiatric disorder. While concern about prenatal exposure to psychotropics has generated vigilance, discontinuation of these medications in patients who have a psychiatric disorder may result in significant morbidity for the patient. Of growing concern, too, is the risk of untreated psychiatric disorder as it may potentially affect fetoplacental integrity. Thus, women maintained on psychiatric medications who plan to become pregnant, as well as those with onset of psychiatric symptoms during pregnancy, should be carefully evaluated.

First trimester exposure to some phenothiazines, lithium, benzodiazepines, and the anticonvulsants carbamazepine and valproic acid, increases the relative risk of a congenital malformation. Data supporting safety of the TCAs and fluoxetine are, however, particularly reassuring.

The potential for long-term behavioral changes after prenatal exposure to psychotropics is relatively unknown. Animal studies suggest changes in brain receptor number and function after in utero exposure to various psychotropic drugs. Large epidemiologic follow-up studies of children exposed to medication in utero may help clinicians better weigh the relative risk of psychotropic drug use during pregnancy. Studies of these children must also include a relevant control group of nonexposed children whose mothers suffer from the disorder for which the medication is prescribed. This type of study may help to distinguish the impact of disorders from prenatal exposure with respect to long-term neurobehavioral function. Given the inevitability of psychotropic use during pregnancy, it is critical that clinicians have a prepared approach to the use of these agents. Coordinated care among patient, husband or partner, obstetrician, and psychiatrist is essential, as is careful medical record documentation. For some patients, however, the decision to accept an increase in teratogenic risk may be appropriate to insure stable maternal
mental health during pregnancy. In general, many psychotropic drugs used in pregnancy offer no discernible adverse consequences. Pending controlled prospective data on the impact of drugs on fetal and later development, clinicians will continue to have to care for patients recognizing uncertainty and weighing partially calculated risks to manage individual clinical dilemmas.

Drug names: alprazolam (Xanax), bupropion (Wellbutrin), carbamazepine (Tegretol and others), clonazepam (Klonopin), clozapine (Clozapril), desipramine (Norpramin and others), diazepam (Valium and others), flunitrazepam (Prosom), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), methylphenidate (Ritalin), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others), valproic acid (Depakene and others), venlafaxine (Effexor).

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