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 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. *(J Clin Psychiatry 1998;59[suppl 2]:18–28)*

The treatment of psychiatric disorders during pregnancy raises a number of clinical challenges.[1] Psychotropic drugs have not been tested or approved by the Food and Drug Administration (FDA) for use during pregnancy, although many women use these medications during this time.[2,3] Psychiatric disorders, particularly mood and anxiety disorders, cluster in women during childbearing years. New-onset illness during pregnancy or concerns about prenatal exposure to psychotropics—among growing numbers of women treated with these agents—are common reasons for consultation. Other concerns that prompt consultation include the risk of recurrence of psychiatric disorders if medication is discontinued. The high prevalence of psychiatric disorders during pregnancy and the evidence that psychiatric patients may be at high risk for relapse when medications are discontinued[4–7] underlie the clinical challenge. To minimize risk of fetal exposure to drugs while limiting risk of untreated psychiatric disorders is the goal of thoughtful treatment planning.[8]

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Over the last decade, reviews[8–13] of the outcome of fetal exposure to antipsychotics,[14–17] antidepressants,[18,19] benzodiazepines,[20–22] and mood stabilizers[23–27] 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.[28–34] 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 clinieSl 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.[35] Fetal exposure to a teratogen results in increased risk of congenital malformations.[36] The incidence of congenital malformations in the United States is about 3% to 4%.[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.[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,[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.[39,42–44] Alterations in noradrenergic, dopaminergic, cholinergic, and serotonergic function have also been observed in animals after in utero exposure to psychoactive agents,[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,[48] benzodiazepines,[49] lithium,[50] and more recently fluoxetine,[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,[52–55] antipsychotics,[56–59] and benzodiazepines[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,[65,66] associated particularly with repeated relapse of psychiatric disorder,[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[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.[28–31,33,34]

PSYCHOTROPIC DRUGS IN PREGNANCY

Antipsychotics

While an early case report describing limb malformations raised concerns regarding first trimester exposure to haloperidol,[69] several studies (but not all) have failed to demonstrate increased teratogenic risk with high-potency neuroleptics.[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.[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.[70,71] No adverse effects were described in one case report of clozapine use during pregnancy.[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[56,59,73,74]; these symptoms have typically been of short duration.[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.[42,76–79]

Antidepressants

Although pregnancy has frequently been thought to offer protection against psychiatric disorder,[80] one prospective study of pregnant and puerperal women described rates of major and minor depression (using RDC criteria)

at about 10%.[81] In another recent prospective study, high rates of relapse were described during pregnancy in women with recurrent affective disorder who reduced or discontinued antidepressants.[82] 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, Altshuler LL, Stowe Z. 1997. Unpublished data). Given the high prevalence of mood disorder during childbearing years,[83] 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,[84] but later studies have failed to confirm these findings. Three prospective and more than 10 retrospective studies have examined the risk for organ dysgenesis after first trimester exposure to TCAs.[18,19,85–94] A combined 500,000 births have been evaluated and over 400 cases of first trimester exposure to TCAs 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 nor 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.[52–54,95] Symptoms of functional bowel obstruction and urinary retention—presumably secondary to anticholinergic effects of TCAs—have also been reported.[55,57] While several animal studies describe a spectrum of behavioral abnormalities during the first 30 days of life after prenatal exposure to TCAs,[74,96–101] 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[102–105] 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.[106] 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[103] 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.[107]

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[108] 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.[109] In one recent study,[103] higher rates of perinatal complications after late trimester exposure to fluoxetine was 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[51] 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.[111] 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 procedure[115,116] 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 l970s 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.[50]

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[9] 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[9] 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.[143,149] The balance of data, although limited, do not support a significant impact on neurobehavioral function.[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[153,154] and increase the risk for impulsivity and dangerous behaviors.[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.[156,157]

Mood Disorders

Major depression. The prevalence of depression during pregnancy appears comparable to rates in matched nongravid women.[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[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[162] or interpersonal therapy[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.[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 bupropion, 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.[158,165,166] 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.[167] 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,[52–54,95] some early reports[8] 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%.[168–172] 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.[173] High rates of relapse are apparent in bipolar patients who abruptly discontinue lithium,[5,174] 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 prepregnancy prophylaxis with lithium to alternative mood stabilizers such as carbamazepine or valproic acid.[23] 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%.[24] Rates of neural tube defects after in utero exposure to valproic acid have been estimated to be as high as 5%.[175] Compared with the revised risk for first trimester exposure to lithium,[27] 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.[176]

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,[27] and that fetal cardiac ultrasonography can be performed at 16 to 18 weeks gestation.[8] 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%.[171] Several investigators have evaluated the extent to which postpartum prophylaxis with lithium attenuates this impressive risk.[177] 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[128] notwithstanding, follow-up studies of children whose mothers have received prophylactic lithium are somewhat reassuring.[129]

Anxiety Disorders

Panic disorder. Panic disorder typically has a chronic and recurrent course,[65] although some patients can successfully taper and discontinue antipanic medication for periods of time during the course of their illness.[178] While a past report suggested a protective effect of pregnancy on the symptoms of panic disorder,[179] recent studies[180,181] describe persistence or worsening of panic symptoms during pregnancy. Pregnancy may ameliorate symptoms of panic in some patients,[179,182–184] but other patients appear to experience persistence or exacerbation of symptoms.[185] 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.[185]

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.[186] 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,[9] 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).[187–189] In one study,[187] 52% of women experienced the onset of OCD during their first pregnancy; other studies have failed to confirm this finding.[190] 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.[95] 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 psychotropics 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 (Clozaril), desipramine (Norpramin and others), diazepam (Valium and others), 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).

REFERENCES

1. Cohen LS, Rosenbaum JF, Heller VH. Psychotropic drug use in pregnancy. In: Gelenberg AJ, Bassuk EL, Schoonover SC, eds. The Practitioner's Guide to Psychoactive Drugs. New York, NY: Plenum Medical Book Company; 1991:389–405
2. Doering JC, Stewart RB. The extent and character of drug consumption during pregnancy. JAMA 1978;239:843–846
3. Kasilo O, Romero M, Bonati M, et al. Information on drug use in pregnancy from the Viewpoint Regional Drug Information Center. Eur J Clin Pharmacol 1988;35:447–453
4. Kupfer D, Frank E, Perel J, et al. Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1992;49:769–773
5. Suppes T, Baldessarini RJ, Faedda GL, et al. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry 1991;48:1082–1088
6. Roy-Byrne PP, Dager SR, Cowley DS, et al. Relapse and rebound following discontinuation of benzodiazepine treatment of panic attacks: alprazolam versus diazepam. Am J Psychiatry 1989;146:860–865
7. Dencker SJ, Malm U, Lepp M. Schizophrenic relapse after drug withdrawal is predictable. Acta Psychiatr Scand 1986;73:181–185
8. Cohen LS, Heller VL, Rosenbaum JF. Treatment guidelines for psychotropic drug use in pregnancy. Psychosomatics 1989;30:25–33
9. Altshuler LL, Cohen LS, Szuba MP, et al. Pharmacologic management of psychiatric illness in pregnancy: dilemmas and guidelines. Am J Psychiatry 1996;153:592–606
10. Calabrese JR, Gulledge AD. Psychotropics during pregnancy and lactation: a review. Psychosomatics 1985;26:413–426
11. Miller L. Clinical strategies for the use of psychotropic drugs during pregnancy. Psychiatr Med 1991;9(2):275–298
12. Mortola J. The use of psychotropic agents in pregnancy and lactation. Psychiatr Clin North Am 1989;12(1):69–87
13. Robinson GE, Stewart DE, Flak E. The rational use of psychotropic drugs in pregnancy and postpartum. Can J Psychiatry 1986;31:183–190
14. Slone D, Siskind V, Heinonen OP, et al. Antenatal exposure to the phenothiazines in relation to congenital malformations, perinatal mortality rate, birth weight, and intelligence quotient score. Am J Obstet Gynecol 1977;128:486–488
15. Rumeau-Rouguette C, Goujard J, Huel G. Possible teratogenic effect of phenothiazines in human beings. Teratology 1977;15:57–64
16. Milkovich L, Van den Berg BJ. An evaluation of the teratogenicity of certain antinauseant drugs. Am J Obstet Gynecol 1976;125:244–248
17. Edlund MJ, Craig TJ. Antipsychotic drug use and birth defects: an epidemiologic reassessment. Compr Psychiatry 1984;25:32–37
18. Kuenssberg EV, Knox JD. Imipramine in pregnancy. BMJ 1972;2:292
19. Idanpaan-Heikkila J, Saxen L. Possible teratogenicity of imipramine-chloropyramine. Lancet 1973;2:282–284
20. Czeizel A, Lendvay A. In-utero exposure to benzodiazepines [letter]. Lancet 1987;1:628
21. Shiono PH, Mills IL. Oral clefts and diazepam use during pregnancy [letter]. N Engl J Med 1984;311:919–920
22. Rosenberg L, Mitchell AA, Parsells JL, et al. Lack of relation of oral clefts to diazepam use during pregnancy. N Engl J Med 1983;309:1282–1285
23. Markovitz PJ, Calabrese JR. Use of anticonvulsants for manic depression in pregnancy [letter]. Psychosomatics 1990;31:118
24. Jones KL, Lacro RV, Johnson KA, et al. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. N Engl J Med 1989;320:1661–1666
25. Lindhout D, Schmidt D. In utero exposure to valproate and neural defects. Lancet 1986;1:329–393
26. Jacobson SJ, Jones K, Johnson K, et al. Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet 1992;339:530–533
27. Cohen LS, Friedman JM, Jefferson JW, et al. A reevaluation of risk of in utero exposure to lithium. JAMA 1994;271:146–150
28. Istvan J. Stress, anxiety, and birth outcome: a critical review of the evidence. Psychol Bull 1986;100(3):331–348
29. Steer RA, Scholl TO, Hediger ML, et al. Self-reported depression and negative pregnancy outcomes. J Clin Epidemiol 1992;45:1093–1099
30. Orr S, Miller C. Maternal depressive symptoms and the risk of poor pregnancy outcome: review of the literature and preliminary findings. Epidemiol Rev 1995;17(1):165–171
31. Perkin MR, Bland JM, Peacock JL, et al. The effect of anxiety and depression during pregnancy on obstetric complications. Br J Obstet Gynaecol 1993;100:629–634
32. Zuckerman B, Bauchner H, Parker S, et al. Maternal depressive symptoms during pregnancy, and newborn irritability. J Dev Behav Pediatr 1990;11(4):190–194
33. Cutrona CE. Causal attributions and perinatal distress. J Abnorm Psychol 1983;92:161–172
34. Sapolski R, Meaney M. Maturation of the adrenotcortical stress response: neuroendocrine control mechanisms and the stress hyporesponsive period. Brain Res Rev 1986;11:65–76
35. Dicke JM. Teratology: principles and practice. Med Clin North Am 1989;73:567–581
36. American Medical Association. Drug interactions and adverse drug reactions. In: American Medical Association Drug Evaluation. Chicago, Ill: American Medical Association; 1983:31–44
37. Fabro SE. Clinical Obstetrics. New York, NY: John Wiley & Sons; 1987
38. Langman J. Human development: normal and abnormals. In: Langman J, ed. Medical Embryology. Baltimore, Md: Williams & Wilkins; 1985:123
39. Coyle I, Wayner M, Singer G. Behavioral teratogenesis: a critical evaluation. Pharmacol Biochem Behav 1976;4:191–200
40. Vorhees C, Brunner R, Butcher R. Psychotropic drugs as behavioral teratogens. Science 1979;205:1220–1225
41. Vernadakis A, Parker K. Drugs and the developing central nervous system. Pharmacol Ther 1980;11:593–647
42. Robertson RT, Majka JA, Peter CP, et al. Effects of prenatal exposure to chlorpromazine on postnatal development and behavior of rats. Toxicol Appl Pharmacol 1980;53:541–549
43. Kellogg CK. Benzodiazepines: influence on the developing brain. Prog Brain Res 1988;73:207–228
44. Kellogg C, Ison J, Miller J. Prenatal diazepam exposure: effects on auditory temporal resolution in rats. Psychopharmacology (Berl) 1983;79:332–337
45. Montero D, DeCeballos M, DelRio J. Down-regulation of 3H-imipramine binding sites in rat cerebral cortex after prenatal exposure to antidepressants. Life Sci 1990;46:1619–1626
46. Miller GC, Friedhoff AG. Prenatal neurotransmitter programming of postnatal receptor function. Prog Brain Res 1987;2:509–522
47. Lauer JA, Adams PM, Johnson KM. Perinatal diazepam exposure: behavioral and neurochemical consequences. Neurotoxicol Teratol 1989;9:213–219
48. Misri S, Sivertz K. Tricyclic drugs in pregnancy and lactation: a preliminary report. Int J Psychiatry Med 1991;21(2):157–171
49. Laegreid L, Hagberg G, Lundberg A. The effect of benzodiazepines on the fetus and the newborn. Neuropediatrics 1992;23:18–23
50. Schou M. What happened later to the lithium babies: a follow-up study of children born without malformations. Acta Psychiatr Scand 1976;54:193–197
51. Nulman I, Rovet J, Stewart D, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997;336:258–262
52. Eggermont E. Withdrawal symptoms in neonates associated with maternal imipramine therapy. Lancet 1973;2:680
53. Schimmel M, Katz E, Shaag Y, et al. Toxic neonatal effects following ma-

ternal clomipramine therapy. Clinical Toxicology 1991;29:479–484
54. Webster PAC. Withdrawal symptoms in neonates associated with maternal antidepressant therapy. Lancet 1973;2:318–319
55. Shearer WT, Schreiner RL, Marshall RE. Urinary retention in a neonate secondary to maternal ingestion of nortriptyline. J Pediatr 1972;81: 570–572
56. Tamer A, McKey R, Arias D, et al. Phenothiazine-induced extrapyramidal dysfunction in the neonate. J Pediatr 1969;75:479–480
57. Falterman LG, Richardson DJ. Small left colon syndrome associated with maternal ingestion of psychotropics. J Pediatr 1980;97:300–310
58. Scokel PW, Jones WD. Infant jaundice after phenothiazine drugs for labour: an enigma. Obstet Gynecol 1962;20:124–127
59. Hill RM, Desmond MM, Kay JL. Extrapyramidal dysfunction in an infant of a schizophrenic mother. J Pediatr 1966;69:589–595
60. Fisher J, Edgren B, Mammel M. Neonatal apnea associated with maternal clonazepam therapy. Obstet Gynecol 1985;66(3, suppl)34S–35S
61. Athinarayanan P, Peirog S, Nigam S. Chlordiazepoxide withdrawal in the neonate. Am J Obstet Gynecol 1976;124:212–213
62. Gillberg C. "Floppy infant death syndrome" and maternal diazepam [letter]. Lancet 1977;2:244
63. Mazzi E. Possible neonatal diazepam withdrawal: a case report. Am J Obstet Gynecol 1977;129:586–587
64. Whitelaw A, Cummings A, McFadyen I. Effect of maternal lorazepam on the neonate. BMJ 1981;282:1106–1108
65. Pollack MH, Otto MW, Rosenbaum JF, et al. Longitudinal course of panic disorder: findings from the Massachusetts General Hospital Naturalistic Study. J Clin Psychiatry 1990;51(12, suppl A):12–16
66. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. Arch Gen Psychiatry 1990;47:1106–1111
67. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992;149:999–1010
68. Cohen LS, Rosenbaum JF, Heller VL. Panic attack-associated placental abruption: a case report. J Clin Psychiatry 1989;50:266–267
69. Kopelman AE, McCullar FW, Heggeness L. Limb malformations following maternal use of haloperidol. JAMA 1975;231:62–64
70. Hanson G, Oakley G. Haloperidol and limb deformity [letter]. JAMA 1975;231:26
71. van Waes A, van de Velde E. Safety evaluation of haloperidol in the treatment of hyperemesis gravidum. J Clin Psychopharmacol 1969;224–237
72. Waldman M, Safferman A. Pregnancy and clozapine. Am J Psychiatry 1993;150:168–169
73. Levy W, Wisniewski K. Chlorpromazine causing extrapyramidal dysfunction in newborn infants of psychotic mothers. New York State Journal of Medicine 1974;74:684–685
74. Auerbach JG, Hans SL, Marcus J, et al. Maternal psychotropic medication and neonatal behavior. Neurotoxicol Teratol 1992;14:399–406
75. Desmond MM, Rudolph AJ, Hill RM. Behavioral alterations in infants born to mothers on psychoactive medication during pregnancy. In: Farrell G, ed. Congenital Mental Retardation. Austin, Tex: University of Texas; 1967
76. Clarke C, Gorman D, Vernadakis A. Effects of prenatal administration of psychotropic drugs on behavior of developing rats. Dev Psychol 1970;3: 225–235
77. Golub M, Kornetsky C. Seizure susceptibility and avoidance conditioning in adult rats treated prenatally with chlorpromazine. Dev Psychobiol 1974; 7:79–88
78. Spear LP, Shalaby IA, Brick J. Chronic administration of haloperidol during development: behavioral and psychopharmacological effects. Psychopharmacology 1980;70:47–58
79 Cagiano R, Barfield R, White N. Subtle behavioral changes produced in rat pups exposed in utero to haloperidol. Eur J Pharmacol 1988;157:45–50
80. Zajicek E. Psychiatric problems during pregnancy. In: Wolkind S, Zajicek E, eds. Pregnancy: a Psychological and Social Study. London, England: Academic Press; 1981:57–73
81. O'Hara MW, Schlechte JA, Lewis DA, et al. Controlled prospective study of postpartum mood disorders: psychological, environmental, and hormonal factors. J Abnorm Psychol 1991;100:63–73
82. Cohen LS, Grush L, Goldstein J, et al. Relapse of recurrent major depression during pregnancy. Presented at the Paper Session of the annual meeting of the American Psychiatric Association; May 17–22, 1997; San Diego, Calif
83. Kessler RC, McGonagle KA, Swartz M, et al. Sex and depression in the National Comorbidity Survey, I: lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29:85–96
84. McBride WG. Limb deformities associated with ininodibenzyl hydrochloride [letter]. Med J Aust 1972;1:492
85. Heinonen O, Sloan D, Shapiro S. Birth Defects and Drugs in Pregnancy. Littleton, Mass: Publishing Services Group; 1977
86. Pastuszak A, Schick-Boschetto B, Zuber C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA 1993;269: 2246–2248
87. Crombie D, Pinsent RJ, Felming D. Imipramine and pregnancy [letter]. BMJ 1972;1:745
88. Rachelefsky G, Flynt J, Ebbin A. Possible teratogenicity of tricyclic antidepressants. Lancet 1972;1:838
89. Sim M. Imipramine and pregnancy. BMJ 1972;2:45
90. Scanlon F. Use of antidepressant drugs first trimester [letter]. Med J Aust 1969;2(21):1077
91. Briggs G, Freeman R, Yaffe S. Drugs in pregnancy and lactation. Baltimore, Md: William & Wilkins; 1994
92. Banister P, Dafoe C, Smith ESO, et al. Possible teratogenicity of tricyclic antidepressants [letter]. Lancet 1972;1:838–839
93. Morrow AW. Imipramine and congenital abnormalities. N Z Med J 1972; 75:228–229
94. Jacobs D. Imipramine (Tofranil) [letter]. S Afr Med J 1972;46:1023
95. Cowe L, Lloyd D, Dawling S. Neonatal convulsions caused by withdrawal from maternal clomipramine. BMJ 1982;284:1837–1838
96. Ali S, Buelkesam J, Newport L. Early neurobehavioral and neurochemical alterations in rats prenatally exposed to imipramine. Neurotoxicology 1986;7:365–380
97. DelRio J, Montero D, DeCeballos M. Long lasting changes after perinatal exposure to antidepressants. Prog Brain Res 1988;73:173–187
98. Coyle LR. Changes in developing behavior following prenatal administration. Pharmacol Biochem Behav 1975;3:799–807
99. File SE, Tucker JC. Prenatal treatment with clomipramine: effects on the behavior of male and female adolescent rats. Psychopharmacology (Berl) 1984;82:221–224
100. Jason K, Cooper T, Friedman E. Prenatal exposure to imipramine alters early behavioral development and beta adrenergic receptors in rats. J Pharmacol Exp Ther 1981;217:461–466
101. DeCeballos M, Benedi A, DeFelipe C, et al. Prenatal exposure of rats to antidepressants enhances agonist affinity of brain dopamine receptors and dopamine-mediated behavior. Eur J Pharmacol 1985;116:257–262
102. Pastuszak AL, Milich V, Can S, et al. Prospective assessment of pregnancy outcome following first trimester exposure to benzodiazepines. Presented at the 6th International Conference on Teratogen Information Services; 1993
103. Chambers C, Johnson K, Dick L, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996;335:1010–1015
104. Nulman I, Koren G. The safety of fluoxetine during pregnancy and lactation. Teratology 1996;53:304–308
105. Goldstein DJ. Effects of third trimester fluoxetine exposure on the newborn. Clinical Psychopharmacology 1995;15:417–420
106. McElhatton P, Garbis H, Elefant E, et al. The outcome of pregnancy in 689 women exposed to therapeutic doses of antidepressants: a collaborative study of the European Network of Teratology Information Services (ENTIS). Reprod Toxicol 1996;10(4):285–294
107. Cohen LS, Rosenbaum JR. Fluoxetine in pregnancy [letter]. N Engl J Med 1997;336:872
108. Inman W, Kobotu K, Pearce G, et al. Prescription event monitoring of paroxetine. Prescription Events Monitoring Reports 1993;PXL 1206: 1–44
109. Spencer M. Fluoxetine hydrochloride (Prozac) toxicity in the neonate. Pediatrics 1993;92:721–722
110. Cohen LS, Grush LR, Bailey JW, et al. Perinatal outcome following fluoxetine exposure: a preliminary report. In: New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatry Association; May 20, 1997; San Diego, Calif. Abstract NR 212:125
111. Chiarello R, Cole J. The use of psychostimulants in general psychiatry: a reconsideration. Arch Gen Psychiatry 1987;44:286–295
112. Goldstein H, Weinberg J, Sankstone M. Shock therapy in psychosis complicating pregnancy: a case report. Am J Psychiatry 1941;98:201–202
113. Remick RA, Maurice WL. ECT in pregnancy [letter]. Am J Psychiatry 1978;135:761–762
114. Impasato DJ, Gabriel AR, Lardara M. Electric and insulin shock therapy

during pregnancy. Dis Nerv Syst 1964;25:542–546
115. Miller LJ. Use of electroconvulsive therapy during pregnancy. Hosp Community Psychiatry 1994;45:444–450
116. Ferrill MJ, Kehoe WA, Jacisin JJ. ECT during pregnancy: physiologic and pharmacologic considerations. Convuls Ther 1992;8(3):186–200
117. Sherer DM, D'Amico LD, Warshal DP, et al. Recurrent mild abruptio placentae occurring immediately after repeated electroconvulsive therapy in pregnancy. Am J Obstet Gynecol 1991;165:652–653
118. Weinstein MR. The International Register of Lithium Babies. Drug Information Journal 1976;10:94–100
119. Schou M, Goldfield MD, Weinstein MR, et al. Lithium and pregnancy, I: report from the register of lithium babies. BMJ 1973;2:135–136
120. Nora JJ, Nora AH, Toews WH. Lithium, Ebstein's anomaly and other congenital heart defects [letter]. Lancet 1974;2:594–595
121. Kallen B, Tandberg A. Lithium and pregnancy: a cohort study on manic-depressive women. Acta Psychiatr Scand 1983;68:134–139
122. Kallen B. Comments on teratogen update: lithium. Teratology 1988;38: 597
123. Edmonds LD, Oakley GP. Ebstein's anomaly and maternal lithium exposure during pregnancy. Teratology 1990;41:551–552
124. Sipek A. Lithium and Ebstein's anomaly. Cor Vasa 1989;31:149–156
125. Zalstein E, Koren G, Einarson T, et al. A case control study on the association between 1st-trimester exposure to lithium and Ebstein's anomaly. Am J Cardiol 1990;65:817–818
126. Schou M, Amdisen A. Lithium and the placenta [letter]. Am J Obstet Gynecol 1975;122:541
127. Woody J, London W, Wilbanks G. Lithium toxicity in a newborn. Pediatrics 1971;47:94–96
128. Ananth J. Side effects of fetus and infant of psychotropic drug use during pregnancy. Pharmacopsychiatry 1976;11:246–260
129. Cohen LS, Sichel DA, Robertson LM, et al. Postpartum prophylaxis for women with bipolar disorder. Am J Psychiatry 1995;152:1641–1645
130. Koch S, Hortman A, Jager-Roman E. Major malformations of children of epileptic parents: due to epilepsy or therapy? In: Janz D, Richens A, eds. Epilepsy, Pregnancy, and the Child. New York, NY: Ram Press; 1982: 313–316
131. Paskind H, Brown M. Constitutional differences between deteriorated and nondeteriorated patient with epilepsy. Archives of Neurology and Psychiatry 1936;36:1037–1044
132. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. N Engl J Med 1991;324:674–677
133. Omtzigt JGC, Los FJ, Grobbee DE, et al. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. Neurology 1992;42(suppl 5):119–125
134. Lammer EJ, Sever LE, Oakley GP. Teratogen update: valproic acid. Teratology 1987;35:465–473
135. Lindhout D, Meinardi H, Meijer J. Antiepileptic drugs and teratogenesis in two consecutive cohorts: changes in prescription policy paralleled by changes in pattern malformations. Neurology 1992;42(suppl 5):94–110
136. Battino D, Binelli S, Caccamo M. Malformation in offspring of 305 epileptic women: a prospective study. Acta Neurol Scand 1992;85:204–207
137. Koch S, Losche G, Jager-Roman E. Major and minor birth malformations and antiepileptic drugs. Neurology 1992;42(suppl 5):83–88
138. Nakane Y, Okuma T, Takahashi R, et al. Multi-institutional study on the teratogenicity and fetal toxicity of antiepileptic drugs: a report of a collaborative study group in Japan. Epilepsia 1980;21:663–680
139. Shaw GM, Wasserman CR, O'Malley CD, et al. Orofacial clefts and maternal anticonvulsant use. Reprod Toxicol 1995;9(1):97–98
140. Aarskog D. Association between maternal intake of diazepam and oral clefts [letter]. Lancet 1975;2:921
141. Safra MJ, Oakley GP. Association between cleft lip with or without cleft palate and prenatal exposure to diazepam. Lancet 1975;2:478–480
142. Saxen I. Association between oral clefts and drugs taken during pregnancy. Int J Epidemiol 1975;4:37–44
143. Milkovich L, van den Berg BJ. Effects of prenatal meprobamate and chlordiazepoxide hydrochloride on human embryonic and fetal development. N Engl J Med 1974;291:1268–1271
144. Crombie D, Pinsent R, Fleming D. Fetal effects of tranquilizers in pregnancy [letter]. N Engl J Med 1975;293:198–199
145. Hartz S, Heinonen O, Shapiro S. Antenatal exposure to meprobamate and chlordiazepoxide in relation to malformations, mental development, and childhood mortality. N Engl J Med 1975;292:726–728
146. Saxen I, Saxen L. Association between maternal intake of diazepam and oral clefts [letter]. Lancet 1975;2:498
147. Czeizel A. Diazepam, phenytoin and aetiology of cleft lip and/or cleft palate [letter]. Lancet 1976;1:810
148. Czeizel A, Racz J. Evaluation of drug intake during pregnancy in the Hungarian case-control surveillance of congenital anomalies. Teratology 1990;42:505–512
149. Laegreid L, Olegard R, Conradi N, et al. Congenital malformations and maternal consumption of benzodiazepines: a case control study. Dev Med Child Neurol 1990;32:432–441
150. Bergman U, Rosa FW, Baum C, et al. Effects of exposure to benzodiazepine during fetal life. Lancet 1992;340:694–696
151. St. Clair SM, Schirmer RG. First-trimester exposure to alprazolam. Obstet Gynecol 1992;80:843–846
152. Weinstock L, Cohen LS, Sichel DA, et al. Clonazepam use during pregnancy. In: Syllabus & Proceedings Summary of the 1996 Annual Meeting of the American Psychiatric Association; May 4–9, 1996; New York, NY. No 24:11
153. Spielvogel A, Wile J. Treatment and outcomes of psychotic patients during pregnancy and childbirth. Birth 1992;19:131–137
154. Wrede G, Mednick S, Huttenen M. Pregnancy and delivery complications in the births of unselected series of Finnish children with schizophrenic mothers. Acta Psychiatr Scand 1980;62:369–381
155. Miller LJ. Psychotic denial of pregnancy: phenomenology and clinical management. Hosp Community Psychiatry 1990;41:1233–1237
156. Carpenter W, Hanlon T, Heinrichs D, et al. Continuous vs targeted medication in schizophrenic outpatients: outcome results. Am J Psychiatry 1990;147:1138–1141
157. Viguera AC, Baldessarini RC. Neuroleptic withdrawal in schizophrenic patients. Arch Gen Psychiatry 1995;52:189–192
158. Gotlib IH, Whiffen VE, Mount JH, et al. Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum period. J Consult Clin Psychol 1989;57:269–274
159. O'Hara MW. Social support, life events, and depression during pregnancy and the pueperium. Arch Gen Psychiatry 1986;43:569–573
160. Cohn JF, Tronick E. Specificity of infants' response to mothers' affective behavior. J Am Acad Child Adolesc Psychiatry 1989;28:242–248
161. Lederman R. Relationship of anxiety, stress, and psychosocial development to reproductive health. Behav Med 1995;21:101–112
162. Beck AT, Rush AJ, Shaw BF, et al. Cognitive therapy of depression. New York, NY: Guilford Press; 1979
163. Klerman GL, Weissman MM, Rounsaville BJ, et al. Interpersonal psychotherapy of depression. New York, NY: Basic Books; 1984
164. Cohen LS, Robertson LM, Goldstein J, et al. Impact of pregnancy on risk for relapse of MDD. In: Syllabus & Proceedings Summary of the 150th Annual Meeting of the American Psychiatric Association; May 17–22, 1997; San Diego, Calif. No. 57:23
165. O'Hara MW, Rehm LP, Campbell SB. Postpartum depression: a role for social network and life stress variables. J Nerv Ment Dis 1983;171: 336–341
166. O'Hara MW, Neunaber DJ, Zekoski EM. A prospective study of postpartum depression: prevalence, course, and predictive factors. J Abnorm Psychol 1984;93:158–171
167. Wisner KL, Wheeler SB. Prevention of recurrent postpartum major depression. Hosp Community Psychiatry 1994;45:1191–1196
168. Brockington IF, Winokur G, Dean C. Puerperal psychosis. In: Brockington IF, Kumar R, eds. Motherhood and Mental Illness. London, England: Academic Press; 1982:37–69
169. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. Br J Psychiatry 1987;150:662–673
170. Paffenbarger RA. Epidemiological aspects of mental illness associated with childbearing. In: Brockington IF, Kumar R, eds. Motherhood and Mental Illness. New York, NY: Grune & Stratton; 1982
171. Reich T, Winokur G. Postpartum psychosis in patients with manic depressive disease. J Nerv Ment Dis 1970;151:60–68
172. Kendell RE, Wainwright S, Hailey A, et al. The influence of childbirth on psychiatric morbidity. Psychol Med 1976;6:297–302
173. Viguera AC, Nonacs RM, Cohen LS, et al. Risks of discontinuing maintenance treatment in pregnant women with bipolar disorder. In: New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatric Association; May 19, 1997; San Diego, Calif. Abstract NR116:97
174. Faedda GL, Tondo L, Baldessarini RJ, et al. Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. Arch

Gen Psychiatry 1993;50:448–455
175. Omtzigt J, Los F, Hagenaars A, et al. Prenatal diagnosis of spina bifida aperta after first-trimester valproate exposure. Prenat Diagn 1992;12: 892–897
176. MRC Vitamin Study Research Group. Prevention of neural-tube defects: results of the medical research council vitamin study. Lancet 1991;338: 131–137
177. Stewart DE, Klompenhouwer JL, Kendall RE, et al. Prophylactic lithium in puerperal psychosis: the experience of three centers. Br J Psychiatry 1991;158:393–397
178. Wheeler EO, White PD, Reed EW, et al. Neurocirculatory anthenia (anxiety neurosis, effort syndrome, neurasthenia): a twenty-year follow-up study of 173 patients. JAMA 1950;142:878–890
179. Cowley DS, Roy-Byrne PP. Panic disorder during pregnancy. J Psychosom Obstet Gynaecol 1989;10:193–210
180. Cohen LS, Sichel DA, Faraone SV, et al. Course of panic disorder during pregnancy and the puerperium: a preliminary study. Biol Psychiatry 1996;39:950–954
181. Northcott CJ, Stein MB. Panic disorder in pregnancy. J Clin Psychiatry 1994;55:539–542
182. Villeponteaux VA, Lydiard RB, Laraia MT, et al. The effects of pregnancy on preexisting panic disorder. J Clin Psychiatry 1992;53:201–203
183. George DT, Ladenheim JA, Nutt DJ. Effect of pregnancy on panic attacks. Am J Psychiatry 1987;144:1078–1079
184. Klein DF, Skrobala AM, Garfinkel DS. Preliminary look at the effects of pregnancy on the course of panic disorder (technical note). Anxiety 1994; 1:227–232
185 Cohen L. Prospective study of panic disorder during pregnancy and the postpartum period. In: Syllabus and Proceedings Summary of the 1996 Annual Meeting of the American Psychiatric Association; New York, NY: May 4–9, 1996; No. 25:11
186. Robinson L, Walker JR, Anderson D. Cognitive-behavioural treatment of panic disorder during pregnancy and lactation. Can J Psychiatry 1992;37: 623–626
187. Buttolph ML, Holland A. Obsessive compulsive disorders in pregnancy and childbirth. In: Jenike M, Baer L, Minichiello WE, eds. Obsessive Compulsive Disorders, Theory and Management. Chicago, Ill: Yearbook Medical Publishers; 1990
188. Ingram IM. Obsessional illness in mental hospital patients. J Ment Sci 1961;107:382–402
189. Neziroglu F, Anemone R, Yaryura-Tobias JA. Onset of obsessive-compulsive disorder in pregnancy. Am J Psychiatry 1992;149:947–950
190. Lo WH. A follow-up study of obsessional neurotics in Hong Kong Chinese. Br J Psychiatry 1967;113:823–832