

Psychiatric disorders during pregnancy

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Summary

Treating women with psychiatric disorders during pregnancy is a challenge for numerous reasons. Balancing the risks and benefits of symptoms and treatments is particularly important during pregnancy because both medication and maternal illness may have adverse effects on the fetus. Communication of options in the management of psychiatric disorders in pregnancy is vital to optimal treatment. One barrier to effective communication has been a paucity of research from which clinicians can draw information, particularly in the area of pharmacological treatment. However, emerging evidence points to the low risk of many psychotropic medications during pregnancy. Uncertainty must not prevent frank risk-benefit discussions from occurring between treating physicians and their pregnant patients. Psychiatrists can prepare themselves for management decisions by reviewing the current literature.

Introduction

Psychiatric disorders, particularly mood and anxiety disorders have the highest prevalence in women during the childbearing years. The lifetime risk for depression in community samples ranges from 10% to 25% for women, with peak prevalence from age 25 through 44 years (Burke *et al.*, 1991). A significant number of women meet diagnostic criteria for mood and anxiety disorders during pregnancy. Symptoms of psychiatric illness such as disturbed sleep, appetite, energy, and interest level may be incorrectly assumed to be symptoms associated with pregnancy. Some women experience the onset of psychiatric symptoms for the first time during pregnancy, while others are already being treated for a psychiatric disorder. Most women are concerned about the safety of prenatal exposure to psychotropic medications.

A major challenge for physicians is that no psychotropic medications have been approved by the Food and Drug Administration for use during pregnancy. Ethical and forensic considerations limit research that includes pregnant women, and pharmaceutical studies routinely exclude pregnant women as participants. Although many pregnant women need medication treatment, they are deterred from taking medication due to lack of information about their safety (Koren *et al.*, 1989). Patients who seek consultation before pregnancy take advantage of the opportunity to review the data on medication exposure, to discuss the potential risk of relapse or symptom exacerbation, and to implement other prophylactic interventions (Hendrick & Altshuler, 2002).

There is no definitive answer to the optimal treatment of women with psychiatric illness in pregnancy. Each woman must be evaluated individually, and the consultation should involve the psychiatrist and the obstetrician as well as the patient's partner and involved family members. Recommendations also depend on the patient's psychiatric history, symptoms in past pregnancies, current severity of symptoms, and response to prior non-pharmacological treatments and medication discontinuation. The risks of pharmacotherapy must be weighed with the risk of illness relapse. Evidence that psychiatric illness, or at least maternal stress, can affect pregnancy outcome and child development is accruing. There are no risk-free decisions; active, informed decisions are the goal. Specific options include continuing medication throughout pregnancy, discontinuing medications before or at conception, and discontinuing medication only for a particular trimester. Ideal treatment planning minimizes risk to the fetus and enables the patient to have few or no psychiatric symptoms during pregnancy.

Teratogenicity overview

Major birth defect incidence in the United States is 2% to 4%, and the cause of 65% to 70% of these defects is unknown (American Medical Association, 1983). Although case reports have served as important sources of linking abnormalities to particular drugs, they cannot establish causality. Case-control or prospective studies are more useful in evaluating the association between exposure and outcome.

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Investigators are working to isolate the effects of medication exposure from other factors that influence pregnancy outcome (Wisner *et al.*, 1999). Existing studies have been criticized due to their non-randomized design, but randomized controlled trials of pregnant women are not conducted for ethical reasons.

Fetal exposure to drugs can be organized into five domains of toxic effects: intrauterine death, physical malformations, growth impairment, behavioral teratology, and neonatal toxicity (Wilson, 1977; Wisner *et al.*, 1999). Insults that produce structural and neurochemical abnormalities of the central nervous system are most likely 14 to 35 days post-conception (Moore & Persaud, 1998). Behavioral teratogen effects, which include learning problems, abnormal activity levels, and impaired problem solving, are not limited to this period of neural tube closure (Hutchings, 1983). In humans, the fetal brain develops throughout gestation and is therefore susceptible to adverse development from medication toxicity even after the first trimester (Vitiello, 1998). This area is of concern when prescribing central nervous system-active drugs during gestation. Behavioral teratogenicity is a poorly understood aspect of teratology because animal behavior models that robustly reflect human drug use are rare (Wisner *et al.*, 1999).

Pregnancy labeling categories by the FDA appear to provide a simple, convenient measure of risk and are often considered by clinicians who make decisions about drug therapy in pregnant women (FDA, 1999). Regulations require that products be classified under one of five letter categories (A, B, C, D, or X) on the basis of risk of reproductive and developmental adverse effects or on the basis of risk weighed against potential benefit. The labeling has been criticized for implying that reproductive risk increases from category A to B to C to D to X, and for creating the impression that drugs within a given category present the same reproductive risk. The FDA classifies most antidepressant medications as pregnancy category C, which includes both drugs for which there is known teratogenicity in animals and drugs with no studies in animals or humans. The established safety of drugs within this category clearly varies. A category C medication for which there is human data showing low risk may be preferable to a category B medication for which there are no human studies. Bupropion is not recommended for pregnant patients since there is little safety data; however, its category B rating might mislead a clinician to use it in pregnant patients as opposed to a better-studied selective serotonin reuptake inhibitor (SSRI) or tricyclic antidepressant.

Depression and pregnancy

The incidence of depression in pregnancy has been estimated at 9–10% (O'Hara *et al.*, 1984; Gotlib *et al.*,

1989). A recent large cohort study suggested that depressive symptoms are actually more common during gestation than in the postpartum period (Evans *et al.*, 2001). Factors that may increase risk for depression in pregnant women include history of depression, younger age, limited social support, a greater number of children, marital conflict, and ambivalence about the pregnancy (Altshuler *et al.*, 1998). In a UK study of 417 hospitalized women (Johanson *et al.*, 2000) given the Edinburgh Postnatal Depression Scale (EPDS), 9.8% of the women were depressed during pregnancy and 7.4% were depressed postpartum. Importantly, only five of the 41 antepartum depressed patients and eight of the 31 postpartum depressed women were identified by their general practitioner as depressed. Patients should be systematically assessed for depressive symptoms, beginning with routine screens in early pregnancy. Self-report or clinician rated scales are measures that can be repeated to evaluate progression of symptoms or response to intervention. Obstetricians often do not explore psychiatric symptomatology, although their patients report a willingness to discuss emotional concerns with them or to accept a referral to a mental health professional (Birndorf *et al.*, 2001).

Severity of maternal depressive symptoms is an important factor in the risk-benefit decision-making process. Uncontrolled maternal depression puts the developing fetus at harm due to substance abuse, poor prenatal care, and suicide attempts (Zuckerman *et al.*, 1989). Fortunately, suicide during pregnancy is rare (Appleby, 1991). There are also multiple psychosocial consequences of depression. Relationship conflicts, decreased ability to care for other children, and loss of employment are examples. Effective treatments for major depression include psychotherapy, antidepressant medication, and electroconvulsive therapy. A reasonable approach is to discuss the strengths and weaknesses of each therapeutic option for major depression in general, and then to describe how pregnancy modifies each option (Wisner *et al.*, 2000). Treatments involve varying degrees of risk, but allowing a woman to be symptomatic during pregnancy also results in costs to the mother and neonate that may be unacceptable. The consequences of no treatment are an important part of the discussion. It is necessary to balance the risk of antidepressant medication exposure with the impact of untreated maternal depression on pregnancy outcome and child development (Cohen & Rosenbaum, 1998). Fetal exposure can be justified by maternal recovery from depression.

Mood disturbance has been associated with poor obstetric outcomes. Fetal heart rate responsivity, as an indicator of fetal well-being, has been shown to be delayed in untreated maternal depression (Allister *et al.*, 2001). Wadhwa *et al.* (1993) demonstrated that perceived life-event stress and anxiety in pregnancy significantly correlated with infant birth weight and

gestational age at birth. Depression and severe stress have been associated with altered fetoplacental function, premature delivery, impaired fetal growth, perinatal complications, and possible long-term childhood behavioral problems (Orr & Miller, 1995; Stott, 1973). Self-reported depression symptoms during the first trimester of pregnancy increase the risk of delivering a low-birth-weight infant, having a pre-term delivery, or having a small-for-gestational age neonate (Steer *et al.*, 1992). Spontaneous pre-term labor was strongly correlated with women with depression and low pre-pregnancy body mass index (Dayan *et al.*, 2002). Kurki *et al.* (2000) reported a significant relationship between score on the Beck Depression Inventory and pre-eclampsia in a prospective study of 623 pregnant women. In a prospective study of 959 women given the Beck Depression Inventory, depression in late pregnancy was associated with increased risk of epidural analgesia, operative delivery, and neonatal care unit admission (Chung *et al.*, 2001). Investigators postulated a relationship between a high score on a Center for Epidemiologic Studies Depression Scale and higher frequency of cesarean or assisted vaginal delivery, but their findings did not support this association (Wu *et al.*, 2002).

The effect of stress or anxiety on pregnancy is presumed to be mediated by the activated hypothalamic-pituitary-adrenal (HPA) axis, including the derived adrenocorticotrophic hormone and β -endorphin (Sandman *et al.*, 1994). Hypothalamic-pituitary-adrenal axis activation is one of the most reliable findings in neuroendocrine studies of non-pregnant patients with major depression. Another recent hypothesis relates depressive and anxiety symptoms in pregnancy to changes in the metabolism of serotonin, such as lower serum tryptophan (Claes *et al.*, 1997). This was further conceptualized by Maes *et al.* (2002) as an increased catabolism of the serotonin precursor, tryptophan, into kynurenine from immune activation in the early puerperium. Maternal stress in animals has been associated with fetal hypoxia, low birth weight, smaller litter size, miscarriage, and fetal hypotension (Istvan, 1986). A recent prospective longitudinal study tested a hypothesis (based on animal experiments) that antenatal stress in humans predisposes infants to behavioral disturbance (O'Connor *et al.*, 2002). The authors reported that maternal antenatal anxiety predicted offspring behavioral problems at four years and that this effect was likely due to a direct causal mechanism in the antepartum period. Another study of pregnant rats showed that developmental delays were incurred from restraint stress, and that this effect could be offset by the use of diazepam (Barlow *et al.*, 1979). This is an important finding because it suggests that untreated maternal illness was more detrimental to offspring development than gestational psychotropic medication.

Treatment decision-making

A four-pronged approach to enhance decision-making by depressed pregnant patients has been proposed by Coverdale *et al.* (2002), and includes: (1) depression screening, (2) assessing the effects of depression on decision-making capacity, (3) counseling about the adverse consequences of depression on pregnancy, and (4) providing information to patients about the options for treatment. Wisner *et al.* (2000) contributed a model for risk-benefit decision-making that emphasized the importance of informed consent, and the physician responsibility to formulate the diagnosis, identify the risks and benefits, and present the options for treatment. Patients prefer that these problem-solving tasks be performed by the physician, while also wanting to actively participate in understanding the possible outcomes and making the final treatment choice (Deber *et al.*, 1996). The mother has to make a decision about her risk and the risk to the fetus, with the possibilities for positive, negative, or mixed outcomes for both. It is important to understand that patients will have their own assessment of the relative value for each outcome (Wisner *et al.*, 2000). Teratogenic risk is often incorrectly magnified based on media influence or intuitive uncertainty and dread. Risk assessment is also influenced by the way physicians present statistics (Slovic, 1987), and by whether the patient feels the risk was voluntarily incurred. Other factors include familiarity with a treatment from prior exposure, permanence of a potential defect, and the time of manifestation of the undesired outcome (Bogardus *et al.*, 1999). Perceptions of risk can be altered by providing information through counseling (Koren *et al.*, 1989). The strongest predictors of patients' treatment decisions are the recommendations directly given by the physician (Siminoff & Fetting, 1989). Physicians must take care to act on behalf of the patient and to be aware of their own biases for overestimating risk based on prior negative outcome cases or fear of malpractice lawsuits. Risk of legal action is minimized by proper documentation of informed consent and evidence that a risk-benefit discussion took place. It is also always preferable for the obstetrician to be involved with the treatment plan.

Antidepressant medications

Antidepressants have been in use for four decades and there are no known birth defects related to antidepressant use during pregnancy (Newport *et al.*, 2001). All antidepressants cross the placenta. Neither tricyclic antidepressants (TCAs) nor selective serotonin reuptake inhibitors (SSRIs) have been associated with serious teratogenic effects. There was no significant association between exposure to tricyclic antidepressants and congenital malformations

in a meta-analysis of 414 cases of first-trimester exposure to tricyclic antidepressants (Altshuler *et al.*, 1996). Four controlled studies have evaluated outcomes of prenatal SSRI and TCA exposure (Pastusczak *et al.*, 1993; Chambers *et al.*, 1996; Nulman *et al.*, 1997; Nulman *et al.*, 2002). Analyses of these studies have shown that exposure to tricyclic antidepressants or SSRIs did not increase risk for intrauterine death, major birth defects, or neuro-behavioral deficits (Wisner *et al.*, 1999; Addis & Koren, 2000). Reports of the association of growth deficits and minor anomalies with prenatal fluoxetine exposure have been inconsistent. Another controlled study by Einarson *et al.* (2001) reported that among 150 prospectively studied women who took venlafaxine during pregnancy, the incidence of major malformations was the general population rate of 1–3%.

Using the Swedish birth registry, Ericson *et al.* (1999) reported 969 cases of prenatal exposure to antidepressants including SSRIs and TCAs. Perinatal complication and congenital malformation rates were comparable to population norms. Premature delivery among singletons was more common in antidepressant-exposed fetuses, but the authors conclude that depression may explain this difference. Cohen *et al.* (2000) evaluated the effects of early versus late pregnancy fluoxetine exposure and found no differences in birth weight and acute neonatal outcome across the two groups, although there was a higher frequency of special care nursery admissions for newborns exposed in late pregnancy. Citalopram is an SSRI that has been less well studied in pregnancy but was included in the study by Ericson *et al.* (1999). Citalopram's use in a sample of 11 pregnant patients has been reported by Heikkinen *et al.* (2002) and the delivery outcome and neuro-development of infants up to the age of one year was normal.

Simon *et al.* (2002) assessed outcomes of prenatal exposure to tricyclics ($n=209$) or SSRIs ($n=185$) and attempted to decrease methodological bias by selecting a non-volunteer population based sample and by blinding clinical examination and data analysis. Major limitations of the study included reliance on pharmacy records rather than verifying actual medication use and reliance on routine pediatric visits to identify malformations or developmental delay. The results showed no differences between matched controls and tricyclic exposed infants in gestational age, birth weight, head circumference, and Apgar scores. In the SSRI exposed group, gestational age, birth weight, and Apgar scores were all significantly lower than unexposed controls. Significant differences in weight were not observed after six months. When analyzed by trimester exposure, Apgar scores were only lower in infants exposed to SSRIs in the third trimester. In either SSRI or tricyclic exposed infants, no differences with unexposed infants were observed

in rates of major or minor malformation, developmental delay, or other neurological disorders.

The Toronto Motherisk Program published another prospective, controlled study of child development following exposure to tricyclic antidepressants or fluoxetine throughout gestation (Nulman *et al.*, 2002). The original 1997 study (Nulman *et al.*, 1997) focused primarily on first-trimester exposure, whereas the current study tested mother-child pairs exposed to tricyclics ($n=46$) or fluoxetine ($n=40$) throughout all trimesters. When compared with an unexposed, non-depressed comparison group ($n=36$), neither tricyclic antidepressants nor fluoxetine adversely affected the child's global IQ, language development, temperament, or behavior by assessment at ages 15–71 months. However, they did find that duration of depression was significantly and negatively associated with IQ, and that the number of depressive episodes after delivery had a negative relationship with language scores. The authors concluded that uncontrolled maternal depression is a risk factor for adverse cognitive and language development, rather than gestational use of antidepressant medication.

Perinatal syndromes in infants exposed to TCAs and SSRIs have been reported in some studies and symptoms were usually mild and transient. Tricyclic antidepressant treatment through delivery has been associated with a neonatal withdrawal syndrome that includes transient jerky movements and seizures (Cowe *et al.*, 1982), tachypnea, tachycardia, irritability, feeding difficulties, and profuse sweating (Webster, 1973). Constipation and urinary retention as a result of the direct anticholinergic effects of TCAs has also been described in newborns (Wisner & Perel, 1988). Cohen *et al.* (2000) observed higher rates of perinatal complications (e.g. tachypnea, jitteriness, premature delivery) in third trimester use of fluoxetine. Neonatal toxicity from SSRIs (i.e., hypotonia and difficulty feeding) was also observed in the study of fluoxetine by Chambers *et al.* (1996), and by Mhanna *et al.* (1997). Similar transient difficulties have been noted in infants prenatally exposed to sertraline (Kent & Laidlaw, 1995). Paroxetine exposure in the third trimester was recently associated with a high rate of neonatal complications including respiratory distress, hypoglycemia, and jaundice which may relate to a discontinuation syndrome (Costei *et al.*, 2002). Tapering the antidepressant prior to delivery is a consideration to reduce the risk of direct drug effects in the newborn, but this may not be clinically appropriate since the mother would then be at risk of depression relapse (Wisner *et al.*, 1999).

Little information is available on the safety of bupropion, nefazodone, and trazodone use in pregnancy. In a case series of seven women who used mirtazapine in pregnancy, Saks (2001) found no perinatal complications or congenital malformations. The use of monoamine oxidase inhibitors (MAOIs)

is not generally recommended during pregnancy, particularly because of the risk of hypertensive crisis. Also, tocolytic agents may be needed during premature labor and are contraindicated in patients on MAOIs. A high relative risk of 3.4 was reported for congenital malformations in a study of 21 infants prenatally exposed to MAOIs (Heinonen *et al.*, 1977). Gracious & Wisner (1997) described the use of phenelzine throughout pregnancy and reviewed obstetrical and analgesic management.

From the reviewed prospective data, it can be gleaned that there is no evidence that exposure to tricyclic antidepressants (as a group), fluoxetine, newer SSRIs (sertraline, paroxetine, fluvoxamine, and citalopram), or venlafaxine during pregnancy increases the risk for intrauterine fetal death or major birth defects. Behavioral teratogenicity risk appears low based on the measures of comprehension, temperament, activity level, and general behavior in the studies by Nulman *et al.* (1997; 2002). The findings of birth weight and growth differences are not consistent across available studies; however, it makes clinical sense to monitor weight gain in pregnant women who are treated with antidepressants (Wisner *et al.*, 1999). Nortriptyline has been identified by Wisner & Perel (1988) as a favorable tricyclic antidepressant during pregnancy because of its long history of use, relatively lower anticholinergic side effect profile, and well-established therapeutic drug levels. Preferential consideration may be given to another tricyclic if it is already known to be effective based on prior response in a given patient. However, SSRIs are commonly used due to low toxicity and many women have had a good response to these medications.

Neonatal complications related to maternal SSRI use have been reported (Chambers *et al.*, 1996). The study of paroxetine by Costei *et al.* (2002) revealed a notably high prevalence of perinatal complications. However, it would be premature to use half-life as a clinical determinant in drug selection for pregnant women. Use of newer agents with limited safety data puts patients at risk for unknown adverse effects. When engaging in the decision-making process, the insufficiency of knowledge about new drugs must be appropriately presented. Additionally, a woman who has responded well to a newer agent that has not been prospectively studied will have to weigh the risk of unknown teratogenicity against the use of a drug that has been studied prospectively but may not be as effective for her (Bogardus *et al.*, 1999).

Dosing

Pregnant women may not receive adequate antidepressant dosing due to the common practice of reducing the dose to decrease exposure. Dose requirements during pregnancy may actually be increased due to physiological changes such as

increased hepatic metabolism and volume of distribution as well as changes in protein binding and gastrointestinal absorption (Livezey & Rayburn, 1992). Serum concentrations may fall below the therapeutic index during pregnancy and depressive symptoms may emerge (Altshuler & Hendrick, 1996). The dosage of tricyclic antidepressant had to be progressively increased in a case series of eight women across gestation for maintenance of clinical response and therapeutic serum levels (Wisner *et al.*, 1993). The final dose achieved had an average increase of 1.6 times the dose when the patient was not pregnant. In the immediate postpartum period, TCA dosage should be decreased to the pre-pregnancy dosage, or, if that dose is unknown, to one third of the current dose (Wisner *et al.*, 1999). In a naturalistic study of depressed pregnant women on SSRI monotherapy, two thirds of the subjects required an increase in medication to maintain euthymia, which may be related to pregnancy related physiological changes (Hostetter *et al.*, 2000).

Psychotherapy

Psychotherapy remains an important treatment that can be used independently of or in addition to medication. Many women refuse any medications when they are pregnant or breastfeeding (Young *et al.*, 2002). Maintenance interpersonal psychotherapy has been shown to significantly increase the median time to recurrence of a major depressive episode (Frank *et al.*, 1990). It can also be successfully adapted to treat pregnant patients with depression (Spinelli, 1997). Difficulties in social environment, especially with regard to friends, partner, and own mother was established as having an independent association with antenatal depression (Pajulo *et al.*, 2001). It is recommended that psychotherapy be incorporated into management of all pregnant women with depression, but additional pharmacotherapy is advisable for severe depression.

Electroconvulsive therapy (ECT)

Electroconvulsive therapy for severe depression, mania and schizophrenia has been used safely and effectively during pregnancy (Miller, 1994). The use of ECT in pregnancy has been described in case reports but has not been examined in controlled studies (Ferrill *et al.*, 1992). Reported complications from case studies include mild vaginal bleeding, abdominal pain, transient uterine contractions, benign fetal arrhythmias, and premature labor. The short-term administration of anesthetic agents with ECT may present less teratogenicity risk than other pharmacological treatment options (Shnider & Levinson, 1993). Succinylcholine is not sufficiently transferred across the placenta, and there is little

effect on the fetus (Guay *et al.*, 1998). Preparation for ECT during pregnancy should include a pelvic examination, discontinuation of anticholinergic medication, uterine tocodynamometry, intravenous hydration, and administration of a non-particulate antacid (Miller, 1994). External fetal cardiac monitoring should occur during ECT, and an obstetrician should be included as a member of the treatment team.

Bipolar disorder and pregnancy

The effect of pregnancy on the course of bipolar disorder is unclear (Altshuler *et al.*, 1998). Some authors report a protective effect of pregnancy in women with bipolar disorder when compared with the period prior to and after pregnancy (Grof *et al.*, 2000). Freeman *et al.* (2002) demonstrated that pregnancy did not confer protection from mood symptoms and noted that depression during pregnancy in bipolar women is significantly associated with postpartum mood episodes. In another large study, almost half of the women with bipolar disorder experienced symptom exacerbation during pregnancy (Blehar *et al.*, 1988). Viguera *et al.* (2000; 2002a; 2002b) reported that pregnancy in bipolar women presents as a risk factor for symptom exacerbation when maintenance treatment is rapidly discontinued. Ideally, women with bipolar disorder who wish to become pregnant should be cautiously tapered off of medication as a trial prior to pregnancy (Viguera *et al.*, 2002a; 2002b). If the patient relapses, this offers valuable information about her ability to have a medication-free pregnancy. Treatment of bipolar disorder in pregnancy presents particular challenges to patients and clinicians due to strong genetic loading, high risk of relapse with treatment discontinuation, and potential teratogenic risks of standard psychotropics. Women with bipolar disorder are particularly prone to relapse after discontinuing maintenance medication, which has important consequences (Baldessarini *et al.*, 1999). A slow taper appears to lessen the risk of mood episode recurrence compared to abrupt discontinuation. Clinicians and patients are not well informed about the rates of relapse in pregnancy without standard treatment (Freeman *et al.*, 2002).

Cohen *et al.* (1994) note that first-trimester exposure to lithium increases the risk of cardiac malformations, primarily Ebstein's anomaly, by several-fold to a risk ranging from 0.05% to 0.1% (1 in 2,000 to 1 in 1,000 live births). This is a lower risk than previously presented (Weinstein & Goldfield, 1975) due to the reporting bias of voluntary registries. Ebstein's anomaly is a defect of the tricuspid valve with a variable prognosis, and management is based on the severity of disease. Lithium use in pregnancy has also been associated

with premature labor, polyhydramnios, neonatal hypothyroidism, and lithium toxicity (Altshuler *et al.*, 1996), as well as rhythm disturbances, nephrogenic diabetes insipidus, hypoglycemia, cyanosis, hypotonia, and hyperbilirubinemia (Pinelli *et al.*, 2002). In a prospective multicenter study, Jacobson *et al.* (1992) did not find lithium exposure to be an important teratogen, although one patient in the lithium group chose to terminate pregnancy after Ebstein's anomaly was detected. Rosa (1994) reported two infants with birth defects in a study of 62 newborns exposed to lithium, and concluded no association between lithium and congenital malformations. The literature on neonatal toxicity with lithium is inconsistent, but a recent survey reported no direct evidence of toxicity (Cohen *et al.*, 1995). No significant behavioral problems or neurocognitive differences were reported in studies of children who had been exposed to lithium *in utero* (Schou, 1976; Viguera *et al.*, 2001). The absolute risk of serious adverse effects to lithium-exposed infants is relatively small, and clinicians must balance the teratogenic risks with the risk of symptom relapse. Current practice favors lithium continuation for pregnant bipolar women with good lithium response (Pinelli *et al.*, 2002).

When compared with lithium, the teratogenic effects associated with valproic acid and carbamazepine occurs more frequently. These risks include 1–5% rates of neural tube defects such as spina bifida, as well as craniofacial abnormalities, cardiac anomalies, microcephaly, limb defects, genital anomalies, growth retardation, and hydrocephalus (Viguera *et al.*, 2002a; 2002b; Altshuler *et al.*, 1996). Valproate exposure *in utero* increases the risk for major and minor congenital anomalies during organogenesis, as well as intrauterine growth retardation, hypoglycemia, and coagulopathy in late pregnancy (Iqbal *et al.*, 2001). Carbamazepine exposure *in utero* is associated with major and minor anomalies, and has other effects on development, growth, IQ, and coagulopathy. Studies of anti-epileptic teratogenicity have occurred in epileptic patients; effects may be different in bipolar women. Yerby (1987) reported that women with epilepsy on anticonvulsants are at two times greater risk for having a child with a major birth defect. Lindhout & Omtzigt (1994) reported an absolute risk of 7–10% for major malformations in the infants of women with epilepsy who were prenatally exposed to anti-epileptic drugs. They specifically recommend dividing and decreasing the daily dose of valproic acid for reduction of teratogenicity. Divided doses have also been recommended for carbamazepine and lithium (Iqbal *et al.*, 2001). High maternal serum anti-convulsant levels and treatment with more than one anticonvulsant may be factors for increased teratogenicity risk (Holmes *et al.*, 2002). Administration of oral vitamin K in the last month of pregnancy is a recommended prophylactic measure to protect the

infant from potential valproate or carbamazepine induced coagulopathy (Iqbal *et al.*, 2001). Data on adverse neurobehavioral effects from gestational anticonvulsants is very limited and difficult to interpret. Scolnick *et al.* (1994) found that phenytoin negatively affected IQ and language development in children exposed *in utero* but carbamazepine did not. Children exposed to valproate prenatally had normal psychomotor development when assessed up to age four (Granstrom, 1982).

Patients who choose to continue on mood stabilizers should receive screening for abnormalities and folic acid supplementation (Delgado-Escueta & Janz, 1992). Maternal serum α -fetoprotein should be measured before the 20th week of gestation as a screening for neural tube defects. Amniocentesis and sonography may then be performed for an elevated value. High-resolution ultrasound examination at 16–18 weeks gestation can detect fetal cardiac abnormalities. After delivery, rapid maternal fluid shifts can markedly increase lithium levels and care should be taken to lower the lithium dose and ensure hydration (Llewellyn *et al.*, 1998). If clinically indicated, newborns with gestational lithium exposure can have two-dimensional echocardiography and an electrocardiogram shortly after birth (Pinelli *et al.*, 2002). Newborns exposed to valproate should receive 1 mg of vitamin K intramuscularly at birth (Delgado-Escueta & Janz, 1992).

Little is known about the potential teratogenicity of newer anticonvulsants including lamotrigine, gabapentin, oxcarbazepine, and topiramate (Ernst & Goldberg, 2002; Lamotrigine pregnancy registry, 2002). At this time, there is not sufficient data to recommend the newer anticonvulsants as first-line agents in the treatment of bipolar disorder in pregnancy.

Verapamil, a calcium channel blocker with substantial safety data, has also been studied for the treatment of bipolar disorder in women (Wisner *et al.*, 2002). Pregnant women who received verapamil responded similarly to those who were not pregnant, and particular benefit was shown for treatment of mania and hypomania in an open series. However, the efficacy of verapamil in patients with bipolar disorder has never been evaluated in controlled trials of sufficient power (Wisner *et al.*, 2002).

Pregnant women with bipolar disorder can best make informed clinical decisions after being presented with the reproductive safety data of the mood stabilizers and with an assessment of the likelihood of illness relapse and the potential effect of such a relapse on fetal development.

Anxiety and pregnancy

Anxiety disorders are among the most common psychiatric disorders and are more prevalent in women than in men (Kessler *et al.*, 1994). It is

therefore probable that a significant number of women suffering from an anxiety disorder will experience a pregnancy in the course of their illness. Weisberg & Paquette (2002) have suggested a thorough assessment of anxiety disorders in pregnant women. Anxiety disorders can be disabling and a case report linked panic attacks with placental abruption in a non-medicated woman with panic disorder (Cohen *et al.*, 1989). Recent research has shown variable effects of pregnancy on anxiety disorders. Some reports speculated that pregnancy precipitates (Neziroglu *et al.*, 1992) or exacerbates obsessive-compulsive disorder (OCD). Pregnancy was retrospectively associated with the onset of OCD in five of 38 interviewed women, and of 29 women with preexisting OCD, 20 described no change during pregnancy, five described worsening, and four described improvement (Williams & Koran, 1997). Retrospective studies have shown that women with panic disorder may experience an improvement during pregnancy (George *et al.*, 1987; Villepontaux *et al.*, 1992), but a prospective study reports that most will continue to experience clinically significant symptoms (Cohen *et al.*, 1996). Northcott & Stein (1994) retrospectively found that pregnancy did not have a consistent effect on the course of panic disorder. In a historical prospective study of 22 women with panic disorder, the most common effect of pregnancy was no change in symptoms from baseline during pregnancy for both panic attacks and depression (Wisner *et al.*, 1996).

Cognitive-behavioral therapy (CBT) is a well-established intervention for anxiety disorders (Chambless *et al.*, 1996), and CBT is particularly effective for panic disorder and OCD. Robinson *et al.* (1992) have reported on the successful use of CBT for panic disorder during pregnancy, and Chelmos & Halfin (1997) described a 'thought stopping' behavioral technique in a case report of OCD in pregnancy. Many advocate for cognitive-behavioral therapy as a first line treatment of anxiety disorders in pregnancy, and for SSRIs as the first line of pharmacotherapy (Shear & Mammen, 1995). Nortriptyline (Hendrick & Altshuler, 1997) and imipramine (Ware & DeVane, 1990) have also been described in case reports for treatment of panic disorder during gestation. Benzodiazepines are used for multiple indications in psychiatry, including anxiety disorders, depression and mania. Because safer treatments (e.g., cognitive-behavioral therapy and SSRIs) are available, anxiolytics should be avoided during pregnancy, particularly in the first trimester. If they are used, the prescription should be for the lowest dose and shortest duration possible. Wisner & Perel (1988) favor lorazepam as the benzodiazepine of choice during gestation.

The studies of benzodiazepine teratogenicity risk are inconsistent (McElhatton, 1994). Benzodiazepine use has been associated with an increase in the incidence of malformations including orofacial clefts

(Safra & Oakley, 1975; Laegreid *et al.*, 1990). However, in a prospective study by St Clair & Schirmer (1992), alprazolam exposure during the first trimester was not associated with increased rates of spontaneous abortion or stillbirth. In a meta-analysis of the risk of oral cleft or major malformations, benzodiazepines were associated with greater risk in the case-control studies but there was no association in the cohort studies (Dolovich *et al.*, 1998). Neonates may exhibit the 'floppy infant syndrome' characterized by hypotonia and sedation if benzodiazepines were used for a prolonged period or near term, and they can also experience a withdrawal syndrome of irritability and hypertonicity (Wisner & Perel, 1988). Behavioral teratogenicity reports are inconsistent. Viggeda *et al.* (1993) found mental and motor developmental delays in toddlers with gestational exposure to benzodiazepines, but Hartz *et al.* (1975) did not show such an association. The safety during gestation of the non-benzodiazepine anxiolytic buspirone has not been studied.

Psychosis and pregnancy

Psychosis can occur during pregnancy in women with major depression, bipolar disorder or schizophrenia. Pregnancy, as defined separately from the puerperium, has not been identified as a period of increased risk for psychosis (Kendell *et al.*, 1987), although Brockington *et al.* (1990) described four case reports of prepartum psychosis and linked the phenomenon to postpartum psychosis. Some reports indicate an improvement in psychotic symptoms during pregnancy (Lier *et al.*, 1989; McNeil & Malmquist-Larsson, 1984).

Women with schizophrenia are at increased risk for poor obstetrical outcome, and many factors contribute to this finding, including cigarette smoking, alcohol use, drug use, and low socioeconomic status (Bennedsen, 1998). In a meta-analysis of infants born to women with schizophrenia, there was evidence of a small but significantly increased risk for low birth weight and poor neonatal condition (Sacker *et al.*, 1996). Nilsson *et al.* (2002) report significantly increased risks for stillbirth, infant death, pre-term delivery, low birth weight, and small-for-gestational-age diagnosis among the infants of women with schizophrenia. The risk was reduced when cigarette smoking and other maternal factors were controlled. A study that utilized the Danish Medical Birth Register (Bennedsen *et al.*, 2001) showed no evidence that women with schizophrenia have a greater frequency of specific obstetric complications, but they are at increased risk for interventions during delivery. Maternal obesity and low folate intake may be predictors of risk for increased neural tube defects in the infants of women with schizophrenia (Koren *et al.*, 2002).

Antipsychotic agents may be required during pregnancy for the treatment of schizophrenia, affective psychosis, or mania. Potential risks include congenital abnormalities, neonatal toxicity, and neurobehavioral sequelae (Patton *et al.*, 2002). A small increase in overall congenital malformations has been seen with low-potency antipsychotics (e.g., chlorpromazine), while higher-potency agents (e.g., haloperidol) appear to create no increased risk (Altshuler *et al.*, 1996). There is no evidence of teratogenicity with exposure to haloperidol, perphenazine, thiothixene, thioridazine, or trifluoperazine (Wisner & Perel, 1988). Fluphenazine exposure has not been associated with an increased risk for congenital anomalies, perinatal mortality or premature birth in a retrospective study by Brougher (1960). The higher potency antipsychotics tend to be recommended clinically because they are less likely to have associated anticholinergic, antihistaminergic, or hypotensive effects compared to the lower potency antipsychotics (Wisner & Perel, 1988). However, when used near term, neonates may show transient extrapyramidal side effects including motor restlessness, tremor, dystonia, and parkinsonism (Auerbach *et al.*, 1992). Platt and colleagues (1988) showed that prenatal exposure to typical antipsychotic medication significantly affected the height and weight of children followed prospectively. Despite abnormal behavior observations up to seven months, subsequent motor development up to age five years was normal in a longitudinal study of children exposed to low-potency neuroleptics *in utero* (Desmond *et al.*, 1967).

There are no adequate human studies to evaluate the risk of clozapine, risperidone, olanzapine, quetiapine, or ziprasidone during pregnancy (Ernst & Goldberg, 2002). A registry from the manufacturer of clozapine (Registry of Clozaril, 2002), the oldest atypical antipsychotic, has been collected on babies exposed to clozapine before birth, and the few reported abnormalities could not be directly associated with clozapine teratogenicity. Clozapine case reports have yielded no evidence of major malformations (Waldman & Safferman, 1993; Stoner *et al.*, 1997; Dickson & Hogg, 1998). Olanzapine's manufacturer has also established a registry for which reported adverse effects of gestational use have been found to fall within the range of normal historic control rates (Goldstein *et al.*, 2000). Gestational diabetes was reported by two women with no family or personal history. Again, manufacturer registries have limited usefulness. Weight gain is a known side effect of the atypical antipsychotics and prenatal exposure may contribute to negative infant outcomes (Koren *et al.*, 2002). Continued maintenance treatment for many women with psychotic disorders is recommended because re-emergence of symptoms may prevent the patient from obtaining prenatal care or may result in direct harm to the fetus

(Cohen & Rosenbaum, 1998). Hospitalization of the acutely psychotic pregnant patient should always be considered.

New research

Complementary and alternative medicine therapies with indications related to psychiatry have become widespread. Despite their popularity, caution is required until more safety and efficacy data are available. The popular herbal antidepressant, Saint John's wort, is not recommended for pregnant women. Studies of mice offspring that received the drug throughout gestation showed no long term behavioral, maturational, or growth deficits (Rayburn *et al.*, 2001; 2000). Omega-3 fatty acids have become an interesting new area of psychiatric research, and have been evaluated in the treatment of depression (Nemets *et al.*, 2002), bipolar disorder (Stoll *et al.*, 1999), borderline personality disorder (Zanarini & Frankenburg, 2003), and schizophrenia (Puri *et al.*, 1998). Hibbeln (2002) has associated insufficient dietary intake of omega-3 fatty acids with depressive symptoms from maternal depletion of these essential fatty acids during pregnancy. Recent case reports discuss the successful use of omega-3 fatty acids as monotherapy treatment in a pregnant woman with major depression (Chiu *et al.*, 2003) and with a pregnant woman with schizophrenia (Su *et al.*, 2001). Omega-3 fatty acid treatment may actually provide health benefits during pregnancy and lactation for both mother and baby (Freeman, 2000). Pregnant women who wish to supplement their diet with omega-3 fatty acids may eat three servings of uncontaminated fish per week, take daily fish oil supplements, or add flaxseed to their diet (Cott, 2000).

Avoidance of drug exposure in pregnancy has created interest in less well-studied novel modalities. Manber and associates (2002) reviewed promising alternative treatments for depression in women including exercise, stress reduction methods, bright light exposure, sleep deprivation, and acupuncture. Bright light therapy has been used to treat seasonal affective disorder, and has been found by Oren *et al.* (2002) to be efficacious in an open pilot study of pregnant women with depression. Mean depression ratings improved by 49% and there was no evidence of adverse effects of light therapy on pregnancy. Partial sleep deprivation has also been suggested as a potential modality in the treatment of antenatal depression (Parry *et al.*, 2000). High-density negative air ionization is another proposed treatment for seasonal depression in pregnant women (Terman *et al.*, 1998). Rapid transcranial magnetic stimulation has also been suggested as a treatment for depression (Nahas *et al.*, 1999), and, unlike ECT, does not require general anesthesia.

Conclusions

In general, many psychotropics have been reported to have no apparent adverse consequences during pregnancy. However, more research is needed to expand our knowledge about the effects of both psychiatric illness and available treatments on maternal and fetal health. More sophisticated understanding of psychotropics already in wide use will provide more confident decision-making when selecting an agent or when deciding to continue an agent through pregnancy. Certainly, areas of research that focus on non-pharmacological interventions may prove useful to patients unable or unwilling to tolerate the risks or side effects of established treatments. The physician and patient should discuss the known teratogenicity data as well as acknowledge the unknown or non-quantifiable risks. The risk of non-treatment should be incorporated with an objective account of the benefits of treatment. Documentation of the risk-benefit discussion, including the patient's perceived understanding and plan agreement, is highly important. The physician can use the available evidence with consultation skills to guide the decision-making process for optimum outcome for the mother and fetus.

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