

Effects of Antimanic Mood-Stabilizing Drugs on Fetuses, Neonates, and Nursing Infants

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ABSTRACT: Pregnancy presents a special problem to the clinician treating bipolar disorders in women. Since the first episode of mania typically occurs before the age of 30, many women in their prime childbearing years may be exposed to potentially teratogenic mood-stabilizing agents. This exposure may also continue for the nursing infant during lactation. Pregnancy itself can exacerbate bipolar symptoms and also alter the pharmacokinetics of mood-stabilizing drugs. Risks to mother and fetus can be reduced with a number of simple strategies, including monotherapy with the lowest effective dose of a drug for the shortest period necessary, periconceptional use of multivitamins with folate, prescription of drugs with established safety records, and avoidance of exposure to antimanic agents during the first trimester of pregnancy. In this article, we review existing evidence on the risks to fetuses and nursing infants of mothers taking specific mood-stabilizing agents, and we present appropriate management guidelines designed to minimize these risks.

UNTREATED BIPOLAR DISORDER can place a pregnant woman and her unborn infant in significant danger. It may cause a serious disruption of functioning that requires a need for prolonged hospitalization; a vulnerability to suicidal ideation and violence; or loss of employment, housing, and social support. Other risks include malnutrition, attempts at premature self-delivery, fetal abuse or infanticide, noncompliance with prenatal care, and a higher risk of postpartum psychosis.

The patient's clinician must make a risk-benefit assessment that weighs the risks of untreated mental illness against the potential harm of using psychotropic medications to manage this condition in both fetus and mother. The clinician should discuss these risks with the patient in a way that considers the wishes of the patient and the experience and level of comfort of the clinician.

All major classes of psychotropic medications, including antimanic drugs, can be assumed to diffuse readily across the placenta to the fetus or

to be excreted into milk. The mechanism of this transfer depends on a number of pharmacokinetic factors, such as (1) the drug's lipid solubility, (2) its molecular weight, (3) maternal blood levels, (4) plasma protein binding, (5) oral bioavailability in the mother and the infant, (6) the pK_a (pH at which the drug is 50% ionized),¹ and (7) the half-life of the drug in maternal and neonatal circulation. Of these many factors, perhaps the two most important and useful are the lipid solubility and the molecular weight of the drug. The transfer of a drug across the placenta is directly proportional to its lipid solubility and inversely proportional to its molecular weight. Compounds with a molecular weight less than 600 are relatively permeable, and those with a molecular weight greater than 1,000 are considered relatively impermeable.²

Antimanic agents are indicated for treatment of acute manic episodes and maintenance of remission in bipolar disorders and make up several classes of pharmacologic agents (Table), including lithium, the first-generation anticonvulsants (carbamazepine and valproic acid [VPA]), the second-generation anticonvulsants (gabapentin, lamotrigine, and topiramate), conventional antipsychotic medications (chlorpromazine, haloperidol, fluphenazine, and thiothixene), atypical antipsychotics (clozapine, risperidone, and olanzapine), and the benzodiazepines (clonazepam).

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TABLE. Drugs Used in Bipolar Disorder

Classification	Pregnancy Category*	Usual Oral Adult Dosage Range (mg/day)
<i>Antimanic and Mood-Stabilizing Drugs</i>		
Lithium (Eskalith, Lithane, Lithobid, Lithonate)	D	1,200-2,400 (acute); 900-1,200 (maintenance)
<i>First-generation anticonvulsants</i>		
Valproic acid (Depakene, Depakote, Depacon)	D	15-40 mg/kg/day (20 mg/kg loading dose)
Carbamazepine (Tegretol, Carbatrol)	C	400-1,600 (10-20 mg/kg/day)
<i>Second-generation anticonvulsants</i>		
Gabapentin (Neurontin)	C	300-3,600
Lamotrigine (Lamictal)	C	50-500
Topiramate (Topamax)	C	50-400
<i>Antimanic Drugs</i>		
<i>Conventional or standard antipsychotic agents</i>		
Chlorpromazine (Thorazine)	C	50-2,000
Haloperidol (Haldol)	C	6-20
Fluphenazine (Prolixin)	C	1-20
Thiothixene (Navane)	C	6-30
<i>Atypical antipsychotic agents</i>		
Clozapine (Clozaril)	C	75-900
Risperidone (Risperdal)	C	4-6
Olanzapine (Zyprexa)	C	10-20
<i>Benzodiazepines</i>		
Clonazepam (Klonopin)	C	0.5-20
<i>Antidepressants</i>		
Lithium (Eskalith, Lithane, Lithobid, Lithonate)	D	1,200-2,400 (acute); 900-1,200 (maintenance)

*The United States Food and Drug Administration (FDA) has derived a system of Pregnancy Categories "based on the degree to which available information has ruled out risk to the fetus, balanced against the drug's potential benefits of the patients." Drugs are assigned to one of the following categories:

A = controlled studies show no risk; B = no evidence of risk in humans; C = risk cannot be ruled out; D = positive evidence of risk; X = contraindicated in pregnancy.

Patients with bipolar disorder often show fluctuations in mood during long-term maintenance. Although conventional antipsychotics can be used to control these episodes, these agents are associated with several concerns.^{3,4} First, no compelling data from controlled trials support the efficacy of these agents as maintenance therapy.^{5,6} Second, maintenance with antipsychotic drugs may be associated with the exacerbation of depressive symptoms in some patients.^{7,8} Third, the risk for development of extrapyramidal movement disorders appears to be higher in patients with bipolar disorder than in schizophrenics.^{9,10}

Lithium, the first modern antimanic agent, was approved in 1970 by the United States Food and Drug Administration (FDA) for treatment of acute mania and for maintenance in bipolar disorder and is widely regarded as the standard antimanic therapy, whether it is used alone or in combination with other anticonvulsant drugs.¹¹ It is different from other psychotropic agents in that it is not a sedative, depressant, or euphoriant.

The two first-generation anticonvulsants, valproate and carbamazepine, have also been shown to be effective in the treatment of acute mania.¹² Valproate was approved in the United

States in 1978 and has poor to moderate antidepressant properties in addition to its antimanic properties.¹³ Bipolar patients with anxiety disorder are best treated often with VPA. Open-label and case study data also support the use of VPA in panic disorder,^{14,15} obsessive-compulsive disorder,^{16,17} and posttraumatic stress disorder.¹⁸ Carbamazepine has been in use for more than 27 years but has been acknowledged as a first-line antiepileptic drug only in the past decade.¹⁹ It has also been found to produce therapeutic responses in manic-depressive patients, including those resistant to lithium. Both VPA and carbamazepine have limited antidepressant effects and may have a tendency to induce mania or decrease cycle lengths.

Second-generation anticonvulsants (gabapentin, lamotrigine, topiramate, vigabatrin, tiagabine, felbamate, and fosphenytoin) approved by the FDA are recommended as adjunctive therapy for seizures.²⁰ Gabapentin, lamotrigine, and topiramate are thought to have possible antidepressant effects in addition to their mood-stabilizing properties with fewer adverse side effects and are used as adjunctive therapy for manic symptoms.²¹⁻²⁴

The atypical antipsychotics such as clozapine, risperidone, and olanzapine may possess thy-

moleptic properties different from those of the conventional antipsychotics. These atypical agents are commonly used in treating bipolar disorders in the United States. Open trials suggest that clozapine may have acute and long-term mood-stabilizing effects in patients with mixed mania or rapid cycling and in those who are refractory to other mood stabilizers, electroconvulsive therapy, and conventional antipsychotics.^{25,26} A recent placebo-controlled trial suggested that olanzapine has antimanic activity, especially in rapid cycling disorder.^{27,28} A small number of open trials and case reports have also described the efficacy of risperidone in the treatment of acute mania and in rapid cycling.^{29,32}

Clonazepam, a high-potency benzodiazepine, is a useful adjunct in the treatment of acute mania because it aids sleep and decreases agitation. It may be used in conjunction with antimanic agents and to replace or permit lower doses of antipsychotic medications. It has been suggested that continued use of clonazepam might have mood-stabilizing effects with improvement in sleep, possibly preventing some manic relapses, though this is not well established.³³

This review will deal primarily with the various effects of specific antimanic drugs on fetuses, neonates, and nursing infants when these drugs are administered during pregnancy and lactation, considering available data from both human and animal models.

LITHIUM

Risk to Fetus

In Animals. Ample evidence indicates that lithium crosses the placenta freely.^{34,38} Reproductive studies in rats and mice given doses higher than those recommended for humans have shown teratogenic effects such as cleft palate and anomalies of heart, external ear, eye, and skeletal system.³⁵ Fetotoxic effects such as increased perinatal mortality, decreased number and weight of the litters,³⁶ decrease in the number of living offspring,³⁷ and embryotoxic effects³⁸ are also noted. Differing results have been found in the offspring of rats, mice, rabbits, and monkeys exposed in utero to lithium.³⁷

In Humans. Numerous studies have noted an association between first trimester administration of lithium carbonate and incidence of cardiovascular malformations such as Ebstein's anomaly in the neonates.³⁹⁻⁴¹ The International Register of Lithium Babies was started in 1968 to assess this potential teratogenicity of lithium in humans.⁴² As of 1980, 225 infants who had been

exposed to lithium during the first 3 months of prenatal life or longer were included in the register. Among these, 18 infants had the rare Ebstein's anomaly (6 cases) and other anomalies of the cardiovascular system (12 cases); 7 were stillborn; 2 had Down syndrome; and 1 had intracerebral toxoplasmosis. The data from the register suggest an incidence rate of 0.1% for Ebstein's anomaly, which is approximately 20 times the risk in the general population. Another report of data from 1970 to 1985 details nine cases of Ebstein's anomaly in the United States out of an estimated 9,000 exposures.³⁹ Therefore, it appears that risk of fetal malformation, especially pertaining to the cardiovascular system, is increased by first trimester lithium administration.⁴³

A number of other abnormalities have also been reported. Kallen and Tandberg⁴⁴ conducted a cohort study of 350 women with manic-depressive disease. They found a non-significant trend toward higher risks of perinatal mortality and congenital malformations among pregnancies in which lithium had been used in the first trimester, and an increase in cardiac defects in particular, but none with Ebstein's anomaly. In a nested, case-control study observing congenital heart defects in children, Kallen⁴⁵ reported that 3 (27%) of the cases and 4 (20%) of the controls (N = 20) were exposed to lithium in utero. Among these cases, a single child, who was not exposed to lithium, had Ebstein's anomaly. This study showed a statistically insignificant association between prenatal exposure to lithium and congenital heart defects. Similarly, several other studies have found that lithium has been safely used during pregnancy by many patients, suggesting a lack of association between cardiovascular anomalies and prenatal lithium.⁴⁶⁻⁴⁸

Lithium is also known to impair the synthesis and release of thyroid hormones and subsequently increase the pituitary secretion of thyroid-stimulating hormone by its inhibitory action on adenosine triphosphatase activity and cyclic adenosine monophosphate.⁴⁹ Many studies have reported nontoxic goiters in both mothers treated with lithium during pregnancy and their infants.⁵⁰⁻⁵² This may result in a difficult vaginal delivery for the mother, may necessitate a cesarean section, or may impair respiration in the neonate after delivery.

Many authors have reported lithium toxicity, characterized by shallow respiration, muscle flaccidity, hypotonia, absent Moro's reflex, lethargy, cyanosis, and poor suck and grasp reflexes in neonates born to women who received toxic or

therapeutic doses of lithium salts near term or during labor. These toxicities may take up to 10 days to resolve.^{53,55} Other adverse effects reported in the neonate include atrial flutter,⁵⁶ functional tricuspid regurgitation, congestive heart failure,⁵¹ and nephrogenic diabetes insipidus, which may persist for 2 months postnatally.⁵⁷

A study of 241 infants from the Lithium Registry observed an association between maternal treatment with lithium carbonate during gestation and the occurrence of premature delivery (39%), macrosomia (36%), and perinatal mortality (8.3%) in newborns.⁵⁸ A statistically significant association was noted between higher dosages of lithium during the first trimester and premature deliveries, with a significantly higher rate of macrosomia in these premature infants.

In contrast to those findings, Rosa⁵⁹ described a study of 229,101 completed pregnancies (1985 to 1992); of the 62 newborns exposed to lithium during the first trimester of pregnancy, only 2 had birth defects. The data gathered from this study do not support an association between the drug and congenital malformations. Isolated cases of other congenital anomalies in newborns exposed to lithium in utero appear in the literature have included malformed right external auditory canal and meatus,⁶⁰ bilateral clubfoot, lumbar meningocele,⁶¹ polyhydramnios, deep-seated ears, bilateral agenesis of kidneys, and a septal defect with transposition of the great vessels.⁶²

In summary, because of the risk of teratogenicity, especially with regard to the cardiovascular system, lithium should be avoided during the period of organogenesis and if possible throughout pregnancy. A dosage that had been increased during pregnancy must be immediately reduced at delivery, or the mother will have a toxic condition, since lithium clearance increases by 50% to 100% early in pregnancy and returns to normal at delivery. Alternative drugs that have less teratogenic effects on the fetus should be used. When the use of lithium is unavoidable, the risk of teratogenicity can be minimized by monotherapy with the lowest effective dose for the shortest duration, use of a sustained-release preparation of lithium,⁶³ careful monitoring of lithium levels, close collaboration with the obstetrician, and screening for anomalies using ultrasonography and fetal echocardiography between 16 and 18 weeks of gestation.

Risk to Infant During Breast-Feeding

Lithium has been found consistently in both breast milk and infants' serum. Lithium concen-

trations in breast milk have been reported to be approximately 40% (range, 24% to 72%) of the mothers' serum concentrations.^{34,64,65}

We found three case reports of nursing infants who had adverse events that were attributed to lithium.^{55,65,66} The first case, reported by Tunnesen and Hertz,⁶⁶ described cyanosis, hypotonia, heart murmur, T-wave changes on electrocardiography, lethargy, and hypothermia in a nursing infant whose mother received lithium (600 to 1,200 mg/day) while nursing. No lithium levels were reported until day 5, when the baby had a cyanotic episode. At that time, the infant's serum level and the breast milk level of lithium (0.6 mEq/L) were within the therapeutic range, and the mother had a serum lithium level of 1.5 mEq/L. The baby's condition was completely normal by day 8. This type of toxicity is more likely to occur during episodes of dehydration and infection and may be due to a combination of high maternal serum levels while nursing and the residual lithium concentration from birth.^{65,66} Similar findings were also reported in two other studies.⁶⁷ On the basis of these reports, nursing by mothers taking lithium should be either partially or totally discontinued because of the immature excretory systems in the infants, particularly during an infant's illness or infection, or when maternal serum lithium levels are high. However, if lithium is to be used, collaboration with a pediatrician is essential, and the risk-benefit ratio must be discussed with mother and her partner.

VALPROIC ACID

Risk to Fetus

In Animals. Valproic acid is a first-generation anticonvulsant drug that readily crosses the placental barrier. Several researchers in their studies of rhesus monkeys, mice, rats, hamsters, and rabbits have noted VPA-induced teratogenic effects such as craniofacial, skeletal, cardiac, limb, renal, and central nervous system anomalies (ie, neural tube defects and encephaloceles).^{67,68} Fetotoxic effects such as low birth weight and delayed development and embryotoxic effects⁶⁹ were also noted with doses higher than those recommended in humans. Also, behavioral alterations have been reported in the offspring of rats treated during pregnancy with VPA in doses equivalent to those in humans.⁷⁰

In Humans. Valproic acid has been shown to cross the placenta and accumulate in fetal tissues.^{71,72} The use of first-generation anticonvulsant drugs such as VPA, carbamazepine, and

phenytoin in women during pregnancy is associated with a two to three times higher rate of congenital malformations in their offspring.⁷³

Many epidemiologic studies have described an association between first trimester VPA therapy and the occurrence of spina bifida.^{74,76} A ten-fold to 20-fold increase in risk of spina bifida when compared with the general prevalence at birth in most populations has been observed.⁷⁴ The administration of VPA during the first trimester of pregnancy carries a 1% to 2% risk of spina bifida in the offspring.⁷⁴ Hence, the fetus should be evaluated for this congenital anomaly if a woman taking valproate becomes pregnant. A substantial proportion of fetal malformations may be detected prenatally using fetal structural high resolution ultrasonography at 16 to 18 weeks of gestation and maternal α -feto-protein (AFP) with amniocentesis to measure amniotic fluid acetylcholinesterase and AFP.⁷⁷ Most neural tube defects (92% to 95%) can be detected by this method. Primary prevention is possible with preconception counseling involving careful discussion of the risks of VPA and possible replacement with another antiepileptic agent.⁷⁸

McMohan and Braddock⁷⁹ described a child with septo-optic dysplasia born to a mother who took 500 mg of valproate twice daily throughout her pregnancy. This child had hypoplasia of the optic chiasma with absence of septum pellucidum. Lindhaut et al⁸⁰ suggested that high daily doses of VPA in excess of 1,000 mg probably carry a higher risk of congenital malformations than do lower doses. In one study, it was found that the offspring of mothers using >1,000 mg of VPA daily were at a significantly increased risk for major congenital anomalies, especially neural tube defects. No congenital anomalies were found among the offspring exposed to ≤ 600 or 600 to 1,000 mg/day.⁸¹

When the benefits of valproate to the mother outweigh the risks to the fetus, a reduction in the total daily dose, if possible, and the division of the daily dose into three or more equal doses, seem to be a prudent measure to reduce fetal risk.⁸⁰ In general, women of childbearing age who are being treated with any anticonvulsant drugs including VPA should also receive 4 mg of folic acid daily to reduce the risk of neural tube defects in children. Folic acid supplements should be started before conception and continued until the 12th week of pregnancy.⁸²

An association has been observed between gestational valproate use and the development of "fetal valproate syndrome," characterized by cardiovascular, craniofacial, urogenital, digital,

and respiratory tract anomalies and developmental delays.^{83,85} In one study, nine of 17 infants (53%) born to epileptic women who took valproate during pregnancy had features of fetal valproate syndrome.⁸⁶ Ardinger et al⁸⁷ observed that up to 90% of children exposed in utero to VPA showed developmental delay.

Deficiencies of vitamin K₁-dependent clotting factors (II, VII, IX, and X), thrombocytopenia, reduced platelet aggregation, and low fibrinogen have been reported in pregnant women taking sodium valproate. This may lead to hemorrhages particularly in the central nervous system, causing permanent neurologic damage in some infants.^{88,90} Therefore, it is prudent to administer oral vitamin K₁ (10 to 20 mg/day) prophylactically to the anticonvulsant-treated mother during the last month of pregnancy as a means of protecting the infant against valproate induced coagulopathy. In addition, all newborns should receive 1 mg of vitamin K intramuscularly at birth as a prophylactic measure.⁸⁹

Both monotherapy and combination therapy with valproate in the first trimester have been reported to be associated with congenital heart defects.^{74,76,91,92} Sodium valproate taken by the mother during pregnancy also has an important role in skeletal, limb, skin, head, neck, and muscle defects in infants.^{83,85,87,91,92}

Growth retardation is a common problem with some anticonvulsants administered during the third trimester of pregnancy. Numerous cases of intrauterine growth retardation in newborns exposed in utero to monotherapy or combination therapy with VPA have been reported.^{77,85,91,92} However, some studies report normal birth weight, height, and head circumference in neonates exposed in utero to valproate monotherapy.^{83,85,87,92} Hence, the relationship between intrauterine growth retardation and valproate is unclear.

Ebbesen et al⁹³ observed that infants exposed in utero to valproate have a significantly higher risk of hypoglycemia than normal term infants. In the study, 20 pregnant epileptic women had been treated with valproate monotherapy and 2 with valproate and carbamazepine. Asymptomatic episodes of hypoglycemia were observed among all 22 infants within the first or second hour of life. There was a significantly negative correlation between blood glucose levels and the maternal median plasma concentration of total valproate, while a positive correlation was observed between withdrawal symptoms and median dose of valproate during the third trimester.

Current knowledge indicates that valproate exposure in utero causes major and minor congenital anomalies in neonates during organogenesis, as well as intrauterine growth retardation, hypoglycemia, and coagulopathy in late pregnancy. The mechanisms for these congenital anomalies are not clearly known, though interference with metabolism of trace elements such as zinc has been hypothesized.⁹⁴ It has also been suggested that teratogenicity may possibly be due to folate antagonism, fetal tissue binding, and toxic effects of metabolic intermediates.⁹⁵ Combination anticonvulsant therapy along with a family history of birth defects carries a higher risk of teratogenicity than monotherapy and an absent family history of birth defects.^{90,96,97}

Manic women of childbearing age should be advised before conception that fetuses exposed in utero to anticonvulsant drugs, particularly VPA, have a significantly higher risk of congenital anomalies.⁹⁸ The use of VPA should be avoided in pregnant women, especially during the first trimester of pregnancy. When valproate cannot be avoided, the therapeutic risk may be diminished by reducing the daily dose or giving three or more divided doses,⁸⁰ carefully monitoring serum VPA levels, performing screening tests including ultrasonography and fetal echocardiography at 16 to 18 weeks' gestation to detect malformations early, and monitoring clotting parameters in late pregnancy.⁹⁹

Risk to Infant During Breast-Feeding

Evidence indicates that VPA is excreted in breast milk in low concentrations ranging from 2% to 8% of maternal serum levels.^{71,100} We found three case reports of nursing infants who had adverse effects attributed to valproate.¹⁰¹⁻¹⁰³ The first report¹⁰¹ described a 3-month-old infant with thrombocytopenia and anemia caused by sodium valproate administration to the nursing mother. The infant had a serum level of 46 $\mu\text{mol/L}$ (6.6 $\mu\text{g/mL}$). Hematologic abnormalities resolved completely between 12 and 35 days after breast-feeding was discontinued. The second and third reports^{102,103} described increased risk of fatal hepatotoxicity in children less than 2 years of age nursed by mothers taking valproate. Thus, mothers should be informed of the signs of toxicity. When such signs are observed, nursing should be discontinued, at least temporarily, and valproate and its metabolite levels in infant and maternal serum should be measured. No conclusion about causation can be drawn from these instances.

Although adverse effects have been reported from the use of VPA during lactation, the bulk of the evidence indicates that these widely used drugs are relatively safe. Monitoring for potential adverse effects and monitoring of infant serum concentrations is advisable but not compulsory.

CARBAMAZEPINE

Risk to Fetus

In Animals. Evidence indicates that carbamazepine crosses the placenta and its concentration in cord blood equals that in maternal serum.¹⁰⁴ In several animal reproductive studies, the use of carbamazepine at doses higher than the recommended dose in humans has been associated with teratogenic effects in rats and mice. These include cleft palate and club-foot^{97,105,106}; fetotoxic effects in mice, such as reduced fetal body weight and brain weight^{105,107}; embryotoxic effects, such as cardiovascular anomalies in chick embryos¹⁰⁸; neural tube defects in rat and mouse embryos^{109,110}; and retardation of growth and development in rat embryos.¹⁰⁹

In Humans. Adequate studies have not yet been done to determine the risk of teratogenicity during pregnancy. However, many authors describe a twofold to threefold increase in the frequency of malformations in offspring exposed to carbamazepine during the first trimester when compared with the general population.^{76,111-113}

An association between spina bifida and monotherapy or combination therapy with carbamazepine during gestation has been noted.^{80,114-116} Rosa¹¹⁶ studied a cohort of 1,490 pregnant women treated with antiepileptic drugs. Of the four infants with spina bifida, three had been exposed to carbamazepine. In one case, the mother was taking valproate in addition to carbamazepine. Rosa's review of all known maternal antiepileptic cohorts receiving carbamazepine revealed a tenfold increase in spina bifida compared with the general population and an absolute risk of spina bifida of 1% without the confounding effect of valproate.¹¹⁶

Combination therapy with carbamazepine during gestation, particularly along with valproate, has been associated with a higher frequency of congenital anomalies than treatment with carbamazepine alone.^{97,117,118} In one report, 10 of 21 infants exposed to carbamazepine alone ($n = 15$) or in combination with other medication ($n = 6$) showed phenotypic abnormalities, such as round facies, hypertelorism, upslanting

palpebral fissures, hypoplastic nasal bridge, nevus flammeus, large anterior fontanelle, and hypoplasia of nails.¹¹⁷ Two infants had microcephaly manifested postnatally. Kaneko et al¹¹⁸ reported seven malformations among 45 patients treated with carbamazepine and another drug during gestation. Sutcliffe et al¹¹⁹ described 4 neonates born to mothers taking carbamazepine during pregnancy; 2 had bilateral severe microphthalmos, 1 had bilateral anophthalmos, and 1 had unilateral optic disk coloboma.

Hiilesmaa et al¹²⁰ reported a study of 133 epileptic pregnant women with matched controls, which showed that gestational carbamazepine was associated with a 10 mm decrease in fetal head circumference when compared with controls and that catch-up growth of the head was not observed by the age of 18 months. Bertollini et al¹²¹ found an association between prenatal exposure to carbamazepine and reduction in head circumference, body length, and overall birth weight.

Kuhnz et al¹²² reported that among 11 infants of mothers taking carbamazepine, 1 had major anomalies while the rest had minor anomalies, which were much less severe than those associated with other antiepileptics. Jones et al¹²³ observed craniofacial defects, fingernail hypoplasia, and developmental delay in the eight children retrospectively ascertained to have been exposed to carbamazepine in utero. This was confirmed by similar findings in a study of 35 children of women exposed to carbamazepine monotherapy during gestation. This prospective study showed facial abnormalities in 11%, developmental delay in 20%, and hypoplastic nails in 26%.

Gaily et al¹²⁴ observed that the prevalence of mental delay is the same or slightly increased among infants of epileptic mothers compared with the general population. The frequency of specific cognitive dysfunction was not higher than that expected in a group of 30 of these children who were tested.¹²⁵ In another study, the frequencies of neurologic dysfunction and school problems were no higher for 23 children between 6 and 13 years exposed in utero to carbamazepine.¹²⁶ However, most of the literature suggests increased developmental delay^{123,127,128} and lower intelligent quotient scores^{125,129} among children exposed in utero to carbamazepine. These findings were attributed to an epoxide intermediate of carbamazepine.¹²⁹

Carbamazepine, like valproate, may cause deficiency of vitamin K during the latter half of gestation, leading to an abnormal coagulation profile that may result in uncontrolled bleeding.

Bleeding in the central nervous system may cause permanent neurologic damage. Therefore, maternal vitamin K supplementation is necessary.⁸⁹

To summarize, carbamazepine should be considered as a suspected human teratogen.¹²³ Monotherapy is less teratogenic than combination therapy.^{96,97} Carbamazepine exposure in utero causes major and minor congenital anomalies and other adverse effects such as developmental problems, growth retardation, subnormal IQ, and bleeding disorders in the fetus and newborn. Hence, carbamazepine should not be used by pregnant women especially during the sensitive phase of organogenesis in the first trimester.

Risk to Infant During Breast-Feeding

Carbamazepine is detected in breast milk^{104,130} but is not found in quantifiable amounts. There have been two clinical reports of transient hepatic toxicity such as cholestasis and jaundice in breast-feeding infants associated with the maternal use of VPA.^{131,132} Also, seizure-like activity,¹³³ drowsiness, irritability, refusal to feed, and a high-pitched cry¹³⁴ have been reported in breast-fed 3-week-old and 10-week-old infants whose mothers were taking carbamazepine along with other drugs, though a causal relationship could not be established. In contrast, one study revealed no adverse outcomes in 94 infants exposed to carbamazepine while nursing.¹⁰⁴

Therefore, if a woman wishes to continue breast-feeding while taking carbamazepine, concentrations of drug and its metabolite 10,11-epoxide in her plasma and breast milk and in the infant's plasma should be monitored. If the infant has adverse reactions such as hepatic and central nervous system dysfunction, nursing should be discontinued, at least temporarily. Neonatal acquisition via nursing does not seem to be harmful for the neonate, and weighing the benefits of breast-feeding against the potential risk, breast-feeding during maternal carbamazepine therapy is considered safe.

GABAPENTIN

Risk to Fetus

In Animals. The potential reproductive toxicity of gabapentin has not been adequately evaluated in animals. However, animal reproductive studies in rodents have revealed evidence of fetotoxic effects such as delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs at oral doses of 1,000 to 3,000 mg/kg/day during organogenesis, which

is approximately one to four times the maximum dose of 3,600 mg/day used with epileptic patients when considered on the basis of milligrams per square meter.^{135,136} Also, there was an increased incidence of hydronephrosis and/or hydronephrosis in rats exposed during organogenesis to doses of 2,000 mg/kg/day, which is approximately one to five times the maximum dose of 3,600 mg/day in terms of milligrams per square meter.^{135,136} In rabbits, there was an increased incidence of postimplantation fetal loss when exposed to 60, 300, and 1,500 mg/kg/day, which is approximately one fourth to eight times the maximum human dose in terms of milligrams per square meter.^{135,136}

In Humans. No adequate and well-controlled studies have been done to determine the gabapentin-associated risk to the human fetus.^{135,136} Because animal reproductive studies are not always accurately predictive of human response, this drug should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Risk to Infant During Breast-Feeding

We found no published reports of breast-feeding infants exposed to gabapentin. However, one unpublished study conducted by the manufacturer analyzed the blood, urine, and breast milk in six healthy women treated with 400 mg of gabapentin. One woman was unable to produce breast milk. In the other five women, the drug levels in breast milk and plasma were equal.¹³⁷ Therefore, caution is advised when gabapentin is administered to mothers nursing infants.

LAMOTRIGINE

Risk to Fetus

In Animals. Studies in rats and rabbits indicate that lamotrigine crosses the placenta, yielding placental and fetal levels comparable with those in maternal plasma. No teratogenic effects were seen in animal studies using increasing doses, up to 1.2 times an equivalent human dose of 500 mg/day. However, rats receiving up to 0.5 times an equivalent human dose of 500 mg/day produced offspring with decreased fetal folate concentrations, an effect known to be associated with teratogenicity in humans and animals. In addition, an increase in stillbirths and postnatal deaths was noted among offspring of rats receiving lamotrigine at doses less than half the equivalent human dose of 500 mg/day and was attributed to in utero exposure to lamotrigine. The clinical significance of these effects is unknown.^{136,138}

In Humans. Evidence indicates that lamotrigine crosses the placenta. One report noted a decrease in plasma level of lamotrigine as pregnancy progressed.¹³⁹ The ratio of dose to plasma concentration was 5.8 times higher at delivery and 3.6 times higher in late pregnancy as compared with 5 months postpartum, suggesting clearance of lamotrigine during pregnancy. The ratio of umbilical cord to maternal plasma level was 1.2, indicating extensive placental passage of lamotrigine.¹³⁹ In another report,¹⁴⁰ maternal plasma lamotrigine concentrations were similar to those in the umbilical cord, and the lamotrigine plasma concentration in the newborn slowly declined. There are still no well-controlled studies of lamotrigine therapy in pregnant women to determine fetal risk.^{136,141} Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Lamotrigine is a dihydrofolate reductase inhibitor, and it decreases fetal folate levels in rats. Therefore, folic acid supplementation should be considered for all women of child-bearing potential who are taking lamotrigine.¹⁴¹ To facilitate monitoring outcomes of pregnant women exposed to lamotrigine, physicians are encouraged to register them in the Anti-epileptic Drug Pregnancy Registry.^{135,136}

Risk to Infant During Breast-Feeding

Considerable amounts of lamotrigine are excreted in breast milk.^{135,136,139-143} In the four reports dealing with breast-feeding infants exposed to lamotrigine and the amount of lamotrigine in breast milk, the milk to maternal serum ratio was approximately 0.6 in all of the cases, with a range of 0.3 to 0.6 in the first case.^{139,142,143} The first infant, followed up for 5 months postpartum, had an estimated daily intake of 2 to 5 mg of lamotrigine, with serum levels ranging from 2.8 $\mu\text{mol/L}$ (at 2 days after birth and exclusively breast-fed) to less than 0.2 $\mu\text{mol/L}$ (when feeding was supplemented with formula in a 3:1 ratio).¹⁴² The second report noted that plasma lamotrigine concentration in the newborn at 48 hours after birth was similar to the plasma levels of the mother at delivery and in the umbilical cord. The ratio of milk to plasma concentration was 0.6 2 weeks after delivery and the plasma concentration was 25% of the mother's plasma level.¹³⁹ The third report showed that the serum levels of three infants were 23% to 33% of the maternal serum levels.¹⁴³ The fourth report showed slow decline in

the lamotrigine plasma concentration in 10 newborns of nine pregnant women.¹⁴⁰ At 72 hours postpartum, median lamotrigine plasma levels in the infants were 75% of the cord plasma levels (range, 50% to 100%). The median milk/plasma concentration ratio was 0.61 (range, 0.47 to 0.77) 2 to 3 weeks after delivery, and nursed infants maintained lamotrigine plasma concentrations of 30% (median, range, 23% to 50%) of the mother's plasma levels. None showed any adverse effects. Nonetheless, exposure of breast-feeding infants to lamotrigine is of some potential concern because of the increased risk of severe life-threatening rashes in children receiving the drug for mood disorder. Therefore, physicians should be alert for lamotrigine's possible side effects, and if they are observed, breast-feeding should be discontinued.

TOPIRAMATE

Risk to Fetus

In Animals. Animal reproductive studies have shown evidence of teratogenic effects such as craniofacial anomalies (at an oral dose of 20, 100, or 500 mg/kg) and skeletal anomalies (at doses of 500 mg/kg) in mice, limb malformations in rats (ectrodactyly, micromelia, and amelia) at doses of 400 mg/kg or greater, and rib and vertebral malformations in rabbits at doses of 120 mg/kg when given during the period of organogenesis. Fetotoxic effects such as decreased fetal weight and increased incidence of structural variations in mice, rats, and rabbits and embryotoxic effects in rabbits have been found to be associated with its use at doses higher than the recommended human dose.^{135,136,141} In addition, clinical signs of maternal toxicity and decreased maternal body weight gain were seen among pregnant rats and rabbits at doses ranging from 35 to 400 mg/kg or greater.^{135,136,141}

In Humans. No well-controlled studies using topiramate in pregnant women have been done.^{136,141} Therefore, topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Risk to Infant During Breast-Feeding

Topiramate is excreted in the milk of lactating rats.^{136,137,141} It is not known whether topiramate is excreted in human milk. Since many drugs are excreted in human milk and because the potential for serious adverse reactions in nursing infants exposed to topiramate is unknown, the

potential benefits to the mother should be weighed against the potential risks to the infant when considering topiramate therapy.

CHLORPROMAZINE

Risk to Fetus

In Animals. Chlorpromazine is a derivative of aliphatic phenothiazines, and it readily crosses the placenta.^{144,145} Animal reproductive studies in rodents and monkeys have shown that doses higher than those recommended in humans cause teratogenic effects such as cleft palate and anomalies of the central nervous system, eye, and skeletal system.¹⁴⁶⁻¹⁴⁸ Also reported are fetotoxic effects such as fetal death, decreased fertility and viability, and decreased fetal weight gain,¹⁴⁶⁻¹⁴⁸ visual disturbances,¹⁴⁹ and behavioral abnormalities,^{150,151} but not embryotoxic effects.

In Humans. Adequate and well-controlled epidemiologic studies to determine the teratogenic potential of chlorpromazine have not been done in pregnant women. Many clinical studies have shown the safety and efficacy of low-dose chlorpromazine when used either to treat nausea and vomiting during all stages of gestation^{152,153} or to promote analgesia, amnesia, and sedation during labor.¹⁵⁴⁻¹⁵⁶ However, there are isolated instances of marked idiosyncratic falls in blood pressure, which could be dangerous to the mother and the fetus.^{153,157}

Sobel¹⁵⁸ observed that among 52 women who were given chlorpromazine during late pregnancy, 3 women receiving high doses (500 to 600 mg daily) gave birth to neonates with respiratory distress and cyanosis. Also, neurologic dysfunction with extrapyramidal signs (ie, muscle rigidity, hypertonia, tremor, dyskinesias, akathisia, weakness, poor sucking, and poor motor maturity) has been reported in several infants born to women who were treated with chlorpromazine during late pregnancy, suggesting a withdrawal syndrome.^{144,159-161} The frequency of these complications appears to be low, and they are usually transient, though some may last for several months.¹⁶²

Levin et al¹⁶³ observed that irrespective of their breast-feeding status, the children of mothers who took chlorpromazine or other neuroleptics for more than 2 months during gestation were significantly taller than unexposed controls at 4 months, 1 year, and 7 years of age.

Sobel¹⁶⁴ reported higher incidences of perinatal mortality and morbidity in neonates born to schizophrenic mothers in a mental hospital, irrespective of their chlorpromazine status. He attributed these adverse effects to the schizo-

phrenia. Similar findings were observed by Reider et al.¹⁶⁵ In one study involving 142 neonates, in utero exposure to chlorpromazine during the first 4 months of pregnancy did not result in a significantly higher risk of congenital anomalies.¹⁶⁶ Similar results were found in neonates of 284 women treated with chlorpromazine during pregnancy.¹⁶⁷ Contrasting results were observed in a prospective study of 12,764 women; a higher number of birth defects occurred in neonates of 189 women receiving phenothiazines, especially chlorpromazine, during the last trimester.¹⁶⁸

In summary, most studies agree that chlorpromazine is safe during gestation and that it is not teratogenic,^{155,169} despite isolated reports describing congenital anomalies. However, it is prudent to avoid this drug near term, if possible, since it has been reported to cause maternal hypotension with adverse effects in neonates.

Risk to Infant During Breast-Feeding

Chlorpromazine is excreted in the breast milk of nursing mothers in low concentrations up to 3% of maternal daily dosage per kilogram of body weight.^{170,171} On a regimen of 600 mg twice daily for 7 days, the drug was not detected in the morning milk samples. Another study found no adverse effects in 6 neonates nursed by mothers taking chlorpromazine, of whom 4 were nursed for 3 months, 1 for 7 weeks, and 1 for 1 month. All the mothers had nursed at least one other child previously and reported no difficulties in the infants nursed while they were taking chlorpromazine.¹⁷²

Estimations based on data collected from five lactating women taking the drug showed that the nursing infant would be expected to ingest between 0.03% and 1.3% of the lowest pediatric dose.^{173,174} Thus, chlorpromazine can be used safely in nursing women.

HALOPERIDOL

Risk to Fetus

In Animals. Haloperidol is a conventional antipsychotic agent that readily crosses the placenta in both animals and humans. The potential reproductive toxicity of haloperidol has not been adequately evaluated in animals. However, reproductive studies at doses higher than the recommended human dose have revealed teratogenic effects such as cleft palate, micromelia, and central nervous system and skull malformations.¹⁷⁵⁻¹⁷⁷ Fetotoxic effects such as fetal death and decreased fetal and postnatal growth have been reported in rats, mice, and hamsters. Long-

lasting alteration of behavior in rats and mice^{177,176} and embryotoxic effects such as embryonic death in hamsters¹⁷⁷ have also been reported.

In Humans. No adequate and well-controlled studies to determine fetal risk associated with haloperidol have been done. However, Van Waes and Van de Velde¹⁷⁸ conducted a large prospective study of 100 women by administering relatively small doses of haloperidol (0.6 mg) twice daily during pregnancy for the treatment of hyperemesis gravidarum. Of the 100 women tested, 2 were lost to follow-up, 92 received haloperidol during the first trimester, and 6 received haloperidol during the second trimester. The pregnancy outcomes for 98 women, when compared with the controls, showed no apparent effect on fertility, duration of gestation, intrauterine survival, neonatal survival, birth weight, or sex ratio. No malformations were observed in the offspring of treated mothers.¹⁷⁸ However, a separate report describes two cases of severe limb malformation in infants of mothers treated with haloperidol during the first trimester. In one of the infants, the mother received a daily dose of 15 mg during the first 7 weeks of pregnancy. Causal relationships were not established.¹⁷⁹

Currently available literature does not reveal a causal relationship between haloperidol and teratogenicity, and the risk of a birth defect attributable to haloperidol is low. Therefore, pregnant women may be treated with haloperidol if the benefits to the mother justify a possible risk to the infant.

Risk to Infant During Breast-Feeding

Although haloperidol is significantly excreted in breast milk,¹⁸⁰ no adverse effects in nursing infants have been reported.^{181,182} Animal studies have shown that haloperidol excreted in milk causes drowsiness and impairment of motor activity in the breast-fed offspring.¹⁸⁰ Therefore, haloperidol should be used in lactating women only if a risk-benefit assessment justifies the potential risk to the infant.

FLUPHENAZINE

Risk to Fetus

In Animals. Fluphenazine belongs to the piperazine phenothiazine group and readily crosses the placenta and accumulates in fetal tissue.¹⁸³ Two studies in which rats were treated with doses up to 100 mg/kg orally throughout pregnancy found no adverse effects in the offspring.¹⁸⁴ Contradictory results were reported in pregnant mice given this drug, with a significantly higher incidence of skeletal defects,

dilated ventricles, and reduction in fetal weight and length.¹⁸⁵ Multiple malformations in chick embryos and cleft palate in fetal mice have been reported in experimental studies involving fluphenazine.¹⁷⁵

In Humans. No adequate, well-controlled studies have determined the teratogenicity of fluphenazine. However, a retrospective study¹⁸⁶ involving 244 patients taking fluphenazine and 150 controls, detected congenital anomalies in 2.7% of the 226 live and stillborn infants in the exposed group compared with 3.5% among 143 live and stillborn deliveries in the control group. Also, the incidences of spontaneous abortion, perinatal mortality, premature birth, and twinning in the two groups were similar.

Currently available clinical data have not shown any teratogenic effects, except for occasional case reports of congenital anomalies,^{187,188} and a case of rhinorrhoea and respiratory distress,¹⁸³ in which causality could not be established. The bulk of the worldwide clinical experience with this drug indicates that pregnant women can be treated with fluphenazine without any ill effects on them or their infants.¹⁸⁹ However, a clinician should weigh the potential risks to the fetus against the probable benefits to the mother when administering this drug to a pregnant patient.

Risk to Infant During Breast-Feeding

Even though fluphenazine, like other phenothiazines, may be excreted into breast milk, neither the drug nor its metabolites have been quantified in human milk, and its effect on nursing infants is unknown. Therefore, it may be administered during nursing if a risk-benefit assessment justifies a possible risk to the infant, and the infant should be observed for development of any adverse effects.

THIOTHIXENE

Risk to Fetus

In Animals. The potential reproductive toxicity of thiothixene has not been adequately evaluated in animals. One reproductive study in mice and rabbits given 90 mg/kg/day showed a decrease in conception rate and litter size and an increase in resorption rate,¹⁹⁰ but revealed no teratogenicity.¹⁹¹

In Humans. To date, no adequate and well-controlled studies on thiothixene therapy during pregnancy have been done. However, this drug should be used during pregnancy only when the physician believes the expected benefits exceed the possible risks to the fetus.

Risk to Infant During Breast-Feeding

There are no reports on the pharmacokinetics of thiothixene in relation to breast milk nor reports on the effects of this drug on nursing infants. Hence, caution is advised, since chemically related phenothiazines are excreted in breast milk and are reported to cause tardive dyskinesia and possible drowsiness in the breast-fed infant.¹⁹⁰

CLOZAPINE

Risk to Fetus

In Animals. Clozapine, a dibenzodiazepine derivative, is an atypical antipsychotic that readily crosses the placenta.¹⁹⁰ Animal reproductive studies in rats and rabbits have shown no teratogenic, fetotoxic, or embryotoxic effect at doses approximately 2 to 4 times the human dose.¹³⁵

In Humans. Presently, no epidemiologic studies show an association between congenital anomalies and gestational clozapine therapy. There are three clinical case reports of no apparent fetal adverse effects associated with the use of clozapine before and during gestation.¹⁹²⁻¹⁹⁴ One of these reports described 14 women who were known to have been exposed to clozapine during gestation with no known adverse sequelae in their newborns.¹⁹⁴ White blood cell counts of all newborn infants of mothers receiving clozapine during pregnancy or while nursing should be monitored carefully to detect agranulocytosis or bone marrow suppression that could result in a life-threatening infection. It has been shown that agranulocytosis develops in the first 6 months of treatment either precipitously or gradually and one third of the patients who had agranulocytosis from clozapine died. Clozapine can be used during pregnancy if the clinical benefit to the mother justifies the possible risk to the fetus.

Risk to Infant During Breast-Feeding

Clozapine is concentrated into breast milk^{135,190,192} and has been known to cause sedation, decreased suckling, restlessness or irritability, seizures, and cardiovascular instability in the nursing infant.¹⁹⁰ Given this potential for serious adverse consequences to infants who are exposed to clozapine, breast-feeding should be avoided during maternal clozapine therapy.

RISPERIDONE

Risk to Fetus

In Animals. Risperidone is a benzisoxazole derivative and an atypical antipsychotic agent

that is chemically unrelated to other antipsychotic agents. Evidence indicates that risperidone easily crosses the placenta. Several animal reproductive studies in rats and rabbits have shown no evidence of teratogenic potential at doses higher than the human recommended dose but have shown fetotoxic effects such as increase in pup deaths and a significant increase in the number of stillborn pups.¹⁹⁰

In Humans. No adequate, well-controlled studies to determine teratogenicity of risperidone in gestational women have been done, even though reports of animal fetotoxicity exist. Hence, risperidone should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus.

Risk to Infant During Breast-Feeding

Risperidone and 9-hydroxy-risperidone are excreted into animal milk in concentrations greater than or equal to plasma concentrations.¹⁹⁰ At present, it is not known whether the drug is excreted in human breast milk, though it is suggested that it may cause adverse effects, such as behavior changes, in breast-fed babies.¹⁹⁰ Caution is thus advised when risperidone is administered to lactating women, and nursing infants should be monitored for any adverse changes.

OLANZAPINE

Risk to Fetus

In Animals. Olanzapine is an atypical antipsychotic agent belonging to the thienobenzodiazepine group chemically and is similar to clozapine both chemically and in its mechanism of action. It is known to cross the placenta.¹³⁵ Animal reproductive studies in rats and rabbits have revealed no evidence of teratogenic effects at doses higher than the human recommended dose but have shown increased resorption, increased number of nonviable fetuses, and decreased fetal weight.

In Humans. Schenker et al¹⁹⁵ described a study in which it was observed that 5% to 14% of olanzapine crosses human placenta unchanged during a period of 4 hours. Goldstein et al¹⁹⁶ described 23 prospectively and 9 retrospectively ascertained pregnancy reports that were collected as a registry in the Lilly Worldwide Pharmacovigilance Safety Database. Outcomes from the 23 prospective reports were as follows: spontaneous abortion in 3 (13%); stillbirth in 1 (5%) after premature rupture of membranes at 37 weeks' gestation in a mother with gestational diabetes, thrombocytopenia,

hepatitis, and polydrug abuse; normal birth in 16 (80%); prematurity in 1 (5%) delivered by cesarean section at 30 weeks because of gestational diabetes, hypothyroidism, preeclampsia, and abnormal liver enzymes in a mother taking insulin, levothyroxine, famotidine, and folic acid; and postmaturity in 2, one delivered by induction 10 days after term because of fetal distress and another who had meconium aspiration after delivery by cesarean section because of postmaturity. These are all within the range of normal historic control rates—ie, these pregnancies did not have an increased risk of spontaneous abortion, stillbirth, prematurity, or major malformation in the offspring.

Among the 9 retrospective reports described by Goldstein et al,¹⁹⁶ there were 2 spontaneous abortions; 1 normal infant; 2 major malformations—Down syndrome (trisomy 21), caused by chromosomal nondysjunction (a defect not considered to be due to a teratogen) and unilateral renal dysplasia unlikely to be related to teratogenicity because a chemical insult would typically be bilateral; 1 therapeutic abortion done at the patient's request; 1 perinatal complication that resulted in neonatal withdrawal because of decreased plasma concentration; 2 postperinatal complications—convulsions in one (despite normal findings on electroencephalogram and laboratory tests) and sudden infant death syndrome in one. Absence of similar events in prospectively identified cases suggests the lack of causation.¹⁹⁶ Therefore, olanzapine should be used in potentially childbearing women, unless, in the opinion of the physician, the potential risk to the fetus or infant outweighs the expected benefit to the patient.

Risk to Infant During Breast-Feeding

Evidence suggests that olanzapine is excreted in rat milk, but its excretion in human breast milk has not been studied.¹⁹⁶ Goldstein et al¹⁹⁶ described two retrospectively identified case reports of lactation exposures. In the first case, a mother with paranoid schizophrenia was taking 10 mg of olanzapine along with trifluoperazine, procyclidine, and paroxetine when her infant was 2 months of age. No adverse effects were noticed in this breast-fed infant. The second report described jaundice, somnolence, cardiomegaly, and heart murmur in a breast-fed infant whose mother had taken 5 mg of olanzapine daily in the first and third trimesters. The infant's birth weight was 3.8 kg, birth length was 50 cm, and Apgar scores were 8 and 9 at 1 minute and 5 minutes, respectively.

The infant had been healthy and fully breast-fed until day 6. On day 7, bottle feeding was initiated, but jaundice and sedation continued, suggesting a lack of relationship to olanzapine. Conclusions cannot be based on only two cases. Hence, until olanzapine in human breast milk is studied more thoroughly, it should be assumed to be readily present, and women should be advised not to breast-feed their infant.

CLONAZEPAM

Risk to Fetus

In Animals. Ample evidence shows that clonazepam, a benzodiazepine, readily crosses the placental barrier. The reproductive toxicity of clonazepam has not been adequately evaluated in animals. However, several reproductive studies in mice, rats, and rabbits have shown no teratogenic, fetotoxic, or embryotoxic effects at usual therapeutic doses.^{73,197,198} A study in rats at oral doses of 100 mg/kg of clonazepam has shown teratogenic, fetotoxic, and embryotoxic effects when administered during the period of organogenesis.¹⁹⁹ There is a report of long lasting immune suppression due to altered T-lymphocyte responsiveness in the offspring of rats treated with a low dose of clonazepam (1.25 mg/kg) during the third week of gestation.²⁰⁰

In Humans. Adequate and well-controlled studies on teratogenicity of clonazepam have not been conducted. Clonazepam is primarily metabolized by hydroxylation, which is impaired in the newborn. The half-life of clonazepam in neonates is not known, but other benzodiazepine derivatives have half-lives two to four times longer in neonates than in adults.²⁰¹ There are a few clinical reports of teratogenic and non-teratogenic adverse effects among the children of epileptic mothers who took clonazepam during pregnancy.²⁰¹⁻²⁰⁵ A study conducted in Turkey observed that among 104 offspring exposed to antiepileptic drugs in utero, 12 (11.53%) showed major congenital malformations.²⁰⁵ Of these 12 infants, 3 (25%) were exposed to combination therapy with clonazepam. It was coupled with phenobarbital in two of them, while the third was exposed to primidone, phenytoin, and clonazepam. A significantly increased risk of congenital heart disease and hip dislocation was only found for clonazepam (doses of 1 to 6 mg/day) and phenobarbital combination therapy.²⁰⁶ This was attributed to the combination therapy²⁰⁶ or increased maternal mean plasma antiepileptic drug concentrations.²⁰⁷ However, contrasting results were found in a study of

10,698 infants with congenital anomalies in which there was a lack of significant association between clonazepam and the anomalies.²⁰²

Johnson et al^{208,209} described 6 cases of major malformations: 1 infant had a ureteropelvic junction obstruction, 2 infants had bilateral inguinal hernias, 1 infant had undescended testicle that required orchidopexy at 4 years of age, and 1 had both a ventricular septal defect and bilateral inguinal hernias. Haeusler et al²⁰³ described a case of paralytic ileus of the small bowel diagnosed prenatally at 32 weeks' gestation after referral for polyhydramnios in a woman taking clonazepam and carbamazepine. All known causes for the ileus were ruled out, and it was concluded that these drugs were the most likely cause of the ileus.

There are reports of flaccidity, lethargy, respiratory difficulties, feeding difficulties, and subnormal temperature in offspring of mothers taking benzodiazepines during late pregnancy.^{201,204} Fisher et al²⁰¹ described a case of neonatal apnea (with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively) in an infant born at 36 weeks to a 40-year-old multiparous myoclonic mother who took clonazepam throughout pregnancy. Six hours after birth, the infant had several episodes of apnea with cyanosis, lethargy, and hypotonia, which resolved in 10 days. The mother's serum clonazepam level at delivery was 32 ng/mL, and the cord blood level was 19 ng/mL. Follow-up at 5 months of age by neurodevelopmental examination revealed no neurologic abnormalities. Therefore, if a woman becomes pregnant during clonazepam therapy, she should be apprised of the potential hazard to the fetus, and serum clonazepam levels should be monitored during pregnancy and lactation. These infants should also be monitored for signs of central nervous system depression and apnea. Another case of respiratory depression has been reported in the newborn of a woman taking 5.5 mg of clonazepam daily during pregnancy and lactation.²⁰⁴ Children born to mothers taking benzodiazepines in late gestation may be at risk of having withdrawal symptoms during the neonatal period. Consequently, clonazepam should be used during pregnancy only if the clinical benefit to the mother justifies the potential risk to the fetus.

Risk to Infant During Breast-Feeding

Like other benzodiazepines, clonazepam may be excreted in human milk in low concentrations.^{201,210} A case of apnea, cyanosis, hypoto-

nia, and excessive periodic breathing was seen in an infant fed breast milk from a clonazepam-treated mother.²⁰¹ This case prompted the authors to suggest that infants exposed to clonazepam in utero or during nursing should be monitored for central nervous system depression or apnea. Therefore, caution is advised when clonazepam is administered to nursing mothers, and it should be avoided especially when nursing premature infants.

CONCLUSION

The ability of drugs to pass from the mother to the fetus and the nursing infant must be considered when administering antimanic drugs. High levels of lithium, VPA, and carbamazepine and low levels of folate in the maternal blood are risk factors for teratogenesis in animals and humans during pregnancy. In utero exposure to these agents and to clonazepam during the first trimester of pregnancy increases the risk of major and minor anomalies. Adverse effects include intrauterine growth retardation, prenatal and postnatal internal bleeding, increased perinatal mortality, apnea, premature labor, neurologic toxicity, developmental delay, hypoglycemia, and psychomotor and mental retardation. Although some studies have shown that lithium can be used safely during pregnancy, these antimanic drugs should be avoided if possible, especially during the sensitive phase of organogenesis (days 18 through 55 after conception).

To date, there is insufficient research to establish whether the new second-generation anticonvulsants (gabapentin, lamotrigine, and topiramate), conventional antipsychotics (chlorpromazine, haloperidol, fluphenazine, and thiothixene), and atypical antipsychotics (clozapine, risperidone, and olanzapine) have any teratogenic effects on the fetus or nursing infant.

Although pregnancy for women with bipolar disorder is considered a high-risk obstetric condition, most women with this disease can have safe pregnancies and healthy babies. To achieve this goal, several steps must be taken. Prenatal counseling should begin at least 3 months before conception. It is necessary to make sure that a woman understands the concept of teratogenic risk and the perinatal risk of nursing associated with treatment of her medical condition. A woman with manic-depressive disorder treated with lithium, VPA, or carbamazepine in the first trimester will need to understand not only the increased

risk of fetal cardiac and neurologic anomalies associated with these drugs, but also the increased genetic risk of bipolar illness in her child. Antimanic drug dosage adjustments should be based on symptoms as well as on serum drug concentrations. Prenatal examinations should include a fetal structural level 2 ultrasound examination at 18 to 20 weeks' gestation. If the anticonvulsant drugs cannot be avoided during pregnancy, monotherapy with the lowest possible dosage is recommended. Electroconvulsive therapy (ECT) may be used for patients who need immediate stabilization of their bipolar condition, those with suicidal thoughts, and those who cannot tolerate or do not respond to medications. The literature contains more than 300 reports of ECT used during pregnancy with no clear evidence of teratogenic effects.²¹¹

Monotherapy is preferable because of the higher risk of congenital malformation associated with combination therapy. If lithium, VPA, or carbamazepine is used, the daily dose should be divided into three or four doses to minimize peak serum levels, since evidence shows that teratogenicity of these drugs is dose-dependent. Folate supplementation of 4 mg/day beginning at 3 months before conception and continuing through 12 weeks of gestation reduces the risk of neural tube defects, especially for those taking any anticonvulsant (particularly VPA or carbamazepine). Although there is no conclusive proof that periconceptional folate supplementation in women using anticonvulsant drugs prevents neural tube defects, we believe that by following these guidelines more than 90% of pregnant women using VPA and carbamazepine today can expect normal infants.²¹²

The antimanic drugs that can be prescribed safely during pregnancy are chlorpromazine, haloperidol, fluphenazine, and clozapine. The remainder have been associated with some adverse effects during pregnancy and are obviously not recommended unless specifically indicated. Whether the new second-generation anticonvulsant drugs, such as gabapentin, lamotrigine, and topiramate, are good choices for the pregnant woman with bipolar disorder remains to be seen. The limited number of human pregnancy exposures to date do not signal a significant number or particular type of adverse outcomes.

Caution should be exercised when antimanic drugs are given to a nursing mother. All products ingested by the mother are excreted in

some form in human milk. The antimanic drug therapy may be discontinued temporarily if it is not essential. The lowest possible dosages may be used in limited time frames with adequate supervision of the infant. Factors that should be considered when prescribing a drug to a nursing mother include the potential acute toxicity of the drug, dosage and duration of therapy, age of the infant, quantity of milk consumed, experience with the drug in infants, pharmacokinetics in the infant, potential long-term effects, and possible interference with lactation. In general, nursing women receiving medication should stop nursing if the drug is known to be harmful to the infant or when using a drug that is so potent that even small amounts could be harmful.

On the basis of data about infant serum levels and reported adverse effects, only VPA and carbamazepine may be used during breast feeding. Other drugs such as thiothixene, risperidone, olanzapine, and clonazepam can be used with caution. Lithium, gabapentin, lamotrigine, topiramate, haloperidol, fluphenazine, and clozapine should be used only when the potential benefits justify the possible risks to the infant.

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