Epilepsy and Pregnancy: Maternal and Fetal Effects of Phenytoin

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In the United States, approximately 1 million women of childbearing age have had epilepsy diagnosed. However, less than 1% of all pregnancies are complicated by seizure disorders.1 The diagnosis of epilepsy can be a devastating event in a woman’s life. She not only is told that she will probably have to take medication for the rest of her life, she also is told that this medication can have serious adverse effects. During her childbearing years she must make difficult decisions, such as whether to become pregnant or terminate a pregnancy, based on her understanding of the possibility of fetal anomalies associated with her medical condition and medication. Although the diagnosis of seizure disorder infrequently leads to admission to a critical care unit, a pregnancy complicated by epilepsy can become a critical care emergency.

The frequency and duration of seizures may change during pregnancy in women with epilepsy.2,3 Epilepsy improves during pregnancy in some women, worsens in others, and appears to be unaffected in most.4 A generalized tonic-clonic seizure occurs in approximately 1% to 2% of women with epilepsy during labor and in another 1% to 2% during the first 24 hours after delivery.5 Status epilepticus, a rare complication of pregnancy, may occur without any preceding increase in the frequency of seizures and may result from the unwise discontinuation of antiepileptic drugs by the mother. Status epilepticus is an immediate threat to both mother and fetus and significantly increases the risk of maternal and fetal death.6

The changes in frequency and duration of seizure activity during pregnancy appear to be due to increased hormonal production and physiological changes in pregnancy that alter or affect absorption of phenytoin. Increases in levels of estrogen and progesterone during pregnancy alter the seizure thresh-
old, estrogens by activating seizure foci and progesterone by dampening activity.7 Seizure activity or susceptibility can also be affected by water and sodium retention, alterations in sleep, and mild respiratory alkalosis associated with pregnancy. These physiological changes of pregnancy often necessitate increasing the dosage of anticonvulsant medication to levels greater than those used before pregnancy.6

Women with epilepsy also have a slightly increased risk for certain obstetric complications. According to Pennell,7 the risk of vaginal bleeding, abruptio placenta, eclampsia, and premature labor is approximately doubled in pregnant women with epilepsy compared with pregnant women without epilepsy.

Women who have epilepsy and become pregnant often do not take their medication as prescribed because of their fear of fetal malformation or their misconception of the importance of taking the medication during pregnancy. According to Yerby and Devinsky,1 the incidence of fetal malformations is increased in women with epilepsy even when antiepilepsy drugs are not used. In this article, we focus on the pharmacokinetics and pharmacodynamics of phenytoin, one of the most widely prescribed antiepilepsy drugs. Both the maternal and fetal effects are reviewed, with an emphasis on information needed by critical care nurses to educate patients and to administer and monitor these medications.

Pharmacokinetics of Phenytoin

Phenytoin was first introduced for the treatment of partial and generalized tonic-clonic seizures in 1938. Rapidly it became one of the most commonly used drugs for the control of epileptic seizures because it had no sedative effects.7 Normally started at a dosage of 300 mg daily, the usual effective maintenance dose of phenytoin is 300 to 400 mg daily.8 Therapeutic plasma levels of phenytoin for most patients are between 10 and 20 µg/mL.9 A loading dose can be given either orally or intravenously. During convulsion or status epilepticus, the preferred route is intravenous, with the infusion given slowly at a dosage of 10 to 15 mg/kg, not to exceed 50 mg/min to reduce the risk of hypotension and cardiac arrhythmias. Intramuscular administration should be avoided because of erratic absorption and because of discomfort at the injection site.3,7

Because phenytoin is poorly soluble in water at an acidic pH, very little drug absorption occurs in the stomach. Absorption takes place primarily in the proximal part of the small intestine, where phenytoin is principally bound to albumin. Both the absorption and metabolism of this drug vary greatly among patients because metabolic rate varies from patient to patient. Careful monitoring of the phenytoin level of patients with renal failure and altered albumin concentrations is necessary because these conditions affect the drug’s concentration. Phenytoin is eliminated primarily by hepatic metabolism and is excreted in urine.9 Doses of phenytoin must be carefully adjusted. The ability of the liver to metabolize the drug tends to reach maximum capacity close to the therapeutic level. At therapeutic levels, phenytoin is safe, with relatively few adverse effects.10,11 If more drug is given than is needed, the maximal capacity for phenytoin metabolism can be approached, causing plasma levels to increase dramatically, resulting in toxic effects such as ataxia, nausea, vomiting, hypotension, motor restlessness, dizziness, and fatigue. Deep coma may also result.10

The time necessary to attain a steady-state level of phenytoin can vary from several days to several weeks, because the half-life of phenytoin varies substantially among patients (8 to 64 hours), depending on the rate at which the patient metabolizes the drug.12 The time to peak absorption in most patients is 4 to 8 hours after an oral dose with bioavailability of 85% to 95%.7 Therapeutic drug monitoring is necessary every 1 to 2 months during pregnancy and more frequently if breakthrough seizures occur. After delivery, as the physiological alterations of pregnancy are reversed, drug levels may fluctuate rapidly, leading to toxic effects.6 Careful monitoring of the phenytoin blood levels during the immediate postpartum period is necessary so that the dosage can be adjusted as needed.

General Adverse Effects of Phenytoin

Phenytoin has a number of general adverse effects, including dysmorphic changes such as acne and hirsutism. These changes can occur in the lips, nose, brow, and other facial structures. Peripheral neuropathy may occur with long-term therapy. These adverse effects are most commonly associated with polytherapy when phenytoin is
combined with other antiepilepsy drugs such as phenobarbital. Another common adverse effect is gingival hyperplasia, an overgrowth of the gums, which is a dose-related effect that often begins within the first 3 months of therapy and progresses during the first year. This condition develops in more than 45% of adults who take this drug. Part of the educational process related to the administration of phenytoin includes emphasizing the need for frequent oral care and regular dental checkups because gingival hyperplasia may progress to the point that gum resection is required. In addition to these general adverse effects, some adverse effects specifically affect pregnant women.

Effects of Phenytoin During Pregnancy

Known adverse effects of phenytoin in pregnant women are listed in Table 1. Antiepileptic drugs interfere with metabolism of folate, and patients taking phenytoin may therefore become deficient in folate, leading to the development of macrocytic anemia and possible complications during pregnancy. During the past decade, it has become widely accepted that maternal deficiency in folate is associated with neural tube defects in the fetus.13 Because the neural tube develops between 18 and 30 days after conception, many women do not know yet that they are pregnant when these defects are occurring.

Folic acid supplements can increase the activity of hepatic microsomal enzymes and thus hasten the clearance of antiepilepsy drugs, leading to a reduced concentration of phenytoin.14 This situation necessitates the careful monitoring of both folate and phenytoin levels after therapy is initiated. The normal range for folate is 5 to 25 ng/mL.15 Additionally, phenytoin therapy may increase the metabolism of vitamin D, leading to a decrease in vitamin D levels that can in turn cause alterations in calcium homeostasis that lead to osteomalacia and osteoporosis. Pregnant women taking phenytoin should receive the recommended 400 IU/day of cholecalciferol throughout pregnancy to prevent problems in vitamin D levels and calcium absorption.

During labor and delivery, women taking antiepilepsy drugs are at increased risk for obstetric complications. Weak uterine contractions may result in increased interventions during labor and delivery, including induction, artificial rupture of membranes, use of forceps, vacuum assistance, and cesarean delivery.4

Effects of Epilepsy and Antiepilepsy Drugs on the Fetus and Newborn Infant

The pathophysiological consequences of maternal seizures are a major risk for the fetus. Maternal grand mal seizures associated with apnea can cause transient hypoxia and acidosis in the fetus.4 Prompt control of breakthrough seizure activity is of utmost importance to minimize the effects of oxygen deprivation on the fetus.

Maternal epilepsy and treatment with antiepilepsy drugs during pregnancy presents increased risk to the fetus and the newborn infant (Table 2). The neonates have an increased risk for stillbirths, congenital malformations, hemorrhagic disease, and hypocalcemia. The long-term cognitive function of offspring of pregnant women taking antiepilepsy drugs is also a concern.

Congenital Malformations

The frequency of congenital malformations increases in pregnancies complicated by maternal epilepsy. This increase occurs in pregnancies in which uncontrolled seizures occur frequently during the first and part of the second trimester of pregnancy. The fetus is most vulnerable to malformations from medication during this time. In the third trimester, seizure activity puts the fetus at risk for hypoxic episodes, which leads to other complications with the pregnancy. Fetal malformations occur in about 10% of pregnant women with epilepsy (1000/year), of which 2% are severe (200/year).16

However, when the frequency of epilepsy and the prevalence of major malformations in the general popu-

Table 1

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<tr>
<th>Known maternal adverse effects of phenytoin</th>
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<tr>
<td>Nystagmus</td>
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<td>Ataxia</td>
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<td>Hirsutism</td>
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<td>Gingival hyperplasia</td>
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<td>Peripheral neuropathy</td>
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<td>Vitamin D and folate deficiency</td>
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<td>Megaloblastic anemia</td>
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Table 2

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<tr>
<th>Known fetal and neonatal adverse effects of phenytoin</th>
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<tr>
<td>Fetal hydantoin syndrome</td>
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<td>Facial clefting</td>
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<tr>
<td>Heart malformations</td>
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<tr>
<td>Limb deformities</td>
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<td>Vitamin K deficiency</td>
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<tr>
<td>Vitamin D deficiency</td>
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<td>Possible cognitive deficit</td>
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with maternal epilepsy. According to Samuels, there is little doubt that anticonvulsant medications are associated with an increase in congenital malformations, but the magnitude of this risk and the association of certain anomalies with specific drugs remain debatable.

Whether the malformations are caused primarily by the maternal epilepsy itself or by exposure to antiepilepsy drugs is controversial. A recent study, however, suggests that antiepilepsy drugs rather than the epilepsy itself are the major contributor to the development of malformations. The dosage and timing of exposure to antiepilepsy drugs during pregnancy are considered major contributing factors. Fetal hydantoin syndrome is a rare disorder that is caused by exposure of a fetus to phenytoin. Major signs of this disorder include abnormalities of the skull and facial features, growth deficiencies, and underdeveloped nails on the fingers and toes. The full-blown syndrome is estimated to occur in approximately 5% to 10% of newborns exposed to phenytoin in utero. An additional 30% have subtle changes compatible with the prenatal effects of hydantoin. The teratogenic mechanism of phenytoin may be related to an accumulation of epoxides, which are highly reactive oxidative metabolites of phenytoin. Fetal hydantoin syndrome does occur with fetal exposure to phenytoin alone, but in most cases, it occurs in offspring of women given several antiepilepsy drugs.

Congenital heart disease and cleft lip or cleft palate are the major malformations most consistently attributed to maternal use of antiepilepsy drugs. Several large-scale studies of infants born to women with epilepsy who were taking antiepilepsy drugs indicated that approximately 2% experienced congenital heart disease and a similar percentage had cleft lip or cleft palate. These rates are 4-fold greater than the rates in the general population for congenital heart disease and 10-fold greater than the rates for cleft lip or cleft palate. Phenytoin was the most commonly implicated antiepilepsy drug in both of these studies.

The risk for neural tube defects is also increased in offspring of women taking anticonvulsant medications. Research indicates that phenytoin causes a decreased plasma concentration of folate in epileptic patients, probably through depletion of total hepatic folate. Serum level of folate decreases when phenytoin therapy is initiated alone with no folic acid supplementation. This situation creates an extraordinarily high degree of risk for women of childbearing age who use phenytoin. Therapy recommendations suggest that women begin taking folic acid supplements before becoming pregnant and continue taking the supplements throughout the first trimester to reduce the risk of neural tube defects.

Hemorrhagic Disease of the Newborn

Phenytoin interferes with vitamin K in the formation of precursor protein for coagulation factors II, VII, IX, and X, resulting in prolongation of either the prothrombin time, the partial thromboplastin time, or both. Women should receive injections of phytonadione early in labor, or phytonadione supplements during the last month of pregnancy to reduce bleeding tendencies in the newborn and during the immediate neonatal period. Additionally, the newborn should receive an injection of phytonadione immediately after birth. Without this additional phytonadione, the newborn is at risk for vitamin K deficiency and hemorrhage, usually within the first 24 hours after birth. Sites of hemorrhage are the skin, liver, gastrointestinal tract, intracranial sites, and thorax. Intracranial hemorrhage has been reported in approximately 25% of these cases. The course may be fulminating, and approximately 40% of infants reported to have intracranial hemorrhage have died. Infants should be monitored carefully for signs of bleeding, including petechiae and large cephalohematomas that indicate collection of blood between the periosteum and the skull. Cephalohematomas generally are due to birth trauma, and if a large cephalohematoma occurs, computed tomography of the head should be ordered to rule out an underlying skull fracture.

Neonatal Hypocalcemia

As discussed previously, phenytoin alters metabolism of vitamin D and inhibits the intestinal absorption of calcium in pregnant women, resulting in osteomalacia with hypocalcemia. Decreased levels of vitamin D in the maternal system can lead to low levels of vitamin D and calcium in the fetus, thus
increasing the risk for neonatal hypocalcemia.\textsuperscript{25,26} In order to reduce the risk related to neonatal hypocalcemia, the pregnant woman should be given cholecalciferol supplements throughout pregnancy. Most infants with hypocalcemia are asymptomatic, and early, mild hypocalcemia often resolves without treatment. If the mother has not received supplemental cholecalciferol during pregnancy or the infant begins to have clinical signs such as jitteriness, the infant’s serum calcium level should be measured. Because neonatal jitteriness can also occur with hypoglycemia, a blood glucose level should also be determined at the same time to help differentiate possible causes.

Cognitive Function

The effect of maternal epilepsy on IQ in the offspring has been studied. Small head size can occur in neonates prenatally exposed to antiepilepsy drugs.\textsuperscript{19} Infants with fetal hydantoin syndrome may have cognitive impairments, but whether these impairments are permanent or disappear over time is unclear.\textsuperscript{27} Research does point to significantly smaller head size in infants who are prenatally exposed to several antiepilepsy drugs as compared with only a single antiepilepsy drug. Most infants exposed to only a single drug have normal intellectual capacity, and the smaller head size does not seem to be related to cognitive functioning in adulthood. In one study,\textsuperscript{28} persistent learning problems were found in approximately 12% of phenytoin-exposed infants as compared with 1% of the general population. On the basis of these results, pregnant women with epilepsy should not be concerned that taking phenytoin will result in lower IQ for the baby, but they must be aware that learning problems may occur.

Management Guidelines: Phenytoin During Pregnancy

Guidelines for the management of women taking phenytoin during pregnancy and for initial monitoring of newborns exposed to phenytoin are summarized in Table 3. It is important to manage the seizure activity of pregnant women while minimizing effects on the fetus and neonate. The major emphasis is prevention and counseling young women with epilepsy about the disease and use of antiepilepsy drugs during pregnancy. Women with epilepsy should be taught that even without medication for their epilepsy, they have a higher risk of delivering an infant with congenital malformation and cognitive impairment. Although the exact mechanism is unknown, it is theorized that genetic factors contribute to the increased prevalence of malformations in infants born to mothers with epilepsy independent of maternal medications.\textsuperscript{21} With anticonvulsant medication, that risk may be even higher. It is equally important, however, and should be stressed to these women, that more than 90% of babies born to women with epilepsy are born with-

### Table 3 Management guidelines for phenytoin during pregnancy\textsuperscript{4-6,19,24}

**Maternal and fetal management**
- Provide counseling before pregnancy about risk of treatment of epilepsy on the developing fetus and neonate and the importance of taking medication
- Attempt to withdraw antiepilepsy drugs from women who wish to become pregnant and have been free of seizures for at least 2 years
- Attempt to use only a single antiepilepsy drug for seizure control
- Use lowest dose and plasma level that prevent tonic-clonic seizures
- Have pregnant women take a folic acid supplement of at least 0.4 mg/day to minimize risk of neural tube defects
- Have pregnant women take a cholecalciferol (vitamin D) supplement of at least 400 IU/day to minimize risk of neonatal hypocalcemia
- Stress the importance of taking prenatal vitamins, which contain folic acid and cholecalciferol
- Advise frequent oral care and regular dental checkups
- Administer oral phytonadione (vitamin K) 10 mg/day to the mother during the last month of pregnancy; if this supplement has not been given, administer parenteral phytonadione to the pregnant woman at the onset of labor to minimize risk of fetal hemorrhage
- Monitor plasma phenytoin levels regularly
- Schedule regular fetal ultrasound examinations during pregnancy to monitor fetal growth and detect malformations
- Determine maternal serum levels of α-fetoprotein to detect fetal neural tube defects
- Management of phenytoin-exposed newborns
  - Carefully observe and monitor for malformations, bleeding, and clinical signs of hypocalcemia
  - Do not discharge early, before 72 hours after birth, because problems may develop during this time
  - Administer phytonadione at birth as recommended for all newborns
  - Measure serum calcium level if jitteriness is observed
  - Measure serum glucose level at same time as serum calcium level to rule out hypoglycemia
  - Allow mother to breast feed if desired

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Toxicology

Conclusion of Case Report

After S.S. was admitted to the high-risk obstetric unit, phenytoin levels in the blood were measured, and fetal monitoring was started. Her blood levels of phenytoin were subtherapeutic. In the next several days, the amount of phenytoin administered was adjusted according to blood levels and clinical status. No further seizure activity was observed, and the status of the fetus remained stable. A fetal ultrasound did not reveal any anomalies. Before discharge, S.S. received counseling about the effects that pregnancy and epilepsy have on each other. The need to take her medication on a regular basis was emphasized, and the importance of routine prenatal care was stressed. An appointment was scheduled with a maternal-fetal specialist for ongoing prenatal care. At 38 weeks’ gestation, S.S. delivered a healthy 2700-g boy with no subsequent problems detected.

Pediatrics suggests that women who have been free of seizures for at least 2 years undergo a medication-free trial before becoming pregnant. The time to begin a medication-free trial is not after a pregnancy has occurred. Once a woman with epilepsy is pregnant, it is best to attempt to decrease the number of anticonvulsant medications carefully to a single antiepilepsy drug at the smallest effective dose possible to minimize the risk. Women who become pregnant should be counseled against discontinuing medication without proper medical guidance.

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References

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