In the United States, approximately 1.1 million women with epilepsy are of childbearing age, and three to five births per thousand will be to women with epilepsy. Epilepsy, by definition, is a chronic condition and as such treatment is typically a daily, long-term regimen. Most people with epilepsy are otherwise healthy and are not restricted from participating fully in life. Thus, the potential risks of fetal exposure to daily antiepileptic drug (AED) treatment during pregnancy is an area of concern.

However, withholding maternal antiepileptic therapy during pregnancy increases the possibility of recurrent seizures and the accompanying medical and neurologic sequelae. This presents a quandary: which is safer, continuing the AED regimen to maintain seizure control or suspending treatment to prevent fetal AED exposure? Although pregnancy is often one of the happiest times in a woman’s life, for women with epilepsy the experience can be fraught with concerns such as these. This article will present the risks and benefits of both AED treatment and seizure occurrence in pregnancy and will discuss potential strategies to minimize both maternal and fetal complications.

Defining Congenital Anomalies
Major malformations in epilepsy studies are characterized as structural abnormalities with medical, surgical or cosmetic importance identified within the first five days of life. The rate of malformations detected increases as ascertainment periods increase; the malformation rate is higher at one month since birth because more malformations are detected by this time, compared to five days since birth.

These include cardiac malformations (ventricular septal defect, coarctation of the
aorta, tetralogy of Fallot, aortic valve stenosis, hypoplasia of mitral valve), neural tube defects (spina bifida, myelomeningocele, anencephaly), craniofacial defects (cleft lip and palate), microcephaly, congenital megacolon and urogenital malformations. Minor anomalies may be outgrown during the first several years of life, such as hypoplasia of the midface and fingers.4-6

Maternal Seizures and Major Malformations
Although there is no debate surrounding the importance of prevention of congenital malformations in women with epilepsy, the separate contributions of maternal seizures and AED treatment to the occurrence of congenital malformations are not so clear. The independent effect of maternal seizures is difficult to determine due to such confounding factors as superimposed AED effect.

In a prospective study, convulsive seizures during the first trimester—which is the type and timing of seizures thought to potentially have the most effect—were associated with malformations in 7.4 percent pregnancies.3 The rates of malformation in offspring of women with minor seizures was 7.8 percent, in women with AED monotherapy was 5.7 percent, in women with AED polytherapy was 8.6 percent.3 Although the association of seizures and malformations is not significantly higher than that with AEDs, these results suggest that seizures during pregnancy at least add to the risk of major malformations imparted by AED treatment.
A historical population-based study showed that seizures during pregnancy were associated with an increased risk of major malformations of 3.8 times greater than the general population. However, this study did not report the timing of seizure occurrence and seizure type. Information about seizures was only available for 40 percent of the study population, which also limits the strength of this association. Another prospective population based study in Rotterdam found an increased risk of malformation (12.3 percent) associated with first trimester seizure occurrence versus a four percent rate of malformation in the seizure-free group.

On the other hand, two large prospective studies have shown no increased risk of malformations in women with seizures in pregnancy. An international, collaborative, prospective study of 983 pregnancies in Japan, Italy and Canada found no association between first trimester seizures and malformations. Another prospective study of 970 pregnancies found no associated risk between first trimester seizures and malformations. A retrospective study from the Mayo clinic showed no increased risk of seizures during pregnancy and malformations.

Based on the previous discussion of the aforementioned six studies, the effect of maternal seizures upon fetal malformations is mixed. Two studies indicate an association, one study suggests an association, and three studies show no association between seizures during pregnancy and the risk of malformations. Since none of these studies included a large proportion of women with epilepsy not taking AEDs, the independent risk of seizures is difficult to sort out. Perhaps the best interpretation of these data is that seizures can add to the risk imparted by AEDs, providing further support for the goal of maintaining seizure freedom during pregnancy.

Maternal Epilepsy and Major Malformations
There is little evidence to indicate that maternal epilepsy as a chronic condition (without seizures during pregnancy) is associated with any major malformations. In a case-controlled study of 57 children born to mothers with epilepsy not on AEDs compared to 57 controls, no statistically significant difference in major malformation rate was seen: 8.7 percent of the study group versus 5.3 percent of the control group. No subject had convulsive seizures during pregnancy but 11/57 mothers had minor seizures during pregnancy. However, the sample size in this study was not determined to detect a difference in malformation rates; the study was aimed toward finding a difference in intellectual outcome. Therefore, the question remains as to whether a larger study would have revealed a difference based on epilepsy alone since AED use was also not a factor in this study. No statistically significant difference in IQ was seen between the study and control group.

An interesting aside is the association of spontaneous abortion and susceptibility to epilepsy. Schupf and Ottman found that spontaneous abortion occurs more frequently in women with epilepsy compared to their siblings, raising the possibility of abortion history as a marker for a genetic predisposition to maternal epilepsy. In addition, a risk of four to five times of having an offspring with epilepsy was noted in women with epilepsy and history of spontaneous abortion. Thus, spontaneous abortion may also be a risk factor for eventual epilepsy in the offspring.

AEDs and Major Malformations
Although the risk of major malformations due to seizures during pregnancy or epilepsy itself is unclear, there is a body of evidence to associate AED exposure with an increased risk of major malformations.

Currently used AEDs carry FDA Category C (adverse effect in animal studies but no human studies) or D (adverse human fetal risk) classifications. Category D AEDs include valproate, carbamazepine and phenytoin. Category C AEDs include gabapentin, oxcarbazepine, lamotrigine, felbamate, levetiracetem, tiagabine, zonisamide and topiramate.

There are many proposed mechanisms of the teratogenesis of AEDs. These include folate deficiency, neuronal suppression, alterations to NMDA/GABA mechanisms and free-radical formation. Certain antiepileptic medications (phenobarbital, phenytoin, valproic acid and primidone) are known to deplete or interfere with folate metabolism. Neuronal suppression models theorize that AEDs may suppress neuronal irritability and, therefore, may also reduce neuronal excitation which may lead to long-term neurodevelopmental deficits.

A theoretical mechanism of alterations in the NMDA/GABA mechanisms (similar to fetal alcohol syndrome) caused by AEDs has been described. Additionally, the reactive intermediates of AEDs, including free-radicals and oxidative metabolites, are thought to be important in teratogenicity. It is thought that AED polytherapy promotes free-radical and epoxide formation.

Evidence of AED teratogenicity has been gained from studies such as the North American AED Pregnancy Registry (1997-2002) which showed a significant increased risk of major malformation in the offspring of mothers taking phenobarbital monotherapy. After 77 birth outcomes, a statistically significant increased risk of phenobarbital monotherapy (6.5 percent) compared to a general hospital population (1.6 percent) was seen. This was four times the risk compared to the general population.

An international survey of malformations (MADRE study) of 299 patients with AED exposure revealed oral clefts associated with phenobarbital and methylphenobarbital. Cardiac malformations were associated with phenobarbital, methylphe-
nobarbital, valproate, and carbamazepine. Valproate was associated with spina bifida, hypospadias, porencephaly and other brain anomalies, and limb reduction defects.

Numerous other studies have confirmed the increased risk of fetal major malformations with the use of category D AEDs. In addition, a total daily dosage greater than 1000mg of valproate posed an increased risk of congenital malformations. Therefore, phenobarbital and valproate have clearly emerged as imparting a risk of malformations of at least double that of the general population.

Polytherapy with greater than one AED increases the overall risk of congenital malformations up to four times compared to monotherapy in separate studies by Holmes et al. and Kaaja et al.

Although large population studies confirm the teratogenicity of the Category D AEDs, particularly with polytherapy, there is incomplete knowledge regarding the newer AEDs and congenital malformations. The current data regarding major malformations from the newer AEDs is based on the available information from current drug-specific pregnancy registries.

Of the newer AEDs (lamotrigine, levetiracetam, oxcarbazepine, topiramate, felbamate, gabapentin, tiagabine, zonisamide), lamotrigine has the most cumulative data. The GlaxoSmithKline International Lamotrigine Pregnancy Registry (11-year study) reported 2.8 percent (10/360 individuals) of first trimester monotherapy births with major malformations. Smaller registries of oxcarbazepine, gabapentin, levetiracetam and topiramate have shown no major malformations. Oxcarbazepine monotherapy exposure in 35 infants revealed no major or minor malformations at birth, three and six months of age. The Gabapentin Pregnancy Registry reported no major malformations in 19 infants exposed to gabapentin monotherapy in early pregnancy. Three cases of levetiracetam monotherapy during pregnancy have shown normal outcome at 12 months postnatally. In 19 prospective cases of fetal topiramate exposure, no malformations have been reported. Although the results of these last four registries look promising, the numbers are yet too small to extrapolate definite conclusions.

**Maternal and Fetal Risks Due to Seizures**

These important risks are among the most compelling for trying to achieve seizure-freedom during pregnancy. Generalized convulsions are known to cause fetal heart rate depression, fetal hypoxia with resultant acidosis, and fetal intracranial hemorrhage. Intrauterine death related to fetal intracranial hemorrhage, which likely occurred after a single seizure, has been reported. Spontaneous abortion, fetal hypoxia, bradycardia and antenatal death have been reported with both partial and generalized convulsive status epilepticus, possibly related to maternal trauma and placental hypoperfusion.

**Table 1. Potential Mechanisms of AED Teratogenesis**

- Suppression of neuronal physiology by AEDs
- Decreased folic acid by AED interference with metabolism or absorption
- Altered NMDA/GABA related mechanisms caused by AEDs (similar to fetal alcohol syndrome)
- Ischemia/hypoxia due to AED effects on cardiac function
- Reactive intermediates
  - Epoxides (but not formed in fetal tissues)
  - Free radicals of bioactivated AEDs

**Table 2. Reasons to Prevent Seizures With AEDs During Pregnancy**

**Why seizures are a risk to the pregnancy:**

- Trauma during pregnancy can result in abruptio placentae (20-50 percent of blunt injuries), premature labor and fetal death
- Generalized convulsions have caused fetal heart rate depression, fetal hypoxia and acidosis, intracranial hemorrhage (Minkoff et al. 1985, Teramo et al. 1979, Hillesmaa et al. 1985)
- One case of decreased fetal heart rate after complex partial seizures (Nei et al. 1998)
- Status epilepticus during pregnancy is associated with high maternal and fetal mortality rate (Teramo et al. 1982)

**Seizures during pregnancy may be associated with:**

- Intrauterine growth retardation
- Miscarriage
- Fetal loss after 20 weeks (fetal wastage)
- Adverse neurocognitive outcome

Expert opinion has also supported an association with seizures during pregnancy and fetal growth retardation. Status epilepticus during pregnancy is associated with both a high fetal (48 percent) and maternal (33 percent) mortality rate. Further, seizure freedom is associated with improved psychosocial as well as physical outcome of the mother and fetus. Patients with seizures during pregnancy may result in loss of employment, loss of driving privileges, increased risk of miscarriage and premature labor.

Recent evidence indicates that another important reason for controlling seizures during pregnancy is to preserve cognitive outcome in offspring. Adab et al. evaluated the long-term cog-
nitive outcome of children born to mothers with epilepsy and reported that more than five convulsive seizures during pregnancy was associated with lower than expected verbal IQ. The use of valproate during pregnancy also was associated with lower verbal IQ in this study.

Management
The foregoing information indicates that optimal seizure control (ideally, seizure-freedom) using the lowest possible AED dose at monotherapy, if possible, will be associated with the least risk of teratogenesis, lowest medical and obstetrical risk, and reduced cognitive risk to the offspring. Some women will not be able to achieve AED monotherapy and still have well-controlled seizures; in these situations seizure control should not be sacrificed in order to reduce AEDs due to the significant risks of seizures to fetal and maternal survival.

Emerging data indicate that phenobarbital and valproate pose risks of malformations that are at least two times greater than in the general population; the use of these AEDs during pregnancy deserves careful consideration as to the risk-to-benefit balance. Definitive risks with the other AED, including the newer AEDs will be forthcoming from the excellent pregnancy registries underway worldwide.

For women with very mild epilepsy and rare seizures, a frequent point of discussion is whether AEDs can be stopped during the first trimester, the period of organogenesis. Although this may seem reasonable for some patients, there is no supporting evidence for the safety of such an approach. It is clear that pregnancy is not a time to change AEDs to an agent the patient has not tried before, due to the risks of side effects such as allergy.

An ongoing tenet of management for all women of reproductive potential, including women with epilepsy, is to ensure adequate folic acid intake. Thus, women taking AEDs should all be on folate supplementation from 0.4mg/day to 4mg/day; usual doses are 1-2mg per day.

Seizure frequency during pregnancy can vary; however, when seizures are well-controlled on AEDs, they usually remain so during pregnancy on AEDs.

Seizure increase, decrease or no change has been reported during pregnancy. The mechanisms for increased seizure activity are multifactorial, including physiologic, hormonal and metabolic changes which can alter the pharmacokinetics of antiepileptic medications.

Seizure exacerbations during pregnancy are most commonly due to decreased AED levels. This can be seen due to decreased plasma protein binding, decreased albumin concentration and increased drug clearance. Other precipitants include stress, sleep-deprivation and noncompliance. However, clinicians can be encouraged and somewhat reassured by the finding that women who are seizure free on medication before pregnancy are likely to remain seizure free while they are pregnant.

Due to the changes in pharmacokinetics of antiepileptic medication as described above, it is imperative that the clinician carefully monitor seizure frequency as well as AED levels during pregnancy, and adjust the AED dose to achieve a serum level appropriate for the individual to maintain seizure freedom. AED levels should be checked at baseline (before conception), at the beginning of every trimester and in the last four weeks of pregnancy in women with well-controlled seizures, and more often for women with recurrent seizures.

Since phenytoin is 90-95 percent protein-bound and the free fraction greatly increases during pregnancy, free levels of phenytoin should be followed during pregnancy rather than only total levels. More frequent monitoring of AED levels may be required if the patient is taking lamotrigine, since serum levels have been shown to decrease by 60-90 percent during pregnancy.

Although there are considerable risks related to seizures and antiepileptic drug therapy, it is important to remember that over 90 percent of women with epilepsy have normal, healthy children. It is imperative to counsel women in the preconception period regarding the underlying issues and risks. By instituting a few measures—striving for the simplest AED regimen that provides seizure control, vigilant testing of AED levels, and supplementing folate—the chances of an uneventful pregnancy are significantly increased.