Published in final edited form as:
Epilepsia. 2008 December ; 49(0 9): . doi:10.1111/j.1528-1167.2008.01926.x.

Antiepileptic drugs during pregnancy: What is known and which AEDs seem to be safest?

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SUMMARY

Most infants born to women with epilepsy are healthy, but there are increased risks related to in utero antiepileptic drug (AED) exposure and seizures. Emerging data from pregnancy registries and other studies allow us to better balance the anatomic teratogenic and neurodevelopmental effects of AEDs against the need to maintain maternal seizure control. Several large prospective pregnancy registries demonstrate a consistent pattern of increased risk for major congenital malformations (MCMs) with valproate (VPA) use as monotherapy, compared to nonexposed populations and to other AEDs used in monotherapy. AED polytherapy likely increases risk for MCMs, but the risk is more pronounced if VPA is included. Reduced cognitive outcomes have been reported with AED polytherapy, and with use of VPA, phenobarbital (PB), and PHT as monotherapy. Dose-dependent risk has been demonstrated with VPA for MCMs and cognitive consequences. CBZ groups show normal neurodevelopment. Increased clearance of most of the AEDs occurs during pregnancy. Use of therapeutic drug monitoring during pregnancy with LTG reduces the risk for seizure worsening. The consistent findings of increased teratogenic risk for VPA should discourage use of this medication as first-line treatment in women of childbearing age.

Keywords

Teratogen; Malformation; Neuro-development; Clearance; Epilepsy; Seizure

Epilepsy is the most common neurologic disorder that requires continuous treatment during pregnancy, and antiepileptic drugs (AEDs) constitute one of the most frequent chronic teratogen exposures (Fairgrieve et al., 2000; Holmes, 2002). Approximately 1.3 million women with epilepsy in the United States are in their active reproductive years and give birth to 25,000 infants each year (Kaplan et al., 2007). Most women with epilepsy will have a normal pregnancy with a favorable outcome, but there are increased maternal and fetal risks compared to the general population (Kaplan et al., 2007). The effects of AEDs on the developing offspring include both anatomic teratogenic and neurodevelopmental consequences.

Offspring of women with epilepsy on AEDs are at an increased risk for intrauterine growth retardation, minor anomalies, major congenital malformations, cognitive dysfunction, microcephaly, and infant mortality (Hvas et al., 2000; Yerby, 2000; Kaplan et al., 2007;

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Disclosure of conflicts of interest: Dr. Page B. Pennell has received research support from Marinus Pharmaceuticals, UCB Pharma, and GlaxoSmithKline, and has served on the Expert Panel for the Keppra Pregnancy Registry.

Meador et al., 2008). The term “fetal anticonvulsant syndrome” is used to include various combinations of these findings. The pregnancy registries are best able to collect information on the major congenital malformations.

Major congenital malformations (MCM) are defined as an abnormality of an essential anatomic structure present at birth that interferes significantly with function and/or requires major intervention. The MCMs most commonly associated with AED exposure include congenital heart disease, cleft lip/palate, urogenital defects, and neural tube defects (Morrell, 1998; Pennell et al., 2004; Meador et al., 2008). The congenital heart defects include atrial septal defect, ventricular septal defect, patent ductus arteriosus, pulmonary stenosis, coarctation of the aorta, and tetralogy of Fallot. Urogenital defects commonly involve glandular hypospadias. Neural tube defects (NTDs) are malformations of the central nervous system and its membranes caused by faulty neurulation or abnormal development of the neural tube. The NTDs associated with AEDs are usually lower defects, but often tend to be severe open defects complicated by hydrocephaly and other midline defects (Lindhout et al., 1992). The neural tube closure usually occurs between the third and fourth weeks of gestation. By the time most women realize they are pregnant, it is too late to make medication adjustments to avoid malformations (Table 1). Neurodevelopmental effects also occur, with the potential for lifelong consequences. This places the practitioner in the clinical dilemma of minimizing teratogenic effects of AED exposure while maintaining maternal seizure control. However, recent pregnancy registry data allow us to begin to differentiate the risks among the AEDs and help guide our selection.

The AED pregnancy registries are studies that collect both normal outcomes and adverse outcomes for the offspring, with a focus on the anatomic defects that are categorized as MCMs. The major prospective registries include The North American AED Pregnancy Registry, which has reported key findings for phenobarbital (PB), valproate (VPA), lamotrigine (LTG), and carbamazepine (CBZ). The UK Pregnancy Register has reported on the MCM rates for VPA, CBZ, LTG, levetiracetam (LEV), and polytherapy. The Australian Register has reported key findings on VPA, LTG, and polytherapy. The International Lamotrigine Pregnancy Registry, sponsored by GlaxoSmithKline, has provided information on LTG as monotherapy and as polytherapy treatment. Studies of large cohorts of epilepsy patients during pregnancy in Finland (Artama et al., 2005) and in The Netherlands (Samrén et al., 1999) have also provided key information.

AED Polytherapy versus Monotherapy during Pregnancy

The reported MCM rates in the general population vary between 1.6% and 2.1%, and women with a history of epilepsy but on no AEDs show similar MCM rates (Holmes et al., 2001; Meador et al., 2008). Estimates of the size of this risk vary between studies, but Holmes et al. (2001) reported that the frequency of MCMs with first-trimester exposure to monotherapy is 4.5% [odds ratio (OR) 2.6; 95% confidence interval (CI) 0.8–8.3] and with AED polytherapy is 8.6% (OR 5.1; 95% CI 1.0–21.1).

Artama et al. (2005) compared the risks for MCMs in offspring born to women on AEDs for epilepsy and women who had chosen to discontinue their AEDs prior to conception. They reported significantly increased risks of MCMs with maternal AED exposure (OR 1.70; 95% CI 1.07–2.68) compared to an untreated group of women with epilepsy (WWE) ($p = 0.02$). However, they noted that the risk was higher specifically in offspring of women taking VPA as monotherapy (OR 4.18; 95% CI 2.31–7.57) or as polytherapy (OR 3.54; 95% CI 1.42–8.11) compared to untreated patients, and that polytherapy without VPA was not associated with increased risk of malformations. The risk did not appear elevated in offspring of women on CBZ, oxcarbazepine (OXC), or PHT, but the number of women on these specific

AEDs could have limited the positive findings. The UK Pregnancy Register (Morrow et al., 2006) demonstrated an increased risk of MCMs with polytherapy AED use compared to untreated women with epilepsy [relative risk (RR) 2.52; 95% CI 1.17–5.44], and they reported an increased risk with AED polytherapy use compared to AED monotherapy use (RR 1.62; 95% CI 1.14–2.31). Dean et al. (2002) also showed an increased risk with polytherapy versus monotherapy use (OR 2.78; 95% CI 1.20–5.87). A prospective study in southeast France reported that the rate of malformations was higher in infants exposed to polytherapy (15%) than in those exposed to monotherapy (5%) ($p < 0.01$) (Dravet et al., 1992). Other studies have consistently demonstrated a trend toward increased risk with polytherapy versus monotherapy use, but the results are often not significant, with wide confidence intervals, possibly because of being underpowered to detect significant differences (Olafsson et al., 1998; Samrén et al., 1999; Holmes et al., 2001; Artama et al., 2005). In one study, the rate of major malformations increased to 25% for those women on four or more AEDs (Lindhout et al., 1992). Comparison of two cohorts of patients from different intervals at the same Canadian institution found that the prevalence of major malformations was significantly different between groups (24.1% vs. 8.8%; $p < 0.01$), and that the decreased prevalence correlated with the proportion of patients receiving AED monotherapy and a smaller mean number of drugs (Oguni et al., 1992). These consistent results have led to the recommendation that AED monotherapy is preferred to polytherapy during pregnancy and should be achieved during the preconception planning phase (Morrell, 1998; Pennell, 2003; Meador et al., 2008).

AED monotherapies during pregnancy

Although features of the fetal anticonvulsant syndrome have been described in association with virtually all of the AEDs, there are some notable differences in the likelihood of MCMs in general and with specific malformations with the different AEDs (Barrett & Richens, 2003; Meador et al., 2008).

Valproate

Other studies in addition to the one by Artama et al. (2005) have consistently demonstrated higher risks with VPA use than with use of other AEDs during the first trimester of pregnancy. The large UK Pregnancy Register (Morrow et al., 2006) also reported that polytherapy combinations containing VPA carried a higher risk of MCMs than combinations not containing VPA (OR 2.49; 95% CI 1.31–4.70). For monotherapy, the MCM rate was specifically greater for pregnancies exposed to VPA (6.2%; 95% CI 4.6–8.2%) than to CBZ [2.2%; 95% CI 1.4–3.4%; OR 2.78 ($p < 0.001$); adjusted OR 2.97 ($p < 0.001$)]. There were also fewer MCMs for pregnancies exposed to LTG compared to those exposed to VPA, but this difference did not reach statistical significance ($p = 0.064$). In addition, a positive dose trend was reported for VPA with a MCM rate of 9.1% (95% CI 5.8–14.1%) for >1,000 mg/day compared to 5.1% for lower doses.

Prospective data from the North American AED Pregnancy Registry (Wyszynski et al., 2005) reported that with first-trimester VPA monotherapy exposures ($n = 149$), major birth defects occurred in 10.7% (95% CI 6.3–16.9%) of infants, as compared with 2.8% in infants exposed to other AED monotherapies and 1.6% in external control infants (RR 7.3; 95% CI 4.4–12.2]). Perhaps more helpful to the clinician choosing between AEDs, the relative risk was 4.0 (95% CI 2.1–7.4%) compared to the internal comparison group, which were offspring of women on other AED monotherapies. Birth defects included cardiac anomalies, NTDs, hypospadias, polydactyly, bilateral inguinal hernia, dysplastic kidney, and equinovarus club foot. The Australian Pregnancy Registry also demonstrated greater risk with VPA in comparison to the other monotherapies combined (16.0% vs. 2.4%) (Vajda et al., 2004; Vajda & Eadie, 2005). In addition, a significant dose-effect was demonstrated; the

incidence of MCMs with VPA doses >1,100 mg was 30.2% versus 3.2% with doses <1,100 mg.

Meador et al. (2006) replicated the findings of increased risk of VPA exposure compared to other monotherapies as a combined group (CBZ, LTG, and PHT) with an RR of 4.59 (95% CI 2.07–10.18%). These significant differences were maintained when individually compared to each of the AED monotherapies, and the effect for VPA was a dose-dependent effect. A study examining the Swedish Medical Birth Registry directly compared VPA and CBZ exposed pregnancies; the authors reported that exposure to VPA monotherapy compared with CBZ monotherapy provided an OR of 2.51 (95% CI 1.43–4.68%) for a diagnosis of MCMs (Wide et al., 2004).

Other studies have supported a dose-relationship for VPA, with an increased risk for MCMs with VPA doses above approximately 1,000 mg/day or with levels above 70 μg/ml (Omtzigt et al., 1992; Samrén et al., 1997, 1999; Canger et al., 1999; Mawer et al., 2002; Artama et al., 2005).

Three studies have reported an increased risk of NTDs with VPA (Bertollini et al., 1985; Samrén et al., 1999; Arpino et al., 2000). One analysis pooling data from five prospective studies suggested that the absolute risk with VPA monotherapy may be as high as 3.8% for neural tube defects, and that offspring of women receiving >1,000 mg/day of VPA were especially at increased risk (Samrén et al., 1997). Two of the studies also reported an increased risk of hypospadias (Samrén et al., 1999; Arpino et al., 2000).

The consistent findings of these large prospective pregnancy registries scattered across different regions of the world reveal a consistent pattern of amplified risk for the development of MCMs in pregnancies exposed to VPA.

Carbamazepine

In an analysis by Samrén et al. (1997) of the European prospective studies, the relative risk for a major congenital malformation in children exposed to CBZ monotherapy was 4.9 (95% CI 1.3–18.0). In the study by Holmes et al. (2001) the frequency of major malformations, microcephaly, and growth retardation, but not of facial or digit hypoplasia, was higher in the 58 infants exposed to CBZ monotherapy. A recent review pooled data from prospective studies of exposure to CBZ (Matalon et al., 2002). Among the CBZ-exposed children, 85 of 1,255 children (6.7%) were described as having major congenital anomalies compared with 88 (2.34%) of 3,756 control children ($p < 0.05$; OR 3.02; 95% CI 2.56–4.56). The major malformations most commonly reported were NTDs, cardiovascular and urinary tract anomalies, and cleft palate. The risk for major congenital anomalies was highest when CBZ was used in polytherapy combinations, with a rate of 18.8% (n = 99) versus 5.28% for those exposed to CBZ monotherapy.

For NTDs, Rosa (1991) reported that 1% of CBZ-exposed infants had spina bifida. Data from an ongoing case-control study in the United States and Canada compared data on 1,242 infants with NTDs with data from a control group of infants with malformations not related to vitamin supplementation. They reported that the adjusted odds ratio of NTDs related to exposure to CBZ was 6.9 (95% CI 1.9–25.7) (Hernandez-Diaz et al., 2001).

Hernandez-Diaz et al. (2007) recently reported on findings with CBZ monotherapy from the North American AED Pregnancy Registry. The rate of MCM was 2.5% (95% CI 1.6–3.7%) in 873 infants, with an RR of 1.6 (95% CI 0.9–2.8) compared to the external comparison group. However, increased risk for cleft lip or cleft palate was noted, occurring in 0.57% of the newborns, with an RR of 24 (95% CI 7.9–74.4). The data set of the large population-

based Hungarian Case-Control Surveillance of Congenital Abnormalities, 1980–1996, was evaluated, and the authors reported an increased risk for posterior cleft palate with CBZ (Puho et al., 2007).

The possible malformation-specific risks with CBZ use during pregnancy need to be considered in light of the relatively small risk for all MCMs combined together; the large UK Pregnancy Register study suggested no increased risk for MCMs for CBZ (n = 927 outcomes) (RR 0.63; 95% CI 0.28–1.41), and CBZ was associated with the lowest risk of MCMs for all monotherapy exposures (Morrow et al., 2006).

Phenobarbital

Prospective data from the North American AED Pregnancy Registry are available for PB; of 77 women receiving PB monotherapy, five of the infants had confirmed MCMs (6.5%; 95% CI 2.1%–14.5%). When compared to the background rate for major malformations in this hospital-based pregnancy registry (1.62%), the relative risk is 4.2 (95% CI 1.5–9.4) (Holmes et al., 2004). The MCMs reported in this study included one cleft lip and palate and four heart defects. Two other studies have reported specifically increased cardiac malformations associated with PB exposure in utero (Canger et al., 1999; Arpino et al., 2000).

Phenytoin

The Australian Pregnancy Registry (Vajda et al., 2004; Vajda & Eadie, 2005) reported an MCM rate for PHT of 4.7%. Other studies have a relatively small number of outcomes for PHT, with the MCM rates varying between 3.4 and 10.7% (Samrén et al., 1997, 1999; Holmes et al., 2001; Meador et al., 2006; Morrow et al., 2006). One study showed an increased risk for cleft palate with PHT (Puho et al., 2007),

Lamotrigine

The North American AED Pregnancy Registry has reported on findings with first trimester exposure to LTG monotherapy; the rate of MCM is 2.3% (95% CI 1.3–3.8%) in 684 infants, with an RR of 1.4 (95% CI 0.9–2.3) compared to the external comparison group (Holmes et al., 2008). However, increased risk for cleft lip or cleft palate was noted, occurring in 0.73% of the newborns, with an RR of 10.4 (95% CI 4.3–24.4). The UK Pregnancy Register reported that the MCM rate for pregnancies exposed to LTG was 3.2% (95% CI 2.1–4.9), but the adjusted OR of 0.59 compared to the VPA group did not reach statistical significance ($p = 0.064$). A positive dose response for MCMs was found for LTG ($p = 0.006$), with reports of an MCM rate for doses >200 mg/day of 5.4% (95% CI 3.3–8.7) (Morrow et al., 2006). The investigators more recently refined their findings to demonstrate that the increased risk appeared above 400 mg/day during the first trimester (platform presentation at 2007 AES Annual Meeting, Pregnancy Outcomes SIG). In contrast to this, no relationship between LTG dose and MCMs could be demonstrated in the International Lamotrigine Pregnancy Registry among 802 exposures (Cunnington et al., 2007). The distribution of dose did not differ between the group of infants with MCMs (mean 248.3 mg/day) and those without MCMs (mean 278.9 mg/day). Median doses of both groups were 200 mg/day.

The overall frequency of MCMs was 2.7% (95% CI 1.8–4.2%) in the International Lamotrigine Pregnancy Registry (Cunnington et al., 2007). Other studies also support a low overall rate of MCMs, including the NEAD study (Meador et al., 2006). Serious adverse outcomes, defined as fetal death and/or major congenital malformations, occurred in only 1.0% of LTG pregnancies, and the RRs of MCMs for VPA versus LTG was 22.82 (95% CI 4.25–424.20) (Meador et al., 2006). The UK study also supports low risk of LTG use for MCMs compared to untreated women with epilepsy (RR 0.92; 95% CI 0.41–2.05), although with relatively wide confidence intervals (Morrow et al., 2006).

Other AEDs

The newer generation of AEDs consists of a large number of structurally diverse compounds, most of which have demonstrated teratogenic effects in preclinical animal experiments. With the possible exception of LTG, none has sufficient human pregnancy experience to assess their safety or teratogenicity. Human birth defects have been reported with OXC, topiramate (TPM), gabapentin (GBP), tiagabine (TGB), LEV, and zonisamide (ZNS), but accurate denominators are not available to calculate rates. Preliminary reports of experience with these agents during pregnancy are reported in the following text, but prospective population-based studies in postmarketing evaluation with larger numbers of outcomes are essential to establish safety in human pregnancies.

A series of GBP exposures during pregnancy evaluated prospective and retrospective outcomes for 51 fetuses of women with epilepsy and other disorders, with 44 live births. No malformations were seen in the 11 patients on GBP monotherapy. Two newborns had MCMs with poly-therapy exposure (VPA, PB) and one had minor anomalies (LTG) (Montouris, 2003). However, the number of outcomes is too small to make any definitive conclusions.

The UK Epilepsy and Pregnancy Registry recently reported outcomes for 117 pregnancies exposed to LEV (Hunt et al., 2006). Three had major congenital malformations (2.7%; 95% CI 0.9–7.7%), but all three of these were exposed to AED polytherapy.

The UK Epilepsy and Pregnancy Register also reported on topiramate in 203 pregnancies and 178 live births (Hunt et al., 2008). Sixteen had an MCM (9.0%; 95% CI 5.6–14.1%). Of the 70 monotherapy cases, 4.8% (95% CI 1.7–13.3%) had an MCM, but of the polytherapy cases, 11.2% (95% CI 6.7–18.2%) had an MCM. Four MCMs were oral clefts (2.2%; 95% CI 0.9–5.6%), which is approximately 11 times the background rate.

A case series from Argentina included 35 women on OXC monotherapy, and all infants were healthy; of the 20 infants exposed to polytherapy with OXC, one had a cardiac malformation (Meischenguiser et al., 2004). The prospective study from Denmark (Sabers et al., 2004) included 37 women on OXC, and two (5%) had infants with major malformations, both ventricular septal defect. One of the mothers was on OXC monotherapy and one on OXC with low-dose LTG. Another small series of nine infants exposed to OXC monotherapy reported one major malformation (Kaaja et al., 2003).

One case series reported on 26 pregnancies with ZNS exposure (Kondo et al., 2004). Two of the 26 fetuses (7.7%) had major malformations, although one of these was exposed to PHT and the other to PHT and VPA.

Information on specific benzodiazepines is limited to relatively small series. However, one larger study utilized the Swedish Medical Birth Register and combined into a single class benzodiazepines and/or hypnotic benzodiazepine receptor agonists (HBRAs), prescribed for a variety of medical conditions (Wikner et al., 2007). Neonatal outcomes were compared for all births. A modest increased risk for preterm birth and low birth weight occurred in the exposed group. The adjusted OR for MCMs in the infants exposed during early pregnancy was 1.24 (95% CI 1.00–1.55). Pyloric stenosis and alimentary tract atresia were noted to occur with an unusual frequency, but earlier reports of orofacial clefts were not confirmed. Reports from the Hungarian Case-Control Surveillance of Congenital Abnormalities (1980–1996), utilizing a case-time-control study design, reported similar risks for valium. The group exposed to valium early in pregnancy had an OR of 1.2 (95% CI 1.0–1.4) for an MCM (Kjaer et al., 2007). Other studies have specifically examined clonazepam. A large retrospective cohort study of women with epilepsy in The Netherlands compared to

nonepilepsy-matched controls reported significantly increased relative risk for MCMs with use of clonazepam in the first trimester when used in combination with other AEDs (Samrén et al., 1999). A report from a hospital-based malformation surveillance program of 43 infants exposed to clonazepam monotherapy (Lin et al., 2004) reported no increase in MCMs; however, this and other studies are not large enough to have adequate power to rule out an increased risk for MCMs with clonazepam exposure during early pregnancy.

Neurodevelopmental Outcomes

Studies investigating cognitive outcome in children of women with epilepsy report an increased risk of mental deficiency, affecting 1.4–6% of children of women with epilepsy, compared to 1% of controls (Granstrom & Gaily, 1992; Leavitt et al., 1992; Yerby, 2000). Verbal scores on neuropsychometric measures may be selectively more involved (Meador & Zupanc, 2004). A variety of factors contribute to the cognitive problems of children of mothers with epilepsy, but AEDs appear to play a role (Meador & Zupanc, 2004). Two studies reported that children of women with epilepsy on no AEDs during pregnancy have no behavioral deficits compare to matched controls (Holmes et al., 2000; Gaily et al., 2004). Exposure during the last trimester may actually be the most detrimental (Reinisch et al., 1995). Factors other than specific AED use have been associated with cognitive impairment, including seizures (Leonard et al., 1997), a high number of minor anomalies, major malformations, decreased maternal education, impaired maternal–child relations, and maternal partial seizure disorder (Meador, 2001). It is possible that these risk factors are not only additive but potentially synergistic. Several small studies do show reduced cognitive outcomes in children exposed to AED polytherapy compared to AED monotherapy (Losche et al., 1994; Koch et al., 1999; Gaily et al., 2004).

The Neurodevelopmental Effect of Antiepileptic Drugs (NEAD) study (Meador et al., 2007) is an ongoing prospective, observational study that spans 25 epilepsy centers in the U.S.A. and U.K. The primary aim of the study is to determine if long-term neurocognitive outcomes are different among four different monotherapy exposures in utero (LTG, CBZ, VPA, and PHT). Blinded cognitive assessments at 2 years of age with analysis of Bayley Mental Developmental scores adjusted for maternal IQ, age, and dose, revealed that the VPA group had significantly lower child IQ scores than each of the other groups, and the effects were VPA blood level and dose dependent ($p \leq 0.009$).

A retrospective survey in the UK also demonstrated an especially high risk of VPA for the neurodevelopment of children exposed in utero (Adab et al., 2001). Compared to children of women with epilepsy on no AEDs, the ORs for additional educational needs were 1.49 for all children exposed to AEDs in utero and 3.4 for children exposed to VPA monotherapy.

A prospective study conducted in Finland (Gaily et al., 2004) tested 182 preschool or school-age children who had prenatal exposure to AEDs and compared them to 141 control children. Eighty-six children were exposed to CBZ monotherapy and 13 to VPA. Significantly reduced verbal IQ scores were found in the VPA monotherapy group as well as the polytherapy group. In this study, the CBZ group actually demonstrated no differences from controls in their mean verbal and nonverbal IQ scores. A follow-up study from the UK group (Adab et al., 2004) performed a battery of neuropsychological tests on mother–child pairs on 249 children ages 6–16 years old. Children with in utero exposure to VPA had a significant reduction in verbal IQ (10–14 points) when compared to children exposed to other AED monotherapies or the general population (Adab et al., 2004; Vinten et al., 2005). Other significant predictors of verbal IQ were the mother's IQ, and the number of convulsive seizures (Vinten et al., 2005). Greater than five convulsive seizures during pregnancy had a negative effect on verbal IQ (Adab et al., 2004). In both of these studies,

risks for VPA were dose-dependent. In the study by Adab et al., the risk for VPA was also greater than that for PHT.

Studies by two other groups support the finding that CBZ does not increase the risk for poor cognitive outcomes, but did demonstrate an increased risk for poor cognitive outcomes with PHT compared to unexposed controls (Scolnik et al., 1994; Wide et al., 2002). The risk for PHT is supported by an additional study (Vanoverloop et al., 1992).

Reinisch et al. (1995) reported on two double-blind studies of independent cohorts of adult men in Copenhagen, Denmark, exposed to PB in utero. The PB was not prescribed for epilepsy and the women had no history of a CNS disorder. The men had had significantly lower verbal intelligence scores [approximately 0.5 standard deviation (SD)] than predicted. Exposure that included the third trimester was the most detrimental, and lower socioeconomic status and being the offspring of an “unwanted” pregnancy increased the magnitude of the negative effects.

The Kerala Registry of Epilepsy and Pregnancy (Thomas et al., 2008) recently reported results from prospective evaluation of developmental quotients of 395 infants of mothers with epilepsy (mean age: 15 months), evaluated with the Indian adaptation of the Bayley Scale of Infant Development. The mean mental and motor developmental quotients were impaired (<84) for 150 (37.6%) and 133 (33.5%) infants of mothers with epilepsy, respectively. Infants not exposed to AEDs (n = 32) had higher quotients than those exposed to an AED. Those exposed to polytherapy had significantly lower developmental quotients than those exposed to monotherapy. VPA monotherapy exposure in utero was associated with significantly lower mental and motor developmental quotients in infants compared to CBZ monotherapy (86.9 and 86.1 vs. 93.1 and 95, respectively).

The findings of increased risk for neurodevelopmental consequences with polytherapy and with VPA exposure, should be considered by the prescribing physician and included in the discussion with women with epilepsy. If possible, avoidance of PHT and PB may also be warranted.

Mortality

Fetal death (fetal loss at greater than 20 weeks of gestation) is another increased risk for women with epilepsy (Kaplan et al., 2007). Reported stillbirth rates vary between 1.3% and 14.0% compared to rates of 1.2–7.8% for women without epilepsy (Yerby, 2000). Perinatal death rates are also up to 2-fold higher for women with epilepsy (1.3–7.8%) compared to controls (1.0–3.9%) (Yerby, 2000). Spontaneous abortions (≤ 20 weeks of gestation) may also occur more frequently, although figures from different studies vary considerably (Yerby & Cawthon, 1996; Yerby & Collins, 1997b; Report of the Quality Standards Subcommittee of the American Academy of Neurology, 1998).

Folic Acid and Vitamin K_1 Supplementation

One treatment paradigm that is generally accepted as being important is the use of supplemental folic acid prior to conception and during pregnancy in women on AEDs (Report of the Quality Standards Subcommittee of the American Academy of Neurology, 1998). However, the established benefits of supplemental folic acid are based on studies of women without epilepsy in the general population (Honein et al., 2001) or women at high risk for neural tube defects, with a positive family history (MRC Vitamin Study Research Group 1991). Studies specifically designed to determine effects of fetal AED exposure have failed to consistently show a protective effect against MCMs with folic acid administration (Hernandez-Diaz et al., 2000; Nambisan et al., 2003; Vajda et al., 2003). These findings

either could be due to folic acid's inability to impact AED teratogenic mechanisms or, possibly, to the prescription of inadequate dosage levels of folic acid.

An association between folate concentrations <4.4 nmol/L and neonatal malformation was reported in one study (adjusted OR 5.8; 95% CI 1.3–27; p = 0.02) (Kaaja et al., 2003). Another study, suggested an increased risk of MCMs with VPA only if folate is not supplemented, but the result is not significant (OR 1.67; 95% CI 0.62–4.50). However, given the proven benefit of folic acid in other populations, all women with epilepsy of childbearing potential should be placed on folate supplementation of at least 0.4 mg per day (Report of the Quality Standards Subcommittee of the American Academy of Neurology, 1998). Previous guidelines recommended administration of 10 mg of vitamin K_1 orally to women during the last month of gestation if they were on an enzyme-inducing AED (Report of the Quality Standards Subcommittee of the American Academy of Neurology, 1998). However, a recent review of the studies does not provide a clear answer as to whether there is an increased risk for hemorrhagic disease in these newborns in light of the current practice of administering 1 mg of vitamin K_1 parenterally to all neonates.

Seizures During Pregnancy

The effect of pregnancy on seizure frequency is variable. Approximately 20–33% of patients will have an increase in their seizures, 7–25% a decrease in seizures, and 50–83% will experience no significant change (Devinsky & Yerby, 1994; Gee et al., 1995; Cantrell, 1997; Yerby & Collins, 1997a).

The physiologic changes and psychosocial adjustments that accompany pregnancy can alter seizure frequency, including changes in sex hormone concentrations, changes in AED metabolism, sleep deprivation, and new stresses. Noncompliance with medications is common during pregnancy, in part because of inadequate patient information and counseling (Crawford & Hudson, 2003; Kampman et al., 2005). Proper education about the risks of AEDs versus the risks of seizures can be very helpful in assuring compliance during pregnancy.

Generalized tonic–clonic seizures (GTCS) can cause maternal and fetal hypoxia and acidosis (Stumpf & Frost, 1978; Yerby, 2000; Kaplan et al., 2007). Fetal intracranial hemorrhages (Minkoff et al., 1985), miscarriages, and stillbirths have been reported (Zahn et al., 1998) after a single GTCS. A single brief tonic–clonic seizure has been shown to cause depression of fetal heart rate for more than 20 min (Teramo et al., 1979), and longer or repetitive tonic–clonic seizures are incrementally more hazardous to the fetus as well as the mother. Status epilepticus is an uncommon complication of pregnancy, but when it does occur it may carry a high maternal and fetal mortality rate. One series of 29 cases reported 9 maternal deaths and 14 infant deaths (Teramo & Hiilesmaa, 1982). However, the EURAP Study Group (2006) reported in the 36 cases of status epilepticus (12 of which were convulsive) that only one still birth occurred and no maternal deaths occurred.

It is not as clear what the effects of nonconvulsive seizures are on the developing fetus. One case report described that during labor a complex partial seizure was associated with strong, prolonged uterine contraction with fetal heart rate deceleration for 3.5 min (Nei et al., 1998). Many types of seizures can cause trauma, which can result in ruptured fetal membranes with an increased risk of infection, premature labor, and even fetal death (Yerby & Devinsky, 1994). Abruptio placenta occurs after 1–5% of minor and 20–50% of major blunt injuries (Pearlman et al., 1990). Restrictions from driving and climbing heights should be reinforced with each patient with special emphasis on the risk to the fetus of what could otherwise seem to be a trivial injury. In addition to the physical risks of seizures to the developing fetus, reemergence of seizures in a woman who had previously experienced seizure control

can be devastating. In addition to the immediate risk to herself and the fetus, the loss of the ability to drive legally can have remarkable psychosocial effects.

AED Management and Seizure Control

Management of AEDs during pregnancy can be complex. Clearance of most of the AEDs increases during pregnancy, resulting in a decrease in serum concentrations (Table 2) (Pennell, 2003, 2008). Several physiologic factors contribute to the decline in AED levels during pregnancy (Table 3). Important mechanisms include decreased albumin concentration and induction of the hepatic microsomal enzymes by the increased sex steroid hormones.

Observations on seizure control and treatment were reported from the international Eurap Study Group (2006). Data was obtained from 1956 pregnancies in 1882 women with epilepsy. Seizure control during the second and third trimesters was compared to that in the first trimester. The majority of women (58.3%) were seizure-free throughout pregnancy. Seizure frequency remained unchanged throughout pregnancy in 63.6%, was increased in 17.3%, and decreased in 15.9%. Factors that were associated with an increased risk for occurrence for all seizures were localization-related epilepsy (OR 2.5; 95% CI 1.7–3.9) and polytherapy (OR 9.0; 95% CI 5.6–14.8). OXC monotherapy was associated with a greater risk for occurrence of convulsive seizures (OR 5.4; 95% CI 1.6–17.1). The number or dosage of AEDs was more often increased in pregnancies with seizures (OR 3.6; 95% CI 2.8–4.7) or pregnancies treated with OXC monotherapy (OR 3.7; CI 1.1–12.9) or LTG monotherapy (OR 3.8; 95% CI 2.1–6.9). This international, observational study did not dictate a protocol to monitor serum levels or make dosage adjustments (2006). The apparently higher risk of convulsive seizures among women treated with OXC and the need to increase dose or other medications with OXC or LTG monotherapy is consistent with similar major routes of elimination via glucuronidation.

Lamotrigine

The magnitude of alterations in LTG concentrations exceeds that described for many of the older AEDs, which are primarily eliminated via the cytochrome P450 system (Tran et al., 2002; Pennell, 2003; Pennell et al., 2004, 2007a, 2007b). Approximately 90% of LTG undergoes hepatic glucuronidation, catalyzed by UGT1A4, an isozyme of the UGT family of enzymes. This elimination pathway appears particularly susceptible to activation during pregnancy, most likely as a result of direct effects of rising sex steroid hormone levels.

An early retrospective study reported an approximately 150% increase in LTG clearance in the second and third trimesters of pregnancy (n = 11) (Petrenaite et al., 2005), associated with seizure worsening in 45% of the pregnancies and specifically occurring in women who had >60% change in level–dose ratio. Other studies also noted up to 75% of women experienced seizure worsening during pregnancies on LTG or complications of convulsive seizures, status epilepticus, and even fetal loss (Tran et al., 2002; de Haan et al., 2004; Pennell, 2005; Vajda et al., 2006).

Two small studies showed an increase in the LTG clearance (Tran et al., 2002; Pennell et al., 2004), but with variable magnitude of >65% to 230% increase in clearance. A more recent larger prospective study by Pennell et al. (2007b) of 53 pregnancies in 53 women, using 305 samples throughout preconception baseline, pregnancy, and postpartum reported that both LTG free and total clearance were increased during all three trimesters, with peaks of 94% (total) and 89% (free) in the third trimester. Clearance of free LTG was significantly higher in whites compared to black patients. These studies noted substantial interindividual variability, which may be related to UGT polymorphism variants (Ehmer et al., 2004). This

study also examined therapeutic drug monitoring and seizure frequency, and changes in LTG dosing to avoid postpartum toxicity. The authors reported that seizure frequency significantly increased when the LTG level decreased to 65% of the preconceptional individualized target LTG concentration. This finding supports the recommendation to monitor levels of LTG and possibly other AEDs for which the levels decrease during pregnancy.

Previous studies on LTG noted a rapid decrease in LTG clearance during the early postpartum period with reports of symptomatic toxicity (Tran et al., 2002; de Haan et al., 2004). Pennell et al. (2007b) also examined the effectiveness of using an empiric postpartum taper schedule for LTG, with steady decreases in dosing at postpartum days 3, 7, and 10, with return to preconception dose or preconception dose plus 50 mg to help counteract the effects of sleep deprivation. Patients were assessed for symptoms of LTG toxicity (dizziness, imbalance, and blurred or double vision). Nonadherence to the standard taper schedule was associated with significantly higher risk of experiencing postpartum toxicity ($p = 0.040$).

Oxcarbazepine

The discovery that glucuronidation can be activated by hormonal shifts may apply to other AEDs. Metabolism of VPA is 30–50% by glucuronidation, and 50–60% of the clearance of OXC is via glucuronidation. Christensen et al. (2006) reported retrospectively on nine pregnancies in seven women. The mean dose-corrected concentration of monohydroxy derivative (MHD) was decreased during pregnancy ($p = 0.0016$), being 72% (SD = 13%) in the first trimester, 74% (SD = 17%) in the second trimester, 64% (SD = 6%) in the third trimester, and 108% (SD = 18%) after pregnancy versus dose-corrected concentration before pregnancy.

Levetiracetam

LEV is primarily eliminated via renal excretion (66%), with the remainder via extrahepatic hydrolysis. Tomson & Battino (2007) prospectively examined LEV trough concentrations in 15 pregnancies in 14 women. In the women without dosage changes, plasma LEV concentrations during the third trimester were only 40% of baseline concentrations outside pregnancy ($p < 0.001$). For all pregnancies, clearance of LEV was significantly higher during the third trimester, with an increase from mean (±SD) 124.7 ± 57.9 L/day at baseline to 427.3 ± 211.3 ($p < 0.0001$), an increase of 243%.

Phenobarbital

Limited studies of PB during pregnancy suggest that clearance increases throughout pregnancy (Lander et al., 1981; Battino et al., 1984; Yerby et al., 1990). Yerby et al. (1990) reported that the mean concentrations of total PB declined by 55% as pregnancy progressed ($p < 0.005$), with the sharpest decline during the first trimester. Free concentration decreases of PB were statistically significant ($p < 0.005$), with a decrease of 50%. Lander et al. (1981) reported that the mean ratio of PB plasma clearance in the third trimester to clearance in the pre- or postpregnancy state was 1.6:1 ($p < 0.001$).

Phenytoin

Previous studies of PHT suggest that apparent clearance increases during pregnancy by 20–150% and is often associated with increased seizures (Bossi et al., 1980; Lander et al., 1981; Chen et al., 1982; Dansky et al., 1982; Bardy et al., 1987; Dickinson et al., 1989; Tomson et al., 1994). PHT clearance decreases again to pre-gestational levels over the first 12 weeks postpartum. Although the ratio of free PHT to total plasma drug concentration increases

during pregnancy, most studies have reported that the actual free-drug concentration still declines significantly (Chen et al., 1982; Perucca & Crema, 1982; Tomson et al., 1994). Tomson et al. (1994) performed a population-based prospective study of 93 pregnancies in 70 women with epilepsy; 29 patients were on PHT monotherapy and 7 were on polytherapy. Doses were kept constant unless poor seizure control occurred. Total PHT levels decreased steadily throughout pregnancy with a nadir of 61% at the end of pregnancy, but free levels only dropped by 16% compared to baseline. Yerby et al. (1990) reported that the mean concentration of PHT declined by 56% ($p \leq 0.005$), with the sharpest decline occurring during the first trimester. Although the free concentrations did not change as dramatically, the free concentrations of PHT during all three trimesters were significantly different from baseline ($p < 0.05$), with an overall decrease in free concentration of 31%.

Many of the AEDs studied are characterized by significant increases in clearance during the course of pregnancy. The evidence is most convincing for gestational-induced alterations in clearance of PHT and LTG, moderately convincing for PB, OXC, and LEV, and contradictory or lacking for CBZ, VPA, ESX, and PRM (Pennell, 2008). However, even for the AEDs, well-studied details of individual predictability of magnitude of alterations and time course of alterations are lacking. Because there is evidence that decreased AED levels during pregnancy are associated with seizure worsening, monitoring of concentrations should be considered for LTG and free PHT, and possibly for free PB, OXC, and LEV. However, because of the myriad factors that can contribute to the decrease in all AED concentrations during pregnancy (including noncompliance, enhanced metabolism, and excretion) and large intraindividual and interindividual variability, some authors have recommended at least monthly monitoring of all AED concentrations, with obtaining free (unbound) measurements for those medications that are highly protein bound (Levy & Yerby, 1985; Yerby, 2000; Krishnamurthy et al., 2002; Pennell, 2003; Tomson & Battino, 2007). For each individual patient, the ideal AED (free) level should be established for each patient prior to conception, and should be the level at which seizure control is the best possible for that patient without debilitating side effects. Future studies with formal pharmacokinetic modeling of each of the AEDs during pregnancy in women with epilepsy could be very helpful in achieving an optimal balance between minimizing neonatal exposure to the deleterious influences of both AEDs and seizures.

Postpartum Care

Most of the antiepileptic drug levels increase after delivery and plateau by 10 weeks postpartum. AED levels should be followed closely during this postpartum period (Report of the Quality Standards Subcommittee of the American Academy of Neurology, 1998). Lamotrigine levels, however, increase immediately and plateau within 2 weeks postpartum. Adjustments in LTG doses may need to be made on an anticipatory basis, beginning within the first few days after delivery (Pennell et al., 2007b). Breast-feeding is considered a viable option for most of these mother–infant pairs, and the benefits of breast-feeding are believed to outweigh the small risk of adverse effects of AEDs (Report of the Quality Standards Subcommittee of the American Academy of Neurology, 1998). The concentrations of the different AEDs in breast milk are considerably less than those in maternal serum, with the exception of LEV (Johannessen et al., 2005; Pennell, 2006). A recent study reported on a cohort of 32 mother–child pairs with 210 breast milk samples of LTG(Newport et al., 2008). The mean milk-to-plasma ratio was 41.3% (33.0–49.9%), but the infant plasma concentrations were only 18.3% (9.5–27.0%) of maternal plasma concentrations, despite the fact that LTG is metabolized primarily via glucuronidation. Mild thrombocytosis was noted in seven of the eight infants, and no other adverse events were noted. Long-term follow-up of infants exposed to AEDs through nursing is needed to exclude the possibility of adverse neurodevelopmental effects. Extensive detailed information of levels of exposure and

potential immediate and long-term consequences is lacking for most of the AEDs (Pennell, 2003; Pennell et al., 2007a).

Summary of Epilepsy and Pregnancy

Improving maternal and fetal outcomes for women with epilepsy involves effective preconceptional counseling and preparation. Before pregnancy, it is important to verify whether that individual patient continues to need AEDs and whether she is on the most appropriate AED to balance control of her seizures against teratogenic risks. For most women with epilepsy, withdrawal of all AEDs prior to pregnancy is not a realistic option. In most cases requiring continued AED therapy, monotherapy with an agent other than VPA, possibly at the lowest effective dose during the first trimester, should be employed. The consistent findings of increased risk for major congenital malformations and neurodevelopmental delay with VPA use during pregnancy should enter into the physician's daily treatment decisions. In addition, avoidance of AED polytherapy, PHT monotherapy, and PB monotherapy throughout all of gestation may be considered to reduce the risk of poor neurodevelopmental outcomes. Given that 50% of pregnancies are unplanned in the USA, prescribing AEDs to females during their reproductive years should be performed with the constant consideration of pregnancy, planned or unplanned. When a patient presents after conception and is not on an ideal AED regimen, it is often too late to alter the risk for anatomic teratogenesis; however, careful changes could be considered to lower the risk for poor neurodevelopmental outcome by reducing the number of AEDs if the patient is on polypharmacy and by reducing the dose of AED. Ongoing studies may provide data to support changing the type of AED during pregnancy to improve neurodevelopmental outcome. Folate supplementation should be encouraged in all women of childbearing age. Maintaining seizure control during pregnancy is desired, and therapeutic drug monitoring of LTG can improve seizure control; the same benefits may be extended to other AEDs. Postpartum toxicity can be avoided with AED tapers to preconception doses.

Future studies of AED use in women with epilepsy during pregnancy are essential. Prospective data from pregnancy registries are needed for most of the second-generation AEDs, with analyses to include not only comparisons to a background population but to other AED choices. The actual risk of different polytherapies is yet to be determined, as it is unlikely that all polytherapy combinations confer the same degree of risk. The role of folic acid and other antioxidants or vitamin supplements is still unclear, and no clear recommendations can be given regarding dosages. Further studies of pharmacokinetic and pharmacodynamic alterations in each of the AEDs, with consideration of individual pharmacogenomics (Sankar, 2007) will provide important information about how to manage the medications throughout the course of pregnancy to minimize fetal risk and maintain maternal seizure control. These advances in our knowledge will allow us to better refine treatment decisions for women during pregnancy, and will permit an individualized approach to improve both maternal and fetal outcomes.

Acknowledgments

Funded in part by a National Institutes of Health (NIH) Specialized Center of Research (P50 MH 68036).

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Table 1

Relative timing and developmental pathology of certain malformations[a]

Tissues	Malformations	Postconceptional age (days)
CNS	Neural tube defect	28
Heart	Ventricular septal defect	42
Face	Cleft lip	36
	Cleft maxillary palate	47–70

[a]From Moore, 1988; Yerby, 2003.

Table 2

Alterations of AED clearance and/or concentrations during pregnancy: Summary of class I, II, and III studies[a]

AED	Reported increases in clearance	Reported decreases in total concentrations	Reported changes in free AED or metabolites
PHT	19–150%	60–70%	Free PHT clearance increased in TM3 by 25%; free PHT concentration decreased by 16–40% in TM3
CBZ	−11 to +27%	0–12%	No change
PB	60%	55%	Decrease in free PB concentration by 50%
PRM	Inconsistent	Inconsistent	Decrease in derived PB concentrations, with lower PB/PRM ratios
VPA	Increased by TM2 and TM3		No change in clearance of free VPA. Free fraction increased by TM2 and TM3
ESX	Inconsistent	Inconsistent	
LTG	65–230%, substantial interindividual variability		89% increase in clearance of free LTG
OXC		MHD and active moiety decreased by 36–61%	
LEV	243%	60% by TM3	

AED, antiepileptic drug; CBZ, carbamazepine; ESX, ethosuximide; LEV, levetiracetam; LTG, lamotrigine; MHD, monohydroxy derivative of oxcarbazepine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; TM, trimester; VPA, valproic acid.

References:

PHT (Lander et al., 1980; Chen et al., 1982; Bardy et al., 1987; Dickinson et al., 1989; Yerby et al., 1990; Tomson et al., 1994).

CBZ (Battino et al., 1985; Yerby et al., 1985, 1992; Tomson et al., 1994).

PB (Lander et al., 1981; Battino et al., 1984; Yerby et al., 1990; Vajda et al., 2006).

PRM (Rating et al., 1982; Battino et al., 1984).

VPA (Koerner et al., 1989).

ESX (Kuhnz et al., 1984; Tomson et al., 1990).

LTG (Ohman et al., 2000; Tran et al., 2002; de Haan et al., 2004; Pennell et al., 2004, 2007b; Petrenaite et al., 2005).

OXC (Christensen et al., 2006; Mazzucchelli et al., 2006).

LEV (Tomson et al., 2007).

[a]From Pennell et al., 2007a.

Table 3

Physiologic changes during pregnancy: Effects on drug disposition[a]

Parameter	Consequences
↑Total body water, extracellular fluid	Altered drug distribution
↑Fat stores	↓Elimination of lipid soluble drugs
↑Cardiac output	↑Hepatic blood flow leading to ↑elimination
↑Renal blood flow and glomerular flow rate	↑Renal clearance of unchanged drug
Altered CYP3A4 activity and UGT activity	Altered systemic absorption & hepatic elimination
↓Maternal albumin	Altered free fraction; increased availability of drug for hepatic extraction

[a]From Pennell, 2003.