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Therapy Insight: clinical management of pregnant women with epilepsy

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SUMMARY

In pregnant women with epilepsy who are being treated with antiepileptic drugs (AEDs), careful clinical management is vital because seizure frequency can change during pregnancy, and both seizure activity and AED treatment can have consequences for the developing fetus. Complications of epilepsy and AED treatment include stillbirths, prematurity, low birth weight, major and minor malformations, and cognitive delay later in life. Certain AEDs probably have more adverse effects than others; data from prospective studies indicate that phenobarbital and valproate are associated with significant increases in major malformations, and retrospective studies show lower verbal IQs and greater need for extra assistance in school for children whose mothers received valproate during pregnancy. Monitoring of AED levels and dosage adjustment are warranted throughout pregnancy, and vitamin K_1 at a dose of 10 mg/day should be given in the last month, particularly when cytochrome P450 enzyme-inducing AEDs are being administered. In the postpartum period, breastfeeding is recommended; however, there is differential transfer of individual AEDs in breast milk, and the infant should be observed clinically. For all women of reproductive age, preconceptual counseling is important, and includes optimization of the AED regimen and advising the mother to take supplemental folic acid.

KEYWORDS antiepileptic drugs, breastfeeding, epilepsy malformations, pregnancy

REVIEW CRITERIA

PubMed was searched using Entrez for articles published up to December 15 2005, including electronic early release publications. Search terms included "epilepsy" or "antiepileptic drug", as well as "pregnancy", "registry", "neurocognitive" or "breastfeeding". The abstracts of retrieved citations were reviewed and prioritized by relative content. Full articles were obtained and references checked for additional material when appropriate.

CME

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INTRODUCTION

Pregnancy is associated with dynamic changes in the body, and for women with epilepsy who are undergoing treatment with antiepileptic drugs (AEDs) there are unique management concerns. This review highlights how seizure frequency can change during pregnancy, and the potential effects of epilepsy and AEDs on the developing fetus, illustrated by results from both retrospective and prospective studies. This article also discusses specific management issues for women with epilepsy during pregnancy, including preconceptual counseling, monitoring of AED levels and vitamin K prophylaxis, and recommendations with regard to breastfeeding.

SEIZURE FREQUENCY DURING PREGNANCY

Seizure frequency can increase or decrease in an unpredictable manner during pregnancy, and the nature of the change is not related to seizure type, duration, or seizures in previous pregnancies. Changes in seizure frequency are thought to be secondary to multiple factors, including alterations in the concentration and type of circulating steroid hormones during pregnancy, changes in maternal physiology that result in alterations in the pharmacokinetics of prescribed AEDs, and poor compliance with the drug regimen if the mother fears potential teratogenesis from AED use.

In the nonpregnant state, the main circulating estrogens in the body are estradiol and estrone. In pregnancy, the concentrations of both of these estrogens increase, and levels of estriol—a peripheral metabolite of estrone and estradiol—show an even more marked increase. Progesterone production also increases dramatically. These hormonal changes might have direct consequences on the presentation of seizures, as it has been suggested that estrogen has proconvulsant properties, whereas progesterone has antiepileptic effects.[1]

PRECONCEPTUAL COUNSELING

Women with epilepsy need to plan their pregnancies carefully, as changes in AED regimens might be beneficial. Ideally, women should be prescribed the most effective and best-tolerated AED regimen at the lowest possible dose before becoming pregnant. Changing medication once pregnant is not always practical—lamotrigine therapy, for example, cannot be initiated quickly—and might subject the mother and developing fetus to additional risks as a secondary consequence of seizures. If possible, women on polytherapy should be switched to monotherapy, as data indicate that polytherapy is associated with a higher risk of teratogenic abnormalities. If a woman has not had a seizure in 2 years or more, tapering off medication can be an option.

Because folic acid fortification in cereal grains has significantly decreased the rates of neural tube defects in the US and Canada, the American Academy of Neurology recommends that all women of childbearing age take folic acid supplementation at a dose of 0.8–4.0 mg/day. No definitive proof exists, however, that folic acid has protective effects in children whose mothers take AEDs.[2] Possible explanations for the lack of effect include an inability to overcome AED-related teratogenic mechanisms, or inadequate doses.

EPILEPSY, ANTIEPILEPTIC DRUGS AND THE DEVELOPING FETUS

Controlling seizures during pregnancy is vital, as seizures are likely to have an adverse effect on the developing fetus. Generalized TONIC–CLONIC SEIZURES might cause hypoxia, leading to damage of the CNS as well as of other organ systems, and sustained hypoxia can result in fetal death. In a study of pregnant rats, induction of seizures resulted in neuronal damage in numerous regions of the fetal CNS, including the hippocampus.[3] In addition to hypoxia, a generalized tonic–clonic seizure could result in trauma to the mother or fetus. Maternal death rates might also be higher in women with epilepsy.[4]

The effect of partial seizures on the developing fetus is not clear. In one case report,[5] a 33-year-old pregnant woman had a complex partial seizure during labor, and intrauterine pressure catheter and fetal heart monitoring during the seizure revealed a strong, prolonged uterine contraction and a simultaneous significant fetal heart rate deceleration for 3.5 min. Another report[6] documented fetal heart rate deceleration during a complex partial seizure in the fetus of a 43-year-old woman in her seventh month of pregnancy. These findings indicate that the fetus might be affected during complex partial seizures, and it is advised that complex partial seizures are controlled throughout pregnancy. Recent studies also indicate that generalized tonic–clonic seizures might result in cognitive problems for the child later in life, a phenomenon that is supported by evidence of significantly decreased verbal IQ scores in children whose mothers had more-frequent generalized tonic–clonic seizures during pregnancy.[4,7]

Older studies indicate that perinatal complications are more prevalent in women with epilepsy.[8,9] Possible complications include stillbirth, prematurity and low birth weight, and stillbirths have even been reported to occur after a single seizure. STATUS EPILEPTICUS carries an increased risk of these complications. A recent historical population-based cohort study in Iceland,[10] however, found no significant difference in perinatal mortality and mean birth weight in offspring of women with epilepsy, as compared with the general population. The risk of perinatal complications has not been studied prospectively.

The most common and worrying adverse effects for pregnant women with epilepsy relate to the potential teratogenesis of AEDs. Teratogenic effects are classified as either major malformations or minor anomalies, and both have been associated with maternal AED use. A major malformation is an abnormality that is present at birth and interferes significantly with life function, and which can require surgical intervention. Possible major malformations include congenital heart disease, urogenital defects, cleft lip or palate, and neural tube defects. Minor anomalies include facial dysmorphism and digital anomalies; these anomalies are typically subtle and are often outgrown.

Factors such as maternal epilepsy have been argued to contribute to the increased risk of defects; indeed, some early studies concluded that the mother's epilepsy itself was the teratogen.[11,12] Little evidence remains, however, that seizures themselves result in increased teratogenicity, and recent studies indicate that potential for teratogenesis is a consequence of AED treatment and not epilepsy per se.[13] Early

GLOSSARY

TONIC–CLONIC SEIZURES
Seizures that begins with rigidity (tonic phase), followed by repetitive clonic activity of all extremities

STATUS EPILEPTICUS
Continuous seizure activity without recovery of consciousness or return to neurological function

retrospective studies identified a higher risk of malformations and anomalies associated with AED use.[8,14,15] These studies included mothers who took the older AEDs; that is, those drugs approved before 1993 (phenobarbital, phenytoin, carbamazepine, primidone, valproic acid and trimethadione). The risk increased further in mothers who were receiving polytherapy.[15] It is important to use prospective studies to identify the risk of malformations, as studies of this nature eliminate potential biases, such as selection and recall bias.

A recent cross-sectional controlled study[13] of 922 infants—316 of whom who were exposed to AEDs through treatment of the mother for seizures, 98 of whom were not exposed to AEDs but whose mothers had a history of epilepsy, and 508 of whom were not exposed to AEDs and whose mothers had no history of epilepsy—uncovered a pattern of physical abnormalities associated with AED use but not with maternal epilepsy. No significant differences in outcome were seen between infants whose mothers had a history of seizures but were not treated with AEDs during pregnancy and infants of mothers with no history of epilepsy. Infants of mothers with a history of epilepsy who received AEDs during pregnancy had a higher frequency of major malformations, including microcephaly, growth retardation, and hypoplasia of the mid-face and fingers, than did infants whose mothers had no history of epilepsy or had a history of epilepsy but did not receive AEDs. Children born to mothers who took multiple AEDs showed the highest frequency of malformations.

A population-based study of over 20,000 patients with epilepsy identified 939 births among 561 untreated patients and 1,411 births among 857 patients using AEDs in the first trimester.[16] In this study, valproate use was associated with excess risk of congenital malformations (monotherapy: odds ratio [OR] 4.18; 95% CI 2.31–7.57; polytherapy: OR 3.54; 95% CI 1.42–8.11) compared with the offspring of untreated patients. The risk of congenital malformations did not increase in the offspring of mothers using carbamazepine, oxcarbazepine or phenytoin (as monotherapy or polytherapy without valproate).

Pregnancy registries for major malformations

To ascertain the frequency of major malformations associated with prenatal exposure to AEDs, pregnancy registries have been established. There are two different types of registry: hospital-based and pharmaceutical-based. The first hospital-based registry to be established was the North American AED Pregnancy Registry. Other hospital-based registries include the Australian Pregnancy Registry of Women Taking Antiepileptic Drugs, the UK Epilepsy and Pregnancy Register, and the European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP), which includes countries throughout Europe and Asia. Several pharmaceutical-based registries are also actively enrolling subjects.

The North American AED Pregnancy Registry was first established in 1997. Eligible women must enroll themselves, and are interviewed three times: at enrollment, at 7 months' gestation, and postpartum (8–12 weeks after the expected delivery).[17] Enrolled women are divided into pure prospective cases (no information about fetus known) and traditional prospective cases (some knowledge of status of fetus known). For analysis only pure prospective cases are used, to reduce potential bias. Positive association is released when the lower end of the confidence interval for the proportion of major malformations is 2.0 or higher. Controls are infants with malformations who are registered by the Active Malformations Surveillance Program at Brigham and Women's Hospital, and the baseline rate of major malformations is 1.62% after exclusion of infants with genetic disorders and chromosome abnormalities (conditions also excluded from the major malformations considered in the AED registry). In addition, the prevalence of malformations found in specific AED-exposed groups is compared with the prevalence of malformations among infants of women exposed to all other AEDs (internal comparison group). The internal comparison group is similar to the studied groups in terms of demographics and prenatal exposures.[17,18]

Using this methodology, it was calculated that 6.5% of 77 infants exposed to phenobarbital (95% CI 2.1%–14.5%) were born with major malformations.[17] Specific malformations of infants exposed to phenobarbital from this registry are described in Box 1. When compared with the external comparison group (control population), the relative risk of having an affected infant after exposure to phenobarbital was 4.2 (95% CI 1.5–9.4). At the time of publication, the internal comparison group consists of 796

Box 1 Malformations reported in children exposed to phenobarbital (North American Antiepileptic Drug Pregnancy Registry).[17]

Cardiac malformations
- COARCTATION of the aorta with abnormal valves
- Ventricular septal defect
- TETRALOGY OF FALLOT
- Pulmonary atresia

Cleft lip and palate

Box 2 Malformations reported in children exposed to valproate (North American Antiepileptic Drug Pregnancy Registry).[18]

Nervous system malformations
- Spina bifida
- SUTURE SYNOSTOSIS

Cardiopulmonary malformations
- Tetralogy of Fallot
- Atrial septal defect
- Ventricular septal defect
- Bicuspid aortic valve
- Pulmonary atresia

Renal malformations
- HYPOSPADIAS
- Multicystic dysplastic kidneys

Limb malformations
- POLYDACTYLY
- Club foot

Developmental delay

Inguinal hernia

GLOSSARY

COARCTATION
A narrowing of the passageway of a blood vessel

TETRALOGY OF FALLOT
A congenital heart anomaly that consists of pulmonary stenosis, ventricular septal defect, dextroposition of the aorta (aorta is on the right side instead of the left) and hypertrophy of the right ventricle

SUTURE SYNOSTOSIS
Union by means of bone; the complete closing up and obliteration of sutures

HYPOSPADIAS
Congenital defect in males where the urethral opening is on the underside of the penis or the perineum, rather than on the glans

POLYDACTYLY
The condition of having more than the normal number of digits

infants exposed to three other AEDs, and the prevalence of malformations in this group is 2.9% (95% CI 1.8–4.3%). Comparison of the two groups yielded a relative risk of 2.0 (95% CI 0.9–4.5).[17]

Of 149 infants exposed to valproate monotherapy, 10.7% (95% CI 6.3–16.9%) had major malformations.[18] Box 2 outlines malformations found in valproate-exposed infants from this registry. The relative risk of having an affected infant when compared with the external comparison group is 7.3 (95% CI 4.4–12.2). The internal comparison group at the time of this analysis consisted of 1,048 women exposed to all other AEDs as monotherapies. The prevalence of malformations in the internal comparison group was 2.9% (95% CI 2.0–4.1%), and the odds ratio when comparing the valproate-exposed group with this group was 4.0 (95% CI 2.1–7.4; $P<0.001$).[18]

The Australian Pregnancy Registry of Women Taking Antiepileptic Drugs, which was established in 1999, is a prospective, voluntary, telephone-based registry that enrolls three groups of pregnant women: those with epilepsy taking AEDs; those with epilepsy not taking AEDs; and those taking AEDs for a nonepileptic indication.[19–22] The third group is important, as AEDs are being prescribed increasingly for multiple indications, including pain, bipolar depression, anxiety and headaches. The pregnancy outcomes are evaluated by follow-up interviews and by reference to hospital and treating doctors' records. To date, 493 pregnancies have been completed including nine sets of twins, giving a total of 502 pregnancy outcomes. The fetal malformation rate was greater in fetuses exposed to valproate in the first trimester than in those exposed to all other AEDs (15.2% vs 2.4%, OR 7.40, 95% CI 3.12–17.5) or no AEDs (17.1% vs 2.5%, OR 9.96, 95% CI 1.26–38.5). The incidence of fetal malformations was significantly lower in those taking valproate doses of 1,400 mg or less per day than in those taking doses of more than 1,400 mg per day (34.5% vs 5.5%, OR 0.109, 95% CI 0.0405–0.295).[20–22]

The UK Epilepsy and Pregnancy Register is a prospective observational registry and, as in the North American and Australian registries, the outcome is not known before enrollment. AED use is not mandatory. Enrollment is either by self-referral or by a healthcare practitioner, and data are obtained 3 months after expected delivery. Full outcome data are currently available on 3,607 cases.[23] The overall major congenital malformation rate was 4.2% (95% CI 3.6–5.0%); therefore, almost 96% of live births born to women with epilepsy did not have a major congenital malformation. The malformation rate was higher for pregnancies exposed to polytherapy (6.0%, $n=770$) than for monotherapy exposure (3.7%, $n=2,598$). Valproate exposure resulted in the highest malformation rate, and carbamazepine exposure was associated with the lowest malformation rate. Table 1 outlines malformation rates for individual AEDs, comparing these drugs with carbamazepine exposure using an OR, and Table 2 provides information on specific types of major congenital malformation,

Table 1 Major congenital malformation rate by monotherapy antiepileptic drug exposure (UK Epilepsy and Pregnancy Register).[23]

Antiepileptic drug	Number of individuals	Number of MCMs	MCM rate (95% CI)	Odds ratio[a] (95% CI)	*P* value
Carbamazepine	900	20	2.2% (1.4–3.4%)	1.0	—
Valproate	715	44	6.2% (4.6–8.2%)	2.78 (1.62–4.76)	<0.001
Lamotrigine	647	21	3.2% (2.1–4.9%)	1.44 (0.77–2.67)	0.253
Phenytoin	82	3	3.7% (1.2–10.2%)	1.64 (0.48–5.62)	0.484
Gabapentin	31	1	3.2% (0.6–16.2%)	1.33 (0.17–10.20)	0.782
Topiramate	28	2	7.1% (2.0-22.6%)	2.75 (0.62–12.20)	0.185
Levetiracetam	22	0	0.0%	—	—

[a]Major congenital malformation rate of individual antiepileptic drug compared with carbamazepine. MCM, major congenital malformation.

Table 2 Types of major congenital malformation listed by antiepileptic drug (UK Epilepsy and Pregnancy Register).[23]

Antiepileptic drug	Number of individuals	NTD[a]	Facial cleft[a]	Cardiac[a]	GU[a]	GI[a]	Skeletal[a]	Other[a]
Carbamazepine	900	2 (0.2%)	4 (0.4%)	6 (0.7%)	2 (0.2%)	2 (0.2%)	3 (0.3%)	1 (0.1%)
Valproate	715	7 (1.0%)	11 (1.5%)	5 (0.7%)	9 (1.3%)	2 (0.3%)	8 (1.1%)	2 (0.3%)
Lamotrigine	647	1 (0.2%)	1 (0.2%)	4 (0.6%)	6 (0.9%)	3 (0.5%)	2 (0.3%)	4 (0.6%)
Phenytoin	82	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)

[a]Percentage values in brackets are the percentages of specific malformations in individual AED groups.
GI, gastrointestinal; GU, genitourinary; NTD, neural tube defect.

listed by AED. Interestingly, this study revealed higher percentages of malformations in association with higher doses of carbamazepine, valproate and lamotrigine, although this finding was statistically significant only for lamotrigine.[23,24]

EURAP is an international registry of AEDs and pregnancy, and includes countries in Europe, Asia, Oceania and South America. Women are enrolled by physicians to a central registry. Women taking AEDs for any indication at the time of conception are included. Like other registries, only individuals registered without prior knowledge of fetal outcome are eligible for inclusion in analyses, and data are collected until 1 year after delivery. Since June 2004, more than 2,000 prospective cases have been enrolled and have completed assessment.[25] Of those enrolled, 81% took a single AED, 16% took two different AEDs, and 2% took three or more AEDs. Overall, the current malformation rate is 6% (5% for monotherapy cases and 8% for polytherapy cases). To date, no formal comparison between AEDs has been made, because there is currently insufficient statistical power in the final analysis to allow inclusion of multiple risk factors that might confound the result.

Several pharmaceutical companies have established registries, most within the past

2 years. Data are available in a peer-reviewed publication for the GlaxoSmithKline-sponsored International Lamotrigine Pregnancy Registry.[26] Pregnant women with unknown outcomes from their pregnancies were enrolled between September 1992 and March 2004. Findings were compared with those from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program. These databases are similar in many respects, because they use the same criteria. The CDC program, however, follows children up to 1 year of age, whereas the lamotrigine registry collects information only up to birth, thereby perhaps underestimating the comparative risk, as some malformations only become evident as the child gets older. In the latter registry, among 414 first-trimester exposures to lamotrigine monotherapy, 12 major malformations were reported, giving a malformation rate of 2.9% (95% CI 1.6–5.1%). Among those exposed to polytherapy including lamotrigine the malformation rate was 12.5% (95% CI 6.7–21.7%) for regimens including valproate, and 2.7% (95% CI 1.0–6.6%) for regimens that did not include valproate. Box 3 presents a list of the malformations that were reported from this registry. The authors conclude that the monotherapy findings are similar to those reported by the CDC's Metropolitan Congenital Defects Program (2–3%), and that there was no specific trend found regarding malformations in association with lamotrigine treatment.[26] The sample size, however, might have limited the ability to detect specific increases.

Box 3 Malformations reported in children exposed to lamotrigine (International Lamotrigine Pregnancy Registry).[26]

- Nervous system malformations
  - Anencephaly
  - Lumbar neural tube defect
  - MYELOMENINGOCELE
  - MENINGOMYELOCELE
  - Microcephaly
- Cardiopulmonary malformations
  - Atrial septal wall defect
  - Ventricular septal defect
  - Transposition of great arteries
  - PATENT FORAMEN OVALE
  - PATENT DUCTUS ARTERIOSUS
  - Pulmonary stenosis
- Renal malformations
  - HYDRONEPHROSIS
  - Absent kidney
- Cleft palate
- Limb malformations
  - Club foot
  - Polydactyly
  - Limb deformities
- Atresia of anus
- Bilateral talipes
- PYLOROSTENOSIS

GLOSSARY

MYELOMENINGOCELE
A congenital defect, usually occurring in the lumbosacral region of the spine (lower back), in which the neural arches fail to close, thereby exposing the contents of the spinal canal posteriorly

MENINGOMYELOCELE
A congenital defect that is characterized by the protrusion of the membranes and cord through a defect in the vertebral column

PATENT FORAMEN OVALE
Incomplete closure of the septum that divides the two atrial chambers of the heart

PATENT DUCTUS ARTERIOSUS
A condition in which the normal channel between the pulmonary artery and the aorta fails to close at birth

HYDRONEPHROSIS
Abnormal enlargement of a kidney

PYLOROSTENOSIS
Stricture or narrowing of the orifice of the pylorus

As discussed, prospective data are available on many AEDs, including carbamazepine, phenytoin, valproate, lamotrigine and phenobarbital. Prospective data are limited for other AEDs (sample sizes <50). It is important to differentiate data ascertained from monotherapy and polytherapy studies, as polytherapy is consistently associated with a higher risk of teratogenesis. Retrospective and prospective studies indicate an increased risk of malformations in association with phenytoin, phenobarbital and valproate monotherapies, and the risk is higher for polytherapy exposure. Multiple studies have shown that of these three drugs, valproate therapy carries the highest risk.

Retrospective studies indicate an increased risk of teratogenesis secondary to carbamazepine exposure. A meta-analysis of 795 children exposed to carbamazepine monotherapy revealed that 5.28% had a major congenital malformation (cardiovascular abnormalities, urinary tract anomalies, cleft palate or neural tube defects), compared with 2.34% of 3,756 control children.[27] Other studies have also identified an increased incidence of neural tube defects in children exposed to carbamazepine.[28,29] Prospective studies published more recently, however, have not found a significantly elevated risk of major malformations in carbamazepine-exposed children.[23]

Retrospective studies have been conducted in children exposed to oxcarbazepine, gabapentin, levetiracetam and zonisamide. A review of all published studies of oxcarbazepine-exposed children found that 6 of 248 children (2.4%) exposed to oxcarbazepine monotherapy had major malformations, and 4 of 61 children (6.6%) exposed to oxcarbazepine in combination with another AED had major malformations.[30]

GLOSSARY

OCULAR HYPERTELORISM
Extreme width between the eyes

Among 48 gabapentin-exposed pregnancies in 39 women, two babies, both of whom were exposed to gabapentin in combination with other AEDs, had major malformations.[31] No abnormalities were reported in a case series of three babies whose mothers received levetiracetam in monotherapy throughout pregnancy.[32] Of 26 children whose mothers took zonisamide with or without other AEDs, malformations were detected in two, both of whom were exposed to zonisamide polytherapy.[33] Further prospective well-controlled studies are needed to fully define and differentiate the potential teratogenesis of these AEDs as given in monotherapy.

Minor malformations

Minor anomalies have been shown to occur in association with all AEDs.[34] Midline craniofacial anomalies, including OCULAR HYPERTELORISM, broad nasal bridge, short upturned nose, altered lips and epicanthal folds, in addition to distal digital and nail hypoplasia, are among the minor anomalies that have been described in children of mothers with epilepsy who took AEDs during pregnancy. These features can be difficult to recognize, and the child might outgrow them. The presence of these anomalies, however, can be associated with developmental and cognitive delay later in life.[35] Seventy-six children whose mothers took AEDs in pregnancy were included in a systematic study of physical features and intelligence testing, as determined by the Wechsler Intelligence Scale for Children® (Harcourt Assessment Inc., San Antonio, TX). Mid-face or digital hypoplasia correlated significantly with deficits in verbal IQ, performance IQ and full-scale IQ. Interestingly, there was no decrease in IQ in association with major malformations.[35]

Cognitive deficits

Understanding the effects of epilepsy and AED exposure during pregnancy on developmental and cognitive outcome has become the focus of recent retrospective and prospective studies. In addition to teratogenic malformations, AED exposure *in utero* might have adverse effects on cognitive development. Studies of cognitive function in children whose mothers took AEDs during pregnancy suggest poorer cognitive development as defined by multiple parameters, including lower IQ scores, and specific cognitive deficits in visuospatial functioning, spelling and linguistic abilities.[4,7,36–39] It is difficult to determine long-term effects from the early studies, however, as these predominantly studied young children. More-recent studies have evaluated older children, and have confirmed the presence of longer term cognitive deficits in some individuals.[4]

Interestingly, a differential effect of individual AEDs has been identified in retrospective and prospective studies of young and older children who were exposed to AEDs *in utero*. Phenobarbital exposure resulted in a 7-point reduction in verbal IQ in adult men who had been exposed to phenobarbital during gestation, compared with controls whose mothers did not take AEDs during pregnancy.[38] In retrospective studies, valproate use is associated with lower verbal IQ scores and additional educational needs, as defined by attendance in special schools and extra assistance in school. Other factors that contributed to this cognitive impairment included mother's IQ and number of tonic–clonic seizures during pregnancy.[4,7,37] A prospective study of 86 children exposed to carbamazepine monotherapy *in utero* did not find any differences between this group and control subjects in verbal and nonverbal IQ scores, whereas children exposed to polytherapy or to valproate *in utero* had significantly reduced verbal intelligence.[36] The authors were not able to separate the independent effects of polytherapy and valproate exposure, as valproate was usually a component of the polytherapy regimen. Lower than expected IQ scores were also found in children exposed to valproate monotherapy *in utero* in a prospective population-based study.[39] The mothers treated with valproate in this study, however, had lower intelligence and schooling level, which could have influenced the findings.

A large-scale international study, Neurodevelopmental Effects of Antiepileptic Drugs (NEAD), is currently underway to prospectively follow children exposed to single AEDs in pregnancy. Children will be followed through to 6 years of age, and the AEDs being studied include valproate, phenytoin, carbamazepine and lamotrigine. Preliminary data indicate that valproate is associated with significantly more adverse outcomes, including fetal death, major congenital malformations and developmental delay, than the other AEDs under investigation.[40]

MANAGEMENT OF WOMEN WITH EPILEPSY DURING PREGNANCY

Once pregnant, a woman with epilepsy who is being treated with AEDs should be followed by an obstetrician who is comfortable with her medical condition and treatment. A high-risk obstetrician or maternal fetal medicine specialist is preferable, although this might not always be possible. Pregnant women should have first-trimester serologic and ultrasonographic studies to assess the risk of neural tube defects.[41,42] A level II or anatomic ultrasound performed between weeks 16 and 20 will provide a detailed view of the fetus. Amniocentesis is not always necessary, although amniotic ALPHA-FETOPROTEIN analysis might provide an additional assessment of the risk of neural tube defects.

During pregnancy, the monitoring of AED levels will help to maintain seizure control. AED pharmacokinetics are affected by the physiological changes of pregnancy. During pregnancy, renal blood flow and glomerular filtration increase as a function of increased cardiac output, and plasma volume, extravascular fluid and adipose tissue increase to create a larger volume of distribution. The level of serum albumin decreases, which reduces drug binding, increases the free fraction and increases drug clearance. These pharmacokinetic alterations can affect AED concentrations, and are most important for AEDs that are highly protein-bound, hepatically metabolized or renally cleared. Both total and free levels of highly protein-bound AEDs, including phenytoin and valproate, should be monitored.

Lamotrigine metabolism and clearance increases during pregnancy, and understanding the effect of pregnancy on lamotrigine concentrations is particularly important as this drug is being used increasingly in women who are considering pregnancy. In a prospective study of 14 women, lamotrigine concentrations were followed before conception and monthly throughout the pregnancy.[43] Lamotrigine clearance increased until 32 weeks' gestation, reaching a peak of >330% of baseline, and the clearance began to decline thereafter. A retrospective study of 11 women found a significant decrease in the ratio of plasma lamotrigine concentration : dose, of 65.1% in the second trimester, and 65.8% during the third trimester, compared with pre-pregnancy values.[44] Clinically, five patients experienced increased seizure frequency, probably a result of decreased concentrations of lamotrigine. Women treated with AEDs during pregnancy should have their drug levels monitored throughout pregnancy, and have their doses adjusted accordingly. The frequency of monitoring depends on the particular AED, with more-frequent monitoring being required for lamotrigine.

Vitamin K prophylaxis is recommended in the last few weeks of pregnancy, starting at approximately week 36. The incidence of hemorrhagic disease in the newborn child has been reported to be increased in infants exposed to AEDs during pregnancy—in particular, AEDs that induce the CYTOCHROME P450 ENZYME SYSTEM. Cytochrome P450 enzyme-inducing AEDs, including phenobarbital, primidone, phenytoin, carbamazepine and, to a lesser extent, oxcarbazepine and topiramate, induce fetal microsomal enzymes, which degrade vitamin K. In addition, these drugs might cause competitive inhibition of the addition of calcium-binding γ-carboxyglutamic-acid residues to the precursors of clotting factors II, VII, IX and X. Bleeding in AED-exposed infants typically occurs early, and includes intra-abdominal, intracranial and intrathoracic locations.

Interestingly, 204 infants who were exposed to cytochrome P450 enzyme-inducing AEDs, and whose mothers, with the exception of one, did not take antenatal vitamin K, had no significant increase in hemorrhage compared with a control group.[45] Similarly, a prospective study of over 600 pregnant women treated with cytochrome P450 enzyme-inducing AEDs, including phenytoin, carbamazepine, phenobarbital, primidone and oxcarbazepine, did not find a statistically significant elevation of bleeding complications.[46] A logistic regression analysis did not find bleeding complications to be associated with exposure to cytochrome P450 enzyme-inducing AEDs. The researchers concluded, however, that administration of vitamin K_1 might still be needed in selected cases.[47] It is recommended, therefore, that women who are taking AEDs—and in particular cytochrome P450 enzyme-inducing AEDs—should take vitamin K_1 10 mg/day orally during the last month of pregnancy, followed by a single dose of 1 mg given intramuscularly or intravenously to the newborn.

GLOSSARY

ALPHA-FETOPROTEIN
Dominant serum protein in early embryonic life; alpha-fetoprotein can be an important marker for the prenatal diagnosis of anencephaly and other open neural tube defects such as spina bifida

CYTOCHROME P450 ENZYME SYSTEM
A pathway involving a superfamily of heme proteins that are present in the inner membrane of mitochondria or in the endoplasmic reticulum of liver cells, where they metabolize endogenous and exogenous toxins, drugs, xenobiotics and other potentially harmful molecules

BREASTFEEDING

Breastfeeding a newborn baby has many advantages, including maternal transfer of antibodies, as well as promoting bonding between mother and child. In addition, for many women, breastfeeding is an integral and important part of the experience of motherhood. Given these considerations, the American Academy of Neurology and the American Academy of Pediatrics advise that women with epilepsy taking AEDs can breastfeed.[48] During breastfeeding the baby will, however, continue to be exposed to the AED in varying concentrations depending on the prescribed AED. If mothers receiving ethosuximide, phenobarbital or primidone choose to breastfeed, they should exercise caution and closely monitor the infant for sedation, lethargy and any significant clinical findings.[49] On the basis of small studies, including single-dose studies, case reports and short-term studies, phenytoin, carbamazepine and valproate are probably safe. These AEDs are all moderately to highly protein-bound, and are not transferred in high concentrations in breast milk. A small study of four infants indicates that lamotrigine might be transferred to the infant through breast milk in concentrations similar to those seen in the mother, as lamotrigine is extensively metabolized by glucuronidation, which is immature in infants.[50] Given these findings, infants who are breastfed by mothers receiving lamotrigine should be monitored.

In eight women receiving levetiracetam, concentrations of the drug were approximately equal in milk and plasma.[51] In their babies, however, levels of levetiracetam in the serum were very low, indicating extensive transfer in milk and rapid elimination of levetiracetam in infants. Similarly, 2–3 weeks after delivery in five mother–child pairs in which the mother was treated with topiramate, the mean milk : maternal plasma concentration ratio of topiramate was 0.86,[52] yet topiramate concentrations of the drug in the infants were very low, indicating efficient elimination by the infant. It should be noted, however, that in this small study four of the five mothers were also taking carbamazepine, which induces metabolism of topiramate, as well as inducing fetal metabolism in general (including metabolism of carbamazepine). The pharmacokinetics of gabapentin during lactation was studied in six infants.[53] The milk : maternal plasma concentration ratio was 1.0 (range 0.7–1.3) from 2 weeks to 3 months. Plasma concentrations were low in suckling infants, however, and no adverse effects were reported. Studies also indicate that oxcarbazepine and zonisamide are transferred extensively in breast milk.

In summary, breastfeeding is a viable option for women with epilepsy who are being treated with AEDs. Caution and clinical monitoring should be exercised if the mother is using phenobarbital, primidone, ethosuximide or lamotrigine. Larger scale studies are needed to better understand drug transfer in breast milk and metabolism in infants for all AEDs.

CONCLUSION

Careful management of pregnant women with epilepsy who are being treated with AEDs is important, as seizure frequency can change during pregnancy, and both seizure activity and AED drug treatment might have consequences for the developing fetus, including increased rates of stillbirth, teratogenesis and cognitive delay. Some AEDs probably have more adverse effects than others. In addition, drug-level monitoring and dosage adjustment throughout pregnancy is warranted. Vitamin K_1 at a dose of 10 mg/day should be given in the last month of pregnancy, particularly in women who are taking cytochrome P450 enzyme-inducing AEDs. Breastfeeding is generally recommended, although there is differential transfer of individual AEDs in breast milk, and the infant should be observed clinically. For all women with epilepsy of reproductive age, preconceptual counseling is important. Such counseling should include optimization of the AED regimen, and advising the women to take supplemental folic acid.

Issues that need to be addressed in further studies include better differentiation of which AEDs result in higher rates of major malformations, defining cognitive effects of *in utero* AED exposure, and establishing better guidelines for breastfeeding. The pregnancy registries discussed are likely to better define potential teratogenicity of individual AEDs, especially of the newer AEDs where information is lacking. The NEAD study will define prospectively the potential cognitive effects of the studied AEDs (phenytoin, carbamazepine, valproate and lamotrigine). Further studies are needed, however, to address cognitive effects of other AEDs; particularly if these agents are used in increasing numbers during pregnancy.

KEY POINTS

- For women with epilepsy, pregnancy raises unique clinical management concerns, as both seizure activity and antiepileptic drug (AED) treatment can have consequences for the developing fetus
- Seizure frequency can increase or decrease in an unpredictable manner during pregnancy because of multiple factors, including hormonal changes, and alterations in maternal physiology that affect the pharmacokinetics of AEDs
- Ideally, women should be prescribed the most effective and best-tolerated AED regimen before becoming pregnant, as changing medication once pregnant might not be practical
- Retrospective and prospective studies indicate that prenatal exposure to AEDs is associated with an increased risk of major and minor malformations, and might also have adverse effects on cognitive development
- Women treated with AEDs during pregnancy should have their drug levels monitored throughout pregnancy, and have their doses adjusted accordingly
- Breastfeeding is a viable option for women with epilepsy who are being treated with AEDs, but careful monitoring is required if the mother is using phenobarbital, primidone, ethosuximide or lamotrigine

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Competing interests
The author declared she has no competing interests.

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