Women's Issues in the Treatment of Epilepsy

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ABSTRACT: ***Background:*** The management of women with epilepsy involves a number of important issues including conception control, sexual dysfunction and fertility, the effect of seizures on the fetus, possible changes in seizure frequency during pregnancy, potential teratogenic effects of antiepileptic drugs and management issues during pregnancy. The primary goal in the treatment of women with epilepsy remains optimal seizure control in the absence of unacceptable adverse effects. The advantages and disadvantages of the new antiepileptic drugs in women remain to be fully established but these new agents allow a wider choice for improved seizure control

RÉSUMÉ: Problèmes particuliers aux femmes dans le traitement de l'épilepsie. Le traitement des femmes épileptiques comporte un nombre important de problèmes incluant la contraception, la dysfonction sexuelle et la fertilité, l'effet des crises sur le fétus, la possibilité d'un changement dans la fréquence des crises pendant la grossesse, les effets tératogènes possibles des médicaments antiépileptiques et le traitement pendant la grossesse. Le but principal du traitement des femmes épileptiques demeure le contrôle optimal des crises en l'absence d'effets secondaires inacceptables. Les avantages et les désavantages des nouveaux médicaments antiépileptiques chez les femmes ne sont pas parfaitement connus, mais ces médicaments permettent un choix plus vaste pour arriver à un meilleur contrôle des crises.

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In the management of the woman with epilepsy a number of important issues have to be addressed. Women with epilepsy have a greater incidence of sexual dysfunction and lower fertility rates. Sex hormones may influence the frequency of seizures and in some women a relationship of seizures to their menstrual cycle can be established (catamenial seizures). Hormonal changes during pregnancy may also influence changes in seizure frequency. Conception control has to be addressed with all patients of childbearing potential. There are a number of other issues in relation to epilepsy and pregnancy that should be appreciated. These include the outcome of pregnancy in women with epilepsy, the teratogenic potential of antiepileptic drugs, breast feeding, and recommendations for management of epilepsy during pregnancy. This review attempts to summarize these issues.

Sexual Dysfunction and Fertility

Fertility in women with epilepsy is generally reduced and this is probably multi-factorial in etiology.[1-5] Psychosocial factors with lower marriage rates, the effect of seizures on hormonal functions, and the effects of antiepileptic drugs on sex hormones may all be important contributing factors to sexual dysfunction and reduced fertility.

Psychosocial factors that may adversely affect sex function and fertility include a decision by the patient not to have children, lack of social interaction because of the epilepsy, and a greater incidence of psychologic and psychiatric disturbances that may influence libido and arousal.

In women with epilepsy there is a higher incidence of menstrual irregularities such as oligomenorrhea, amenorrhea, and anovulatory cycles.[3] Hypogonadotropic and hypergonadotropic hypogonadism and polycystic ovary disease are more common than in the general population. The effect of seizures on hypothalamic and pituitary functions may be an important factor.[6] Antiepileptic drug therapy itself, particularly valproate, may contribute to the development of polycystic ovary disease[7]. Hepatic enzyme inducers such as carbamazepine may result in an increase in the level of sex hormone binding globulin which may influence fertility and the menstrual cycle.[8,9] The reasons for decreased fertility are summarized in Table 1.Sexual dysfunction in epilepsy may be related to psychosocial factors, the effect of epilepsy on arousal and libido, and the effect of antiepileptic drugs on sex hormones metabolism.[10]

The Effects of Sex Hormones on Epilepsy

In animal models both estrogen and progesterone may influence neuronal excitability. Estrogen decreases the electroshock

Table 1: Reasons for Reduced Fertility

- Psychosocial factors
- Increased anovulatory cycles
- Hypogonadotropic and hypergonadotropic hypogonadism
- Polycystic ovary disease
- Enhanced sex hormone metabolism secondary to Cytochrome P450 stimulation by inducing antiepileptic drugs

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seizure threshold in rats[11] and progesterone has a protective effect in experimental models of epilepsy.[12] Estrogen inhibits the inhibitory neurotransmitter GABA, promotes the development of kindling and potentiates glutaminergic transmission.[13] Progesterone reduces neuronal discharge rates, suppresses kindling, and potentiates GABA receptor activity.[13] The role of steroid hormone effect on other transmitter systems is less clear. A direct membrane effect is another possible site of action of sex hormones and steroid receptors have been identified in certain brain regions.[14-15] A protective effect of progesterone has also been shown in partial seizures.[16,17]

A relationship between seizure frequency and the menstrual cycle has been recognized. [13, 18-22] Such seizures are frequently termed catamenial seizures and most often an exacerbation is observed just before the onset of menstruation or in the first few days of the menstrual flow. This exacerbation is thought to be related to progesterone withdrawal and a change in the estrogen: progesterone ratio which may be more important than the concentration of the individual hormones themselves.

Three distinct patterns of catamenial epilepsy have been proposed.[13] In the evaluation of 1324 seizures recorded during ovulatory cycles and 1523 seizures recorded during anovulatory cycles three distinct patterns of seizure exacerbation were observed:

1) premenstrual (C1, days - 3 to 3)
2) peri-ovulatory (C2, days 10 to -13) in normal cycles and
3) luteal (C3, days 10 to 3) in anovulatory cycles.

Both generalized and complex partial seizures showed these patterns of seizure exacerbation. Specific antiepileptic drug therapy including both enzyme-inhibiting and enzyme-inducing drugs did not alter these patterns.

Table 2: Catamenial Seizures

- Occur in approximately one-third of women with intractable partial seizures
- Exacerbation postulated secondary to change in estrogen: progesterone ratio
- Estrogen epileptogenic
- Progesterone protective
- Anovulatory cycles common[3,13]
- Three patterns identified

Contraception

Generally contraceptive hormones can be used by women with epilepsy without causing an aggravation in their epilepsy. In early studies, the risk of contraceptive failure with hepatic enzyme-inducing antiepileptic drugs was increased 25 fold. There is also a greater risk of breakthrough bleeding. The increase in risk may be related to increase in the protein binding of estrogen and enhanced metabolism by the mixed oxidase hepatic enzymes.[23] Women using hepatic enzyme inducing antiepileptic drugs should be prescribed an oral contraceptive containing at least 50 micrograms of estrogen in an attempt to maintain a more satisfactory estrogen level in the presence of enhanced metabolism. Failure of implantable hormone contraception has also been described.

Table 3: Antiepileptic Drug Effect

Hepatic enzyme inducers	Non enzyme inducers
Phenytoin	Benzodiazepines
Barbiturates	Valproate
Carbamazepine	Vigabatrin
Topiramate	Gabapentin
	Lamotrigine
	Tiagabine

Effect of Pregnancy on Epilepsy - Changes in Seizure Frequency

Although a relationship can often be established in seizure exacerbation in relation to the menstrual cycle in some women, one cannot predict if there will be a change in seizure frequency during pregnancy. In addition the change in seizure frequency during one pregnancy may be different than the change in seizure frequency in subsequent pregnancies.

There is no aggravation of seizure frequency or severity during pregnancy in the majority of patients. In the majority seizure frequency will either remain unchanged or decrease.[24-26] Up to twenty-five percent may experience an increase in seizure frequency. Generally, patients who have an increase in seizures are likely to be more refractory patients.

Seizure frequency may increase during various stages of pregnancy and there are different etiologic factors that may be responsible. Early in pregnancy seizures may increase due to sleep deprivation, stress, and reduced drug compliance due to fear of possible teratogenic effects of medication. As the pregnancy advances, factors such as increased volume of distribution of antiepileptic drugs, hormonal changes, and changes in protein binding and drug metabolism may result in an aggravation of seizures. The risk of status epilepticus is low, approximately one percent but carries a high mortality.

When seizures occur for the first time during pregnancy careful evaluation in determining a possible underlying etiology is required. Investigation of seizures that develop in pregnancy should follow general principles.

Table 4: New Onset Seizures

- Eclamptic seizures
- Gestational epilepsy
- Cerebrovascular
  - embolic - amniotic fluid, air
  - cortical venous thrombosis
  - arteriovenous malformation
  - subarachnoid hemorrhage
- Toxic-metabolic
- Psychogenic
- Other causes of epilepsy

Effect of Pregnancy on Epilepsy - Changes in Drug Metabolism

Total antiepileptic drug levels during pregnancy may be different than those observed during the non-gravid state. One of the causes of lower drug levels is non-compliance. Antiepileptic drug levels may also decline during pregnancy because of reduced protein binding, enhanced metabolism, and changes in

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volume of distribution.[27,28] Although the total plasma concentration of some antiepileptic drugs (eg., phenytoin, or valproate) may decline during pregnancy, there is an increase in the free fraction and the "pharmacologically active" portion may not always be significantly reduced.[29]

The effect of pregnancy on the elimination of the new antiepileptic drugs such as vigabatrin, gabapentin, lamotrigine, and topiramate is unknown. Gabapentin and vigabatrin are eliminated by renal excretion, and metabolic and hormonal changes would not be expected to cause changes in their elimination. These antiepileptic drugs are not significantly protein bound.

Effects of Epilepsy on Pregnancy

Women with epilepsy are more likely to have obstetric complications, such as increased incidence of vaginal bleeding, premature labor, induced abortion, induction of labor and perinatal mortality.[30-32] Some studies suggest that there is an increased risk of hyperemesis gravidarum and pre-eclampsia. A one and one-half to four-fold increase of these complications has been reported.

Generally low birth weight and neonatal seizures are not increased in the offspring of women with epilepsy. Bleeding during delivery may be increased in patients treated with enzyme-inducing drugs because of interaction with the vitamin K dependent clotting factor, II, VII, IX, and X.[33]. In the last four weeks of pregnancy the patient should receive oral vital K supplementation. Stillbirth and perinatal mortality rates are approximately twice those found in the general population.[26,34,35] There is a 5 percent to 10 percent risk of prematurity.[35,36]

Epileptic seizures are potentially hazardous to the fetus and the mother, resulting in injury and potential hypoxia. Hemorrhagic disease may be observed in the newborn again because of a deficiency in vitamin K dependent clotting factors (a 10 percent risk).

The effects of maternal epilepsy and antiepileptic drug therapy during pregnancy on neurodevelopmental outcome of the fetus are controversial.[37-39] The potential teratogenic effects will be discussed in a subsequent section.

Teratogenicity of Antiepileptic Drugs

Clinical studies support the conclusion that minor congenital anomalies and major malformations (defects of surgical, medical, or cosmetic importance) occur with greater frequency in the offspring of mothers with epilepsy, although more than 90 percent of women with epilepsy have a normal outcome. Both genetic and drug related factors are important contributors. The overall risk of major birth defects in the general population is approximately 2 percent, in untreated patients with epilepsy it is approximately 4 percent, and in treated patients it is between 5 percent and 10 percent. Orofacial cleft defects and congenital heart disease are the most common malformations and hypoplastic phalanges and nails are the most common minor anomalies.[31,40-44] No single abnormality, however, is specific to antiepileptic drugs. One has to be cautious in the interpretation of these studies since the majority of these studies were retrospective and patients were often on polytherapy.

Most of the traditional antiepileptic drugs have not been associated with a specific pattern of anomalies and malformations, with the exception of a 1 percent to 2 percent risk of spina bifida with valproic acid and a 0.5 percent to a 1 percent risk of spina bifida with carbamazepine exposure during the first trimester of pregnancy. The overall incidence and the risk of congenital anomalies rises with the number of antiepileptic drugs used in pregnancy.[45,46]

The mechanisms of teratogenesis are poorly understood. Folate deficiency and teratogenicity of unstable arene oxide metabolites of some antiepileptic drugs such as phenytoin may be important factors but these mechanisms do not explain the whole spectrum of antiepileptic drug - associated teratogenicity.[47,48] To minimize high peak concentrations of antiepileptic drugs medications should be administered in divided doses. Folic acid supplementation during pregnancy is recommended.

Seizures during pregnancy do not appear to be a risk factor for congenital anomalies and malformations.[36] Epilepsy in the father has not been shown to be a significant risk factor for the occurrence of congenital anomalies.[49]

There are limited data on the new antiepileptic drugs. In phase 2 and phase 3 clinical trials with gabapentin 14 pregnancies were reported. Five healthy babies were born. Pregnancy was terminated electively in six patients. There was one missed abortion, one pregnancy was on-going and one infant out of the 14 had respiratory distress, pyloric stenosis and an inguinal hernia with normal development at thirteen months.[50]

As of March 31, 1997, 103 pregnancies exposed to lamotrigine have been prospectively reported to the Lamotrigine Pregnancy Registry, resulting in 106 outcomes. Of these 103 pregnancies, 100 involved earliest exposure in the first trimester and resulted in 101 outcomes. Outcomes included 4 infants with birth defects, 6 spontaneous pregnancy losses, 19 induced abortions (no fetal anomalies were reported) and 72 infants (including 1 set of twins) born without birth defects. Of the 4 infants with birth defects, 1 infant had an extra digit (mother also took carbamazepine, and had a previous infant born with cardiac septal defect and multiple extra bones in the left thumb and distortion of the penis), 1 infant had bilateral talipes, 1 infant had skin tags on the left ear and no opening to the ear canal on the right ear (mother also took gabapentin), and 1 infant had a lumbar neural tube defect[51]. Thus although currently there is no signal suggesting teratogenicity the number of outcomes to date represent an insufficient sample size for reaching definite conclusions.

Forty-eight pregnancy outcomes with exposure to vigabatrin have been reported.[52] There were thirty-five normal offspring. There were five spontaneous miscarriages, four major abnormalities and four minor anomalies. All these patients were receiving vigabatrin in combination with other antiepileptic drugs and the relative contribution of vigabatrin is unknown.

The number of pregnancy outcomes with exposure to topiramate to date is unknown; however five women have delivered healthy infants.[53]

The issues of the teratogenicity of antiepileptic drugs have recently been reviewed.[15,54-56]

The care of the mother with epilepsy is a joint effort between neurologist and obstetrician and close communication and collaboration should be encouraged. The neurologist should educate the patient and document the information given. In an attempt to obtain prospective data on pregnancy outcome with exposure to antiepileptic drugs, neurologists are encouraged to

Table 5: Principles of Management[57]

- Counsel and educate the patient
- Re-evaluate the need for antiepileptic drug therapy
- Use monotherapy at lowest effective dose whenever possible choose the antiepileptic drug that is most appropriate for the type of epilepsy
- Avoid non-compliance and sleep deprivation
- Optimize nutritional status
- Dose antiepileptic drugs in divided doses
- Monitor drug concentrations and make proper dose increases based on the patient's seizure control
- Monitor patients at high risk of neural tube defects with plasma alphafetoprotein and level II ultrasound examinations at 16 and 20 weeks
- All women of childbearing potential should receive 0.4-1mg folic acid supplementation daily and this should be increased to 5mg during pregnancy.[58,59]
- Prescribe oral vitamin K (20mg daily) during the last 4 weeks of pregnancy.(Tablets of vitamin K are not available in Canada, therefore, the parenteral form can be added to juice and taken orally).
- Administer 1mg-2mg vitamin K parenterally to the infant at birth
- Monitor blood levels during the post-partum period
- Counsel patient about child safety
- Advise that breast feeding is generally safe[60-63]
- Provide contraceptive advice
- Monitor infant development

register pregnancies with the North American Antiepileptic Drug Epilepsy Pregnancy Registry.

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