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REPRODUCTIVE HEALTH CONCERNS FOR WOMEN WITH EPILEPSY

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SUMMARY – Pregnancy has some important implications for women with epilepsy. Appropriate counseling and support for women with epilepsy who are pregnant or contemplating pregnancy have raised a number of issues about their proper treatment. The impact of epilepsy on fertility and pregnancy must be carefully managed. This includes the effect of pregnancy on seizure frequency, the effect of seizures on the fetus, birth defects and possible teratogenic effect of antiepileptic drugs, complications of pregnancy, the implications for breast feeding, and precautions for the mothers having seizures when taking care of their newborn and young children. Understanding of the risk associated with epilepsy in pregnancy, use of appropriate therapy, and close teamwork of the neurologist, obstetrician, pediatrician and the woman herself will help ensure a safe pregnancy and delivery outcome. The knowledge and awareness of these issues are of great importance for optimal care of these women.

Key words: *Pregnancy, complications; Pregnancy, prevention and control; Epilepsy, drug therapy; Women's health*

Introduction

Epilepsy is a very common and serious neurologic condition, with a 10-fold prevalence of multiple sclerosis and 100-fold that of motor neuron disease. The incidence of epilepsy (annual rate of occurrence of new cases) is a measure of the number of cases *per* 100,000 inhabitants *per* year. It ranges between 40 and 70 *per* 100,000 in most developed countries, and between 100 and 190 *per* 100,000 in developing countries. This makes epilepsy the third most common neurologic disorder, immediately following stroke and Alzheimer's disease. Epilepsy is an episodic and paroxysmal condition. It is a frightening condition, misunderstood by many, including health care professionals. This has placed an extra burden on patients with epilepsy who often face discrimination in everyday life[1,2]. Despite the fact that about 50% of patients with epilepsy are women, it is only during the last two decades that the interest in special issues concerning epilepsy in women has risen and has been systematically studied[3].

Fertility and Reproductive Dysfunction

Men and women with epilepsy are at a risk of reproductive dysfunction. Birth rates equal only one third to two thirds of those among persons without epilepsy. For women with epilepsy, infertility has been attributed to menstrual irregularity, pituitary hormone abnormalities, anovulatory cycles, and polycystic ovaries. Both men and women experience disturbances and disorders of sexual desire and arousal, which may affect even 40% of persons with epilepsy. Reproductive dysfunction is common in women with epilepsy[3,4].

The prevalence of menstrual cycle disruption, anovulatory cycles, disturbances of hypothalamic hormones, pituitary hormones, or both, and disturbances of gonadal steroids is increased in women with epilepsy. The mecha-

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nism of reproductive dysfunction is not fully understood. Reproductive dysfunction may be due to psychologic, pharmacologic, or physiologic factors. However, epilepsy related brain dysfunction in the regions mediating reproductive physiology and behavior is likely to be partly responsible for this phenomenon. In addition, antiepileptic drugs (AEDs) contribute to reproductive health disorders by decreasing plasma steroid levels (carbamazepine, phenytoin, phenobarbital), or by increasing plasma levels of gonadal androgens (valproate)[5,6].

Polycystic ovaries and menstrual cycle irregularities are more common in women receiving valproate, probably related to valproate association with weight gain and hyperinsulinemia[3,5,6].

Birth Control

Counseling about contraception is important for two reasons. First, the enzymes inducing AEDs (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, and topiramate) lower the efficacy of oral contraception by increasing steroid hormone-binding globulin with reduction of free hormone levels. This leads to the reduction of exogenous estradiol and progesterone levels in women using hormonal contraception, and to failure of hormonal contraception. A combination of oral contraceptives with an estrogen content higher than normally recommended is therefore advisable. Birth control drugs containing at least 50 mg of estradiol or mestranol are recommended. Enzyme induction does not seem to be a problem with valproic acid, lamotrigine, felbamate, gabapentine, tiagabine or zonisamide.

About 10% of women with epilepsy experience a peak in seizure frequency around the time of menstruation (catamenial epilepsy), some patients also experience such an increase at ovulation. The possible explanation may be related to hormonal changes, however, despite several attempts to find an efficacious treatment for these problems, only a limited success has been achieved[1,5].

Pregnancy and Childbirth

Seizure frequency during pregnancy

Epilepsy is the most commonly encountered neurologic disorder during pregnancy. About one third of women with epilepsy experience an increased frequency of seizures during pregnancy. Seizure exacerbation usually occur at the end of the first and at the beginning of the second trimester, mainly as the result of a variety of physiologic changes and noncompliance. Some women have seizures only during pregnancy. The likelihood of change in the seizure frequency appears to be independent of seizure type and their pregestational frequency. Seizures may occur *de novo* in pregnancy as the result of idiopathic epilepsy, occurring in pregnancy for the first time (gestational epilepsy). Seizures may also occur following cerebrovascular disease, eclampsia, hyponatremia caused by water retention from oxytoin, i.v. lidocaine during epidural anesthesia, syncope with seizures, or as psychogenic seizures[8-11].

Pharmacological Changes

Pregnancy is associated with a number of physiologic, endocrine and psychological changes, any or all of which might contribute to lowering the seizure threshold. A major factor is poor compliance in taking antiepileptic medication because of the fear concerning malformations in the offspring. Psychological stress factors such as anxiety leading to the lack of sleep have been postulated as important in lowering the seizure threshold. Although some pregnant women have an exacerbation of their seizures because of noncompliance or sleep deprivation, in the majority of these women a number of physiologic changes are responsible for the increase in seizure frequency. Women often gain weight during pregnancy, which may be partly caused by the increased retention of water and sodium. An increase of the volume into which the drug is distributed may result in lower plasma concentrations, even if the rate of drug metabolism or renal excretion is not altered. Lower plasma concentrations of AEDs during pregnancy, therefore, appear to be related to the combined effect of enhanced hepatic metabolism and an increased volume of distribution. The greatest change in plasma levels occur during the first trimester with phenobarbital and phenytoin, and during the third trimester with carbamazepine. During gestation, changes occur in protein binding of AEDs. Plasma albumin concentrations tend to decline during pregnancy, which leads to a proportional reduction in protein binding of drugs. The free (non-protein bound) levels of the drug may even increase, so the free drug concentration, which is the pharmacologically active portion, may change very little. That is why it is sometimes necessary to monitor the effective drug concentrations, measuring the concentrations of free drug, especially in case of phenytoin and valproate. After pregnancy, the pharma-

cokinetic values of the drug usually return to the pregestational values within 8 weeks[1,12-15].

Unfavorable pregnancy and fetal outcomes are more likely to occur in women with epilepsy. The developing fetus in epileptic patients is exposed to two risk sources: metabolic and mechanical stresses from generalized tonic-clonic seizures, and problems caused by antiepileptic medication and their metabolites. A balanced risk from medication against the risk from increased seizures requires the exercise of careful judgment based on the most current information[1,12,13,16].

Teratogenicity of AEDs

Antiepileptic drugs are associated with an increased risk of birth defect. The risk of both major fetal malformations and minor anomalies is increased in epileptic women taking AEDs, probably because of the complex inter-relationship among undefined genetic factors related to epilepsy itself, the AEDs used, and major seizures occurring during pregnancy. The overall risk of having a baby with some major malformation is about 2% to 3% in healthy population, and is increased in women with epilepsy. Although AEDs increase the risk of congenital anomalies, the risk of malformations is increased in mothers with epilepsy regardless of whether or not they are taking AEDs. The risk is even higher if the mother is on AED. Interestingly enough, the incidence of malformations was highest (12.7%) in medicated patients who had seizures during pregnancy. Thus, the highest risks of fetal injury occur in women whose seizures are incompletely controlled with multiple drug use[1,3,12,13].

The risk of malformation in any individual pregnancy in women with epilepsy on antiepileptic monotherapy is estimated to be between 4% and 6%. In other words, women with epilepsy on monotherapy have a nearly 95% chance of having a healthy baby. The risk is increased, perhaps even doubled, by use of two or more drugs, and also by very high plasma levels of AEDs. All of the AEDs have been associated with congenital malformations, although the incidence and type of malformations may vary with the drugs used. The major malformations encountered most often are cardiac and 'midline' defects (cleft lip/palate), however, others involving the brain and spine may also occur. Current evidence suggest that, with the exception of trimethadione and valproate, all current AEDs from the older group of AEDs carry similar risks of malformation. Trimethadione, which should never be used in pregnancy, results in major malformations or fetal loss in 87% of pregnancies. Valproate, both as monotherapy and in polytherapy, has been associated with a 1% to 2% risk of neural tube defects. The risk of spina bifida appears to be significantly higher in infants exposed not only to valproate but also to carbamazepine (approximately 0.5% to 1%). Infants born to mothers on AEDs are at an increased risk of minor anomalies (prominent lips, fingernail hypoplasia, hypertelorism, etc.). The risk of spina bifida is increased with a family history of a prior child with spina bifida, folate deficiency, high diurnal fluctuations in blood levels of AEDs, and polytherapy. Primidone appears to be more teratogenic than phenobarbital itself. However, the claims that barbiturates are less teratogenic than other AEDs, with the exception of trimethadione, cannot be substantiated by the available literature data[10,14,17].

While some of the increased risk is attributable to AEDs, the more likely cause is the complex interaction of genetic factors and environmental factors (drugs, vitamin deficiencies, etc.) working in connection. Little data are available on the teratogenicity of newer AEDs in humans. However, animal studies in equivalent species have shown that gabapentine, lamotrigine, topiramate, tiagabine, vigabatrine and felbamate do not have significant teratogenicity, but limited experience in patients prevents giving any definite statement about their safety[9,18-20].

There appears to be a strong association between maternal folic acid deficiency and fetal malformation, spontaneous abortion and placental abruption[2,14].

Labor and Delivery

Hemorrhagic disease of the newborn can occur due to the induction of vitamin K metabolism by inducing AEDs and deficiency of vitamin K-dependent clotting factors. It tends to occur in the first 24 hours postpartum, involves abdominal hemorrhages, and is associated with a 30% mortality. The mechanism underlying this deficit is thought to be the induction of hepatic enzymes by AEDs. Vitamin D levels may often be below normal. The prevalence of complications of labor and delivery, such as preeclampsia, vaginal bleeding, placenta previa, abruptio placentae, polyhydramnion, assisted delivery, cesarean section, prematurity and intrauterine growth retardation, may be slightly increased in women with epilepsy. An increase in perinatal mortality (stillbirth or death in the first week postpartum) is most consistently reported.

The fetus is protected from the physiologic effect of maternal seizures, but miscarriages can occur with prolonged seizures or status epilepticus. The factors involved in these unfavorable outcomes may be socioeconomic or genetic, and may be related to seizures or AEDs.

Only 1.2% of the women with epilepsy will experience seizures during labor or in the first 24 hours after delivery. As in all mothers, breast feeding is encouraged. Most AEDs are extracted in the milk but it seldom causes problems. The benefits of breast feeding (reduced risk of infections) must be weighted against the immediate and long-term risk of exposure of the infant to AEDs.

Management for Epilepsy in Pregnancy

A decision on AED therapy should be made before the woman becomes pregnant. The issue must be discussed with all epileptic women of childbearing potential. The woman and her partner have the responsibility to decide whether or not to bear the children. The role of physician should focus on providing information on the risks of childbearing and on providing medical care to reduce the risks as much as possible before the patients become pregnant. The most critical step in caring for an epileptic woman of childbearing age is to properly diagnose the syndrome. Consideration must be given to whether AEDs are needed. Has the woman been seizure-free for 2 to 5 years, the need to continue drug therapy should be reconsidered. If the woman receives polytherapy, regimen simplification and dose optimization should be considered before pregnancy. Monotherapy should be reduced to the lowest effective dose. Generally, AEDs that are effective and well tolerated should not be changed. Initial selection of drugs with the least teratogenic potentials, such as carbamazepine, clobazam, or possibly some of the newer drugs such as gabapentine, lamotrigine, topiramate, tiagabine, vigabatrine, is recommended in women who wish to be pregnant. However, the women with a family history of spina bifida should probably avoid valproic acid and carbamazepine. During pregnancy, toxic and subtherapeutic concentrations should be avoided. Blood levels of AED (especially free drug levels) must be monitored. Dose adjustments may be necessary if significant declines occur. The necessity of good compliance should be constantly reinforced[1,3,7,9,11].

Folate, 0.5-1.0 mg *per* day, should be given to women with childbearing potential who are on AEDs. The doses could be increased to 5 mg *per* day in patients trying to conceive[20].

Fetal high-resolution ultrasonography should be performed to rule out spina bifida, cardiac anomalies, or limb defects at the gestational age of 16 to 18 weeks. If ultrasound raises suspicion of spina bifida, amniocentesis should be performed, and alfa-fetoprotein levels should be obtained[3,21].

Proper nutrition and adequate sleep are essential. The patients should avoid the use of any other medication except for that prescribed by the physician. Cigarette smoking and alcohol consumption should be avoided, because they have been associated with fetal anomalies[18].

To prevent hemorrhagic disease of the newborn (possibly due to the induction of enzymes degrading vitamin K), vitamin K oral supplementation at a dose of 20 mg *per* day should be administered for 4 weeks prepartum[6,10].

Breast feeding is generally safe. Epileptic women taking anticonvulsant drugs who want to nurse should not be discouraged. Unless the mother is taking barbiturates, which may sedate babies, there are not many reasons to prevent breast feeding, even though small quantities of AEDs will appear in the breast milk. A fetus exposed prepartum to barbiturates may have withdrawal symptoms after the first week postpartum. Mothers with seizures are able to take care of their infants, but they must think of precautions when taking care of them and performing some tasks[9,10,21].

Conclusion

Preconception counseling is arguably the most important information a woman with epilepsy receives. The most important aspect for a woman with epilepsy is maintaining an open dialogue between the physician and the patient. There is a consensus today that more than 90% of women with epilepsy who receive AED therapy will deliver normal children. Compared to women in the general population, the risk for infants of developing malformations if having an epileptic mother is significantly higher. The risk of malformation in any individual pregnancy in a woman with epilepsy on single AED is estimated to range between 4% and 6%. The risk of a major malformation development is also increased in mothers on polytherapy or in those receiving toxic levels of AEDs. To ensure the best outcome, only those women with an established diagnosis of epilepsy should receive medication. Understanding the risks associated with epilepsy in

pregnancy, use of appropriate therapy, and close teamwork among the neurologist, obstetrician, pediatrician and the woman herself will help ensure an uneventful pregnancy and delivery for most epileptic women.

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Sažetak

REPRODUKCIJSKI ZDRAVSTVENI PROBLEMI U ŽENA S EPILEPSIJOM

S. Miškov

Za žene koje boluju od epilepsije trudnoća ima veliko značenje. Potreba za prikladnim savjetovanjem i potporom u ovih bolesnica potakla je brojna istraživanja. U liječenju ovih bolesnica treba uzeti u obzir utjecaj epilepsije na fertilitet i trudnoću. Osobito je važno obratiti pozornost na utjecaj trudnoće na učestalost epileptičnih napadaja, utjecaj napadaja na fetus, moguću teratogenost antiepileptičnih lijekova, njihov utjecaj na dojenje, utjecaj napadaja na sposobnost majke da se brine o svom novorođenčetu i malom djetetu. Sigurniji ishod trudnoće i poroda može se osigurati razumijevanjem rizika povezanog s epilepsijom u trudnoći, uporabom prikladne specifične antiepileptične terapije, kao i timskom suradnjom između neurologa, ginekologa, pedijatra i same trudnice koja boluje od epilepsije.

Ključne riječi: *Trudnoća, komplikacije; Trudnoća, prevencija i kontrola; Epilepsija, medikamentna terapija; Zdravlje u žena*