

Managing Epilepsy in Women of Reproductive Age: A Review

HABIB R^a, ISLAM R^b, RAHMAN A^c, BHOWMIK NB^d, HAQUE A^e

Abstract

Despite all of our advances, women with epilepsy face obstacles when it comes to pregnancy and childbearing. Many of these obstacles are social, based on incorrect and inappropriate attitudes of the public towards persons with epilepsy. Most women with epilepsy can conceive and bear healthy children. They have higher probabilities of infertility but this is often amenable to treatment. Complications of pregnancy are higher and revolve primarily around the increased risk of maternal seizures. Careful monitoring of the clinical condition of the patient and the free anticonvulsant levels will obviate much of this difficulty. Maternal seizures themselves can pose hazards for women with epilepsy and their offspring and generalized convulsive seizures are clearly to be avoided. Adverse pregnancy

outcomes tend to be seen more often in particular: congenital malformations, dysmorphic features, neonatal hemorrhage and fetal death. Neonatal and infant mortality is increased to two to threefold over the general population; and an uncertain risk of developmental delay particularly in the area of language acquisition. Risks can be reduced by ensuring good seizure control, monotherapy, preconceptual use of multivitamins with folate. The plethora of new anticonvulsants offers us new opportunities for improving the function and control of persons with epilepsy. All of the risks aside, the majority of women with epilepsy can and will have healthy children.

Keywords: Epilepsy, Menstrual cycle, Fertility, Contraception, Reproduction, Pregnancy, Antiepileptic drug

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Introduction

Epilepsy is a group of neurologic conditions characterized by recurrent unprovoked seizures. Approximately one percent of the population has epilepsy, making this one of the most common chronic health conditions affecting reproductive-aged women.¹ Although epilepsy affects men and women equally, there are many women's health issues in epilepsy, especially for women of childbearing age. These issues, which include menstrual cycle influences on seizure activity (catamenial epilepsy), interactions of contraceptives with antiepileptic drugs (AEDs), pharmacokinetic changes during pregnancy, teratogenicity and the safety of breastfeeding,

challenge both the woman with epilepsy and healthcare providers involved in her care.²

Menstrual cycle and fertility:

The association between the menstrual cycle and seizures has been extensively investigated. Catamenial epilepsy occurs in about 12% of women with epilepsy.³ In ovulatory cycles, two peaks can be seen around the time of ovulation and in the few days before menstruation.⁴ Seizures are more likely to occur near the time of menstrual flow because of progesterone withdrawal and with the estrogen surge at ovulation.⁵ There are also alterations in AED concentrations, as seen with phenytoin and lamotrigine, throughout the menstrual cycle.⁶⁻⁹ In anovulatory cycles, there is an increase in seizures during the second half of the menstrual cycle. Seizure control may also change during perimenopause because of fluctuations in estrogen and progesterone.

For women on AEDs, intermittent use of perimenstrual clobazam (5 or 10 mg) or acetazolamide is suggested when a seizure increase is anticipated.¹⁰⁻¹¹ For women with catamenial epilepsy in whom low premenstrual progesterone levels may be a factor, an intermittent perimenstrual progesterone supplement, or a synthetic progestogen during days 10 to 26 of the menstrual cycle

- a. Dr. Rumana Habib, Registrar, Department of Neurology, BIRDEM General Hospital, Dhaka
- b. Dr. Rashedul Islam, Registrar, Department of Neurology, BIRDEM General Hospital, Dhaka
- c. Dr. Aminur Rahman, Associate Professor, Department of Neurology, BIRDEM General Hospital, Dhaka
- d. Dr. N.B.Bhowmik, Associate Professor, Department of Neurology, BIRDEM General Hospital, Dhaka
- e. Dr. Amirul Haque, Professor, Department of Neurology, BIRDEM General Hospital, Dhaka

Address of Correspondence : Dr. Rumana Habib, Registrar, Department of Neurology, BIRDEM General Hospital, Dhaka, E-mail: drhrumana4@gmail.com

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is suggested¹². A combined oral contraceptive pill (COCP) may be prescribed¹².

- For women not already taking AEDs, the following are alternatives: intermittent perimenstrual clobazam (5 to 30 mg/day); COCP; depot progestogen therapy; or perimenstrual progestogen.¹⁰

Fertility rates in women with epilepsy are reduced by one to two thirds when compared with their nonepileptic female siblings.^{13,14} Lower birth rates may reflect some of the social and psychologic pressures experienced by women with epilepsy. Misinformation about epilepsy fuels many of these fears.¹⁵ In addition to these social pressures, there is a physiologic basis for infertility in women with epilepsy. Up to one third of women with epilepsy have an abnormal menstrual cycle length (less than 23 days or more than 35 days). One third or more of menstrual cycles in women with generalized seizures are anovulatory.¹⁶ Reproductive endocrine disorders in women with epilepsy include disturbances in luteinizing hormone concentration and pulsatile release and abnormalities in prolactin and steroid hormone levels.^{17,18} Pituitary hormone abnormalities are probably associated with disruptions in hypothalamic input to the pituitary as a consequence of seizures.

Polycystic ovaries are described in 20 to 40 percent of women with epilepsy who were evaluated with transvaginal ovarian ultrasound.¹⁹ These women often have an elevated body mass index ($> 25 \text{ kg / m}^2$), hirsutism, abnormal menstrual cycle length, and anovulatory cycles. It is not known whether this condition is the same as polycystic ovary syndrome. Some investigators found that valproate is associated with polycystic ovaries, elevated androgen levels, obesity, and insulin resistance more often than are other antiepileptic drugs.¹⁹ This phenomenon was reversible in a small number of women when their medication was changed from valproate to lamotrigine.²⁰ To identify and treat reproductive disorders, women with epilepsy should be asked routinely about commonly occurring problems such as weight gain, abnormal menstrual cycle length or irregularity, mid-cycle spotting, hirsutism, or acne. Suspicion of antiepileptic drug-induced polycystic ovarian syndrome may warrant an endocrine screen, including luteinizing hormone, testosterone and prolactin levels, pelvic examination, and ovarian ultrasound.²¹

Contraceptive Choices:

Women receiving a liver enzyme-inducing antiepileptic medication have at least a 6 percent failure rate per year for oral hormonal contraceptive pills.²² Cytochrome P450-inducing antiepileptic drugs enhance hepatic metabolism of contraceptive steroids and increase binding of steroids to serum proteins. This reduces the concentration of biologically active steroid hormone. Most commonly used oral contraceptives contain 35 mcg or less of estrogenic compounds and may be ineffective in women who take some antiepileptic drugs. Subdermal levonorgestrel implants (Norplant) are also less effective in women receiving enzyme-inducing antiepileptic drugs.²³ Consideration of antiepileptic drugs that do not induce liver enzymes may also be an option in some patients (Table 1).

Table-I

Antiepileptic Drug Effects on Oral Contraceptives

- Agents that induce liver enzymes and may compromise OC efficacy
 - Carbamazepine
 - Phenytoin
 - Phenobarbital
 - Primidone
 - Oxcarbazepine
 - Topiramate
- Agents that do not compromise OC efficacy
 - Gabapentin
 - Levetiracetam
 - Lamotrigine
 - Tiagabine
 - Valproate

Women taking enzyme-inducing antiepileptic drugs should use nonhormonal methods of contraception or receive contraceptives containing 50 mcg or more of the estrogenic component.²

For women on nonenzyme-inducing AEDs (valproate sodium, benzodiazepines, vigabatrin, ethosuximide, zonisamide, gabapentin, tiagabine, levetiracetam, pregabalin) all current contraceptive methods are suitable.²⁴ A recent study has suggested a fall of norethisterone concentrations in patients receiving

lamotrigine; therefore, women on a normal-dose COCP and lamotrigine may be at risk of unplanned pregnancies.²⁵

For women on enzyme-inducing AEDs wishing to take the COCP: start with 50 µg/day ethinyl oestradiol dosage, if breakthrough bleeding occurs, increase the dose of ethinyl oestradiol to 75 or 100 µg/day or consider giving three packs of the pill without a break ("tricycling"). Even on a higher-dose COCP with normal cycles, full oral contraceptive efficacy cannot be guaranteed in women with epilepsy taking enzyme-inducing AEDs. The progesterone only pill is likely to be ineffective in women taking enzyme-induced AEDs •^{11,24}

Medroxyprogesterone injections appear to be an effective contraceptive in women with epilepsy, but patients are usually advised for these injections to be given every 10 weeks rather than 12 weeks if used in combination with enzyme-inducing AEDs ¹¹. Levonorgestrel implants are contraindicated in women taking enzyme-inducing AEDs, since there is an unacceptably high failure rate ¹¹. There are no contraindications to the Mirena coil in women with epilepsy, because progestogen acts by being released locally in the uterus²⁴.

If appropriate, the emergency contraceptive pill can be used in women with epilepsy after unprotected sexual intercourse. There are no data on whether a change in the dose of the morning-after contraceptive pill is required in women taking AED medication; some practitioners suggest a higher dose in those women taking enzyme-inducing AEDs ^{11,24}.

Pregnancy:

Planned pregnancy and pre-conception counseling before conception is crucial. This counselling should include issues relating to the future pregnancy, including methods and consequences of prenatal screening, fertility, genetics of their seizure disorder, folic acid supplementation and vitamin K supplements, medication adherence, the risk of teratogenicity of AEDs, labour, breast feeding and care of a child. ⁴

There is a risk of increased seizure frequency in pregnancy irrespective of whether anticonvulsant treatment is taken. Seizure frequency is increased during pregnancy in about one third of women with epilepsy, which is partly caused by poorer medication compliance

and changes in antiepileptic drug pharmacokinetics.^{26,27} Serum drug levels may be reduced because of increases in volume of distribution, hepatic metabolism, or renal clearance. Protein binding of antiepileptic drugs is reduced because of a drop in serum albumin levels and increased binding by sex steroid hormones, which leads to a relative increase in the nonprotein-bound (free) fraction of drug.²⁷ For antiepileptic drugs that are highly protein bound, the total antiepileptic concentration may not accurately portray the brain concentration. Therefore, monitoring and adjusting the free level of antiepileptic drug is recommended during pregnancy.²¹

Individual seizures carry little risk to the mother or the fetus but status epilepticus has a significant maternal and fetal mortality. The risk of status epilepticus must be taken into account when deciding whether to stop anticonvulsant treatment before pregnancy.

Before achieving pregnancy a woman should be on optimum treatment, preferably on one anticonvulsant.²⁸ If a patient has been seizure free for at least 2–3 years and does not have juvenile myoclonic epilepsy (JME), consideration may be given to withdrawing AEDs to reduce the potential teratogenic risk.¹¹ Otherwise during pregnancy, the lowest effective dose of the most appropriate AED should be used, aiming for monotherapy where possible.⁴

Women with epilepsy have a 4 to 8 percent chance of giving birth to a child with a major malformation, compared with 2 to 4 percent in the general population.^{2,21,29,30} Malformations associated with exposure to the older antiepileptic drugs include cleft lip and palate (phenytoin) and ventricular septal defect (Phenobarbitone)¹¹. Neural tube defects are associated with exposure to valproate and carbamazepine at a frequency of 1 to 2 percent and 0.5 to 1 percent, respectively.³⁰ Minor congenital anomalies affect 7 to 15 percent of infants exposed to antiepileptic drugs, which represents a twofold increase over that in the general population.³¹ These anomalies principally involve the face and digits, including hypertelorism, epicanthal folds, broad nasal bridge, elongated philtrum, distal digital, and nail bed hypoplasia. The risk of teratogenicity is significantly increased in women taking multiple antiepileptic drugs and in those on high doses of antiepileptic medication. Recent pregnancy databases have suggested that valproate is significantly more

teratogenic than carbamazepine, and the combination of valproate and lamotrigine is particularly teratogenic.³⁰ The newer generation of antiepileptic drugs is not teratogenic in animals, but there is not sufficient reporting in human pregnancy experience to accurately portray risk.

The American Academy of Neurology (AAN) issued a practice parameter advocating single-drug therapy at the lowest possible dose that effectively controls seizures (Table-II) Folic acid supplementation should be provided to all women of childbearing potential. The recommended dosage range is between 0.4 to 4 mg per day,³² with many neurologists routinely supplementing at 1 mg per day.¹¹ Suggested prenatal diagnostic testing includes a maternal serum alpha-fetoprotein test at 15 to 20 weeks of gestation and an anatomic ultrasound at 16 to 18 weeks of gestation. This detects neural tube defects with more than 95 percent sensitivity.^{21,29} Finally, the AAN recommends that the mother receive 10 mg of oral vitamin K per day during the final month of gestation as hemorrhagic disease of the newborn is more likely to occur in infants whose mothers are taking hepatic microsomal enzyme-inducing AEDs.³³ This is in addition to the intramuscular vitamin K routinely provided to the neonate at birth.

Table-II^{21,29}

*Guidelines for the Use of Antiepileptic Drugs
During Pregnancy*

Use the most effective antiepileptic drug in monotherapy and at the lowest possible dose.

If there is a family history of neural tube defects, and there are acceptable treatment alternatives, avoid valproate and carbamazepine.

Monitor the free (nonprotein-bound) fraction of the antiepileptic drug at each trimester, before delivery, and four to eight weeks after delivery.

Adjust the antiepileptic drug dosage according to the nonprotein-bound (free) level.

Provide folate supplementation at a dosage of 0.4 to 4 mg per day before conception and throughout gestation.

Offer prenatal testing with anatomic ultrasound and maternal serum alpha-fetoprotein at 15 to 20 weeks of gestation.

Provide the pregnant woman with vitamin K, 10 mg per day during the last month of gestation. Infants should receive 1 mg of vitamin K intramuscularly at birth

Over breathing, sleep deprivation, pain, and emotional stress increase the risk of seizures during labor, and it is appropriate to consider epidural anesthesia early on. One to two percent of women with active epilepsy will have a tonic-clonic seizure during labor, and a further 1–2% will have a seizure in the following 24 hour³⁴. Generalized tonic-clonic seizures are likely to result in hypoxia, and this may have deleterious effects on the fetus¹¹. Therefore, the delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation¹¹. The patient's regular AED should be continued throughout labor.

Breastfeeding :

Breastfeeding is advocated for women with epilepsy, according to the AAN and the American Academy of Pediatrics (AAP).²¹ The benefits of breastfeeding are felt to outweigh the potential risk of continued exposure of the neonate and infant to antiepileptic drugs. Antiepileptic drugs cross into breast milk in inverse proportion to their extent of protein binding. Therefore, phenytoin, tiagabine, and valproate, which are all extensively protein bound, have very low concentrations in breast milk. Carbamazepine, phenobarbital, lamotrigine, topiramate, and zonisamide have low to moderate protein binding and can be anticipated to have low to moderate concentrations in breast milk in relation to maternal concentrations. Gabapentin and levetiracetam have no protein binding and therefore have equivalent concentrations in maternal serum and breast milk. However, as drug elimination mechanisms are not fully developed in early infancy, repeated administration of a drug such as lamotrigine via breast milk may lead to accumulation in the infant.¹¹ It is advised that the breastfed infant of a mother receiving antiepileptic drugs be observed for irritability, poor sleep patterns, or inadequate weight gain.

Conclusion:

Epilepsy and AEDs can affect each aspect of the female human life cycle- menstrual cycle, contraception, fertility, conception, pregnancy, and menopause (including hormone replacement therapy and bone health). These have been discussed under their respective sections in this article. The current level of quality research is limited. Hopefully over 90% of epileptic women who become pregnant will have uneventful pregnancies and will produce healthy infants.

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