Women, epilepsy and anti–epileptic drugs

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ABSTRACT

Epilepsy is a chronic disease interlinked with many aspects of a woman's life. The objective for this syllabus is to review these aspects and update physicians treating epileptic women on the recent management recommendations in this population. Epilepsy is more common in males except in adolescence and the elderly. Certain epileptic syndromes are exclusively seen in females such as Rett syndrome, Aicardi syndrome and periventricular nodular heterotopia. Female sex hormones may alter seizure threshold in epileptic women and form the basis for catamenial epilepsy. Seizures particularly those of temporal lobe may influence the normal hormonal balance leading to menstrual irregularities and probable reduced fertility. Although most pregnant epileptic women have successful outcomes of their pregnancies, there is an increased risk of maternal and fetal complications during pregnancy and labor in comparison to non-epileptic women. Menopausal epileptic women receiving anti-epileptic drugs that interfere with calcium and vitamin metabolism are at a higher risk for osteoporosis.

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Although epileptic disorders are similar in males and females, special issues are female specific.[1] Significant social and physiological differences between males and females require a modified approach towards female patients.[1,2] This approach should consider a variety of factors such as age, relationships, diagnosis, female specific syndromes, the influence of female sex hormones and cosmotic effects of anti-epileptic drugs.[1-3]

Epilepsy and gender. Epilepsy predominates in men except in adolescence, and the elderly population.[1] Explanations for epilepsy male preponderance include increased head trauma as an epilepsy risk factor in males in comparison to females, epilepsies without generalized tonic clonic seizures are often ignored by women in some cultures and the female brain is less vulnerable to perinatal anoxia in the intrauterine life with some evidence that male and female sex hormones have a differential effect on brain development.[4] Few epileptic syndromes occur exclusively in females such as Rett syndrome (a neurodevelopmental disorder with neurological and cognitive regression, intractable epilepsy and autistic behavior), Aicardi syndrome (a neonatal syndrome characterized by absence of the corpus callosum, retinal pigmentation and infantile spasms with hypsarrhythmias on the electroencephalogram) and periventricular nodular heterotopia (a neuronal migration disorder).[1] Idiopathic generalized epilepsies show clear female preponderance.[5]

Epilepsy and female sex hormones. Ovarian steroid hormones affect the excitability of the cerebral cortex and therefore alter the seizure threshold. Seizures in turn alter the endocrine environment through actions on the hypothalamic–pituitary axis.[1,6] Estrogens are considered to be proconvulsant, while progestogens to be anticonvulsants. Prolactin has no effect on seizure control but may be transiently elevated after generalized tonic clonic seizures.[6] Estrogens also cause structural and functional changes in the hippocampus. Animal models showed that estrogens increased hippocampal kindling in rats. There is increase in the dendritic spine density on their corno Ammonis 1 (CA1) pyramidal cells. The density of the excitatory NMDA (N methyl D aspartate) receptor binding sites also increased in

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the CA1 region.[7] Seizures disturb the hypothalamic pituitary axis through the cerebral and limbic cortex particularly the amygdala which has extensive interconnections with the hypothalamus.[1,6,7]

Epilepsy and puberty. Existing epilepsy may be exacerbated or change its character by puberty. Some prepubertal epilepsy such as childhood absences usually disappears at puberty or shortly after menarche. Other epilepsies such as juvenile myoclonic epilepsy may start around puberty. The alteration of seizure control at puberty is related mainly to the establishment of the female pattern of cyclic changes in the hypothalamic pituitary gonadal hormone release.[8] Puberty is rarely delayed by epilepsy.[1,8]

Epilepsy and fertility. Most studies reveal reduced fertility in epileptic women in comparison to normal women.[9] Several factors contribute to the reduced fertility in epileptic women. Seizures alter the secretion of the hypothalamic pituitary gonadal axis thus affecting the normal balance of hormones and fertility. Epileptic women experience increased number of anovulatory cycles and more menstrual irregularities in comparison to normal women.[9,10] This is particularly seen in patients with temporal lobe epilepsy.[1,6,7,10] Psychosocial disabilities add to the problem.[1,9,10] The effect of anti-epileptic drugs on fertility is discussed in subsequent paragraphs.

Epilepsy and sexuality. Epilepsy may impair sexuality in women through several factors. These include psychosocial factors such as poor self-image and lack of sexual identity. Neuroendocrine factors such as changes in the luteinizing hormone releasing hormone LHRH pulsatility and prolactin release, anti-epileptic drugs and neurophysiological factors such as inhibition of the sexual arousal centers.[1,11]

Catamenial epilepsy. Although no standard definition for catamenial epilepsy exists, it is proposed that a 2 fold or greater increase in daily seizures during a particular phase of the menstrual cycle is accepted as catamenial epilepsy.[12] Three distinct patterns of catamenial epilepsy are recognized. Pattern I (perimenstrual), pattern II (preovulatory) and pattern III (luteal).[12] Clinical experience suggest that in some women the peak period is at ovulation.[13] Catamenial seizures patterns may affect 30-50% of women with epilepsy.[12,13]

Epilepsy and menopause. There is no evidence that the menopause is affected by epilepsy.[14] Endogenous and exogenous factors may influence seizure frequency in women with epilepsy as they pass through their perimenopausal and menopausal years.[11] As an external factor the use of hormonal replacement therapy HRT may be associated with an increase in seizures. Many women pass through menopause with unchanged seizure frequency. Seizures may increase or decrease at menopause. Approximately 10-12% of menopausal women report their first seizure to occur at menopause. The reason for this is unclear. At menopause, the incidence of cerebrovascular disease is more than in the younger age and therefore makes menopausal women more susceptible to have epilepsy. At menopause women may receive estrogen as hormone replacement therapy. Altered estrogen and progesterone receptors associated with lowered sex hormones at menopause may lead to altered brain excitability. All these factors lower seizure threshold at menopause and seizures may occur for the first time.[15] Long-term treatment with anti-epileptic drugs decreases bone mineral density through a combination of factors. This includes altered vitamin D metabolism, and bone cell growth.[15] Epileptic women at menopause are at a higher risk of osteoporosis.[15] Therefore, it is advised to test bone mineral density for menopausal epileptic women and consider hormonal replacement therapy, calcium and vitamin D supplementation as required.[14,15]

Epilepsy with pregnancy, labor and puerperium. Although most pregnant women with epilepsy achieve successful pregnancies and good outcomes they face increased risks during pregnancy and labor.[16] Pregnant women with epilepsy are at risk of congenital malformations.[16] The rate of birth defects in infants born to epileptic mothers is 4-8%, which is double the rate in the general population.[16] Although the major risk of fetal congenital malformations in pregnant women with epilepsy is due to anti-epileptic drugs (see below) a small risk is attributed to the maternal epilepsy itself.[16] Paternal epilepsy seems to have no effect on fetal development. The direct risk of maternal epilepsy is possibly genetic.[17] Epilepsy may cause an increase in the minor anomalies such as dysmorphic features especially epicanthal folds.[17] Spina bifida, and cleft palate can rarely occur as a direct effect of epilepsy and usually occur as an effect of anti-epileptic drugs.[17] Other possible effects of epilepsy on the fetal development include prematurity, stillbirth, neonatal or perinatal death, hemorrhagic disease of the newborn, low apgar scores, low birth weight and small head circumference.[17] Major congenital malformations are usually due to the exposure to the anti-epileptic drugs. In the majority of women seizure control does not change during pregnancy.[18] Catamenial seizures may decrease significantly during pregnancy. A third of women will have an increase in seizure frequency. This increase is attributable to several factors such as poor compliance with anti-epileptic drugs, sleep deprivation, changes in anti-epileptic drug kinetics, weight gain, metabolic changes, vomiting and altered albumen levels.[18] Generalized tonic clonic seizures result in profound acid base imbalance, which is probably transferred to the fetus, as there are changes in the fetal heart rate after a maternal

tonic clonic seizure suggesting fetal distress possibly secondary to fetal hypoxia or acidosis. There is a high maternal and fetal mortality with convulsive status epilepticus.[18] There is a minor but a significant increase of maternal obstetric complications in women with epilepsy.[16-18] The rate of spontaneous abortions in women with epilepsy is comparable to the general population. Other obstetric complications such as pre-eclampsia are more frequent and more severe in women with epilepsy in comparison to normal women.[16-18] Induction of labor, instrumental delivery, antenatal hemorrhage and premature labor are more common in epileptic women.[16-18] In general it is not necessary to apply any obstetric measures on epileptic women during labor, however, if the patient has intractable epilepsy a cesarean section may be necessary. Epidural anesthesia is possible and should be handled as in any other women.[16] Epileptic mothers should be encouraged to breast-feed their babies. The effects of anti-epileptic drugs on lactation are discussed below. In the puerperium, there may be a transient seizure increase due to stress and exhaustion.[18] If anti-epileptic drugs were increased during pregnancy it is advised to check for side effects and to check blood levels to avoid anti-epileptic drug toxicity (see below).[18]

Anti-epileptic drugs and pregnancy. At constant anti-epileptic drug dosage, the serum levels of most known anti-epileptic drugs tend to decrease during pregnancy and this usually starts within 10 weeks of conception and returns to pre-pregnancy levels within one month of delivery.[19] This is particularly true for phenytoin. The return to pre-pregnancy levels appears to be slower for carbamazepine and phenobarbitone. There is no current evidence of new anti-epileptic drugs to have similar changes during pregnancy. However, lamotrigine level seems to fall in pregnancy in a similar manner and quickly rises again in the puerperium.[19] Possible causes of changed anti-epileptic pharmacokinetics in pregnancy include reduction of gastric motility, vomiting, malabsorption, increased plasma volume, increased cardiac output, increased body water, change in liver function and reduction in binding protein.[19] Enzyme inducing anti-epileptic drugs increases the risk of maternal and fetal hemorrhagic complications. Therefore, oral vitamin K (20mg) should be given to pregnant women on these anti-epileptic drugs in the last month of pregnancy to protect both the mother and the fetus from hemorrhagic complications. The risk of hemorrhagic disease in the newborn extends for at least a week into the puerperium; therefore, it may be advised to continue oral vitamin K for the baby for another week.[20] Infants born to epileptic mothers on anti-epileptic drugs have at least double the risk of being born with a congenital malformation or anomaly when compared to non-epileptic women.[21] The 4 major anti-epileptic drugs (barbiturates, phenytoin, carbamazepine and sodium valproate) are teratogenic in animal studies. Abnormalities seen in animal studies are similar to those in human fetuses born to mothers taking these drugs.[21] The majority of the malformations are minor and these include facial abnormalities such as hypertelorism, abnormal midface, epicanthal folds and other skeletal abnormalities such as transverse palmer creases and digital abnormalities.[21] The incidence of these minor anomalies varies between 1.25-11.5% in exposed infants compared to 2.3% in the general population.[21] Major congenital malformations (CNS malformations, congenital heart defects, orofacial clefts and skeletal malformations) are attributable to the teratogenic effects of the anti-epileptic drugs instead of to the maternal epilepsy (**Table 1**).[21] Several mechanisms have been proposed for the teratogenic effects of the anti-epileptic drugs such as disturbance of folate metabolism or absorption, exposure to the toxic metabolites of anti-epileptic drugs, free radical intermediates, altered vitamin A-retinoid metabolism and adverse effects on the embryonic heart leading to fetal bradycardia and hypoxia.[21] Current international experience suggests that new anti-epileptic drugs are probably safer in pregnancy when compared to old anti-epileptic drugs.[22] This is particularly true for lamotrigine where animal studies show no abnormal data.[22] Published data report that major congenital malformations with lamotrigine monotherapy are 1.8-4%.[22] Major congenital malformations with other common anti-epileptic drugs monotherapies range between 3.6-9.6%.[22] Anti-epileptic drugs polytherapies especially when containing valproate significantly increases the risk of major congenital malformations.[23,24] Therefore it is proposed to avoid anti-epileptic drug polytherapy combinations containing valproate during pregnancy if possible and if needed to prescribe valproate at the minimal effective dose as the risk of major congenital malformations increases with large doses of valproate (>1000 mg/day).[22-24] It is also proposed to prescribe folic acid before conception (0.4-5mg/day) to protect the fetus from the teratogenic effects of folic acid impairment secondary to anti-epileptic drugs.[24]

Anti-epileptic drugs and lactation. Concentrations of anti-epileptic drugs in breast milk are minimal and are seldom harmful to the infant. The breast milk concentration of anti-epileptic drug is 5-10% of the blood concentration. Anti-epileptic drugs such as phenytoin and carbamazepine are highly protein bound and are poorly excreted in the breast milk, in fact, breast feeding is encouraged as it ensures that the baby is slowly withdrawn from the anti-epileptic drug.[25] Anti-epileptic drugs such

Table 1 - Potential congenital malformations from common anti-epileptic drugs.

Medication	Characteristic possible neonatal /fetal effect
Carbamazepine	Neural tube defects (0.5-1%), congenital heart disease, hypospadias, inguinal hernia, hip dislocation, reduced birth weight head circumference
Phenytoin	Congenital heart disease, facial clefts, nail and distal phalanx hypoplasia, dysmorphic craniofacial abnormalities, developmental delay, microcephaly, growth deficiency
Phenobarbitone	Congenital heart disease, facial deficiency, growth deficiency, dysmorphic cranial facial abnormalities, distal limb abnormalities, neonatal withdrawal
Primidone	Congenital heart disease, facial deficiency, growth deficiency, dysmorphic cranial facial abnormalities, distal limb abnormalities, neonatal withdrawal
Valproate	Neural tube defects (1-2%), dysmorphic craniofacial abnormalities, skeletal abnormalities, hypospadias, cardiovascular, facial dysmorphisms
Ethosuximide	Possible dysmorphic craniofacial features
Benzodiazepines	Possible craniofacial dysmorphisms

Table 2 - Guidelines for the use of anti-epileptic drugs in women.

Category	Recommendations
Girls	Avoid phenytoin if possible (cosmotic side effects)
Women in the childbearing period	Avoid phenytoin if possible (cosmotic side effects) Suitable anti-epileptic drug monotherapy in the lowest effective dose to control seizures Avoid oral contraceptive pills with liver enzyme inducing anti-epileptic drugs Avoid excessive weight gain
Pregnancy	***Preconception:*** Good seizure control Suitable anti-epileptic drug monotherapy (if possible) Lowest effective doses of anti-epileptic drugs Avoid anti-epileptic drugs polytherapies containing valproate (if possible) Use valproate at doses < 1g/day (if possible) ***Pregnancy:*** Folic acid (0.4 or 5mg/day) one month before conception Adequate sleep and anti-epileptic drugs compliance Monitor anti-epileptic drug levels every 3 months adjust doses if needed Avoid alteration of anti-epileptic drug during pregnancy Close obstetric and neurology follow-up With the use of liver enzyme inducing anti-epileptic drug vitamin K (10-20mg/day) in the last month of pregnancy and the infant should receive 1mg of vitamin K intramuscularly at birth and continue the infant with vitamin K for one week ***Labor:*** Same anti-epileptic drugs as during pregnancy ***Puerperium:*** Encourage breast-feeding (except phenobarbitone and benzodiazepines if sedating the infant). Monitor anti-epileptic drug serum levels (for 8 weeks)
Menopausal women	Monitor calcium and vitamin D levels Consider vitamin D supplementation if required Bone mineral density testing (osteoporosis diagnosis) Hormonal replacement therapy and calcium supplementation (osteoporosis treatment)

as phenobarbitone, primidone or benzodiazepines may cause sedation in the newborn. In this instance, breast-feeding has to be stopped.[25]

Anti-epileptic drugs and fertility. In addition to the effect of epilepsy anti-epileptic drugs can disturb the hypothalamic pituitary gonadal axis and therefore induce menstrual irregularities and infertility.[26] Valproate therapy may often cause menstrual irregularities especially in women who began taking the drug before the age of 20. Retrospective studies revealed that valproate monotherapy may be associated with menstrual irregularities in up to 45% of patients while with carbamazepine monotherapy in 19% and in 25% with valproate and carbamazepine combination and in 13% of women taking other anti-epileptic drugs.[26] However, this observation was not confirmed in subsequent studies. Recent studies have shown that there is no convincing evidence that anti-epileptic drugs may induce specific morphological changes in the ovaries.[27] Therefore, no conclusion can be drawn on a direct link between valproate and polycystic ovary disease. In a prospective study, the incidence of polycystic ovary disease in epileptic women is approximately 10% whether they are on valproate or carbamazepine monotherapies or epileptics on no anti-epileptic drugs.[27] Although the mechanism of polycystic ovaries caused by valproate is unclear, it is suggested that valproate may inhibit the conversion of testosterone to estradiol since estradiol serum concentration is not elevated in patients receiving valproate despite their elevated serum testosterone levels.[26,27] Weight gain has been observed to be a common undesirable effect associated with the use of some anti-epileptic drugs such as valproate and to less extent carbamazepine, vigabatrin and gabapentin. Weight gain in patients receiving these anti-epileptic drugs has been observed to exacerbate or induce symptoms, and signs of polycystic ovary disease in some genetically predisposed women and weight loss ameliorate the clinical, endocrine and metabolic profiles of polycystic ovary disease in these patients. Therefore, weight should be monitored in women receiving these anti-epileptic drugs.[28] Genetic and environmental factors seem also to play a role in the pathogenesis of polycystic ovary disease.[28]

Anti-epileptic drugs and contraception. Anti-epileptic drugs (Phenobarbitone, primidone, phenytoin, carbamazepine, felbamate and probably topiramate) that induce liver enzymes (P-450 isoenzyme and CYP3A4), which are responsible for metabolism of estrogen and progesterone.[29] This results in increased metabolism of exogenous estrogens and leads to contraceptive failure.[29] Valproate, gabapentin, lamotrigine, vigabatrin and levetiracetam do not interact with oral contraceptive pills; therefore, no special measures are required.[29] Oral contraceptive pills can reduce serum levels of lamotrigine significantly.[29] It is preferred for epileptic women on enzyme inducing anti-epileptic drug if she desires contraception to use other methods of contraception. A less preferred option is to use contraceptive pills containing higher concentration of estrogen (50 microgram per tablet) instead of the regular tablets that contain 30 microgram per tablet). However, the oral contraceptive pill with higher estrogen concentration is associated with increased risk of deep venous thrombosis.[30]

Anti-epileptic drugs and cosmotic effects. Women are usually emotionally sensitive to the cosmotic side effects of anti-epileptic drugs. In particular weight gain can occur with sodium valproate, carbamazepine, vigabatrin and gabapentin; acne with phenytoin and phenobarbitone; hirsutism and gingival hyperplasia with phenytoin.[1]

In conclusion, treating epileptic females presents several unique challenges. Therefore, it is advised to follow the standard guidelines for the use of anti-epileptic drugs in women during her life span from puberty to menopause (**Table 2**).

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