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Women with Epilepsy

Review Article

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Introduction

Epilepsy by definition if the occurrence of recurrent, unprovoked seizures. Therefore, a single seizure or seizures brought on by specific circumstances (for example, febrile seizures) do not constitute epilepsy.

Epilepsy affects approximately 0.5 to 1% of the population. Therefore women with epilepsy (WWE) would be a very large affected population.

Seizures are classified either as partial if they arise from a focal area of the brain and generalized if they affect both hemispheres. Partial seizures are sub-classified as simple partial (SP) if consciousness is preserved or as complex partial (CP) if the patient is unaware or unresponsive during the episode. Any partial seizure if it spreads can become a secondarily generalized tonic (SGT) or secondarily generalized tonic and clonic (SGTC) seizure. As opposed to this there are seizures which could be primarily generalized where there is no preceding partial onset. Thus a person could have primary GT (PGT) or primary GTC (PGTC), where there is no preceding partial onset. The other primary generalized seizure types are myoclonic seizures, absence seizures and atonic seizures.

Epilepsy is treated by anti-epileptic drugs (AEDs). The main-line or older drugs are - Phenobarb (PB), Primidone (PMD), Diphenylhydantoin (DPH), Carbamazepine (CBZ), and Valproic acid (VA). The newer AEDs are Clonazepam (CZP), Clobazam (CLB), Gabapentin (GBP), Lamotrigine (LTG), Vigabatrin (VGB), Tiagabine (TGB), Topiramate (TPM), and Zonisamide (ZSM).

As a general principle treatment is begun with a single appropriate main-line drug and gradually increased to the lowest does at which the seizures are fully controlled. If control is not achieved before a toxic dose is reached then a second AED is instituted and the first AED gradually withdrawn. Monotherapy is preferred to polytherapy to reduced the potential side-effects and to avoid the complex drug-drug interaction. After a seizure free period of two to three years tapering of the AED can be attempted and will be successful in around 60%. There are certain seizure syndromes where lifelong treatment is necessary, like juvenile myoclonic epilepsy. (JME). In general, partial seizures especially CP are more difficult to control. Also, withdrawal is less frequently successful if there is an abnormal EEG (with frank epileptogenic activity) at the end of the seizure-free period, or if there is mental retardation or an abnormal neurological examination.

Specific issues make this female population more vulnerable to the effects of epilepsy and treatment with anti-epileptic drugs (AEDs). These include various hormonal changes during the menstrual cycle and pregnancy and the effect of AEDs on oral contraceptive (OC) treatment and most importantly on the fetus during pregnancy. Finally, socioeconomic factors like gender discrimination of females in the form of less food intake, lower education, less access to health facilities and lower purchasing power also play an important role.

This review is based on an extensive literature search from Medline, Pubmed CINAHL, EMBASE, Journals@Ovid, Psycinfo and AMED.

Epilepsy affects the female in several special ways.

A) *Effect of hormonal changes on epilepsy*

1. Puberty
2. Menstrual cycle
3. Pregnancy
4. Menopause

B) Effects of seizures and AEDS on women

1. Reproductive endocrine system
2. Menstrual cycle
3. Fertility
4. PCOS
5. Oral contraceptives (OCs)
6. Menopause
7. Calcium and bone mass
8. Fetus
9. Breast feeding
10. Other health risks

A) Effect of hormonal changes on epilepsy

Puberty

Very little is known of the interaction between puberty and epilepsy but some epilepsies to start during this period epecially JME. Other remit around this period like the benign focal epilepsies. Still others may experience a change in expression of the seizures during this period and these will probably later have varied seizure expression with their menstrual cycle.

Menstrual cycle effect on seizures

Many women do find a cyclicity of their seizures with their periods and this is termed as catamenial epilepsy. It was first described in the 19th century[1]. Herzog described three patterns[2]. There are following patterns: perimenstrual pattern day – 3 to + 3, periovulatory pattern during ovulatory phase of day 10 to 13 and luteal pattern.

The incidence varies from 10 to 70% due to varying methodology in classification [3-12]. Several mechanisms are attributed to this phenomenon mostly relating to hormonal influence:

The excitatory effect and proconvulsant effect of estrogen - estrogens are known to lower the seizure threshold in most experimental models including kindling, electroshock and pentylenetetrazol amongst other agents[13-19]. The inhibitory or anticonvulsant effect of progesterone is well documented. It reduces spontaneous and induced epileptogenic discharges in experimental animals and has an action like that of barbiturates. It acts on the GABA and glutamate reponsivenss[14,20-25].

Conjugated estrogens have been used intravenously and activated epileptic discharges in about 63% (11 out of 16) of women; with clinical seizures in 25% (4/16)[26]. On the other hand intravenous administration of progesterone in women; with epilepsy reduced the interictal spike frequency in four out of seven women[27]. Water retention has been mooted as a causative factor but not borne out by studies [5, 28]. In the management acetazolamide has been used but tolerance develops commonly and necessitates an increase in doseage[29] Cyclical AEDs have been used. CLB has been effective in 14/18 patients (78%). Nine were treated for more than one year and tolerance did not occur [30]. Clobazam CLB has been used with good success 80%.

Oral contraceptives (OC) - Controlled studies have not borne out the promise of the stray reports of efficacy of estrogen progesterone combination[31].

Not very favorable outcome has been found in studies with medroxyprogesterone [32,33]. Intermittent natura' progesterone has been used as lozenges in the dose of 200 mg three times a day and a reduction of 57% to 68% has been seen in seizure frequency[34,35]. Antiestrogens clomiphene is an estrogen anologue used in ovulatory dysfunction to treat women who desire pregnancy. Herzog treated 12 WWE and found favorable results in 10[36].

Stray reports of a few patients have been recorded with equivocal results using androgens and gonadotrophin analogues, neuroactive steroid ganoxolone.

3. Pregnancy

Seizures may be precipitated denovo in the pregnancy and postpartum period due to eclampsia, metabolic problems and cortical venous sinus thrombosis. However, as mentioned above these are regarded as special epilepsy syndromes as these have specifdic provoking factors[27]. Some may develop seizures denovo without any provocation and this is termed asgestational epilepsy. They may further develop recurrent seizurs in

future pregnancies, too. Gestational onset spilepsy refers to those who develop seizures for the first time in the first trimester and have recurrent spontaneous seizures later.

During pregnancy it is estimated that around 35% of WWF have an increase in seizure frequency[38]. Further, one-third will have a decrease in frequency and the rest will have no change in frequency. The exact cause is unknown but could be due to increased volume distribution due to weight increase, increased rate of drug metabolism, increased renal clearance[39] decreased absorption and change in hormonal balance. Non-compliance is also an important factor especially for those not properly counseled[40]. Also, in India there is a general misconception that no medication should be taken during pregnancy. It has to be emphasized that a seizure has a higher risk of causing harm to the fetus than AEDs. There is three-fold increase in the risk of a major malformation in those one first trimester seizure as compared to those whose seizures are well controlled[41]. The increased risk is due to several factors including trauma, especially abdominal and hypoxic ischemic damage caused in turn by a combination of factors including decreased placental perfusion, changes in fetal heart rate and maternal hypoxia[42].

During labor there is a three-fold risk of seizure breakthrough due to drug default, lack of sleep, fasting and dehydration. Also concomitant medication may play a contributory role.

One percent may have status epilepticus (SE) and vigorous treatment should be undertaken as the effect on the fetus is deleterious. SE and even GTC seizures cause fetal asphyxia, bradycardia and other rhythm disturbances which last for 10 –15 minutes after the seizure activity ceases.

Postpartum period is especially stressful and besides there is lack of sleep or frequent interruption in sleep. This can cause an exacerbation of seizures. Family counseling is required to share the burden of the care of the newborn.

4. Menopause

The excitatory effect of estrogens may exacerbate seizures in menopausal WWF. The elevated ratio of estrogen to progesterone also may cause similar exacerbation in the perimenopausal period. Those who experience catamenial seizures will have a reduction of seizures in the menopausal period.

3. Effect of seizures and AEDs on women

1) General effects of seizures on reproductive endocrine system

There is an in0crease in secretion of prolactin after complex partial seizures and generalized seizures and gonadotrophins are also transiently increased[43]. Further it is possible that recurrent seizures and even subclinical epileptic activity may lead to endocrine disorders by permanent changes in regulation of endocrine function[44].

2) Menstrual cycle

Menstrual abnormalities are seen more commonly and include the gamut of oligomenorrhea, menorrhagia, metrorrhagia and abnormal cycle length[45]. This is both due to the epilepsy itself and also to the AEDs. Polycystic ovary or polycystic ovary syndrome (PCOS) is also seen and is associated with use of certain AEDs, notably valproic acid (VA) though others like carbamazepine and lamotrigine do not show this effet[45-47].

Temporal lobe epilepsy (TLE) manifesting as simple partial (SP) or complex partial seizures (CP) is especially associated with menstrual irregularities (up to 50%) [48].

3. Fertility

Fertility is impaired and is reduced to around 85% as compared to the fertility in the general population [49,50]. Also 37% less persons with epilepsy are likely to conceive as compared to a general population. This is probably due to multiple factors like affection of regions of the brain like temporal and frontal lobes and hypothalamus that are intimately involved in regulating the reproductive cycle. Functional epileptogenic lesions and structural lesions cause changes in brain function. Ictal and even interictal discharge can also cause reproductive dysfunction[51].

Those with partial epilepsies are even less likely to conceive but this again could be due to the fact that the partial epilepsies are more difficult to control and often require multiple AEDs. After becoming pregnant there is a higher risk of problems like spontaneous abortion, miscarriages and other pregnancy complications[52]. However some studies from other countries have not found any difference in abortion rates.

The basis for infertility is probably multifactorial and includes -

a) AED effect on contral mechanisms for the regulation of the reproductive cycle and other neuroendocrine systems.

b) Changes in the release of luteinising hormone (LH), prolactin and the adrenal and gonadal steroids are seen [51].

4) Polycystic ovaries and the PCOS

This syndrome is characterized by hyperadrogenism, hirsutism, follicular arrest, structural changes in the ovaries. Anovular cyclicity is caused by hypersecretion of LH, hyperactivity of ovarian theca stromal cells and hypofunction of FSH granulose cell axis.

It is offen seen in the general population (5-6%) but is seen more often in those on AEDs, especially in persons on VA and is being reported between 30% to 80%[52,53], being more in those on a combination of VA and CBZ. In those on enzyme inducing (CYP-450) drugs namely CBZ ,PB, PH, and PMD the effect is less and there is theoretically a protective action by the androgen reducing action of these drugs[54,55].

5) Effect on oral contraception (OC)

The enzyme reducing drugs mentioned above have a synthetic sex hormones reducing action of approximately 40%[55]. This makes the low-dose OCs less effective thus being a potential risk for unwanted pregnancy. This in turn makes the use of high-dose, OCs mandatory[56]. The Americal academy of neurology recommends at least 50 µg estrogen[56]. A instances of OC failure have been reported even with 50 to 80 µg estrogen with no warning of irregular menstrual bleeding. However the AEDs which are non-enzyme-inducing like VA, lamotrigine (LTG), clobazam (CLB) and topiramate (TPM) do not have this side effect and low dose OCs can be safely used. If midcycle bleeding occurs it is probably a warning that the OC is not working [55,56]. However, absence of breakthrough bleeding is not a sign that the OC is working at best efficacy[57]. If IM medroxyprogesterone is used then the efficacy is better and not affected by AEDs but interval will be 3 months instead of the usual 6 months[58]. Also subdermal levonorgestrol may have reduced effectiveness[59]. Additional protection in the form of condom, IUD etc is advisable[60].

6) Menopause

There is still insufficient data on whether there is premature menopause due to early aging of the hypothalamic – pituitary – gonadal axis[61]. However in one report 4% of the women had primary gonadal failure and amenorrhea with high FSH before the age of 30 and in another the incidence of menopause before 40 was 14% compared to 4% in a control population[62]. This was bourn bone out in another large series with 1.7% rate very near the usual rate of 1%. Further the effect of menopause on seizures is also unclear with some reports of worsening of the seizure control[63].

7) Calcium and bone mass

The enzyme-inducing AEDs mentioned earlier cause a lowered bone mass which has important implications especially in menopausal women. Some studies have implicated all AEDs albeit not equally significantly with DPH being the worst offender [64-68].

This could be due to lowering of calcium absorption or interference with vitamin D function. Vitamin D levels are lower in most studies with normal calcium levels and elevated parathormone (PTH) signifying that calcium is being mobilized from the bone. The report by Sato et al[68], however found DPH caused low calcium levels and normal vitamin D levels.

This lack of consistency in reports suggests that complex factors are at play. Further, the risk of fractures is reported

but not with absolute uniformity[65, 69-72]. Management issues for calcium: It is recommended that all WWE take 1000 mg of calcium, ideally as the citrate salt in between meals. They should also receive vitamin D 400 IU per day[73].

8) Effect of AEDs on fetus

The term fetal anticonvulsant syndrome (FAS) includes the following -

a) Intrauterine growth retardation

b) Minor anomalies

c) Major congenital abnormalities

d) Microcephaly

and e) Cognitive dysfunction.

These have been described with the use of almost all AEDs, especially the older AEDs like PB, DPH, CBZ and VA. It is especially more in those on polytherapy[74-76]. The cause of this teratogenicity is not clear and could be due to direct drug toxicity, drug-induced folate deficiency[77] or the genetically-determined lack of epoxide detoxifying enzyme (epoxide hydrolase)[78]. The mechanism of these teratogenic effects is probably multifaceted with AED related folate deficiency and/or disturbances in folic acid mediated metabolic proesses. Also free radicals may in part affect the fetus and the effect would be more pronounced in fetuses with low enzyme levels due to a homozygous gene. Polytherapy promotes free radical formation and therefore is the worst offender. With one AED the risk for birth defects is around 2.5% but rises to 25% with more than 4 AEDs[76]. With newer AEDs the risks are reportedly less [79-81]. However, as they have been around for a shorter period and the series up to now involve lower numbers the actual teratogenic effect could be higher. Dedicated ultrasound tests and alpha-fetoprotein (maternal serum) in the first trimester or latest at 16-18 weeks can identify 90-95% of NTDs and heart malformations. Rarely, amniocentesis may be needed in high-risk pregnancy.

Effects on fetal growth and anthropometric features -

Some variations have been seen in infants of mothers with epilepsy (IME). These include lower birth weight, and reduced, length and head circumference. There are also minor differences in facial anthropometric measures[82]. Many of these remit to normal with age. No specific AED is found to be a causative factor nor is polytherapy as compared to monotherapy more likely to cause these variations. A lower Apgar score and failure to thrive was also found in some neonates. IME on PB may have irritability due to PB withdrawal or due to the effect of PB received from the mother during breast feeding (see below). Rarely, PB withdrawal seizures have been seen. In addition those who had epilepsy and also smoked had the additional risk of preterm delivery.

Minor anomalies were seen in up to 20% of children born of mothers on AEDs. These included hypoplasia of nails, anomalous digits, hypertelorism and low-set ears.

Major anomalies are those malformations which require surgery in the first year of life or are associated with significant disability. These include neural tube defects (NTDs) and cardiovascular anomalies. Also seen are cleft palate and lip and urogenital defects. Around 5% may have a major malformation. However few prospective studies have found higher frequencies of up to 10%. These are most commonly seen with the older AEDs namely PB, DPH, CBZ and VA. VA are especially associated with NTDs and CBZ with NTDs and cardiac anomalies[83-85].

Microcephaly has been variously described albeit with a mild effect.

Cognitivie problems are seen more IME with lower IQs and a higher incidence of LD as compared to the general population. However there are few conflicting report[86-87],

Effect of folate deficiency on the fetus

NTDs are especially thought to be linked to folate deficiency[88,89]. Supplement of folic acid is routinely advised in all women of child bearing age on AEDs[89]. Folic acid 5 mg is often administered though the definitive requirement is not known. Studies mention anywhere from 1 to 4 mg per day[90,91]. As the folate

effect is related to the first 25 days and most pregnancies are unplanned routine administration is prudent[83].

Strategies to reduce the teratogenic effects of AEDs.

In a planned pregnancy several strategies are employed.

Correct use of AED. This is crucial as the most efficacious AED should be used in order to ensure the best possible control of seizures with the least risk to a potential fetus. The four older AEDs (PB, DPH, CBZ and VA) are teratogenic but if they are the best AED for the person then it is prudent to continue the same with proper counseling. The newer AEDs like LTG, OCZ, GBP, CZP have not been found to be teratogenic in animals[83]. The only exception is TPM which is associated with limb agenesis in rodents. A word of caution is that these newer AEDs have been around for a shorter period and the series have fewer patients enrolled which could partially account for the lower teratogenic effects found till now.

Review of the need for continuation of AED.

In those who have not had a seizure for up to three years it may be possible to gradually taper the AED concerned over a period of 3 to 6 months. Certain seizure types like juvenile myoclonic epilepsy (JME) are unlikely to remit and therefore withdrawal is not to be attempted in even a seizure free person. Those with a high risk for recurrence namely with abnormal neurological findings on examination, structural abnormality on MRI and a history of prolonged seizures or status epilepticus also should not be considered for AED withdrawal[92]. After withdrawal of AEDs and before conceiving a further seizure free peiod of over 6 months and preferably one year is advisable as the chance of seizure-recurrence is highest in this period.[92]. If withdrawal is not possible then use of an AED with a safer profile as mentioned above is advisable.

Monitoring of free AED levels during the beginning of each trimester is necessary. The drug level does vary due to the various factors mentioned above. To maintain the same drug level throughout pregnancy it is advisable to check the levels every trimester as proposed by the American Academy of Neurology[95]. Also the same should be done at term and one month after delivery. However, this should ideally be the free drug level which is not available freely in India. Most centres test the combined free and bound level. Increase in the folic acid dose before conception is advised. As mentioned above the dose of folic acid required per day is still controversial but general practice is to double the folic acid dose to 10 mg per day[92].

Judicious use must be made of ultrasound monitoring of the fetus for birth defects and medical termination of pregnancy, if indicated, especially by NTDs or cardiac anomalies are is necessary.

In unplanned pregnancy changes of AED should not be attempted as the major anomalies arise during the early weeks. Also addition of a second AED increases the teratogenic risk while also increasing the risk of a seizure during the change-over period. A person on polytherapy who is seizure-free should be switched over to monotherapy if possible to reduce the risk to the fetus. This has to be very closely monitored with drug levels both free and total. Due to interaction between AEDs there is a possibility of a fall as well an increase in drug levels depending on the AED being withdrawn and the one being continued. Withdrawal can be attempted in the circumstances mentioned above but with much more caution. If the person is not on folic acid this should be started immediately and if already on folic acid it should be increased to 10 mg per day. In India where the majority of the pregnancies are still unplanned or even if planned are not with prior intimation to the Obstetrician / Neurologist then the first four avenues are not available.

Enzyme-inducing AEDs may cause Vit K deficiency and there is a higher frequency of detection of PIVKA (protein induced by vitamin K absence for factor II) with lower levels of vitamin K in the cord blood of newborns prenatally exposed to AEDs as compared to controls[93]. This can be counteracted by administration of Injection Vit K 10 mg intramuscularly twice in the last month. Alternatively, oral vitamin K 20 mg per day may be given during the entire last month. The latter gives higher cord

vitamin K levels than the intramuscular route. The neonats may be given intramuscular vitamin K 1 mg immediately after birth [94].

Although, this is the practice parameter recommended in a review of current textbooks a recent trial has called for a judicious use of vitamin K to only those who are on PB or DPH or on polytherapy. Their prospective series reported in 2002 showed a risk of bleeding in neonates of mothers on enzyme-inducing AEDs similar to that in the controls. The rider to this is that their population of patients being more recent was rarely on polytherapy or on PB and PMD (which are more likely to cause vitamin K deficiency due to their high enzyme-reducing potential). Also, there is no study to show that antenatal administration of vitamin K actually reduces either incidence or severity of neonatal bleeding[95]. In spite of the above it is wiser to use the inexpensive and potentially helpful vitamin K routinely in all mother s and neonates.

9) Breast Feeding

Though AEDs cross into breast milk this is no contraindication to breast-feeding. The amount of AED secreted is in inverse proportion to their protein binding. The newer AEDs cross over to a greater extent than the older[96]. They do not cause any adverse effect though a few infants may feed poorly, become irritable or drowsy. The American Academy of Pediatrics committee on Drugs recommends withdrawal of breast feeding in these neonates. PB is the drug most likely to cause these symptoms[96]. Proper counseling is required as it was found in a survey on mothers with epilepsy that they tended to initiate breast feeding less commonly and also weaned off the baby earlier[97].

10) Miscellaneaus

HRT There are stray reports of some HRT regimen worsening seizure control but in the absence of clear data the only probable route is to stop HRT if this occurs[63]. Reports suggest that menopause may occur three to four years earlier in WWE on AEDs[98].

There is decreased libido associated with epilepsy and also with the use of AEDs[63].

Both DPH and CBZ have been reported to cause lowered levels of serum thyroid hormones[99].

The weight increases especially in a large number of persons with epilepsy on VA, but this drug can also cause weight loss in others due to a loss of appetite and/or nausea and vomiting. On the other hand TPM causes weight loss in many.

Cosmetic effects The effects of DPH are legend and include gum hypertrophy, a hypersensitive problem not related to dose. Other problems are hirsutism, skin thickening and acne. VA causes hair loss which can be embarrassing in women and in some hirsutism.

The Indian Scenario

Marriage, especially an arranged one is a difficult proposition in women with epilepsy. The lack of family support in the in-laws house to ensure full sleep to nursing mother and unplanned pregnancies are still problematic. Visit to the Gynecologist is usually late in pregnancy after the first trimester.

Conclusions

A majority of women with epilepsy can lead normal lives. A team effort including the Gynecologist / Obstetrician, Neurologist and Counselor can ensure a healthy and fruitful life. The important considerations are :

1) Need for high dose estrogen OCs.

2) Supplement of folic acid throughout childbearing age and use of AEDs with less potential for teratogenicity.

3) Supplement of folic acid throughout childbearing age and use of AEDs with less potential for teratogenicity.

4) Judicious use of ultrasound and AFP levels to monitor the fetus

5) Supplement of Vit K in the last month to the mother and on birth to the neonate.

6) Supplement of calcium and vitamin D to all WWE.

and 7) Counselling should highlight the positive aspects namely that most WWE can marry, have normal children and bring up a family.

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