Review Article

Epilepsy: Clinical Considerations In Women Of Childbearing Age

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Abstract

Epilepsy is the commonest chronic neurological disorder to complicate pregnancy, having an incidence of 0.15% to 10%. Sudden unexpected death in epilepsy is the principal cause of death, and seizure control is the key to minimizing this risk. The aim of antenatal care is to optimize seizure control. The lowest dose of antiepileptic medication that protects against seizures should be chosen. Non-adherence to treatment may present a greater risk to the developing fetus than antiepileptic drug exposure. Adequate rest and sleep is mandatory for epileptic women. The normal anti epileptic drug regimen should be continued during labor. An elective cesarean section should be considered if there have been frequent tonic clonic or prolonged complex partial seizures towards the end of pregnancy. Breast feeding is not contraindicated. Appropriate contraceptive advice should be given. The importance of pre conceptual care in a subsequent pregnancy should be reiterated.

Key Words: Epilepsy, Anti-Epileptic Drugs, Seizures

Introduction

Epilepsy is defined as a medical condition characterized by a minimum of two epileptic seizures unprovoked by any immediately identifiable cause. [1] Women with epilepsy (WWE) comprise a special group of patients with specific needs both in the biological and social spheres. Not only are they exposed to the brunt of social stigma associated with the disease, but they also have to face unique aspects of epilepsy right from sub-fertility, contraceptive issues and adverse effects of anti epileptic drugs [AEDs] on pregnancy and baby. [2]

Epilepsy is the commonest chronic neurological disorder worldwide with estimated statistics of around 50 million people suffering from the disease. Of these, around half of the sufferers are women. Therefore it is also the most common neurological disorder to complicate pregnancy. The incidence has been quoted to range from 0.15% in some studies to as high as 10% in others. [3, 4] Sudden unexpected death in epilepsy (SUDEP) is an important cause of maternal mortality, and seizure control is the key to minimizing this risk.[5] Pregnant women with poorly controlled epilepsy, especially where seizure frequency exceeds once a month, are more likely to be the ones whose epilepsy deteriorates in pregnancy. These women are candidates for poor fetal and obstetric outcomes.

Effect of pregnancy on seizure control

In most of the women pregnancy does not affect the frequency of seizures. However, about one third of patients will have an increase in frequency of seizures. [4] The risk of seizures is highest in the peripartum period.

Precipitating factors of seizures

The main reasons behind deterioration of seizure control during pregnancy are a poor compliance with medication, increased volume of distribution in pregnancy leading to decreased drug level, increased drug clearance, lack of sleep, lack of absorption of anticonvulsant drugs and hyperventilation during labor. [6,7] A woman who has been seizure-free for many years is unlikely to have seizures in pregnancy unless she discontinues her medication.

Effect of seizures on pregnancy

There is no evidence of adverse effect of a single episode of seizure on the fetus. However, trauma to the abdomen associated with fall during an epileptic attack may give rise to complications. There is a slightly increased risk of obstetric complications including pre-eclampsia, non-proteinuric hypertension, bleeding in late pregnancy and delivery before 34 weeks of gestation.

Effect of epilepsy and AEDs on fetus

The adverse effects of epilepsy and AEDs on the

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baby are numerous. They can be classified into four major categories- anthropometric, physiological, teratogenic and long term cognitive effects. It has been observed in various studies that WWE on antiepileptic drugs have a higher incidence of intra uterine growth retardation, preterm birth, low Apgar scores and low birth weight. [8-12]

There is an increased risk of congenital malformations [With a single drug, it is 6-7%, with two or more drugs the risk rises to 10-15%. It rises to 50% in women who are taking a combination of Valproate, Carbamazepine & Phenytoin]. The risk of epilepsy in the neonate is increased by about 4-5% in epileptic women. [13,14,15]

Researches investigating long term effects of AEDs on children have suggested that exposure of the fetus to valproate during intra uterine life is associated with impaired cognitive outcomes in the children. This has prompted the US Food and Drug Administration (FDA) to issue a warning to the effect. [16, 17]

Pre conceptual care

There is much controversy regarding the effectiveness of preconception counseling. As yet, there is no evidence that it is associated with improved pregnancy outcomes for women with epilepsy and their babies.[18] Nevertheless, WWE should be informed by their health care providers the consequences of epilepsy and AEDs on pregnancy, especially with respect to maternal and fetal outcome. [19] They should be reassured that most of them will have a normal pregnancy and delivery.

However the risk of teratogenesis posed by anti epileptic drugs [AEDs] and the risks and benefits of treatment, the possibility of development of status epilepticus and sudden death in epilepsy (SUDEP) especially if treatment is ceased are important points for discussion in the pre conception clinic. As some of these risks may have a genetic predisposition, the outcome of pregnancies cannot be anticipated in entirety.

Based on the present knowledge, it is advisable for women to continue medication during pregnancy using monotherapy at the lowest dose required to achieve seizure control. It has been recommended to avoid polytherapy wherever possible.[20] For women who have been seizure free for at least 2 years, supervised withdrawal of AED's over a 3-6 month period may be deemed appropriate by the concerned neurologist.

Drug withdrawal is not recommended in women who have not been seizure free for 2 years or those whose specific epilepsy syndrome is known to require continual drug treatment or those unwilling to accept a risk of seizure recurrence. For these women, consideration should be given to converting a multiple drug regimen to a single drug regimen.
Where sodium valproate is the single agent of choice, high plasma levels should be avoided by dividing the required daily dose over at least two administrations or by using a slow release preparation. However the long term cognitive effects of valproate on the child should be reiterated.

Folic acid should be prescribed in a dosage of 5mg for at least 3 months prior to conception and it should be continued till at least 12 weeks post conception.

Antenatal care

The aim of antenatal care is to optimize seizure control. This demands the involvement of a neurologist at the earliest and working in collaboration with the obstetrician.

Administration of AEDs:[2]

WWE need to continue AEDs during pregnancy under supervision. The treatment chosen for each woman should be at the lowest dose that protects against seizures. For women who first present when already pregnant, particularly those beyond first trimester when organogenesis is complete, there is probably little to be gained in terms of avoiding teratogenesis by altering treatment.

Routine measurement of blood levels of anticonvulsants is not usually indicated. Not only can the total plasma levels be misleading but there is no evidence of a clear cut relationship between free levels and seizure control. Rarely, measurement of plasma levels may be of use where there is concern regarding toxicity or compliance or where multiple drug regimens are used.

An increase in seizure frequency is an indication for increased dosage and/or addition of a new anticonvulsant [providing that poor compliance has been excluded]. Some women, especially those who are

taking oxcarbazepine or lamotrigine, may require dose escalation in the second half of pregnancy. It has been observed that blood levels of these AEDs have a tendency to drop significantly with increase in period of gestation. In the postpartum period, the blood levels of lamotrigine increase rapidly, therefore, its dosage may require adjustment post delivery.

It should be emphasized to all women that non-adherence to antiepileptic medication may present a greater risk to the developing fetus than AED exposure. Besides medical management, for the pregnant epileptic adequate rest and sleep is mandatory.

Assessment for congenital anomalies in the fetus:[21]
WWE should be offered testing for serum alpha fetoprotein at 16 weeks gestation. The pre screening counselling should emphasise on increased incidence of neural tube defects in pregnancies complicated with epilepsy. The couples should be informed the implications of screening, the sensitivity of screening test and the options available in case of abnormal results.

WWE should be offered Level II USG at 18-22 weeks gestation to screen for structural anomalies in the baby. Pre screening counselling should also emphasise on the fact that USG does not reveal all congenital anomalies in the baby.

Preterm labor in WWE:[21]
AEDs are hepatic enzyme inducers, therefore they potentiate the metabolism of steroids. As a result, the usual doses of betamethasone are inadequate for WWE. The steroid regimen advised is two doses of betamethasone, 24mg, given 12 hours apart [providing a total steroid dosage of 48mg].

Management of seizures in the antenatal period:[21]
The management of seizures during pregnancy remains same as in the non pregnant state. Prolonged seizures should be treated with diazepam 10-20mg IV [the first 10mg as a bolus with slow injection of further 2mg boluses, as required]. Diazepam can also be given per rectally. If needed, phenytoin can also be administered in a dosage of 15mg/Kg IV at a rate no greater than 50mg / minute.

Prevention against hemorrhagic disease of newborn: The maternal use of enzyme inducing AEDs has been known to be associated with increased risk of neonatal bleeding. 22 Many doctors believe in treating these women prophylactically with Vitamin K. This can be administered in two ways. Two doses of Vitamin K [Inj. Vit K, 10mg] can be given to mothers at 34 and 36 weeks of pregnancy, followed by 1mg vitamin K to neonate at birth. 2Alternatively, women can receive oral vitamin K [20mg/ day] from 36 weeks of gestation to delivery.[23]

However, a prospective cohort study found no significant difference in neonatal hemorrhage with antenatal administration of vitamin K to mothers, provided that neonates receive 1mg injection vitamin K at birth. Therefore, the recommendation of National Institute for Health and Clinical Excellence [NICE] remains to administer 1mg of vitamin K at birth to all babies of mothers on enzyme inducing AEDs.

Intrapartum care:
Besides the routine information, it should be recorded in the case sheet that the woman is suffering from epilepsy. A detailed drug history should be recorded. The paediatrician should be duly informed.

AEDs during labor
The woman's normal anti epileptic regimen should be continued during labor. However, where this is not possible (due to nausea or vomiting or after anesthetic) then an intravenous regimen of phenytoin comprising an initial dose of 10mg/Kg followed 2 hours later by a second dose of 5mg/Kg is recommended.[24]

Mode of delivery
Reassurance should be given to WWE that most of them will be able to deliver vaginally. However, if there have been frequent tonic clonic or prolonged complex partial seizures towards the end of pregnancy, an elective cesarean section should be considered.

Type of analgesia:[21]
The same type of analgesia, including epidural analgesia should be offered to women with epilepsy as to a non epileptic woman. Pethidine may have a convulsant effect in some patients; therefore it should be administered with extreme caution.

Seizures in labor:[21]
Around 1-2% of women with epilepsy can have tonic clonic seizures during labor. They can be man-

aged by intravenous diazepam or lorazepam. A CTG should be performed for at least 30 minutes following any seizure.

In case of persistent seizures, the woman should be managed as for status epilepticus. If there is doubt regarding intrapartum seizure, whether it is due to eclampsia or epilepsy, then, in addition to intravenous lorazepam or diazepam, a slow intravenous bolus of 4 g magnesium sulphate followed by 1g/hour is recommended. Repeated seizures place the fetus at risk of anoxia and distress. These women should be taken up for a Cesarean section under general anaesthesia.

Postnatal care: [21]
Babies of mothers taking AEDs are at increased risk of developing hemorrhagic disease of the newborn. Therefore, it is recommended that they receive Vitamin K [1mg] intramuscularly, at birth.

The use of AEDs does not contraindicate breast feeding, despite the fact that most anticonvulsants are excreted in breast milk. The resulting dose to the breast fed infant is usually sub therapeutic, however, sedative anticonvulsants have been known to cause sedation in the infant. If the baby of a mother taking anticonvulsants is unusually sleepy or has to be woken up to feeds, the mother should be advised to feed before, rather than after taking the medicines.

Seizures in the post natal period:[21]
Sleep deprivation has been known to increase the risk of seizures in the post partum period. Therefore the importance of adequate sleep and rest should be emphasised to the mother. In the event of seizures in the post partum period, provided adequate precautions are taken, the risk of injury to the infant remains low. The woman should be advised as to how she can reduce the risk of accidents. This advice may include minimal carrying of baby by mother, arrangement for feeding the baby and changing nappies and clothes while seated on the floor and not to bathe the baby whilst alone.

Post natal advice:
The obstetrician should confirm an appointment with the neurologist around 3-4 months later, prior to discharging the mother. She should be advised about appropriate methods of contraception. The importance of pre conceptual care in a subsequent pregnancy should also be reiterated.

Contraception:
The commonly used AEDs are hepatic enzyme inducers, and increase the metabolism of both estrogen and progesterone. Therefore hormonal methods of contraception might not prove to have a similar efficacy in women on AEDs as compared to other women.

Progesterone only pills/ Progesterone implants:[23]
Progestogen only pills [POP] are not recommended for epileptic women. However, if no other method of contraception is acceptable in a given situation, the dose of daily POP may be doubled to ensure a more effective contraception.

Fixed dosage release progestogen implants are not recommended for epileptic women. However if DMPA is being administered, it should be given at a 10 week interval instead of the usual 12 week one.

Combined oral contraceptive pill:[COC][23]
A minimum initial dose of 50 micrograms of estrogen is recommended if the epileptic woman is taking combined oral contraceptive pill. However, if breakthrough bleeding occurs, the dose of estrogen may be increased to 80 or 100 [maximum] micrograms/day.

The use of 4 packs of COCs consecutively with a reduced pill-free interval of 4 days after the fourth pack is recommended. Such a regimen provides enhanced contraceptive cover and can reduce the frequency of seizures if hormonally triggered. It is important to note that even after enzyme inducers are withdrawn, an extra contraceptive cover for 8 weeks is recommended.

Emergency contraception:[23]
An intrauterine contraceptive device is the most reliable choice for emergency contraception in women taking AEDs. In case hormonal methods of emergency contraception are planned for a woman who is taking enzyme inducing AEDs, the dose should be accordingly doubled.

Conclusion:
The management of pregnancies in women with epilepsy demands a multidisciplinary approach with the obstetrician working in collaboration with the neurologist. There remain many issues to be attended to, starting from the periconception period itself. An institution needs to formulate its own set of

guidelines as there are many grey areas regarding management. It remains undisputed that babies of women on anti epileptic drugs have a higher risk of congenital anomalies as compared to other babies. There is no anti epileptic absolutely safe during pregnancy and this is an important fact that should be explained to the couple. The antenatal management basically remains similar to non epileptic pregnancies. However, these pregnancies remain at a higher risk of complications such as intrauterine growth retardation, pre eclampsia and preterm birth. One should anticipate these complications, detect them early and manage them appropriately. Intrapartum period is important in epileptic pregnancies because the stress of labor can precipitate convulsions, resulting in maternal and fetal morbidity and mortality. Post partum issues relate to breast-feeding, contraception and appropriate follow up care.

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