Women with Epilepsy: Management Issues

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It was estimated that epilepsy affects ~ 4/1000 of the population in Hong Kong and 3 to 5 births per thousand belong to women with epilepsy. Health issues for women with epilepsy are complex and requires special attention.

The use of antiepileptic drug (AED) interferes with the efficacy of hormonal contraception and has been associated with certain congenital malformations. The fertility rate is also lower among women with epilepsy. In addition, frequent convulsive seizures may damage the foetus by impairment of placental blood flow and foetal oxygenation.

This article provides an up-to-date recommendation for the optimal AED management and the supportive care for women with epilepsy.

Table1: Management issues for women with epilepsy

During reproductive years
- What is the best AED regiment during reproductive years?
- What is the best contraceptive plan?
- What is the role of folic acid supplementation during reproductive years?
- How should seizures related to cyclic hormonal fluctuation be managed?
- What are the appropriate topics for prepregnancy counselling?

During and after pregnancy
- How should AED levels be monitored and adjusted during pregnancy?
- What is the role of vitamin K use during pregnancy?
- What recommendations can be made regarding breast-feeding?
- How should AED dosages be altered in the postpartum period?

AED = antiepileptic drug

A) Women with Epilepsy at Their Reproductive Age

AED regimen:

The ideal AED for women with epilepsy is the one which is appropriate for her seizure type achieving optimal control with least side effects. Scientific evidence is available for the teratogenic effects of AEDs in animals but data for human beings are less clear. There is substantial risk of neural tube defects for infants exposed to valproic acid (1%) and carbamazepine (0.5%). Multiple AEDs are associated with higher risk of congenital malformations and developmental delay. At present, insufficient data are available for the newer AEDs, eg felbamate, gabapentin, lamotrigine, tiagabine, topiramate, and vigabatrin.

AED discontinuation may be considered in a woman who has been seizure free for 2 to 5 years with a single type of seizure, normal neurological examination and EEG before withdrawal. The teratogenic risks of AEDs and their potential drug interactions with hormonal contraception are other factors which affect the decision to withdraw AED. After appropriate counselling, women with epilepsy who are contemplating pregnancy may consider drug withdrawal if they fulfill the above criteria. Since the risk of seizure recurrence is cumulative and greatest during the first six months after discontinuing AEDs, AED withdrawal shall be completed, if possible, at least six months before planned conception. Nevertheless, it must be emphasised that AED withdrawal is not a prerequisite for a planned pregnancy.

Contraception

All women with epilepsy must be counselled for contraception as they approach reproductive age. Phenobarbital, primidone, phenytoin, and carbamazepine are liver enzyme inducers causing a reduction of exogenous estradiol and progesterone levels; and an elevation in steroid hormone binding globulins causing a decrease in free hormone levels leading to contraceptive failure. Higher-dose formulations containing at least 50 £gg of estradiol or mestranol are more efficacious.

In contrast, valproic acid inhibits the hepatic microsomal enzyme system, and the newer AEDs e.g. gabapentin, vigabatrin, and lamotrigine have no significant effect on liver enzyme metabolism. These AEDs have not been reported to result in failure of hormonal contraception.

Folic acid

Low serum and red blood cell folate levels have been associated with spontaneous abortion and foetal malformations in both animal models and in humans. Some AEDs such as phenytoin, carbamazepine, and barbiturates, can impair folate absorption. In addition, studies have confirmed that folic acid supplementation reduces primary and secondary risk of neural tube

defects in infants not exposed to AEDs. Therefore, there is a scientific basis for the recommendation of folate supplementation for pregnant women with epilepsy. The optimal dosage is unclear but most studies use folate supplement between 0.36mg and 5 mg daily.

Seizures and hormonal fluctuations

Fluctuation of seizure control is not uncommonly seen in women with epilepsy. Information from animal experiments suggests that estrogens lower and progestins raise the seizure threshold. The true frequency of this problem is unclear, and management strategies are unproved. According to some uncontrolled case series, add-on AEDs e.g. clobazam during peri-menstrual period appears to be effective.

Counselling

The current level of risk for poor pregnancy outcome with optimal care does not constitute a contraindication to pregnancy in women with epilepsy. Over 90% of women with epilepsy can expect good pregnancy outcomes. A minority of women with epilepsy will experience a worsening of seizure control during pregnancy.

A coordinated approach to the care of women with epilepsy is crucial. Contributions from general practitioner, obstetrician, and neurologist, are equally important. Communication and documentation of discussions are essential.

Although figures are not consistent among studies, there is a higher rate of spontaneous abortion and other complications of pregnancy in women with epilepsy. These complications are probably multifactorial (eg: secondary to AEDs, psychosocial or socioeconomic factors, or the effects of seizures on gonadotropin levels).

The incidence of birth defects is higher in the offspring of women with epilepsy compared to the general population. Major malformations occur in 2 to 3% of infants born to mothers without epilepsy, whereas children of women taking AEDs carry a 4 - 6% risk of major malformations. Again, this increase in risk is likely multifactorial.

Retrospective studies indicate a genetic factor in some forms of epilepsy, e.g. primary generalised seizures which would therefore increase the risk of epilepsy in the next generation. On the contrary, the increased risk for symptomatic epilepsy (e.g. post-traumatic) in the offspring is negligible compared with that of the general population risk of 0.7 to 1%.

Table 2: Prepregnancy counselling should include the topics listed below: -

- Prepregnancy and pregnancy folic acid supplementation;
- Teratogenic potential of AEDs, including risk levels and discussion of major and minor birth defects;
- Options for considering AED discontinuation before pregnancy;
- Possibility for change in seizure frequency during pregnancy;
- Importance of medication compliance during pregnancy;
- Need for regular follow-up during pregnancy with AED level monitoring;
- Inheritance risks for seizures;
- Vitamin K supplementation in the last month of pregnancy; and
- Advantages and disadvantages of breast-feeding.

Table 3: For women with epilepsy During Reproductive Years

There is strong evidence you should:
- Choose AED most appropriate for seizure type
- Target at monotherapy with lowest possible dose
- Counsel patients entering reproductive years about the decreased effectiveness of hormonal contraception with enzyme-inducing AEDs (eg carbamazepine).
- Begin folic acid supplementation with at least 0.4 mg/day; and continue throughout pregnancy.

There is evidence you should:
- If your patient's preferred method of birth controls hormonal contraception and treatment involves an enzyme-inducing AED, such as carbamazepine, a formulation containing 50 ug of ethinyl estradiol or mestranol is recommended to prevent contraceptive failure.
- Counsel women with epilepsy on the following issues:
  - o Folic acid supplementation
  - o Teratogenic potential of AEDs
  - o Possible change in seizure frequency during pregnancy
  - o Importance of compliance and AED level monitoring during pregnancy
  - o Inheritance risks for seizures
  - o Vitamin K supplementation last month of pregnancy
  - o Pros/cons of breast feeding

B) Women with Epilepsy During and After Pregnancy

AED monitoring and adjustment

The physical and psychosocial risks of maternal and foetal injury with convulsions during pregnancy support the practices of optimising AED therapy before pregnancy, counselling women concerning compliance and monitoring AED levels. If seizures are well controlled with a single AED, this should be continued during pregnancy. Changes in AEDs during pregnancy with a view to reduce the teratogenic risk may be inappropriate. First, there is risk for precipitation of seizures upon changing of AED. Second, consultation is often sought several weeks following established pregnancy when the benefit of switching is uncertain. Third, overlapping AEDs exposes the foetus to the teratogenic effect of the additional AED.

Compliance with AED regimen by women with epilepsy during pregnancy may be reduced. Some women may stop AEDs due to fears about their side-effects on the foetus, hence resulting in seizure or even status epilepticus.

AED levels determined at the beginning of each trimester and during the last four weeks of pregnancy are sufficient for women with good seizure control. In selected cases, more frequent AED level assays may be necessary to monitor side-effects and compliance.

Vitamin K

AED therapy with enzyme-inducing agents has been shown to cause vitamin K deficiency in neonates born to women with epilepsy. The pathogenesis is unclear. The antenatal administration of oral vitamin K to pregnant women taking AEDs to prevent early (in the first 24 hours of life) haemorrhagic disease of the newborn is theoretically useful. Outcome studies are required to confirm the clinical usefulness of vitamin K1 supplementation (10 mg per day starting from the 36th week of gestation until delivery).

Breast-feeding

Current AEDs are compatible with breast-feeding and do not contraindicate breast-feeding. There has been one report of methemoglobinaemia occurring in a breast-fed infant of a woman taking phenytoin and a case report of an infant with thrombocytopenic purpura and anemia related to valproic acid excreted via breast milk. There have been no other reports of hepatic or hematologic toxicity to breast-fed infants of women taking AEDs. In summary, the benefits of breast-feeding appeared to outweigh the small risks of adverse effects caused by AEDs.

Postpartum AED adjustment

AED dosage increment is necessary for some women during pregnancy. With the reversal of physiologic changes of pregnancy, AED dosages usually can be reduced to prepregnancy levels at eight weeks after delivery. Continuing the higher AED regime during pregnancy may result in toxicity.

Table 4: For women with epilepsy During and After Pregnancy

There is strong evidence you should:
- Optimise therapy before conception.
- If possible, complete AED modification at least six months before planned conception.
- Don't change to an alternate AED during pregnancy for the sole purpose of reducing teratogenic risk.
- Offer patients being treated with carbamazepine, divalproex sodium or valproic acid:
  - o Prenatal testing with alpha-fetoprotein levels at 14 to 16 weeks gestation.
  - o Structural ultrasound at 16 to 20 weeks gestation; and
  - o If appropriate, amniocentesis for amniotic fluid alpha-fetoprotein and acetylcholinesterase levels
- Encourage breast-feeding; monitor the neonate for sedation or feeding difficulties.

There is evidence you should consider:
- Monitoring AED levels throughout pregnancy.
- Monitoring AED levels through the eighth postpartum week.
- Prescribing vitamin K 10 mg per day of in the last month of pregnancy for women with epilepsy taking enzyme-inducing AEDs (eg carbamazepine).