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Therapeutic issues in women with epilepsy

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Abstract

Approximately 20% of people with epilepsy are of childbearing potential and about 3 to 5 births per thousand will be to women with epilepsy. Both epilepsy and antiepileptic drugs can cause specific problems in women and embryos (less than 8 weeks of gestational age) or fœtuses (more than 8 weeks of gestational age). The aim of this paper is to discuss therapeutic issues for the management of women with epilepsy : initiation of antiepileptic therapy, contraception, pregnancy, breast feeding and menopause. Some fertility issues are also discussed.

Introduction

Epilepsy is a common disorder, usually treated medically with antiepileptic drugs (AEDs). Approximately 20% of people with epilepsy are of childbearing potential and about 3 to 5 births per thousand will be to women with epilepsy (1). Both epilepsy and AEDs can cause specific problems in women. Special management strategies are required for women's health, regarding contraception, fertility, pregnancy and menopause (2). The aim of this paper is to propose practical guidelines for the management of women with epilepsy.

Initiation of antiepileptic therapy

In every patient with epilepsy, including women and adolescents, the most appropriate AED is determined by knowledge of the seizure type and the specific epilepsy syndrome. The profile of side effects has also to be taken into account. In our country, carbamazepine (CBZ) is recommended as the first line drug for partial epilepsy and valproate (VPA) for generalized epilepsy. This is based on a published consensus between french-speaking belgian academic epileptologists, data from the litterature, advice of international experts and reimbursement constraints (3, 4, 5, 6). In a recent meta-analysis, Marson et al found significant advantages for CBZ in partial-onset seizures, but no evidence for an advantage of using VPA as the treatment of choice for generalized-onset tonic clonic seizures (7). However, it should be taken into account that in many generalized syndromes, CBZ may worsen other seizure types such as absence or myoclonic seizures.

Those guidelines are also true in women (of childbearing potentials or not). Contraception and pregnancy issues (cf lower in the text) should be discussed with the patient at the initiation of therapy. Modification of dosage and change of AED should be performed according to efficacy and tolerance. Although the teratogenic effects of newer AEDs are not yet known in humans, they globally have a more favorable side effect profile and the practitioner should be allowed to employ them if clinically indicated. As a general rule, phenytoin (PHT) and phenobarbital (PB) should not be used as first choice drugs, because of their potential long term side effects. This is particularly true in women in whom, for example, the cosmetic effects of PHT (gingival hyperplasia, hirsutism) or osteoporosis may be an important problem.

Contraception

Therapeutic guidelines are summarized in table 1.

Although ovarian sex steroid hormones can alter neuronal excitability, there have been no reports of worsening of seizure control for women who use hormonal contraception (8).

Proper counselling is essential. An adolescent with epilepsy starting an AED should have detailed information about the inducing effects of AEDs on liver metabolism and the absolute necessity of increasing oestrogen dosage in the contraceptive pill. The adolescent should also be educated about pregnancy issues as soon as the AED is started. Those issues are discussed lower in the text. Institutionalized girls with developmental delay and their caregivers should be educated too.

Classic inducing AEDs include CBZ, oxcarbazepine (OXC), phenobarbital (PB), phenytoin

Table 1

Contraception

- Important role of information
  - About inducing effects of some AEDs and the necessity of increasing oestrogen dosages
  - About pregnancy
  - Even in developmentally delayed patient
- If using inducing AEDs (CBZ, OXC, PB, PHT, PRM, TPM*): dosage of oestrogen should be ≥ 50 µg
  - An alternative is the use of non-inducing AEDs (GBP, LEV, LTG, TGB, VPA)
- Breakthrough bleeding at midcycle is a sign of non-efficacy but ovulation can happen without this warning
- IM medroxyprogesterone can be used but interval between injections should be reduced from 3 months to 6-8 weeks
- Levonorgestrel implants have a reduced efficacy and should be avoided

AEDs : antiepileptic drugs ; CBZ : Carbamazepine ; OXC : Oxcarbazepine ; PHT : Phenytoin ; PB : Phenobarbital ; PRM : primidone, TPM : Topiramate ; VPA : Valproic acid ; LTG : Lamotrigine ; LEV : Levetiracetam ; TGB : Tiagabine ; GBP : Gabapentin.

* for doses > 200 mg/day in monotherapy.

(PHT), and primidone (PRM). Topiramate (TPM) is a weak hepatic inducer too. Inducing AEDs reduce serum oestrogen concentration by 40-50%. They also increase the serum concentration of the sex hormone binding globulin, which increases binding of progesterone and reduces the level of free progesterone (8). Thus, with enzyme inducing AEDs, the contraceptive pill should contain at least 50 µg of oestrogen. With TPM, enzyme induction is significant only after 200 mg per day in monotherapy (9). Midcycle bleeding is a sign of non-efficacy but ovulation remains possible without this warning. With the use of IM medroxyprogesterone, the interval between injections should be reduced from 3 months to 6-8 weeks. In women who take inducing AEDs, subcutaneous implants of levonorgestrel have a reduced efficacy and should be avoided (10).

An alternative strategy is the use of non-inducing AEDs.

Fertility

Women with epilepsy have reduced fertility, compared to healthy non-epileptic women. Fertility may be as low as two thirds of that expected in the general population (11, 12, 13, 14). This is probably multifactorial, including the direct effect of seizures on the hypothalamus and pituitary gland, social pressure, endocrine disturbances (hypo and hypergonadotropic hypogonadism, micropolycystic ovaries), decreased libido (8, 15). The potential role of epilepsy and AEDs on micropolycystic ovaries and micropolycystic ovarian syndrome has been widely discussed in the literature and remains controversial. It seems that their prevalence is increased in epileptic women, even without AEDs and that valproate can increase the risk (15, 16).

Table 2

Fertility : Situations when women should be referred to gynaecologists

- Intervals between menstruation < 21 days or > 35 days
- Metrorrhagia
- Duration of menstruation > 7 days
- Infertility > 1 year
- Clinical features of the micropolycystic ovary syndrome (signs of hyperandrogenism, obesity, diabetes, high blood pressure)
- History of miscarriage

Table 2 summarizes the situations the neurologist should refer the patient to her gynaecologist for fertility problems (17).

Pregnancy

Women with epilepsy, and the foetus, have increased risks during pregnancy: risk of maternal seizures, risk of complicated pregnancy, risk of foetal malformation, risk of complicated labor and delivery, etc. About one-third of epileptic women will have an increase in seizure frequency (18). The cause of this is multifactorial, including a decrease in AEDs serum concentration, an increase in oestrogen concentration, an increase in total blood volume, compliance issues, vomiting and disturbances of bowel motility. For example, pregnancy increases lamotrigine clearance by more than 50%. This effect occurs early in pregnancy and reverts after delivery (18). Maternal seizures may have adverse effects on the foetus, i.e. foetal death, due to foetal anoxia secondary to severe systemic maternal acidemia and reduced uteroplacental perfusion as well as maternal abdominal trauma resulting in placental abruption. Foetal bradycardia has also been observed after maternal seizures (17). Generalized tonic-clonic seizures are more dangerous than complex partial seizures in term of hypoxia and risk of abdominal trauma. In a recent paper, primary generalised epilepsy has been found to be a risk factor for seizures during labour and delivery, if compared with localization-related epilepsy (20). It is posible that maintaining therapeutic AED levels in late pregnancy and delivery may help prevent seizures in labor and delivery (20).

Pregnant women with epilepsy have an increased risk of vaginal bleeding in 5% of the cases.

There is a 3.8 to 8% risk of major foetal malformations, which is two to three times greater than that of the general population (17, 21). All of the older AEDs have been associated with malformations, including congenital heart disease, cleft lip-palate, neural tube defects, and genitourinary malformations (17). Closure anomalies of the neural tube take place between the third and the fourth

Table 3

Pregnancy

- Low dose monotherapy, if possible
- Consider stopping AEDs before pregnancy
  - No seizure in the last 2-5 years
  - Only one seizure type
  - Normal neurological examination
  - Normal EEG
  - At least 6 months before conception period
- Usual polyvitamin complexes + 4 mg of folic acid per day
- Minimum visit schedule : One per trimester + one visit during the last 4 weeks of pregnancy
- Minimum AEDs blood level measurment schedule (when available) : one per trimester + one blood level during the last 4 weeks of pregnancy
- Fractionating AEDs intake often helps in maintaining AED blood level
- 10 mg of vitamin K per day in the last month of pregnancy ; 10 mg of vitamin K IM to the mother in case of premature delivery
- High definition ultrasonography at 16-20 weeks of pregnancy
- Dosage of alpha-fetoprotein at 14-16 weeks
- Acute IV treatment of generalized seizures during labour should be immediately available with appropriate AED (generally benzodiazepines, PHT or VPA)

AEDs : Antiepileptic drugs ; PHT : Phenytoin, VPA : Valproic acid.

week of foetal development (17). When using VPA, there is a 1 to 2% risk of neural tube defect in the offspring and 0.5 to 1% in the case of CBZ (18). There is a lack of data for newer AEDs, due to still limited experience. Thus, it is reasonable to employ them if a pregnancy is planned only if the potential benefit outweighs the risk. This means that the clinician should be sure that the newer drug will bring significant additional seizure control. The efficacy should be proven before the conception. The patient should also have the time to stop the drug in case of uneffectiveness before trying to be pregnant. Outcome of pregnancies in women under new AEDs have already been published but the number of pregnancies is still too small to draw any conclusions. For example, in recent papers, there were 200 exposures to LTG in monotherapy during the first trimester resulting in a live birth, 51 pregnancies on GBP and 42 pregnancies on OXC (22, 23). If a pregnancy occurs while on these AEDs, it should be reported to a pregnancy data bank or a registry. Those data banks are organized at a european or world level and the easier way to report a case is to directly contact the pharmaceutical company that produces the involved AED.

Without supplements of vitamin K, there is a 10% risk of neonatal bleeding, due to vitamin K deficiency secondary to induction of hepatic microsomal enzymes in the foetal liver (17). Without vitamin K supplements, haemorrhagic disease of the newborn may occur in the first 24 hours of life (24).

Practical guidelines for management of pregnancy in a woman with epilepsy are summarized in table 3. As a general rule, the most effective drug to control the patient's seizures should be used, at the minimal effective dose. Monotherapy is preferred as teratogenic risks increase with polytherapy (2). In case of pregnancy wish, the neurologist should try to diminish the dosages and to reduce the number of drugs taken by the patient, but this has to be done at least 6 months before conception, in order to exclude seizure worsening. Medication may be stopped in some syndromes, but only if the woman accepts to wait at least 6 months before trying to be pregnant in order to evaluate the safety of drug withdrawal. In addition, she should be free of seizures for 2-5 years, should have a single seizure type, a normal neurological examination and a normal EEG under AED therapy (25). In syndromes such as juvenile myoclonic epilepsy, where it is known that the woman will continue to have seizures, drug withdrawal should be avoided. Low serum folate levels are associated with an increased risk of foetal malformations, and AEDs reduce or interfere with folate metabolism (17, 21). Thus, in addition to the usual polyvitamin complexes, the woman should receive 4 mg of folic acid, ideally given as 2 mg twice a day. This treatment should be started 6 weeks *before* the conception in order to avoid very early toxicity of AEDs on the neural tube. If there is a personal or familial history of spina bifida, valproic acid and carbamazepine should not be prescribed. However, there is no proof that folic acid could have a beneficial effect in preventing non-neural tube defect malformations (26). During the pregnancy, the clinician should attempt not to change the current medication, in order to avoid precipitating seizures. Due to pharmacokinetic alterations during pregnancy, the total daily dose and the number of doses may be changed in order to maintain optimal blood levels. Blood level monitoring of AEDs should be performed every trimester and during the last four weeks of pregnancy. Increasing the number of doses sometimes helps in maintaining stable blood levels and could decrease the risk of foetal malformations, often related to the maximum concentration, at least in animals. The pregnant woman must take 10 mg of vitamin K per day during the last month of pregnancy, in order to avoid neonatal bleeding. In case of premature delivery, 10 mg of vitamin K should be given intramuscularly to the woman 3 to 4 hours before the birth. Intramuscular vitamin K given to the newborn is still necessary even if the mother did take her vitamin K treatment. In case of premature delivery, the baby should receive vitamin K intravenously. At 16-20 weeks of pregnancy, a high resolution ultrasonogram should be performed by an experienced physician, aware of the AED treatment. Measurement of alpha-fetoprotein should be done at 14-16 weeks. We do not recommend a compulsory amniocentesis in women taking AEDs. Modern ultrasonographic techniques and blood

Table 4

Breast feeding

AED	Milk : plasma ratio	Concentrations in infants
CBZ	0.17-0.69	Non therapeutic
ESM	0.77-1	Therapeutic
FBM	UN	UN
GBP	0.73	UN
LEV	UN	UN
LTG	0.35-0.77	Therapeutic
OXC	0.5	UN
PB	0.11-0.46	Therapeutic
PHT	0.06-0.69	Not therapeutic
PRM	0.4-0.96	Therapeutic
TGB	UN	UN
TPM	0.86	Not therapeutic
VGB	0.04-0.22	UN
VPA	0.01-0.1	Not therapeutic

Adapted from references 29, 30, 31.

CBZ : carbamazepine ; ESM : ethosuccimide ; FBM : felbamate ; GBP : gabapentin ; LEV : levetiracetam ; LTG : lamotrigine ; OXC : oxcarbazepin ; PB : phenobarbital ; PHT : phenytoin ; PRM : primidone ; TGB : tiagabine ; TPM : topiramate ; VGB : vigabatrin ; VPA : valproic acid ; UN : unknown.

alpha-fetoprotein help in selecting women who eventually need measurement of amniotic alpha-fetoprotein. It is the recommendation of our group that a pregnant epileptic woman should be referred for the delivery to a centre with adult and neonatal intensive care facilities. Acute IV treatment of generalized seizures during labour should be immediately available with appropriate AED (generally benzodiazepines, PHT or VPA).

Blood monitoring of AEDs is still necessary after the delivery because the dose has to be lowered very often, especially when it had to be increased during pregnancy.

Breast feeding

Breast feeding is allowed in the vast majority of the cases. Some AEDs diffuse to the milk. Protein binding is the most important variable in determining the concentration of AED in breast milk. Some AEDs can reach therapeutic levels in the baby. Data concerning this point is summarized in table 4. PB, PRM and benzodiazepines can cause sedation in the newborn. Excessive neonatal sedation is a contraindication to breast-feeding (17). Barbiturate withdrawal syndromes have been described in babies of mothers taking PB and stopping breast-feeding. This is easily resolved by giving low decreasing dose of PB to the baby (17). Because of the possibility of reaching therapeutic levels of AED in the baby, advantages and disadvantages of breast feeding should be discussed with the mother. If breastfed, the baby must be carefully observed in order to detect excessive sedation or poor sucking.

Menopause

Menopause has variable effects on the course of epilepsy (17). There is increasing evidence that most of the AEDs increase the risk of osteoporosis (27, 16). This disorder should be recognized early, by regular bone density monitoring, and treated with vitamin D and calcium supplementation as soon as there is evidence of bone disease. The place of treatment with bisphosphonates is still being debated.

Conclusion

Women with epilepsy often need a multidisciplinary approach. Contraception issues are crucial in adolescents and young women. Management during pregnancy requires strong collaboration between gynaecologists and neurologists. Managed appropriately, the vast majority of women with epilepsy will have a successful pregnancy and outcome (28).

Still, several issues in women with epilepsy remain to be elucidated, including teratogenicity of newer AEDs, effects of AEDs on polycystic ovarian syndrome and the correct management of postmenopausal epileptic women.

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