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Managing Epilepsy in Women of Childbearing Age

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Contents

Abstract

Epilepsy affects the menstrual cycle, aspects of contraception, fertility, pregnancy and bone health in women.

It is common for seizure frequency to vary throughout the menstrual cycle. In ovulatory cycles, two peaks can be seen around the time of ovulation and in the few days before menstruation. In anovulatory cycles, there is an increase in seizures during the second half of the menstrual cycle. There is also an increase in polycystic ovaries and hyperandrogenism associated with valproate therapy.

There are no contraindications to the use of non-hormonal methods of contraception in women with epilepsy. Non-enzyme-inducing antiepileptic drugs (AEDs) [valproate, benzodiazepines, ethosuximide, levetiracetam, tiagabine and zonisamide] do not show any interactions with the combined oral contraceptive (OC). There are interactions between the combined OC and hepatic microsomal-inducing AEDs (phenytoin, barbiturates, carbamazepine, topiramate [dosages >200 mg/day], oxcarbazepine) and lamotrigine.

Pre-conception counselling should be available to all women with epilepsy who are considering pregnancy. Women with epilepsy should be informed about issues relating to the future pregnancy, including methods and consequences of prenatal screening, fertility, genetics of their seizure disorder, teratogenicity of AEDs, folic acid and vitamin K supplements, labour, breast feeding and care of a child.

During pregnancy, the lowest effective dose of the most appropriate AED should be used, aiming for monotherapy where possible. Recent pregnancy databases have suggested that valproate is significantly more teratogenic than carbamazepine, and the combination of valproate and lamotrigine is particularly teratogenic. Most pregnancies in women with epilepsy are without complications, and the majority of infants are delivered healthy with no increased risk of obstetric complications in women.

There is no medical reason why a woman with epilepsy cannot breastfeed her child. The AED concentration profiled in breast milk follows the plasma concentration curve. The total amount of drug transferred to infants via breast milk is usually much smaller than the amount transferred via the placenta during pregnancy. However, as drug elimination mechanisms are not fully developed in early infancy, repeated administration of a drug such as lamotrigine via breast milk may lead to accumulation in the infant.

Studies have suggested that women with epilepsy are at increased risk of fractures, osteoporosis and osteomalacia. No studies have been undertaken looking at preventative therapies for these co-morbidities.

Epilepsy is one of the most common neurological disorders, with a lifetime prevalence of 2–7%.[1] At any one time approximately 0.5% of the population are taking antiepileptic drugs (AEDs).[2]

In women, epilepsy and AEDs can affect many aspects of the female human life cycle – appearance, menstrual cycle, contraception, fertility, conception, pregnancy and menopause.

This article reviews current knowledge and opinion about the management of women with epilepsy at various stages of their lives. The literature was searched using MEDLINE (up to June 2008). Current epilepsy journals, recent reviews and books on the topic were sourced.

1. Adolescence

Adolescence is an important time to review the diagnosis of both epilepsy and the epilepsy syndrome, because of the implications and decisions that should be made regarding AED treatment.[3] Many childhood seizure disorders cease at puberty and therapy can therefore be stopped.[4] Conversely, there are specific syndromes that begin at this time, the most common being juvenile myoclonic epilepsy. This syndrome has an excellent prognosis in that the majority of individuals will become seizure free but the most effective therapy appears to be valproate, although major problems are associated with

its use in women of childbearing age (discussed in section 9.1.4).[5]

Once someone is receiving AED therapy and is seizure free and driving, it becomes difficult to change therapy because of the risk of breakthrough seizures and the possibility that the new AED may not be as effective as the first.[6] A treatment choice made in adolescence is often lifelong. Therefore, women need to start treatment with an AED that appears to be the most suitable for their seizure type and syndrome, has a low teratogenic risk and preferably does not interact with the combined oral contraceptive (OC).[6] Advice on relationships, contraception, the consequences of AED treatment, employment, driving and psychosocial issues needs to be provided at this time.[3,6]

Also, some drugs can affect physical appearance. Phenytoin classically causes coarsening of the features, hirsutism and gum hypertrophy,[7] and drugs such as valproate, gabapentin and pregabalin stimulate the appetite and cause weight gain.[8]

2. Catamenial Epilepsy

Catamenial epilepsy refers to an increase in seizures around the time of the menses, either just before or during the first few days of menstruation. Catamenial epilepsy appears to be uncommon. Studies suggest that between 10% and 12.5% of epileptic women have catamenial epilepsy, despite 78% of women with epilepsy claiming that their seizures occurred near the time of menstruation.[9] Anovulatory cycles tend to be associated with an increase in seizure frequency during the second half of the menstrual cycle, whilst ovulatory cycles can have one or two peaks in seizure frequency around the time of menstruation and/or ovulation.[10] Catamenial seizure exacerbations are, in part, related to the changing oestrogen and progesterone levels during the menstrual cycle but these hormonal changes do not appear to be entirely responsible for the changes in seizure frequency during the menstrual cycle in women with epilepsy.[11-13]

Many therapeutic interventions have been evaluated in catamenial epilepsy with varying degrees of success. In the 1950s, acetazolamide was advocated[14] and a recent study suggests that it is effective.[15] Over the past two decades, there has been research on hormonal manipulation, with the aim of increasing relative progesterone levels or converting anovulatory to ovulatory cycles. In women with catamenial epilepsy, progesterone produced a decrease in seizure frequency[16] but norethisterone failed to show any antiepileptic benefit.[17]

Successful open-label trials using a cyclic natural progesterone supplement, depot medroxyprogesterone and gonadotropin-releasing hormone analogues in women with catamenial epilepsy have been reported.[18] A combined OC[6] or medroxyprogesterone injections[19] may be prescribed. It has also been suggested that the OC can be given in a tricyclic regimen (three cycles of combined OC consecutively without a break followed by a shorter pill-free interval of 4 days) [off-label use].[20] For women already receiving AEDs, intermittent use of perimenstrual clobazam or acetazolamide is suggested when an increase in seizures is anticipated.[6,15,21] All of these regimens can decrease or prevent catamenial exacerbations of epilepsy.

3. Polycystic Ovary Syndrome

Polycystic ovary syndrome includes hyperandrogenism (with raised testosterone levels), multiple ovarian cysts, anovulatory cycles, hirsutism and, in 30–50% of patients, obesity. Moreover, it predisposes patients to the metabolic syndrome. The prevalence of polycystic ovary syndrome in women without epilepsy is between 4% and 19%, depending on how the syndrome is defined and assessed.[22]

The majority of studies suggest that women taking valproate have an increased incidence of polycystic ovaries and hyperandrogenism.[23,24] In a study of 65 women with epilepsy, polycystic ovaries were present in 64% of women taking valproate monotherapy (14/23 women).[23] However, another study in 93 women was unable to confirm these findings.[25]

In a study of 238 women with epilepsy, 45% receiving valproate monotherapy (13/29 women) displayed menstrual irregularities (amenorrhoea, oligomenorrhoea, prolonged cycles and irregular menstruation); 43% of these women also had polycystic ovaries and 16% had elevated serum testosterone concentrations. These effects were more common (80%) in women beginning valproate therapy before the age of 20 years.[26,27] Studies suggest that stopping valproate therapy and substituting either lamotrigine[28] or levetiracetam[29] leads to a reversal of hyper-insulinaemia, hyperandrogenism and low serum high-density lipoprotein cholesterol levels.

4. Contraception

There are no contraindications to the use of non-hormonal methods of contraception in women with epilepsy (table I).[43] Non-enzyme-inducing AEDs do not show any interactions with the combined OC (table II).

A higher incidence of breakthrough bleeding and contraceptive failure has been noted amongst women with epilepsy taking an OC[46,49] and hepatic microsomal-inducing AEDs (barbiturates,[32] phenytoin,[30] carbamazepine,[30] topiramate [dose >200 mg/day],[39] felbamate[50] and oxcarbazepine[36,37]). In women taking these AEDs, a combined OC containing a progestin dose above that required to inhibit ovulation should be prescribed and used without a pill-free interval (off-label use).[51] Even on a higher dose of combined OC, full contraceptive efficacy cannot be guaranteed.

Table I. Methods of contraception and antiepileptic drugs (AEDs)

Methods of contraception that are not affected by enzyme-inducing AEDs[43]
Medroxyprogesterone depot injection (Depo-Provera®)
Copper intrauterine devices
Hormone-releasing intrauterine system (levonorgestrel-releasing intrauterine system [Mirena®])[45]
Barrier methods
Methods of contraception that are affected by enzyme-inducing AEDs[43]
Combined contraceptive pill/patch[30,32,39,46]
Progestogen-only oral contraceptive
Progestogen implant (Implanon™)[47]

Table II. Antiepileptic drugs (AEDs) and hormonal contraception

AEDs that cause enzyme induction and reduce hormonal contraception efficacy	AEDs that do not affect hormonal contraception
Phenytoin[30]	Valproate[31]
Phenobarbital (phenobarbitone)[32]	Gabapentin[33]
Primidone[32]	Levetiracetam[34]
Carbamazepine[30]	Vigabatrin[35]
Oxcarbazepine[36,37]	Tiagabine[38]
Topiramate (little effect below 200 mg/day)[39]	Pregabalin[40]
Lamotrigine[a][41,42]	Benzodiazepines[48]
	Zonisamide[44]
	Ethosuximide[48]
	Acetazolamide[43]

a Lamotrigine is not considered a traditional enzyme-inducing AED but it may induce the metabolism of progesterone and therefore is included in this table.

Studies of lamotrigine and a combined OC have shown a modest decrease in levonorgestrel and a reduced suppression of the hypothalamic pituitary axis. Although ovulation did not occur, contraceptive efficacy cannot be guaranteed, especially if higher lamotrigine doses or other combined OCs with different progestins are used.[41,42]

It can be deduced from clinical studies looking at the interactions between combined OCs and hepatic microsomal enzyme-inducing AEDs that the efficacy of progesterone-only OCs and contraceptive patches would also be affected by enzyme-inducing AEDs.[20,43]

Medroxyprogesterone injections appear to be effective in women with epilepsy.[20] However, in adolescent girls, there is some evidence to suggest that depot medroxyprogesterone (Depo-Provera®) may interfere with the achievement of peak bone mass.[20]

Levonorgestrel implants (Implanon™,[47] Norplant®[52]) are contraindicated in women taking enzyme-inducing AEDs as there is an unacceptably high failure rate. There should be no such problems with the Mirena® coil as the progestogen acts locally and is therefore unaffected by hepatic microsomal-inducing AEDs.[45]

Recent studies suggest that the OC can reduce concentrations of lamotrigine[53,54] and valproate,[55] and breakthrough seizures or a deterioration in seizure control can result when it is added to a stable antiepileptic regimen.

The progestogen-only emergency contraceptive pill (Levonelle One Step®) can be taken up to 72 hours after unprotected intercourse, and prevents more than 90% of pregnancies if taken within 24 hours. The copper intrauterine contraceptive device can be used as emergency contraception within 5 days of having unprotected sexual intercourse and has a success rate approaching 100%.[56] Women should be informed about the lack of data on the efficacy of the progestogen-only emergency contraceptive pill when using enzyme-inducing AEDs and should be offered an intrauterine device as an alternative.[20] It is suggested that women taking enzyme-inducing AEDs who require progestogen-only emergency contraception should use twice the normal dose for post-coital contraception (off-label use).[20,57,58]

5. Sexuality

Between 20% and 30% of women with epilepsy have sexual dysfunction.[59-61] Women with epilepsy have a marked decrease in sexual interest and orgasmic dysfunction is more frequent, compared with control subjects.[60] There is an association between sexual dysfunction and epilepsy of temporal lobe origin, and enzyme-inducing AEDs decrease biologically active testosterone.[62] However, the majority of women with epilepsy appear to have normal sex lives. It has been suggested that a short standard sexual history should be part of the assessment of all women with epilepsy.[6]

6. Fertility

Many studies have suggested that fertility is reduced in women with epilepsy.[63,64] This may partly be related to anovulatory cycles and/or hyperandrogenism. However, it mostly appears to be due to psychosocial factors,[64] largely because of the difficulties that some individuals with epilepsy have in finding a long-term partner.[65] An American study interviewed 1558 adults with epilepsy identified from the voluntary epilepsy organisations, and 316 sibling controls. The study found that women with epilepsy were only 37% as likely to have a pregnancy, compared with control individuals.[66] However, it has to be recognised that patients with epilepsy who belong to the various epilepsy organisations are not necessarily representative of all people with epilepsy. A general practice-based study in the UK suggested that fertility rates in women treated for epilepsy were reduced (47.1 vs 62.6 live births/1000 women for those with vs without epilepsy).[64] Another population-based study in Finland revealed that fertility was reduced in both sexes but more significantly in men.[63] The evidence therefore suggests that epilepsy is associated with a modest reduction in fertility, some of which can be explained by a subgroup of patients with epilepsy who do not enter a sexual relationship.

7. Pre-Conception Counselling

Pre-conception counselling should be available to all women with epilepsy who are considering pregnancy. Women with epilepsy need to be aware of a number of issues relating to future pregnancy, including methods and consequences of prenatal screening, folic acid supplements, genetics of their seizure disorder, teratogenicity of AEDs, labour and issues relating to caring for children. The main aim of pre-conception counselling is to ensure that women embark on pregnancy with a minimum of risk factors, fully aware of any risks and benefits of treatment, and able to make informed decisions about the pregnancy.[6]

As with all women contemplating pregnancy, advice should be given about maintaining good general health in relation to exercise, diet, smoking and alcohol consumption. Although a major concern of women with epilepsy who are contemplating pregnancy is the teratogenic potential of AEDs, it is important to put these risks in perspective. Recent studies suggest that the risk of significant fetal malformation is approximately 3–5% if one AED is taken, slightly above the

background risk of 1–2%[67], and up to 15% if two or more are taken.[67-72,73]

8. Seizure and Antiepileptic Drug (AED) Management During Pregnancy

Before conception, the continuing need for AED treatment should be reviewed. Women should enter pregnancy having complete seizure control or as few seizures as possible. If a patient has been seizure free for at least 4 years or only has simple or short-lived complex partial seizures and does not have primary generalized epilepsy and tonic-clonic seizures, consideration may be given to withdrawing AEDs to reduce the potential teratogenic risk. The lowest effective dose of the most appropriate AED should be continued, aiming for monotherapy where possible and avoiding valproate, particularly in polytherapy.[57,58,74,75]

9. Fetal Development

Infants born to women receiving AEDs, compared with those born to women without epilepsy, have at least double the risk of being born with an anomaly or malformation. Paternal epilepsy does not influence this. The most likely aetiological factor to account for the increase in malformations in infants born to women with epilepsy appears to be AED therapy,[67] but one recent retrospective study suggested frequent tonic-clonic seizures in pregnancy may also be a risk factor.[76] The four older standard AEDs (barbiturates, phenytoin, carbamazepine and valproate) are all teratogenic in animal studies.[77] The abnormalities reported are similar to those seen in humans. Studies from Japan have clearly demonstrated that the risk of an abnormal fetus is related to the number and dosage of the AEDs.[78] A prospective study showed that the risk of a malformed infant could be decreased from 13.5% to 6.2% by ensuring that more women receive monotherapy at the lowest possible dose.[78]

Gestational days 21–56 are the time when the fetus is considered to be most sensitive to the induction of malformations by exogenous agents.[79] The organs in the body are sensitive to exogenous agents that cause or are suspected of causing teratogenic effects at different stages of gestation.[79] For example, cleft palate cannot be caused by drugs administered after 60 days' post-conception, by which date the palate is closed.[79] After the eighth week, exposure to teratogens is not considered to result in any major morphological malformations.[79] However, development is a continuum and any particular drug may affect processes in the embryonic as well as the fetal period. Receptors and other molecular drug targets for future functions are continually developing, possibly making the fetus even more sensitive than the embryo to some pharmacological effects.[79]

Although there has been no randomized study of the effect of folic acid supplementation on the risk of neural tube defects and other congenital malformations in women taking valproate or other AEDs, extrapolations have been made from published studies of sporadic spina bifida in the general population.[80] Accordingly, a daily dose of 5 mg of folic acid is recommended for all women taking AEDs, starting before conception and continuing until at least the end of the first trimester.[57] A recent population-based study suggested some benefit from folic acid supplements in women taking AEDs in that, compared with infants not exposed to either AEDs or folic acid, the odds ratio of congenital abnormalities was 1.47 (95% CI 1.13, 1.90) for infants exposed to AEDs without folic acid and 1.27 (95% CI 0.85, 1.89) for infants exposed to AEDs with folic acid supplementation.[81] However, the total number of children exposed to AEDs was only 148 and other factors may account for some of this difference. Another study showed that 85 women with epilepsy who had been for preconception counselling and took folic acid (5 mg) in early pregnancy had a decreased risk of having an infant with a malformation, with no such occurrences, compared with a rate of 18% in 59 women who presented when they were pregnant.[82]

9.1 Major Malformation Patterns Associated with AEDs

Routine screening of the fetus can detect the majority of major malformations (about 50% at

11–14 weeks' gestation) depending on type and severity. It may provide the mother the option of terminating the pregnancy.[83] However, not all malformations can be detected prenatally, and even when detected, it may not be possible to give a prognosis.

9.1.1 Phenytoin

Hydantoins in monotherapy have been associated with a pattern of malformations called the fetal hydantoin syndrome.[84] This consists of pre- and post-natal growth deficiency, microcephaly and developmental delay, in combination with dysmorphic craniofacial abnormalities, and nail and distal pharyngeal hypoplasia. Major congenital malformations associated with phenytoin include facial clefts and congenital heart defects. The Australian pregnancy register quotes a major malformation rate of 10.5% for phenytoin.[70] There appears to be no consistent relationship between phenytoin dose or maternal AED plasma concentrations and major or minor malformations.

9.1.2 Barbiturates

Barbiturates in monotherapy have also been associated with congenital heart defects and facial clefts. There also appears to be a specific pattern of minor anomalies and dysmorphic features such as growth deficiency and craniofacial and/or limb abnormalities associated with barbiturates.[85,86] There may be a dose-related risk of teratogenicity with these drugs.[87]

9.1.3 Carbamazapine

Recent studies have suggested there may be an association between carbamazapine and congenital malformations, although this is slightly less than for barbiturates and phenytoin, and the patterns of malformation are different.[69,70] Studies have suggested that carbamazapine therapy is associated with abnormal growth parameters such as reduced head circumference, weight and length at birth, hip dislocation, inguinal hernia, hypospadias, congenital heart defects and neural tube defects (0.5–1%, compared with a prevalence in the general population of 0.05–0.3%).[88] The incidence of a major malformation is 3.3% in the Australian pregnancy register and 2.2% (95% CI 1.4, 3.4) in the UK register.[69,70]

9.1.4 Valproate

The teratogenicity of valproate appears to be dose related. A daily dose above 1000 mg/day or high peak plasma concentrations both appear to increase the risk of major congenital malformations.[89,90] Animal studies suggest that valproate-induced malformations may be related to high peak concentrations,[89] and it has been suggested three- or four-times-daily treatment or slow-release preparations may decrease these risks by reducing peak plasma concentrations. However, the UK pregnancy database has failed to show any benefit of a slow-release formulation.[69]

Malformations associated with valproate include neural tube (2.5%), craniofacial, skeletal, cardiovascular, urogenital and cerebral defects.[89] A relationship between valproate and radial ray aplasia and rib and vertebral anomalies has also been reported.[91] Data from the UK pregnancy register have shown that valproate is significantly more teratogenic than carbamazepine (6.2% [95% CI 4.6, 8.2] vs 2.2% [95% CI 1.4, 3.4]).[69] The Australian pregnancy database suggests an even higher risk of major malformation of 15%.[70]

Valproate is also associated with a fetal antiepileptic syndrome with a characteristic facial appearance.[92,93] Many of these children also have specific educational needs, particularly language problems, and need additional help at school.[93]

Valproate should be avoided in pregnancy if possible. Although valproate is a very effective drug for women with generalized epilepsies, the risks and benefits should be carefully considered and discussed with the patient. If valproate must be prescribed, the dose should be maintained at a level that is as low as possible and certainly <1000 mg/day, unless this is associated with an unacceptably poor degree of seizure control.[69]

9.1.5 Lamotrigine

The UK and Australian pregnancy databases currently suggest that the risk of fetal malformations with lamotrigine monotherapy is similar to that of carbamazepine.[69,70] A recent analysis of the UK pregnancy database suggests

that lamotrigine in dosages of 200 mg/day or less carries a teratogenic risk similar to that of carbamazepine.[69] The North American registry has reported an increased incidence of non-syndromic facial clefts with lamotrigine, although the other registries have not replicated this finding.[94] The UK database suggests that lamotrigine dosages of >200 mg/day increase the teratogenic risk to a rate similar to that of low-dosage valproate (1000 mg/day or less).[69]

9.1.6 Ethosuximide

Major congenital malformations, such as facial clefts, have been associated with ethosuximide, but ethosuximide was mainly used in combination therapies such as with barbiturates.[95]

9.1.7 Benzodiazepines

Initial reports suggested an association between orofacial clefts and benzodiazepines[96] but later studies have not been able to confirm these findings.[97,98] Another study suggests that the combination of valproate and benzodiazepines may lead to more pronounced dysmorphism, compared with valproate monotherapy. This may be due to an amplifying action of benzodiazepines on valproate teratogenicity.[99]

9.1.8 Other AEDs

There are not yet enough data relating to monotherapy during pregnancy with any of the other newer AEDs to be able to accurately advise women, although a recent review of oxcarbazepine does not appear to show an increased risk or any specific pattern of malformations.[100] Although monotherapy data are limited, no increase in teratogenicity has been seen with levetiracetam (70 pregnancies).[101] However, a recent study has shown that topiramate is teratogenic,[102] and zonisamide is teratogenic in animal studies.[103]

9.2 Which AED during Pregnancy?

An important question is which AED carries the lowest risk during pregnancy. Studies suggest that of the older first-line therapies, carbamazepine carries slightly less risk than valproate, phenytoin, phenobarbital (phenobarbitone) or primidone.[69,70] If therapy cannot be changed it is best to use a single AED at the lowest possible dose.

The risk of valproate teratogenicity may be decreased by keeping the total dosage <1000 mg/day[69] and using controlled-release tablets, as animal studies suggest that the peak plasma concentration of valproate may be important with regard to teratogenicity.[89] However, as data from the UK pregnancy register have shown that valproate is significantly more teratogenic than carbamazepine,[69] and another study has shown later educational problems in many of the children exposed to valproate during pregnancy,[93] valproate should be avoided if possible in pregnant women.

Lamotrigine at dosages of 200 mg/day or lower carries a similar teratogenic risk to carbamazepine but is more difficult to use in pregnancy due to falling drug concentrations and the risk of breakthrough seizures.[69,104]

Literature reviews suggest that drug combinations, especially those including valproate, should also be avoided; valproate and lamotrigine appear to be a particularly teratogenic combination with a teratogenic risk of 9.6%.[69]

In conclusion, carbamazepine and lamotrigine (200 mg/day or less) are treatments of choice for localization-related epilepsy. Treatment of primary generalized epilepsy is more difficult as valproate is the most effective AED but carries a significantly higher risk of teratogenicity. In the recent SANAD (Standard and New Antiepileptic Drugs) study, lamotrigine has not been shown to be effective for these epilepsies,[105] and levetiracetam, although effective, has scanty pregnancy data (approximately 70 pregnancies with no infant with a malformation to date).[101]

10. Vitamin K Prophylaxis

Haemorrhagic disease of the newborn is more likely to occur in infants whose mothers are taking hepatic microsomal enzyme-inducing AEDs. The Scottish Intercollegiate Guidelines Network (SIGN) guidelines suggest that an oral dose of 10 mg/day vitamin K should be given daily in the last month of pregnancy to these mothers, but there are no data of benefit to the infant to

support this.[58] Infants should receive 1 mg of vitamin K intramuscularly at birth.[57,106]

11. Management of Pregnancy and Birth

Many women with epilepsy do not experience an increase in seizures during pregnancy but there is an 8-fold increase in seizures around the time of delivery.[106] Of those women who do have an increase in seizures (between 8% and 58%),[107] the increase can often be attributed to factors such as poor compliance with prescribed AEDs (sometimes compounded by vomiting), inappropriate reduction in AED therapy, a pregnancy-related fall in plasma drug concentrations and sleep deprivation.[107-110] Consequently, the patients' seizures and AED concentrations (especially for lamotrigine[111] and oxcarbazepine[112]) should be monitored and AEDs altered accordingly.

Most pregnancies are not adversely affected by the presence of epilepsy in the mother, and most infants are delivered healthy. Recent studies have not indicated any increased risk of obstetric complications in women with epilepsy.[113]

Overbreathing, sleep deprivation, pain and emotional stress increase the risk of seizures during labour, and it is appropriate to consider epidural anaesthesia at an early stage. One to two percent of women with active epilepsy will have a tonic-clonic seizure during labour, and a further 1–2% will have a seizure in the following 24 hours.[113] In patients with frequent seizures or those who are anxious about seizures during delivery, oral clobazam (5 or 10 mg) can be useful in preventing seizures. Generalized tonic-clonic seizures are likely to result in hypoxia, and this may have deleterious effects on the fetus.[114] Therefore, the delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation. The patient's regular AED therapy should be continued throughout labour. If a corticosteroid is necessary due to premature labour, women taking hepatic microsomal enzyme-inducing AEDs will need an increased corticosteroid dose (e.g. 48 mg of beclomethasone) for prophylaxis against respiratory distress syndrome in the baby.[57,115]

12. Infant Development

When a woman with epilepsy is pregnant, the greater risk of adverse outcome of pregnancy also extends to the child. There is an increased risk of prematurity (9–11%), stillbirth, neonatal and perinatal death, haemorrhagic disease of the newborn, low Apgar scores and low birth weight.[116] The perinatal mortality in infants of women with epilepsy has been found to be 2- to 3-fold higher than in the general population in several studies, both retrospective and prospective.[115] A fall in the perinatal mortality rate was found when the outcomes of pregnancy were compared from two periods, 1977–81 and 1987–91, with a decrease from 4.7% to 2.1%, respectively. However, the mortality rate was consistently 2- to 3-fold that of the control group, reflecting improved perinatal care in more recent years rather than an effect of changing AED prescriptions.[117]

Although the potential problem of neonatal withdrawal from AEDs is well recognized, there is little recent literature about this. Neonatal withdrawal from barbiturates occurred within 2–3 days following delivery and included irritability, hypotonia and vomiting.[118,119] Neonatal hypoglycaemia after maternal valproate treatment was common (13/22 infants) in a prospective study, with the lowest blood glucose level being 1 nmol/L, but all infants were asymptomatic. Ten infants developed withdrawal symptoms that correlated with the mean dose of valproate in the third trimester.[120] Benzodiazepines have also been associated with neonatal withdrawal symptoms, and hypotonia and hypoventilation.[121]

13. Breastfeeding and AEDs

The majority of women with epilepsy can safely breastfeed their infants. Drug concentration profiles in breast milk follow the plasma concentration curve, but a delay can often be seen.[122] The drug concentrations in milk can substantially differ between the first and last portion of the feed, and between the left and right breast, depending on the fat and protein content.[122,123] The total amounts of drug transferred to the

infant via breast milk are usually much smaller than the amounts transferred via the placenta during pregnancy.[124,125]

Relatively small amounts of phenytoin are transferred via breast milk and the serum levels of phenytoin in breastfeeding infants are generally considerably below maternal levels.[124] Phenobarbital and primidone can accumulate in the plasma of the breastfed infant due to slow elimination.[124] It is therefore recommended that the infant is closely monitored and monitoring of serum concentrations may be indicated. Carbamazapine concentrations in breastfed infants are usually low and below the level where pharmacological effects might be anticipated.[124,125] However, very rarely, adverse reactions such as hepatitis have occurred.[126] Ethosuximide can be transferred via breast milk in relatively high daily doses, and plasma concentrations in breastfed infants can be close to maternal levels.[125] Valproate concentrations in breastfed infants are low.[124] Vigabatrin and gabapentin are excreted mainly unchanged in the urine and therefore, in infants with fully developed renal function, accumulation of these drugs is unlikely.[125]

However, as drug elimination mechanisms are not fully developed in early infancy, repeated administration of a drug such as lamotrigine via breast milk may lead to accumulation in the infant and pharmacological effects, and it has been suggested that lamotrigine concentrations should be monitored in breastfed children whose mothers are taking high-dose lamotrigine.[127,128] One study showed infant lamotrigine concentrations to be 30% of those in maternal plasma 2 weeks after delivery.[128]

Maternal benzodiazepine therapy can cause infant respiratory depression.[129,130] Levetiracetam concentrations have been shown to be significantly lower in breast milk than in maternal blood.[131] Zonisamide, on the other hand, is excreted in breast milk at a concentration similar to that in maternal plasma.[132]

14. Bone Health

Women, men and children with epilepsy, who are receiving treatment, are at increased risk of fractures, osteoporosis and osteomalacia.[133] This is multi-factorial in nature. There are adverse effects of AEDs (barbiturates, phenytoin, carbamazepine and valproate) on bone metabolism, vitamin D and bone turnover. AEDs that inhibit carbonic anhydrase (topiramate, zonisamide and acetazolamide) may theoretically affect bone health by producing metabolic acidosis, resulting in secondary abnormalities in bone.[134] However, a study with topiramate did not show any significant changes in bone markers.[135] There is also the trauma of seizures and subtle effects of AEDs on coordination.[133]

A study in the US showed that nearly 90% of people with epilepsy took some form of calcium/vitamin D supplement, but only 47% had undergone dual-energy x-ray absorptiometry scans, as a result of managed care in the US.[136] The commonly advised prophylactic therapy of vitamin D and calcium has not been shown to decrease hip fractures in women without epilepsy,[137] and calcium supplements may increase the risk of vascular disease.[138] The most effective therapy for AED-induced osteoporosis has not been established, but it has been suggested that women taking long-term AEDs should have bone density monitored on a regular basis.[136]

15. Conclusions

There are many issues facing women of childbearing age with epilepsy. Women need to be given relevant information at appropriate times in their lives but studies have consistently shown that this fails to happen.[139,140] The most difficult area is that of choosing the most effective AED for seizure type, taking into consideration the teratogenicity of the drug and its interactions with combined OCs.

In women with localization-related epilepsy, carbamazepine is a very effective AED and carries a low risk of teratogenicity but has major interactions with combined OCs. Levetiracetam has proven to be an effective AED, has no interactions with combined OCs and appears to be associated with a low risk of major malformation; however, more pregnancy data are needed. Lamotrigine has proven to be a very effective AED but has complex

interactions with combined OCs, a dose-related risk of major malformation, a requirement for changes in dosage during pregnancy and high concentrations excreted in breast milk.

In women with generalized epilepsies, the choice of AED is even more difficult. Valproate is the most effective AED but treatment carries with it a high dose-related risk of fetal valproate syndrome and major malformations, and a predisposition towards polycystic ovaries, hyperandrogenism and weight gain, although there is no interaction with the OC. As a result of these problems, the majority of clinicians advocate alternative therapies, but lamotrigine is not as effective and more data are needed for levetiracetam.

Women of childbearing age therefore need advice about the various therapeutic options and should be advised to attend pre-pregnancy counselling as information changes. However, the majority of women are reluctant to change treatment once seizure-free and driving, and therefore the optimum therapy at the time needs to be chosen.

The issue of bone health and the choice of AED therapy is likely to become more important in the future. However, there are no good community-based studies looking at the risk of osteoporosis/osteomalacia and fractures with the different AEDs, and none evaluating the effectiveness of different forms of therapy for AED-induced bone problems.

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