

Epilepsy and women

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Women, of all ages, with epilepsy have their own considerations which must be taken into account if their care is to be optimised. Although the issues are usually considered when a female becomes of childbearing age, therapy with antiepileptic drugs (AEDs) during childhood may influence choices in adult life. From the time of diagnosis the important issues should therefore be considered. The main areas to consider are:

- AEDs and appearance
- Female hormones and seizure control
- Fertility
- Contraception
- Pregnancy
 - the effects of epilepsy and AEDs on pregnancy
 - the effects of pregnancy on AEDs and seizure control
 - the effects of epilepsy and, in particular, seizures on the developing embryo/fetus
 - the effects of AEDs on the developing fetus/embryo
 - management of labour and postpartum management of mother and child
- Epilepsy and the menopause.

AEDs and appearance

Phenytoin therapy in childhood can lead to hirsutism, gingival hyperplasia and coarsening of facial features. Sodium valproate can cause hair loss, acne and hirsutism. Sodium valproate can also stimulate appetite leading to obesity, as can vigabatrin, gabapentin and pregabalin. Conversely, topiramate can cause significant weight loss. While for some this may have a beneficial impact, on occasions it can be extreme. The occurrence of these side effects, which are mostly undesirable in all, can have a particularly detrimental effect during adolescence, with all of its associated problems. For some their impact may be so great as to lead to poor compliance with AEDs, resulting in loss of seizure control.

Female hormones and seizure control

An increase in seizure frequency around the time of menstruation (catamenial epilepsy) was first clinically documented by Gowers in 1885 but cyclical variations in seizure frequency have been known about since antiquity and were initially attributed to the cycles of the moon.

Various authors have reported an increase in seizures perimenstrually. Many of these studies are poorly documented, use a less than strict definition of what seizures to include in the calculation of perimenstrual attacks and are unrepresentative of the female population with

epilepsy. Using the strict definition for catamenial epilepsy that $\geq 75\%$ of seizures have to occur within four days preceding and within six days of the onset of menstruation, Duncan et al showed that only 12.5% of 40 women met this criterion¹. However, 31 (78%) claimed that most of their seizures occurred around the time of menstruation.

Experimental evidence from animal studies suggests that the change in seizure frequency during the menstrual cycle may be related to the relative oestrogen and progesterone concentrations, with oestrogens being considered to have proconvulsant and progestogens anticonvulsant properties, respectively^{2,3}. Human data tend to support this hypothesis, though there appear to be no clear differences in hormonal changes in women with and without catamenial seizures⁴.

An increase in seizure frequency has been reported during the follicular phase when oestrogen concentrations are highest⁵. Anovulatory cycles tend to be associated with higher seizure frequencies, in particular during times of peak oestrogen concentration⁶. Anovulatory cycles tend to be associated with an increase in seizure frequency in the second half of the menstrual cycle while ovulatory cycles can have one or two peaks in seizure frequency, at around the time of menstruation and/or ovulation⁷.

Other influences around the time of menstruation, such as premenstrual tension and mood changes, may also be important and may have an effect on seizure control. For example, premenstrual tension is more common in women with catamenial epilepsy (75%) compared with other women with epilepsy (43%)⁸.

Treatment

Over the last century, many therapeutic agents have been tried with various degrees of success. Bromides were introduced by Locock in 1857 for the treatment of catamenial and hysterical epilepsies. By the turn of the century, it had been noted that seizure frequency occasionally decreased at the menopause or after oophorectomy. In the 1950s acetazolamide became available, which is advocated by some for use in catamenial epilepsy. Data, on which this supposition is based, are however scant with conflicting views on its effectiveness^{9,10}.

Over the last decade or so one of the main areas of therapeutic research has been hormonal manipulation. Here the aim is either to increase relative progesterone concentrations or to convert anovulatory to ovulatory cycles^{11,12}. In an open study of progesterone therapy in 25 women with catamenial epilepsy 72% experienced a decline in seizure frequency¹³. Reports suggest that the reduced metabolite of progesterone, tetrahydroprogesterone, rather than progesterone itself, is responsible for improved seizure control¹⁴⁻¹⁶, through modulation of GABA_A chloride conductance.

Other approaches have involved the intermittent use of AEDs perimenstrually. Many of the problems of tolerance, in particular those of benzodiazepines, can be overcome using this treatment model. In a double-blind crossover study of 20 mg clobazam versus placebo over a predetermined ten-day period in each menstrual cycle, clobazam was found to be superior to placebo in 14 women (78%) and completely prevented catamenial seizures in the majority¹⁷.

With regard to therapy it should first be established whether the seizures are truly catamenial. If so, intermittent therapy with clobazam 10 mg at night perimenstrually is the simplest and most useful therapy for the majority of women. If this fails, it may be worth considering the use of acetazolamide perimenstrually or increasing the dose of the AED around the time at risk.

Finally, hormonal manipulation could be considered with medroxyprogesterone or clomiphene¹⁸.

Fertility

It has been reported that women with epilepsy have reduced fertility. The potential reasons for this are likely to be complex, and include social and economic factors. It has also been reported that sexual arousal may be reduced in women with epilepsy. However the situation is far from resolved, with other studies showing that when women with epilepsy marry they have near normal fertility.

It is recognised that there is a high incidence of menstrual disorders among women with epilepsy¹⁹. Over 35% of women with partial seizures of temporal lobe origin had anovulatory cycles when studied over three cycles, compared to 8% of controls²⁰. Treatment has been tried with progesterone suppositories in the appropriate phase of the menstrual cycle²¹, as well as clomiphene¹⁸, and medroxyprogesterone¹³, with some success.

A recent prospective study showed that women with epilepsy have an increased risk of infertility, particularly if they are using polytherapy. Infertility was least (7.1%) for those with no AED exposure and higher ($P = 0.001$) for those with AED exposure (31.8% with one AED, 40.7% with two AEDs and 60.3% with three or more AEDs). In this study women with epilepsy exposed to phenobarbitone had significant risk of infertility, but no such trend was observed for valproate or other AEDs²².

Particular emphasis has however been placed on valproate. In 1993, Isojarvi reported that polycystic ovaries and hyperandrogenism are frequently detected in women on valproate²³. Subsequently they reported that these abnormalities are more common in women on valproate who gain weight²⁴, especially if this is during pubertal maturation²⁵. However, their initial study was retrospectively based in a selected population and did not concentrate on clinical endocrine status. More recently, Betts et al have shown that women who had taken valproate for at least a year were more likely to have biochemical evidence of hyperandrogenaemia than those who had taken carbamazepine or lamotrigine²⁶. However, others have not been able to replicate their results, reporting that the occurrence of polycystic ovaries in women taking AEDs is not higher than the general population²⁷. The occurrence of polycystic ovarian syndrome (PCOS), which is associated with menstrual disturbance, has also been shown to be similar for women with epilepsy taking either carbamazepine or valproate, and similar to women with epilepsy on no treatment²⁸. Furthermore a recent study performed in monkeys did not indicate that exposure to valproate for 12–15 months induced hormonal or morphological ovarian abnormalities or characteristics of PCOS²⁹. In conclusion there is no definite evidence to implicate valproate as more likely to reduce fertility than other AEDs³⁰, but women should be informed about weight gain and its association with PCOS.

Contraception

The AEDs phenobarbitone, primidone, phenytoin, carbamazepine,³¹ topiramate³² and eslicarbazepine acetate are inducers of the hepatic P-450 microsomal isoenzyme CYP3A4 which is responsible for the metabolism of oestrogens and progestogens. This results in an increased metabolism of the combined oral contraceptive pill (OCP) which may lead to a higher rate of breakthrough bleeding and contraceptive failure. Sodium valproate and the newer AEDs, vigabatrin, gabapentin, tiagabine, pregabalin, levetiracetam and zonisamide do not

induce hepatic enzymes and hence do not react with the OCP. Oxcarbazepine is considered a weak enzyme-inducing agent³³. The situation for lamotrigine is less clear. While initially not thought to interfere with the OCP, there is one report in which lamotrigine was associated with a small decrease in the levels of the progestin used in this study, levonorgesterol, with the AUC reduced by 19% and maximal concentration by 12%³⁴.

It is recommended that women taking enzyme-inducing AEDs increase their ethinyl oestradiol dose from 20–35 µg to 50 µg. If breakthrough bleeding occurs ethinyl oestradiol dosages may need to be increased to 75 or 100 µg or the 50 µg pill may be tricycled (three packets taken continuously, then a four-day break). Women also need counselling that even on a higher dose combined OCP, efficacy may be reduced. Breakthrough bleeding occurring in the middle of a cycle of contraceptive use is generally due to a relative oestrogen deficiency and usually taken as a sign of incipient failure of contraception. However, pregnancy rates (approximately 7% per year) still appear to be lower compared with barrier methods which have a failure rate of between 15 and 20%.

Levonorgestrol implants have an increased failure rate in women taking enzyme-inducing AEDs³⁵, and although the data are not available it can only be assumed that the efficacy of progesterone-only OCPs is also reduced. Medroxyprogesterone injections may be effective in women with epilepsy, with their elimination being dependent on hepatic blood flow instead of hepatic metabolism, but data proving this are not as yet available. Whether the dose of the morning-after pill should be changed in those on enzyme-inducing drugs is unknown.

Of note, OCPs can reduce the levels of lamotrigine and to a clinically significant level³⁶.

Pregnancy

The management of pregnant women with epilepsy is becoming of increasing importance as the risk factors for adverse outcomes of pregnancy become more clearly delineated³⁷. The majority of women with epilepsy will have a normal pregnancy and delivery, an unchanged seizure frequency and over a 90% chance of a healthy baby. However, considering the incidence of epilepsy many pregnancies are still at risk for an adverse outcome. Because of this, pregnancies in women with epilepsy are considered high risk and need careful management by both medical and obstetric teams.

Preconception

Preconception counselling should be available to all women with epilepsy contemplating a pregnancy. This should start at the time of diagnosis and at subsequent reviews. While it may not always be appropriate to discuss the many relevant issues (for example in paediatric practice) it should certainly be considered in female adolescents with epilepsy, including those whose care is being transferred from a paediatrician to an adult physician. The fact that the relevant issues have been discussed should always be clearly recorded in the notes. Women with epilepsy of childbearing years do not always recall being given relevant information, hence the need to repeat this regularly. For example, the results of a postal survey of women showed that only between 38 and 48% recalled being given information on contraception, pre-pregnancy planning, folic acid and teratogenicity³⁸.

Ideally an organised joint obstetric/neurology pre-conceptual counselling service should be available to allow rapid assessment of women actively contemplating pregnancy and to coordinate care during pregnancy. At present, given the numbers of neurologists and those

other specialists with an interest in epilepsy, this is not always available and waiting times are long. Nevertheless, a re-configuration of clinics and additional resources to allow for this service should be actively considered.

During counselling a re-evaluation of the diagnosis and the need for continued antiepileptic medication should take place. Consideration should be given to the AED and indeed the dosage of any AED that is prescribed. The risks and benefits of reducing or changing medication should be fully discussed with each individual patient. That the risk of major congenital malformations is at least doubled to trebled (4–9%) in women receiving AEDs, compared with the general population (2–3%) must be discussed. Details of particular malformations occurring with specific AEDs, with the levels of risk (where known), should also be mentioned. As well as major malformations the risk of cognitive and developmental delay should also be discussed.

The genetics of the seizure disorder may also need to be taken into consideration. For example, for autosomal dominant conditions such as tuberous sclerosis there is a 1:2 risk of a child inheriting the condition. Most of the inheritable syndromes which include epilepsy in their phenotype are autosomal recessive and there is therefore a low risk of children developing the condition. The risk of a child developing epilepsy is dependent on the type of seizure disorder and the number of affected relatives. For primary generalised seizure disorders there is up to a 10% chance of offspring developing epilepsy, but this is increased if both parents have epilepsy or if the child's siblings develop epilepsy. The risk seems to be lower if only the father has epilepsy compared with if only the mother has epilepsy³⁹.

Folic acid

The prescription of folic acid before conception and at least until the end of the first trimester is recommended in patients taking antiepileptic medication, as it is for all women. This followed the recognition that there is an increased risk of neural tube defect in children born to mothers taking AEDs, in particular sodium valproate and carbamazepine⁴⁰⁻⁴². Large community-based studies have demonstrated a reduction in the rate of neural tube defects in women taking folic acid pre-conceptually⁴³⁻⁴⁵. It has been inferred from this that folic acid will protect women with epilepsy who are also at increased risk of this complication. The optimum dosage of folic acid remains undetermined. Community-based studies have used dosages ranging from 0.5–4.0 mg daily, the higher dosage being suggested for women considered at higher risk. It is the higher dosage that is generally recommended in the UK for women with epilepsy (5 mg daily).

Some concerns have been raised that folic acid may exacerbate seizures but these fears have generally been felt to be unfounded. There is as yet no direct evidence that folic acid will protect against the neural tube defects or other malformations seen in association with AEDs. There is some evidence that the neural tube defects which occur in association with sodium valproate are somewhat different from those seen in the general population. They tend to be low lumbar or sacral in site⁴⁶. Other abnormalities are less common and the defect may be the result of altered canalisation rather than folding of the developing neural crest. It remains uncertain as to whether folic acid will protect against this form of neural tube defect⁴⁷, or other defects associated with AEDs⁴⁸. The potential effect of folate supplementation was reported for 4680 cases from the *UK Epilepsy and Pregnancy Register*⁴⁹. Those patients who received preconceptual folic acid, approximately three-quarters of whom received 5 mg each day, appeared more likely to have a child with a major congenital malformation (MCM) than those who did not (3.9% vs 2.2% ; odds ratio 1.8 [95% CI 1.2–2.5]). While the above results clearly do not mean that we should stop prescribing folate periconceptionally to women with epilepsy they do question the validity of information contained in current guidelines.

The effects of epilepsy and AEDs on pregnancy

Data on whether women with epilepsy are at increased risk of obstetric complications are conflicting. Complications that have been reported as being increased compared with control mothers are vaginal bleeding, spontaneous abortion, pre-eclampsia, and premature or prolonged labour⁵⁰. Higher frequencies of labour induction and artificial labour have also been reported⁵¹, but whether this is due to a greater frequency of medical indications or is due to increased concern on the part of obstetricians or mothers-to-be is uncertain⁵². The adverse outcomes most consistently reported are increased stillbirths and neonatal deaths^{53,54}, though there is some evidence that the latter has been improving⁵⁵.

Since 1958 over 40 cases of neonatal bleeding associated with maternal AED treatment have been reported⁵⁶. It is felt that this is due to reduced clotting factors, consequent to alterations in vitamin K metabolism, in infants exposed to enzyme-inducing AEDs, such as phenytoin, phenobarbitone and carbamazepine. There is evidence that newborn infants that have been exposed to enzyme-inducing AEDs *in utero* may show increased levels of PIVKA II (protein induced by vitamin K absence of factor II), an indirect marker of vitamin K deficiency^{57,58}. While there is no evidence directly linking this biochemical marker to a clinically increased risk of bleeding in the neonate, its suppression with vitamin K₁ supplementation given as 10 mg orally each day from the 36th week of gestation⁵⁹ has resulted in most guidelines for best practice advocating maternal supplementation with vitamin K₁, with all infants also being given 1 mg vitamin K₁ intramuscularly at birth^{60,61}. However, the results from a recent case-control study did not show that there was an increased risk for bleeding in infants exposed *in utero* to enzyme-inducing AEDs (mainly carbamazepine and phenytoin)⁶², though it was felt that supplementation might be necessary in selected cases, such as when prematurity is anticipated. Nevertheless, although the risk of haemorrhagic disease of the newborn is small, UK and other best practice guidelines recommend the prescription of 10–20 mg/day of vitamin K given orally to women with epilepsy in the last month of pregnancy^{60,61}, especially if an enzyme-inducing AED is being taken. This is not possible in the UK at present as no oral preparation of vitamin K is available which can be prescribed in pregnancy. At birth it is also recommended, as is the case for all newborns, that infants receive vitamin K, with 1 mg of vitamin K given intramuscularly^{60,61}.

The effects of pregnancy on AEDs and seizure control

Studies documenting the natural history of epilepsy during pregnancy have given a wide range of results.

It is however usually held that women with well controlled epilepsy are unlikely to experience a significant change in their seizure frequency. This has been confirmed in a report from the EURAP study group, who reported on the outcomes of 1956 prospectively studied pregnancies. Using first trimester as reference, seizure control remained unchanged throughout pregnancy in 63.6% of those studied, 92.7% of whom were seizure free during the entire pregnancy⁶³.

However, poor compliance with AED treatment because of nausea or the fear of the potential risks from AEDs to the fetus can result in loss of seizure control. Measuring compliance is problematic and monitoring serum levels or self-reporting may not be reliable. A study comparing longer-term AED ingestion in pregnant and non-pregnant women using hair samples is therefore of interest. In this study it was shown that AED levels of carbamazepine and

lamotrigine varied more often in women who were pregnant, with 15% of the cohort of pregnant women having little or no AED in their proximal compared with distal hair measurements of AEDs⁶⁴.

During pregnancy total serum AED levels may fall with less marked reductions in non-protein bound (free) drug concentrations^{65,66}. Many factors may contribute to this fall, including increased metabolism/excretion, increased plasma volume and reduced protein binding. Total AED concentrations do not predict response during pregnancy and therefore if serum assessments are to be made, measurement of the unbound fraction is the method of choice⁶⁷. This is especially relevant for those AEDs, such as valproate and phenytoin, that are moderately or highly protein bound.

Several studies have demonstrated pronounced alterations in the pharmacokinetics of lamotrigine during pregnancy⁶⁸⁻⁷². Apparent clearance increases steadily throughout pregnancy, peaking at about the 32nd week of gestation, when a 330% increase from baseline has been observed. The observed fall in lamotrigine levels during pregnancy has been reported as being associated with a decline in seizure control.

There is currently no consensus on how best to monitor AED levels during pregnancy. It has been advocated that a baseline, preconception, unbound (free) AED level, repeated at the beginning of each trimester and in the last four weeks of pregnancy should be the minimum level of monitoring⁶⁰. More frequent measurements will be necessary if seizure control deteriorates, side effects ensue, or compliance is an issue. For most AEDs routine monitoring of serum levels is not necessary. For lamotrigine some are of the opinion that close monitoring is mandatory and that drug levels should be increased if serum levels fall, to prevent deterioration in seizure control⁷³. That close monitoring may be effective in minimising seizure deterioration was shown in 42 women receiving lamotrigine, where monthly monitoring and dose adjustment was associated with only 19% having an increased seizure frequency⁷⁴. Whether such practices expose the fetus to additional risk has not however been established.

AED levels quickly revert to pre-pregnancy levels after birth⁶⁹. Hence, if the dose of an AED has been increased during pregnancy because of falling AED levels it may be useful to measure serum levels during the first month after delivery to predict for toxicity. If the increase has been made solely because of worsening seizure control during pregnancy the decision to reduce the AED dosage should be made on an individual basis. In particular, if the increase has resulted in a sustained improvement in seizure control with no evidence of toxicity the dose should not be changed.

The effects of epilepsy and in particular seizures on the developing embryo/fetus

The fetus seems relatively resistant to the effects of seizures, though anecdotal evidence suggests that tonic-clonic seizures may cause fetal bradycardia⁷⁵ or miscarriage but definitive data are lacking. There is no evidence that simple partial, complex partial, absence or myoclonic seizures are harmful to the fetus⁷⁶. Likewise, prospective studies have not shown an association between tonic-clonic seizures and malformations^{77,78}. Nevertheless, the risk of seizure recurrence, injury, status epilepticus, or even death needs to be considered. That the effects of status epilepticus in pregnancy were previously felt to be particularly dramatic is well illustrated by Teramo and Hiilesmaa who compiled 29 cases from the literature, of which nine of the mothers and 14 of the fetuses died⁷⁹. In contrast, in the prospective study of seizure control during pregnancy, the EURAP study group did not find such an effect. Of 36 cases of

status epilepticus (12 convulsive) there was one stillbirth, but no cases of miscarriage or maternal mortality⁶³.

That women with epilepsy who have seizures during pregnancy may be more likely to have preterm, a small or low birth weight baby compared with women without epilepsy has also been shown in a study from Taiwan⁸⁰.

The effects of AEDs on the developing fetus/embryo

There is some, albeit largely indirect, evidence from human pregnancies that AEDs have an effect on fetal and embryonic development. For example, it is a consistent finding that women with epilepsy who are not on AEDs have a lower risk of having children with major malformations than those who are taking AEDs⁸¹. However, whether the two groups are directly comparable is controversial, as women reported as having epilepsy, but who do not require AEDs, usually either have very mild epilepsy or epilepsy in remission. It has also been consistently reported that women who take polytherapy are more at risk than those who take monotherapy⁸²⁻⁸⁴. Again this could be argued as simply being a reflection of the severity of the epilepsy. Finally, animal studies have demonstrated teratogenicity with all of the older AEDs⁸⁵.

Overall, based on current information, it is generally accepted that women with epilepsy who are taking an AED in monotherapy have at least a 2–3 times increased risk over the background population of having an infant with a major congenital malformation. This is equivalent to a 4–9% chance of a major congenital malformation for each pregnancy occurring in a woman taking an AED^{81,82,86,87}.

With regard to the safety of AEDs taken in monotherapy, there is now well established evidence from multiple sources of differences between AEDs, with the greatest risks consistently being found for valproate. Data is also now available for the newer AEDs, with the greatest number of outcomes being reported to date for lamotrigine⁸⁸.

Barbiturates (phenobarbitone, primidone) and phenytoin have been associated with congenital heart defects and facial clefts⁸⁹⁻⁹¹. A few studies have found a positive dose-response relationship for barbiturates. Phenytoin has also been implicated as causing urogenital defects, and dysmorphic facial and other features such as distal phalangeal hypoplasia⁹². The *North American AED Pregnancy Registry* has published data on 146 women who had used phenobarbitone as monotherapy during the first trimester of pregnancy. The incidence of major birth defects for the 77 of these women who had no knowledge of the fetus at the time of registration was 6.5% (95% CI 2.1%–14.5%). Compared with the background risk of 1.62%, this was significantly increased (relative risk 4.2, 95% CI 1.5–9.4%, one-sided $P = 0.001$)⁹³.

In a recent case-control study the rate of major congenital malformations for infants exposed to carbamazepine was approximately twice that in the control group (relative risk 2.24; 95% CI 1.1–4.56)⁹⁴. Such an increase was not found by the *UK Epilepsy and Pregnancy Register*, where the major malformation rate for carbamazepine monotherapy exposures among 927 prospectively collected pregnancies was 2.2%, not that different from the background rate⁹⁵. Carbamazepine has been reported to be associated with major malformations, including neural tube defects (at a rate of anything between 0.2% and 1% of exposed pregnancies⁹⁶), heart defects, inguinal hernia, hypospadias and hip dislocations. There have also been reports of reduced head circumference, weight and length at birth. In a recent systematic review and case

control study the *EUROCAT Antiepileptic Study Working Group* reported that for carbamazepine teratogenicity appeared to be relatively specific to spina bifida⁹⁷.

Valproate has been shown to increase the risk of major congenital malformations in both preclinical studies and in human pregnancies. Results from the *North American AED Pregnancy Registry* described 16 major malformations among 149 valproate-exposed women (10.7%; 95% CI 6.3–16.9%). Assuming a background prevalence of 1.62% for major malformations, they calculated a relative risk for major malformations in valproate-exposed pregnancies of 7.3 (95% CI 4.4–12.2%)⁹⁸. Figures from the *Australian Pregnancy Registry for Women on Anti-epileptic Medication* revealed a higher malformation rate of 15.2% for pregnancies exposed to valproate in monotherapy (n = 224)⁹⁹. That pregnancies exposed to valproate alone have the highest risk for a major congenital malformation was also shown by the *UK Epilepsy and Pregnancy Register*. Of 762 pregnancies exposed to valproate alone, 6.2% had a major malformation⁹⁵. This was also shown by the Neurodevelopmental Effects of Antiepileptic Drugs Study in which 12 of 69 (17.4%) prospectively recruited pregnancies exposed to valproate had a congenital malformation¹⁰⁰.

Studies have indicated that exposure to valproate during early pregnancy is associated with a significant incidence (1–2%) of spina bifida aperta^{41,89}, with the greatest risk for those exposed to doses of greater than 1000 mg per day⁴². It has also been reported that there is a greater risk of cardiovascular and urogenital malformations, skeletal defects (including radial ray aplasia and rib and vertebral anomalies¹⁰¹), and a combination of facial dysmorphic patterns¹⁰², which is possibly distinct from that seen with other AEDs such as phenytoin. However, the dysmorphic features, such as epicanthal folds, long philtrum, flat nasal bridge, and hypertelorism, occur with other AEDs and their significance for long-term development is unknown. There is evidence of a pharmacogenetic susceptibility to the teratogenic effects of valproate, both from human reports^{103,104} and preclinical studies¹⁰⁵. There is also a suggestion from preclinical studies that for valproate, at least, high peak plasma concentrations are associated with an increased risk of malformations¹⁰⁶. This finding was replicated in the Australian study where the mean daily dose of valproate was higher in those with a major malformation⁹⁹. Thus, it has been suggested that a sustained-release preparation may be preferable, with the total daily dose being divided into two or three administrations per day.

Considering the newer AEDs, most human data are available for lamotrigine. The *International Lamotrigine Pregnancy Registry* has recently reported the outcomes of 414 first trimester lamotrigine-exposed pregnancies⁸⁸. The percentage of outcomes exposed to lamotrigine monotherapy with major birth defects was 2.9% (95% CI 1.6–5.1%). For polytherapy outcomes containing lamotrigine the occurrence of birth defects varied according to whether sodium valproate was included in the polytherapy regimen. For combinations containing sodium valproate in addition to lamotrigine (n = 88) the rate of major birth defects was 12.5% (95% CI 6.7–21.7%). This compared with a rate of 2.7% (95% CI 1.0–6.6%) for polytherapy combinations which included lamotrigine but not sodium valproate (n = 182). No distinctive pattern of malformations was reported in this study. Data from the *UK Epilepsy and Pregnancy Register* revealed a similar malformation rate for pregnancies exposed to lamotrigine alone, with 21 of 647 (3.2%) infants having a major congenital malformation. A positive dose-response was seen with 5.4% of pregnancies exposed to more than 200 mg a day of lamotrigine having a major congenital malformation⁹⁵. A positive dose response has not been reported by other registers including the *International Lamotrigine Registry*¹⁰⁷. The *North American AED Pregnancy Registry* reported a total of 16 (2.3%) of 684 infants exposed to lamotrigine to have a major congenital malformation (MCM). No dose response was found but a 10.4-fold (95% CI

4.3–24.9) increase in the rate of clefting abnormalities was noted¹⁰⁸. In contrast the *UK Epilepsy and Pregnancy Register*¹⁰¹ and the *European Surveillance of Congenital Anomalies* found no evidence of increased isolated oro-facial clefts relative to other MCMs for lamotrigine¹⁰⁹.

Reported data on the other new AEDs are sparse. A report of 55 exposures to oxcarbazepine (35 monotherapy and 20 polytherapy) noted only one major malformation¹¹⁰. Six malformations from the outcomes of the 248 monotherapy exposures to oxcarbazepine (2.4%), either reported in the literature or held by the Novartis Germany database, have also been recently reported¹¹¹. In a post-marketing surveillance study of gabapentin as add-on therapy for 3100 patients in England no congenital abnormalities were seen in the 11 infants born to women who used gabapentin in the first trimester of pregnancy¹¹². In the tiagabine clinical trials 22 patients who received the drug became pregnant, of whom nine carried to term. In one of these a hip displacement was noted, though this was a breech delivery¹¹³. In a small study of five women who received topiramate during pregnancy and lactation all women had uneventful deliveries and gave birth to healthy children, although one had a premature delivery at 36 weeks' gestation¹¹⁴. The *UK Epilepsy and Pregnancy Register* reported on 203 pregnancies exposed to topiramate. Of the 70 cases that had just received topiramate, three (4.8%) had a MCM, of which two were clefting abnormalities and one a case of hypospadias¹¹⁵. In contrast in another study of 52 pregnancies exposed to topiramate, no concerns were raised¹¹⁶. With regard to levetiracetam published cases are also limited. Two small reports of pregnancies exposed to levetiracetam have not raised any obvious concerns with regard to major malformations^{117,118}, with preliminary experience from the *UK Epilepsy and Pregnancy Register* in 39 pregnancies exposed to levetiracetam alone also not revealing any concerns¹¹⁹.

The *North American AED Pregnancy Registry* has published data in abstract form for 197 monotherapy exposures to both topiramate and levetiracetam in which eight and four MCMs were noted, equating to rates of 4.1% and 2.0%, respectively. Of interest and in keeping with results from the UK two of the eight MCMs with topiramate were cleft lip deformities¹²⁰. Many more pregnancies are clearly required however to permit any conclusions to be drawn on the safety on these AEDs in pregnancy.

For zonisamide, data for exposed pregnancies is even more limited. The only report published to date includes 25 pregnancies¹²¹. Considering some concerns were expressed in this small study, not to have further information from many more pregnancies is clearly of concern in itself.

For all the newer AEDs, preclinical models are therefore of interest. In these studies topiramate was teratogenic in mice, rats and rabbits at high doses, with limb and digital malformations, including right-sided ectrodactyly observed in rats and rib and vertebral malformations in rabbits. Vigabatrin was also shown to be teratogenic in rabbits, inducing cleft defects¹²². Gabapentin was associated with skeletal malformations, including delayed ossification of the calcaneus and hindlimb digits in mice, and incomplete fusion of skull bones and sternabrae in rats. However, the type and incidence of these abnormalities were not felt to be indicative of developmental toxicity¹²³. Tiagabine, oxcarbazepine and levetiracetam have not been shown to be teratogenic.

When considering the effect of AEDs on embryonic and fetal development, most of the emphasis to date has been on the risk of major congenital malformations. However, there is good evidence that minor anomalies, learning difficulties and other problems may also be

related to AED therapy. It has been found that the children of women with epilepsy, whether or not they are taking AEDs, are at increased risk of minor anomalies¹²⁴, and specific AED-related fetal syndromes have been suggested for most of the older AEDs^{92,102,125}. The types of abnormalities found have included minor craniofacial and digital anomalies and growth retardation. However, possibly except for valproate^{102,126}, there is no real convincing evidence that specific syndromes are associated with specific AEDs, hence the term ‘fetal-AED’ syndrome may be more appropriate. It is unclear what the influence of other variables is, such as maternal epilepsy and hereditary factors. In any case such abnormalities, though undesirable, have usually been felt in themselves to cause little disability. However, whether or not they are markers for more diffuse problems, or cognitive and behavioral upset is increasingly being questioned in particular.

Long-term follow-up studies of children exposed to AEDs *in utero* have been limited, with a Cochrane review concluding that the majority of studies in this area are of limited quality and that there is little evidence overall implicating one drug over another with respect to a detrimental effect on development¹²⁷. While previous studies have shown mean IQ to be significantly lower in the children of women with epilepsy^{53,128,129}, it is suggested that this is independent of AED exposure. However, a growing number of retrospective and prospective studies have found that developmental delay is more common in children born to mothers or fathers with epilepsy. What the influence of the AEDs is, and whether or not there are differences between the drugs, is the subject of much study. One study found that 16% of 224 children who had been exposed to AEDs prenatally had additional educational needs compared with 11% of 176 exposed to no drugs (odds ratio 1.49, 95% CI 0.83–2.67%)¹³⁰. A total of 30% of those exposed to valproate, and 20% exposed to polytherapy containing valproate, had additional educational needs. This compared with 3.2% and 6.5% exposed to carbamazepine and other monotherapy regimes, respectively. In a more thorough investigation of partly the same cohort of children the authors found that verbal IQ was significantly lower in children exposed to valproate monotherapy (mean 83.6, 95% CI 78.2–89.0%; n = 41) than in unexposed children (90.9, CI 87.2–94.6%; n = 80) or in children exposed to carbamazepine (94.1, CI 89.6–98.5; n = 52) or phenytoin (98.5, CI 90.6–106.4; n = 21). Multiple regression analysis revealed exposure to valproate, five or more tonic-clonic seizures in pregnancy and low maternal IQ to be associated with lower verbal IQ after adjustment for confounding factors. Doses of valproate above 800 mg/day were associated with lower verbal IQ than lower doses. There was also a significant negative correlation between dysmorphic features and verbal IQ in children exposed to valproate¹³¹. These results compare with those from previous studies which have shown higher rates for developmental delay for infants exposed prenatally to carbamazepine of between 8% and 20%^{128,132,133}. In another study, 24% of AED-exposed infants had a developmental disorder compared with 10.5% of non-exposed siblings. Differences were noted between AEDs. However, infants exposed to carbamazepine, phenytoin and valproate had significantly higher rates of developmental delay than infants not exposed to AEDs¹³⁴.

In a study from Finland the authors reported similar findings among a small number of exposed infants where full-scale IQ was low (< 80) in four of 21 infants that had been exposed to valproate (19%), and exceptionally low (< 70) in two infants (10%). Of importance however, the mothers of the valproate-exposed group performed significantly worse on IQ tests and also had significantly lower educational levels¹³⁵.

A study from India recently addressed some of the above concerns. Using an Indian adaptation of the Bayley Scale of Infant Development, motor and mental development were measured in 395 infants born to women with epilepsy¹³⁶. In addition to paediatricians being blinded to AED

exposure, multiple confounders were taken into account. Unfortunately these did not include maternal IQ. Valproate was associated with significantly lower mental and motor developmental scores compared with carbamazepine, but not with other AEDs used in monotherapy. While maternal educational status was significantly correlated with motor development in infants, mental development was not. The importance of including all confounding variables was shown in a prior study from the same group where low maternal IQ and maternal education, as well as AED exposure, were found to be associated with significant impairment of intellectual and language functions in children of mothers with epilepsy¹³⁷.

The situation for the newer AEDs is even less clear, with very limited data being available on their influence on cognitive functioning and other aspects of development. With regard to lamotrigine, data to date suggests less of an effect than for valproate. The Neurodevelopmental Effects of Antiepileptic drugs (NEAD) study using the Bayley Mental Developmental Scale showed that at three years that the valproate group was reduced by 9 points compared with the lamotrigine group, 7 points compared with the phenytoin group and 6 points compared with the carbamazepine group¹³⁸. The association between valproate use and IQ was dose dependent. Children's IQs were significantly related to maternal IQs among children exposed to carbamazepine, lamotrigine and phenytoin but not among those exposed to valproate. That valproate seems to be associated with worse cognitive outcomes compared with lamotrigine and carbamazepine, in particular with regard to language skills, has also recently been reported by other authors¹³⁹⁻¹⁴¹.

Data for the other newer AEDs are restricted to levetiracetam. In a study from the Liverpool and Manchester Neurodevelopmental Group and the *UK Epilepsy and Pregnancy Register* which compared cognitive development in children exposed to levetiracetam and valproate, children exposed to levetiracetam *in utero* were not at an increased risk of delayed early development compared with control children. In contrast, those exposed to valproate scored significantly worse¹⁴².

Management of labour and postpartum management of mother and child

Most women with epilepsy will have a normal uncomplicated vaginal delivery⁵⁰. However, in approximately 2–4% the stress of labour may result in an increased risk of seizures during labour or in the following 24 hours^{82,143}. Tonic-clonic seizures may result in fetal hypoxia and it is therefore generally recommended that delivery takes place in a unit equipped with facilities for maternal and neonatal resuscitation^{60,61}.

Breastfeeding is generally to be encouraged and may even have the additional advantage that it ensures the baby is gradually withdrawn from the AED. AEDs are excreted in breast milk at a level inversely proportional to the degree of maternal serum protein binding. Hence the amount transferred to the infant in breast milk varies substantially between AEDs. In addition, concentrations of AEDs can differ substantially between the start and end of a meal, and between the right and left breast depending on the fat and protein contents of the milk. For some AEDs, such as phenobarbitone and primidone, reduced neonatal serum protein binding and immature elimination mechanisms can also result in drug accumulation. This can result in sedation of the infant and necessitate the discontinuation of breastfeeding. However, for most AEDs, including phenytoin, carbamazepine and valproate, breastfeeding is usually without problems as these drugs are highly protein bound and therefore are poorly excreted into breast milk. Information on the concentration in breast milk of the newer AEDs is rather limited as yet¹⁴⁴, however preliminary data indicate that lamotrigine passes into breast milk at 40–45% of

the level in plasma, with levels comparable to those seen in patients having been noted¹⁴⁵. For levetiracetam, plasma concentrations in breastfed infants are low despite extensive transfer of levetiracetam into breast milk¹⁴⁶.

There has been some concern that breastfeeding during AED therapy might have a detrimental effect on cognitive development. Data from the Neurodevelopmental Effects of Antiepileptic Drugs Study is therefore reassuring, though the numbers studied were small. IQs for breastfed children did not differ from those that were not breastfed either for all AEDs combined or for those exposed to the individual AEDs studied (phenytoin, carbamazepine, lamotrigine and valproate)¹⁴⁷.

Risk of injury to the infant largely depends on seizure type and frequency. Any such risk can be minimised if time is allocated to training mothers with epilepsy on safe handling, bathing techniques, feeding, and safe practice around the home.

Epilepsy and the menopause

The effects of epilepsy on the menopause and the effects of the hormonal changes of the menopause on epilepsy cannot be reliably predicted. Women with epilepsy are at increased risk of bone demineralisation, especially if they are receiving a hepatic enzyme-inducing AED (phenobarbitone, phenytoin, or carbamazepine), which can accelerate vitamin D metabolism^{148,149}. Both seizures and AEDs affect the hypothalamic-pituitary-adrenal axis, which can have an adverse impact on bone health. No assessment has been made of the optimal frequency with which women on long-term AEDs should have bone density monitored. In the general population, hormone replacement therapy (combined oestrogen and progesterone) appears to have beneficial effects in postmenopausal women and it should be offered to postmenopausal women with epilepsy if it is clinically indicated¹⁵⁰.

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