Chapter 44

Epilepsy and women

JOHN CRAIG and ELLEN CAMPBELL

Department of Neurology, Belfast Health and Social Care Trust, Belfast

---

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, antiepileptic drug (AED) therapy 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

Epilepsy and AEDs are associated with changes in female hormones that may result in menstrual irregularity, reproductive problems, and abnormalities of bone health. Female hormones may also affect seizure threshold, resulting in increased frequency of seizures at certain times of the menstrual cycle.

Hormonal alterations, including changes in prolactin, follicle-stimulating hormone and luteinising hormone have been observed following generalised and focal seizures.[1] They are thought to arise as a result of connections between the hypothalamic-pituitary axis and areas of the brain involved in seizures, although the precise mechanisms are unclear[1-3]. These

hormonal problems can result in reproductive dysfunction, with the most common disorders being polycystic ovarian syndrome (PCOS) and hypothalamic amenorrhoea[1,4].

It is estimated that PCOS occurs in 20% of women with epilepsy, compared to 5% of those without. However, this relationship is complicated by the potentially confounding effects of AEDs, in particular valproate, which will be outlined later.

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.

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[5,6]. Human data tend to support this hypothesis, although there appear to be no clear differences in hormonal changes in women with and without catamenial seizures[7].

Increased seizure frequency has been reported during the follicular phase when oestrogen concentrations are highest[8]. Anovulatory cycles tend to be associated with higher seizure frequencies, in particular during times of peak oestrogen concentration[9]. 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 ovulation[10].

There is no agreement on the degree of seizure exacerbation required to meet a definition of catamenial epilepsy. Various authors have reported an increase in seizures perimenstrually, however 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 ≥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 criterion[11]. However, 31 (78%) claimed that most of their seizures occurred around the time of menstruation.

Physiological changes to gamma-aminobutyric acid A ($GABA_A$) receptor function as a result of progesterone and its active metabolite allopregnanolone withdrawal at the time of menstruation provide one possible mechanism for exacerbation of seizures perimenstrually, although other mechanisms have also been suggested[12].

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%)[13].

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 oopherectomy. In the 1950s acetazolamide became available, which is advocated by some for use in catamenial epilepsy. Data, on which this supposition is based, however are scant with conflicting views on its effectiveness[14,15].

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[16,17]. In an open study of progesterone therapy in 25 women with catamenial epilepsy 72% experienced a decline in seizure frequency[18]. Reports suggest that the reduced metabolite of progesterone, tetrahydroprogesterone, rather than progesterone itself, is responsible for improved seizure control[19-21], 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 majority[22].

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 clomiphene[23]. However, good evidence for the effectiveness of these therapeutic options is lacking.

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 epilepsy[24]. Over 35% of women with partial seizures of temporal lobe origin had anovulatory cycles when studied over three cycles, compared to 8% of controls[25]. Treatment has been tried with progesterone suppositories in the appropriate phase of the menstrual cycle[26], as well as clomiphene[23], and medroxyprogesterone[18], 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 phenobarbital had significant risk of infertility, but no such trend was observed for valproate or other AEDs[27].

Particular emphasis has been placed on valproate. In 1993, Isojarvi reported that polycystic ovaries and hyperandrogenism are frequently detected in women on valproate[28]. Subsequently they reported that these abnormalities are more common in women on valproate who gain weight[29], especially if this is during pubertal maturation[30]. However, their initial study was retrospectively based in a selected population and did not concentrate on clinical endocrine status. More recently, studies have been conflicting, reporting both significant associations between valproate and PCOS and reporting no significant associations. 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 lamotrigine[31]. 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 population[32]. 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 treatment[33]. Furthermore a subsequent study performed in monkeys did not indicate that exposure to valproate for 12–15 months induced hormonal or morphological ovarian abnormalities or characteristics of PCOS[34]. Morrell et al conducted a recent prospective, randomised, longitudinal evaluation for the impact of valproate on the development of PCOS. Women with epilepsy and regular menstrual cycles were randomised to treatment with valproate or lamotrigine and followed up for 12 months. Women taking valproate were significantly more likely to develop PCOS than those taking lamotrigine (9% vs 2% respectively, $P = 0.007$)[35]. These observations, together with data showing that valproate associated changes are reversible when valproate is discontinued[36,37] suggest that a reasonable treatment option in women who develop PCOS and/or ovulatory dysfunction while taking valproate is to consider discontinuation of the drug and treatment with an alternative AED, if possible.

Contraception

The AEDs phenobarbital, primidone, phenytoin, carbamazepine[38], topiramate[39] and eslicarbazepine acetate are inducers of the hepatic P450 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 agent[40]. 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, levonorgestrel, with the AUC reduced by 19% and maximal concentration by 12%[41]. As a result of this data, the manufacturer of lamotrigine released new guidance and the Summary of Product Characteristics (SPC) now comments that 'the possibility of reduced contraceptive effectiveness cannot be excluded'. It suggests that 'the use of alternative non-hormonal methods should be encouraged' and, 'a hormonal contraceptive should only be used as a sole method of contraception if there is no other alternative'. A statement regarding this change was issued by the Faculty of Family Planning and Reproductive Healthcare Clinical Effectiveness Unit, concluding that there was 'no evidence that lamotrigine reduces the effectiveness of hormonal contraceptives' and that 'there is no good evidence to suggest that non-hormonal methods should be used in favour of hormonal methods'[42]. Further studies in larger numbers of women are needed to clarify this possible effect.

The manufacturers of the new AED perampanel state that it is not a strong inducer or inhibitor of cytochrome P450. However there is evidence that concomitant use of the OCP with doses of perampanel 12 mg per day result in reduction in levonorgestrel exposure (AUC and mean peak serum concentration both reduced by 40%), and an 18% reduction in the mean peak serum concentration of ethinyl oestradiol, which may result in reduced efficacy of progesterone-containing oral contraceptives. No such effect was seen at lower doses[43].

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%.

Levonorgestrel implants have an increased failure rate in women taking enzyme-inducing AEDs[44], 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 level[45].

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 delineated[46]. 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 prevalence 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 teratogenicity[47].

Ideally an organised joint obstetric/neurology preconceptual 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.

Prior pregnancy outcome may be an important factor to consider during preconceptual counselling. There is some evidence that women who have previously had a child with a major malformation are at higher risk of future children also having major malformations if the same AED is taken in subsequent pregnancies. Small studies of infants with fetal anticonvulsant syndromes quoted this risk as between 39% and 55%, but more recent studies have estimated the recurrence risk of major malformations as between 15.8% and 35.7%. In studies by the UK Epilepsy and Pregnancy Register[48] and the Australian Register of Antiepileptic Drugs in Pregnancy[49] the recurrence risk for congenital malformations was higher for women taking valproate (21.9% and 57.2%) than for those on other AEDs. Women attending for preconceptual counselling who have had a previous child with a major malformation, particularly on valproate, should be informed that they may have a higher risk of major malformations in subsequent pregnancies if the AED is not changed. The magnitude of this increase in risk remains to be clarified.

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 epilepsy[50].

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 carbamazepine[51-53]. Large community-based studies have demonstrated a reduction in the rate of neural tube defects in women taking folic acid preconceptually[54-56]. 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 site[57]. 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 defect[58], or other defects associated with AEDs[59]. The potential effect of folate supplementation was reported for 4680 cases from the UK Epilepsy and Pregnancy Register[60]. 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 than those who did not (3.9% vs 2.2%; odds ratio 1.8; 95% CI 1.2–2.5). However, periconceptual folic acid was associated with a reduction in the incidence of valproate-associated neural tube defects (0.8% vs 1.6%). The EURAP pregnancy registry has reported similar findings, with

folic acid use three months prior to conception and in the first trimester carrying an odds ratio of 1.4 (95% CI 1.02–1.82, $P = 0.035$) of major congenital malformations over those not adhering to this regimen[61]. While the above results clearly do not mean that we should stop prescribing folate periconceptually to women with epilepsy they do question the validity of this approach for reducing the risk of major malformations.

Recent data from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study group has suggested that periconceptual folic acid may have a positive effect on mean IQ in infants exposed to AEDs *in utero*[62]. In this study of 225 children, periconceptual folic acid was associated with higher child IQ at age six (mean IQ 108 vs 101, $P = 0.0002$). This effect was seen across all AEDs studied (carbamazepine, lamotrigine, valproate and phenytoin). Together with results from studies in the general population showing reduced risk of severe language delay with folic acid supplementation in early pregnancy[63], and improved measures of verbal communication with preconceptual folic acid at high dose (5 mg daily)[64], these data would suggest that it may be of benefit to continue high dose folic acid supplementation throughout pregnancy.

The effects of epilepsy and AEDs on pregnancy

Data on whether women with epilepsy are at increased risk of obstetric complications are unclear. Complications that have been reported as being increased compared with control mothers are vaginal bleeding, spontaneous abortion, pre-eclampsia, and premature or prolonged labour[65]. Higher frequencies of labour induction and artificial labour have also been reported[66], 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 uncertain[67]. The adverse outcomes most consistently reported are increased stillbirths and neonatal deaths[68,69], although there is some evidence that the latter has been improving[70]. Data on whether women with epilepsy are at increased risk of early pregnancy loss are conflicting. A recent population-based study from the Danish Medical Birth Registry identified a 13 % increase in risk of spontaneous abortion in women taking AEDs during pregnancy. However, no increase in risk was seen when this analysis was limited to women with epilepsy, suggesting this effect may be due to confounding factors rather than seizures or AED consumption[71]. Clearly research into early pregnancy loss is difficult and the authors highlight that this study was designed to look only at clinically recognised pregnancies and that if AED consumption caused an increase in very early spontaneous abortion, this would not have been identified.

Since 1958 over 40 cases of neonatal bleeding associated with maternal AED treatment have been reported[72]. 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[73,74]. While there is no evidence directly linking this biochemical marker to a clinically increased risk of bleeding in the neonate, its suppression with vitamin K_1 supplementation given as 10 mg orally each day from the 36th week of gestation[75] has resulted in most guidelines for best practice advocating maternal supplementation with vitamin K_1, with all infants also being given 1 mg vitamin K_1 intramuscularly at birth[76,77]. 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)[78], although 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, early UK and other best practice guidelines recommended the prescription of 10–20 mg/day of vitamin K given orally to women with epilepsy in the last month of pregnancy[76,77],

especially if an enzyme-inducing AED is being taken. However, the American Academy of Neurology updated its practice parameter in 2009, stating that there was insufficient evidence to determine if infants born to women with epilepsy had increased risk of haemorrhagic complications, or if prenatal supplementation of vitamin K reduced these risks[79]. At present it is not possible to give oral supplementation in the UK as there is no orally available preparation of vitamin K which can be prescribed in pregnancy. At birth it is recommended, as is the case for all newborns, that infants receive vitamin K, with 1 mg of vitamin K given intramuscularly[76,77].

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 pregnancy[80].

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 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 AEDs[81].

During pregnancy total serum AED levels may fall with less marked reductions in non-protein bound (free) drug concentrations[82,83]. 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 choice[84]. 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 pregnancy[85-89]. 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 compared to preconception baseline in up to 39% of women[90].

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 monitoring[76]. 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 control[90]. Close monitoring may be effective at minimising

seizure deterioration. In a study of 42 women receiving lamotrigine, monthly monitoring followed by a 20–25% increase in lamotrigine dose if levels fell below preconception or first trimester baseline was associated with only 19% having an increased seizure frequency[91]. Whether such practices expose the fetus to additional risk has not however been established.

AED levels quickly revert to pre-pregnancy levels after birth[85]. 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. The decision to reduce the AED dosage if the increase has been made solely because of worsening seizure control during pregnancy 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 although anecdotal evidence suggests that tonic-clonic seizures may cause fetal bradycardia[92] or miscarriage but definitive data are lacking. There is no evidence that simple partial, complex partial, absence or myoclonic seizures are harmful to the fetus[93]. Likewise, prospective studies have not shown an association between tonic-clonic seizures and malformations[94,95]. 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 cased from the literature, of which nine of the mothers and 14 of the fetuses died[96]. 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 mortality[80].

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 Taiwan[97]. More recent studies of the Danish Medical Birth Registry[98] and the Medical Birth Registry of Norway[99] have also observed higher risk of infants with low birth weight (<2500 g) or small for gestational age in women with epilepsy who were taking an AED during pregnancy. In both studies this effect was most pronounced in the children of women taking topiramate, with topiramate also being associated with microcephaly in the Norwegian study. A smaller study from the Oppland Perinantal Database[100] also found increased risk of infants born to mothers with epilepsy being small for gestational age and having lower ponderal index (kg/m^3) compared to controls. This risk was highest for mothers taking carbamazepine and lamotrigine, although the numbers in individual drug groups were small. Only three pregnancies exposed to topiramate were included but these had the lowest values for mean head circumference and birth weight in the epilepsy group. Unfortunately, information on seizure control during pregnancy was not included in these studies and it remains unclear whether this effect was due to AED consumption or seizures.

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 AEDs[97,101]. 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 monotherapy[102-104]. 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 AEDs[105].

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 malformations. This is equivalent to a 4–9% chance of a major congenital malformation for each pregnancy occurring to a woman taking an AED[101, 102, 106, 107].

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. There is now also data available for the newer AEDs, with the greatest number of outcomes being reported to date for lamotrigine[108].

Barbiturates (phenobarbital, primidone) and phenytoin have been associated with congenital heart defects and facial clefts[109-111]. 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 hypoplasia[112]. The North American AED Pregnancy Registry has published data on 199 women who had used phenobarbital as monotherapy during the first trimester of pregnancy. The incidence of major birth defects was 5.5% (95% CI 2.8%–9.7%). Compared with the background risk of 1.1%, this was significantly increased (relative risk 5.1; 95% CI 1.8–14.9%)[113].

An early case-control study found the rate of major congenital malformations for 210 infants exposed to carbamazepine was approximately twice that in the control group (relative risk 2.24; 95% CI 1.1–4.56)[114]. Such an increase was not found by the UK Epilepsy and Pregnancy Register, where the major malformation rate for carbamazepine monotherapy exposures among 1657 prospectively collected pregnancies was 2.6%, with no significant increase in risk from the control group[115]. 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 pregnancies[116], 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 bifida[117].

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 Pregnancy Registry described 30 major malformations among 323 valproate-exposed women (9.3%; 95% CI 6.4–13.0%). Compared to the background prevalence of 1.1% for major malformations, they calculated a relative risk for major malformations in valproate-exposed pregnancies of 9.0 (95% CI 3.4–23.3%)[113]. 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 and the EURAP Epilepsy and Pregnancy Registry. In the UK Epilepsy and Pregnancy Register, of 1220 pregnancies exposed to valproate alone, 6.7% had a major malformation[115]. In EURAP, of 1010 pregnancies exposed to valproate alone, 98 had a major malformation (9.7%)[61]. There is also growing data to suggest that total daily dose of valproate is an important determinant for risk of major malformations. Data from all three of the main epilepsy and pregnancy registries has shown a dose-related increase in rates of major congenital malformations with higher valproate doses[61,113,115].

Studies have indicated that exposure to valproate during early pregnancy is associated with a significant incidence (1–2%) of spina bifida aperta[52,109], with the greatest risk for those exposed to doses of greater than 1000 mg per day[53]. 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 anomalies[118]), and a combination of facial dysmorphic patterns[119], 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[120,121]and preclinical studies[122]. There is also a suggestion from preclinical studies that for valproate, at least, high peak plasma concentrations are associated with an increased risk of malformations[123]. This finding was replicated in the Australian study were the mean daily dose of valproate was higher in those with a major malformation[124]. 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. This approach, however, failed to show any benefit in a retrospective analysis by the UK Epilepsy and Pregnancy Register, which showed similar rates of major congenital malformations in women taking standard valproate once daily compared to those taking prolonged-release valproate or standard-release valproate in multiple daily administrations (relative risk 1.1; 95% CI 0.7–1.8)[125]. In January 2015 the MHRA published new warnings regarding valproate exposure during pregnancy, advising that, in view of the risk of major congenital malformations and neurodevelopmental delay associated with the drug, it should not be used unless other alternatives are ineffective or not tolerated. It was also advised that valproate should be started and supervised by a clinician with experience in treating epilepsy and that the risks and benefits of treatment should be considered both on commencing valproate and frequently at subsequent reviews, especially when a girl reaches puberty and when pregnancy is being planned[126].

Considering the newer AEDs, most human data are available for lamotrigine. The International Lamotrigine Pregnancy Registry has recently reported the outcomes of 1558 first trimester lamotrigine-exposed pregnancies[108]. The percentage of outcomes exposed to lamotrigine monotherapy with major birth defects was 2.2% (95% CI 1.6–3.1%). 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 = 150) the rate of major birth defects was 10.7% (95% CI 6.4–17.0%). This compared with a rate of 2.8% (95% CI 1.5–5.0%) for polytherapy combinations which included lamotrigine but not sodium valproate (n = 430). No distinctive pattern of malformations was reported in this study. Data from the pregnancy register revealed a similar malformation rate for pregnancies exposed to lamotrigine alone, with 49 of 2098 (2.3%) infants having a major congenital malformation. In contrast to earlier results, only a small dose-response was seen, with 3.4% of pregnancies exposed to more than 400 mg a day of lamotrigine having a major congenital malformation, compared to 2.1% of those exposed to less than 200 mg daily[115]. This did not reach statistical significance. A positive dose-response has not been reported by some other registers including the International Lamotrigine Registry[108]. The North American Pregnancy Register reported a total of 31 (2.0%) of 1562 infants exposed to lamotrigine to have a major congenital malformation. No dose response was found but a 10.4-fold (95% C.I. 4.3–24.9) increase in the rate of clefting abnormalities was noted[127]. In contrast the UK Epilepsy and Pregnancy Register[115,128] and the European Surveillance of Congenital Anomalies found no evidence of increased isolated oro-facial clefts relative to other major congenital malformations for lamotrigine[129].

Reported data on the other new AEDs are sparse. The North American AED Pregnancy Registry has reported four major malformations of 182 first trimester exposures to oxcarbazepine (2.2%)[113]. These are similar to figures published by EURAP, reporting six malformations of 184 pregnancies (3.3%) exposed to oxcarbazepine[61]. Another report of 55 exposures to oxcarbazepine (35 monotherapy and 20 polytherapy) noted only one major malformation[130]. 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 reported[131]. 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 pregnancy[132]. 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 delivery[133]. Preliminary data for topiramate appears concerning. 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' gestation[134]. 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 major congenital malformation, of which two were clefting abnormalities and one a case of hypospadias[135]. Results from the North American AED Pregnancy Registry (15 from 359 pregnancies, 4.2%)[113] and EURAP (five from 73 pregnancies, 6.8%)[61] were similarly concerning, and in 2011 topiramate was reclassified as a category D drug by the FDA to reflect these results. Earlier results published by the North American AED Pregnancy Registry in abstract form were in keeping with results from the UK Epilepsy and Pregnancy Register, with two of eight major congenital malformations from 197 exposures to topiramate being cleft lip deformities[136]. More recent population-based studies from Norway[98] and Denmark[99] have also suggested an association between topiramate exposure in pregnancy and fetal growth restriction, infants being born small for gestational age and microcephaly. Increasing data is now available for levetiracetam. The UK Epilepsy and Pregnancy Register reported a 0.7% risk of major malformations from 304 pregnancies exposed to levetiracetam in monotherapy[137]. Similarly reassuring results have also been published by the North American AED Pregnancy Registry (11 from 450 pregnancies, 2.4%)[113] and EURAP (two from 126 pregnancies, 1.6%)[61]. Collation of many more pregnancies would clearly be beneficial to clarify the safety of these AEDs in pregnancy.

For zonisamide data for exposed pregnancies is limited. Animal and early human studies previously raised concerns regarding use of zonisamide during pregnancy. However, data recently published by the North American AED Pregnancy Registry is less concerning, with no malformations observed among 90 monotherapy-exposed pregnancies (95 % CI 0–3.3)[113]. Study of much larger numbers of pregnancies is required to confirm the validity of these findings.

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 being observed in rats and rib and vertebral malformations in rabbits. Vigabatrin was also shown to be teratogenic in rabbits, inducing cleft defects[138]. 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 toxicity[139]. 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 anomalies[140], and specific AED-related fetal syndromes have been suggested for most of the older AEDs[129,120,141]. The types of abnormalities found have included minor craniofacial and digital anomalies and growth retardation. However, possibly except for valproate[120,142], 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, although undesirable, have usually been felt in themselves to cause little disability. However, whether or not they are markers for more diffuse problems, cognitive and behavioral upset is increasingly being questioned in particular.

The effects of AEDs on long-term cognitive functioning of children exposed to AEDs *in utero* have not been studied as extensively as major congenital malformations. An early Cochrane review concluded 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 development[143]. While previous studies have shown mean IQ to be significantly lower in the children of women with epilepsy[68,144,145] 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. There is also an increasing body of evidence to suggest that these effects vary by AED exposure, with valproate consistently being associated with poorer outcomes, which are likely to persist long term. 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%)[146]. 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 valproate[147]. 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%[143,148,149]. 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 AEDs[150].

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 levels[151].

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 epilepsy[152]. 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 epilepsy[153].

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 assessed IQ and multiple other cognitive domains in children at six years of age. Mean IQ in the valproate group was reduced by 11 points compared with the lamotrigine group, 11 points compared with the phenytoin group and 8 points compared with the carbamazepine group[62]. The association between valproate use and IQ was dose dependent. Fetal valproate exposure was also significantly associated with a wide range of cognitive deficits, including reduced measures of verbal ability, non-verbal ability, memory and executive function that were also dose-related. 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 is associated with worse cognitive outcomes compared with lamotrigine and carbamazepine, in particular with regard to language skills, has also recently been reported by other authors[154-157]. A Cochrane review published in 2014 included 22 prospective cohort studies and six registry-based studies. It concluded that the IQ of children exposed to valproate during pregnancy was lower than in children born to women without epilepsy or with untreated epilepsy. IQ for children exposed to valproate was on average 8.69 points lower than those exposed to carbamazepine, 10.8 points lower than those exposed to lamotrigine and 9.25 points lower compared to phenytoin, with a dose effect being reported in six studies. The magnitude of these results was felt to be sufficient to affect educational and occupational outcomes later in life. No significant association was found between carbamazepine exposure and development quotient or IQ[158].

Recent data published by the Liverpool and Manchester Neurodevelopment Group suggests that there may also an association between AED use during pregnancy and other neurodevelopmental disorders such as Aspergers, ADHD, autistic spectrum disorders (ASD) and dyspraxia. Neurodevelopmental disorders were more frequently seen in the children of women with epilepsy (15 of 201, 7.46%) compared to control women (four of 214, 1.87%). Although the numbers in each group were small, a differential effect of AED exposure was seen, with valproate exposure being associated with an odds ratio for neurodevelopmental disorders of 6.05 compared to the control group ($P = 0.007$). Lamotrigine was also associated with a higher incidence of neurodevelopmental disorders than the control group (6.67%, odds ratio 4.06), but this was not statistically significant ($P = 0.1$)[159].

Similar results were described in a recent population-based study from Denmark, which also found a higher incidence of ASD and childhood autism in children exposed to valproate during pregnancy. In this study, from all children born alive in Denmark from 1996 to 2006 (total 665,615) 5437 children were identified with ASD, including 2067 with childhood autism. In this population, 2644 were exposed to AEDs during pregnancy and 508 were exposed to valproate. In women with epilepsy, the use of valproate during pregnancy was associated with an increased absolute risk for ASD (4.15%; 95% CI 2.20–7.81%) and

childhood autism (2.95%; 95% CI 1.42–6.11%) compared to those exposed to other AEDs (2.44%; 95% CI 1.88–3.16% and 1.02%; 95% CI 0.70–1.49% respectively). Exposure to carbamazepine, lamotrigine, oxcarbazepine or clonazepam was not associated with a significantly higher risk for these disorders[160].

Data for the other newer AEDs are restricted to levetiracetam. Studies from the Liverpool and Manchester Neurodevelopmental Group and the UK Epilepsy and Pregnancy Register, which compared cognitive development up to three years of age 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 worse[161].

Management of labour and postpartum management of mother and child

Most women with epilepsy will have a normal uncomplicated vaginal delivery[65]. 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[102,162]. 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[76,77].

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 yet[163], 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 noted[164]. For levetiracetam, plasma concentrations in breastfed infants are low despite extensive transfer of levetiracetam into breast milk[165].

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, albeit the numbers studied were small. At age six years, breastfed children had higher IQ and enhanced verbal abilities compared to those that were not breastfed. The analysis found no evidence of an adverse effect on cognitive development either for all AEDs combined or for those exposed to the individual AEDs studied (phenytoin, carbamazepine, lamotrigine or valproate)[166].

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, and carbamazepine), which can accelerate vitamin D metabolism[167,168]. Both seizures and AEDs affect the hypothalamic-pituitary-adrenal axis, which can have an adverse impact on bone health. No assessment has been made on 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 indicated[169].

References

1. LUEF G (2010) Hormonal alterations following seizures. *Epilepsy Behav* 19, 131-133.
2. PACK AM, REDDY DS, DUNCAN S, HERZOG A (2011) Neuroendocrinological aspects of epilepsy: Important issues and trends for future research. *Epilepsy Behav* 94, 102-122.
3. VEROTTI A, D'EGIDIO C, MOHN A, COPPOLA G, PARISI P, CHIARELLI F (2011) Antiepileptic drugs, sex hormones, and PCOS. *Epilepsia* 52(2), 199-211.
4. PACK AM (2010) Implications of hormonal and neuro-endocrine changes associated with seizures and antiepilepsy drugs: a clinical perspective. *Epilepsia* 51(Suppl.3). 150-153.
5. LOGOTHETIS J, HARNER R, MORRELL F, TORRES F (1958) The role of estrogens in catamenial exacerbation of epilepsy. *Neurology* 9, 353-360.
6. BACKSTROM T, ZETTERLUND B, BLOM S, ROMANO M (1984) Effects of intravenous progesterone infusions on the epileptic discharge frequency in women with partial epilepsy. *Acta Neurol Scand* 69, 240-248.
7. BETTS T and CRAWFORD PM (1999) *Epilepsy in Women.* Martin Dunitz, London.
8. BACKSTROM T (1976) Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle. *Acta Neurol Scand* 54, 321-347.
9. MATTSON RH, KRAMER JA, CALDWELL BVV et al (1981) Seizure frequency and the menstrual cycle: a clinical study. *Epilepsia* 22, 242.
10. HERZOG AG, KLEIN P and RANSIL BJ (1997) Three patterns of catamenial epilepsy. *Epilepsia* 38, 1082-1088.
11. DUNCAN S, READ CL, BRODIE MJ (1993) How common is catamenial epilepsy? *Epilepsia* 34, 827-831.
12. REDDY DS, ROGAWSKI MA (2009) Neurosteroid replacement therapy for catamenial epilepsy. *Neurotherapeutics* 6, 392-401.
13. ROSCISZEWSKA D, BUNTNER B, GUZ I et al (1986) Ovarian hormones, anticonvulsant drugs and seizures during the menstrual cycle in women with epilepsy. *J Neurol Neurosurg Psychiatr* 49, 47-51.
14. CRAWFORD PM (1991) Catamenial epilepsy. In: *Epilepsy and Women* (Ed. MR Trimble), pp.159-165. J. Wiley & Sons, Chichester.
15. LIM LL, FOLDVARY N, MASCHA E, LEE J (2001) Acetazolamide in women with catamenial epilepsy. *Epilepsia* 42, 746-749.
16. DANA-HAERI J, RICHENS A (1983) Effects of norethisterone on seizures associated with menstruation. *Epilepsia* 24, 377-381.
17. HERZOG AG (1999) Progesterone therapy in women with epilepsy: a 3-year follow-up. *Neurology* 52, 1917-1918.
18. MATTSON RH, CRAMER JA, CALDWELL BV et al (1984) Treatment of seizures with medroxyprogesterone acetate: preliminary report. *Neurology (Cleveland)* 34, 1255-1258.
19. HERZOG AG, FRYE CA (2003) Seizure exacerbation associated with inhibition of progesterone metabolism. *Ann Neurol* 53, 390-391.
20. REDDY DS, CASTANEDA DC, O'MALLEY BW, ROGAWSKI MA (2004) Anticonvulsant activity of progesterone and neurosteroids in progesterone receptor knockout mice. *J Pharmacol Exp Ther* 310, 230-239.
21. HERZOG AG, FRYE CA (2003) Seizure exacerbation associated with inhibition of progesterone metabolism. *Ann Neurol* 53, 390-391.
22. FEELY M, GIBSON J (1984) Intermittent clobazam for catamenial epilepsy: tolerance avoided. *J Neurol Neurosurg Psychiatry* 47, 1279-1282.
23. HERZOG AG (1988) Clomiphene therapy in epileptic women with menstrual disorders. *Neurology* 38, 432-434.
24. HERZOG AG, SEIBEL MM, SCHOMER DL, VAITUKAITIS JL, GESCHWIND N (1986) Reproductive endocrine disorders in women with partial seizures of temporal lobe origin. *Arch Neurol* 43, 341-345.
25. CUMMINGS LN, GIUDICE L, MORRELL MJ (1995) Ovulatory function in epilepsy. *Epilepsia* 36, 353-357.
26. HERZOG AG (1986) Intermittent progesterone therapy and frequency of complex partial seizures in women with menstrual disorders. *Neurology* 36, 1607-1610.
27. SUKUMARAN SC, SARMA PS, THOMAS SV (2010) Polytherapy increases the risk of infertility in women with epilepsy. *Neurology* 75, 1351-1355.
28. ISOJARVI JI, LAATIKAINEN TJ, PAKARINEN AJ, JUNTUNEN KT, MYLLYLA VV (1993) Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med* 329, 1383-1388.

29. ISOJARVI JI, LAATIKAINEN TJ, KNIP M, PAKARINEN AJ, JUNTUNEN KT, MYLLYLA VV (1996) Obesity and endocrine disorders in women taking valproate for epilepsy. *Ann Neurol* 39, 579-584.
30. VAINIONPAA LK, RATTYA J, KNIP M et al (1999) Valproate-induced hyperandrogenism during pubertal maturation in girls with epilepsy. *Ann Neurol* 45, 444-450.
31. BETTS T, YARROW H, DUTTON N et al (2003) A study of anticonvulsant medication on ovarian function in a group of women with epilepsy who have only ever taken one anticonvulsant compared with a group of women without epilepsy. *Seizure* 12, 323-329.
32. MURIALDO G, GALIMBERTI CA, MAGRI F et al (1997) Menstrual cycle and ovary alterations in women with epilepsy on antiepileptic therapy. *J Endocrinol Invest* 20, 519-526.
33. BAUER J, JARRED A, KLINGMULLER D, ELGER CE (2000) Polycystic ovary syndrome in patients with focal epilepsy: a study in 93 women. *Epilepsy Res* 41, 163-167.
34. FERIN M, MORRELL M, XIAO E et al (2003) Endocrine and metabolic responses to long-term monotherapy with the antiepileptic drug valproate in the normally cycling rhesus monkey. *J Clin Endocrinol Metab* 88, 2908-2915.
35. MORRELL MJ, HAYES FJ, SLUSS PM et al (2008) Hyperandrogenism, ovulatory dysfunction, and polycystic ovary syndrome with valproate versus lamotrigine. *Ann Neurol* 64, 200-211.
36. ISOJARVI JI, RATTYA J, MYLLYLA VV et al (1998) Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. *Ann Neurol* 43, 446-451.
37. MIKKONEN K, VAINIONPAA LK, PAKARINEN AJ et al (2004) Long-term reproductive endocrine health in young women with epilepsy during puberty. *Neurology* 62(3), 445-450.
38. COULAM BB, ANNEGERS JF (1979) Do anticonvulsants reduce the efficacy of oral contraceptives? *Epilepsia* 20, 519-526.
39. ROSENFELD WE, DOOSE DR, WALKER SA et al (1997) Effects of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia* 38, 317-323.
40. BARUZZI A, ALBANI R, RIVA R (1994) Oxcarbazepine: pharmacokinetic interactions and their clinical relevance. *Epilepsia* 35 (suppl 3), S14-S19.
41. SIDHU J, BULSARA S, JOB S et al (2004) A bidirectional pharmacokinetic interaction study of lamotrigine and the combined oral contraceptive pill in healthy subjects. *Epilepsia* 45 (suppl 7), 330.
42. www.fsrh.org/pdfs/CEUStatementADC0110.pdf
43. www.fsrh.org/pdfs/CEUstatementUpdateNewerAntiepilepticAntiretroviralDrugs.pdf
44. HAUKKAMAA M (1986) Contraception by Norplant subdermal capsules is not reliable in epileptic patients on anticonvulsant therapy. *Contraception* 33, 559-565.
45. SABERS A, BUCHOLT JM, ULDALL P, HANSEN EL (2001) Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Res* 47, 151-154.
46. Scottish Obstetric Guidelines and Audit Project (1997) The management of pregnancy in women with epilepsy. SPC & RLI Publications, No. 5. UPDATE.
47. BELL GS, NASHEF L, KENDALL S et al (2002) Information recalled by women taking anti-epileptic drugs for epilepsy: a questionnaire study. *Epilepsy Res* 52, 139-146.
48. CAMPBELL E, DEVENNEY E, MORROW J et al (2013) Recurrence risk of congenital malformations in infants exposed to antiepileptic drugs in utero. *Epilepsia* 54(1), 165-171.
49. VADJA F, O'BRIEN T, LANDER CM, GRAHAM J, ROTEN A, EADIE MJ (2013) Teratogenesis in repeated pregnancies in antiepileptic drug treated women. *Epilepsia* 54(1), 181-186.
50. SHORVON S (1995) The classical genetics of the epilepsies. In: *Epilepsy*, 2nd Edition (Eds A Hopkins, S Shorvon and G Cascino), pp.87-92. Chapman & Hall, London.
51. ROSA FW (1991) Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Eng J Med* 324, 674-677.
52. OMTZIGT JG, LOS FJ, GROBBEE DE et al (1992) The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. *Neurology* 42 (suppl 5), 119-125.
53. LINDHOUT D, OMTZIGT JGC, CORNEL MC (1992) Spectrum of neural-tube defects in 34 infants prenatally exposed to antiepileptic drugs. *Neurology* 42 (suppl 5), 111-118.
54. MEDICAL RESEARCH COUNCIL RESEARCH GROUP (MRC) VITAMIN STUDY RESEARCH GROUP (1991) Prevention of neural-tube defects: results of the Medical research council vitamin study. *Lancet* 338, 131-137.
55. CZEIZEL AE, DUDAS I (1992) Prevention of the first occurrence of neural-tube defects by periconceptual vitamin supplementation. *N Engl J Med* 327, 1832-1835.
56. ROSENBERG IH (1992) Folic acid and neural-tube defects – time for action? *N Engl J Med* 327, 1875-1876.
57. VAN ALLEN MI, KALOUSEK DK, CHERNOFF GF et al (1993) Evidence for multi-site closure of the neural tube in humans. *Am J Med Genet* 47, 723-743.
58. CRAIG J, MORRISON P, MORROW J et al (1999) Failure of periconceptual folic acid to prevent a neural tube defect in the offspring of a mother taking sodium valproate. *Seizure* 8, 253-254.
59. HERNANDEZ-DIAZ S, WERLER MM, WALKER AM, MITCHELL AA (2000) Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med* 343, 1608-1614.
60. MORROW JI, HUNT SJ, RUSSELL AJ, et al (2008) Folic acid use and congenital malformations in offspring of women with epilepsy. A prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 80, 506-511.
61. TOMSON T, BATTINO D, BONIZZONI E et al For the EURAP Study Group (2011) Dose-dependent risk of malformations with anti-epileptic drugs: an analysis from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* 10, 609-617.

62. MEADOR KJ, BAKER GA, BROWNING N (2013) Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 12, 244-252.
63. ROTH C, MAGNUS P, SCHJOLBERG S et al (2011) Folic acid supplements in pregnancy and severe language delay in children. *JAMA* 306(14), 1566-1573.
64. CHATZI L, PAPADOPOULOU E, KOUTRA K et al (2012) Effect of high doses of folic acid supplementation in early pregnancy on child neurodevelopment at 18 months of age: the mother-child cohort 'Rhea' study in Crete, Greece. *Public Health Nutr* 15(9), 1728-1736.
65. SABERS A: Complications during pregnancy and delivery. In: *Epilepsy and Pregnancy.* Tomson T, Gram L, Sillanpaa M, Johannessen SI (Eds) Wrightson Biomedical Publishing Ltd, Petersfield, UK (1997): 105-111.
66. YERBY M, KOEPSELL T, DALING J (1985) Pregnancy complications and outcomes in a cohort of women with epilepsy. *Epilepsy* 26, 631-635.
67. HIILESMAA VK, BARDY A, TERAMO K (1985) Obstetric outcome in women with epilepsy. *Am J Obstet Gynecol* 152, 499-504.
68. NELSON KB, ELLENBERG JH (1982) Maternal seizure disorder, outcome of pregnancy, and neurologic abnormalities in the children. *Neurology* 32, 1247-1254.
69. YERBY MS, CAWTHORN L (1994) Mortality rates in infants of mothers with epilepsy. *Ann Neurol* 36, 330.
70. MARTIN PJ, MILLAC PAH (1993) Pregnancy, epilepsy, management and outcome: a 10 year perspective. *Seizure* 2, 277-280.
71. BECH BH, KJAERSGAARD MIS, PEDERSEN HS et al (2014) Use of antiepileptic drugs during pregnancy and risk of spontaneous abortion and stillbirth: population based cohort study. *BMJ* 349, g5159.
72. LAOSOMBAT V (1988) Hemorrhagic disease of the newborn after maternal anticonvulsant therapy: a case report and literature review. *J Med Assoc Thai* 71, 643-648.
73. CORNELISSEN M, STEEGERS-THEUNISSEN R, KOLLEE L et al (1993) Increased incidence of neonatal vitamin K deficiency resulting from maternal anticonvulsant therapy. *Am J Obstet Gynecol* 168, 923-928.
74. HOWE AM, OAKES DJ, WOODMAN PDC, WEBSTER WS (1999) Prothrombin and PIVKA-II levels in cord blood from newborns exposed to anticonvulsants during pregnancy. *Epilepsia* 40, 980-984.
75. CORNELISSEN M, STEEGERS-THEUNISSEN R, KOLLEE L, ESKES T, MOTOHARA K, MONNENS L (1993) Supplementation of vitamin K in pregnant women receiving anticonvulsant therapy prevents neonatal vitamin K deficiency. *Am J Obstet Gynecol* 168, 884-888.
76. QUALITY STANDARDS SUBCOMMITTEE OF THE AMERICAN ACADEMY OF NEUROLOGY (1998) Practice parameter: Management issues for women with epilepsy (summary statement). *Neurology* 51, 944-948.
77. CRAWFORD P, APPLETON R, BETTS T et al (1999) Best practice guidelines for the management of women with epilepsy. *Seizure* 8, 201-217.
78. KAAJA E KAAJA R, MATILA R, HIILESMAA V. Enzyme-inducing antiepileptic drugs in pregnancy and the risk of bleeding in the neonate. *Neurology* 58, 549-553.
79. HARDEN CL, PENNELL PB, KOPPEL S et al (2009) Practice parameter update: management issues for women with epilepsy- Focus on pregnancy (an evidence based review): Vitamin K, folic acid, blood levels and breastfeeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 73, 142-149.
80. THE EURAP STUDY GROUP (2006) Seizure control and treatment in pregnancy. Observations from the EURAP Epilepsy Pregnancy Registry. *Neurology* 66, 354-360.
81. WILLIAMS J, MYSON V, STERARD S et al (2002) Self-discontinuation of antiepileptic medication in pregnancy: detection by hair analysis. *Epilepsia* 43, 824-831.
82. PERUCCA E, CREMA A (1982) Plasma protein binding of drugs in pregnancy. *Clin Pharmacokinet* 7, 336-352.
83. LANDER CM, EADIE MJ (1991) Plasma antiepileptic drug concentrations during pregnancy. *Epilepsia* 32, 257-266.
84. YERBY MS, FRIEL PN, MCCORMACK K: Antiepileptic drug disposition during pregnancy. *Neurology* (1992) 42 (Suppl 5):12-16.
85. TOMSON T, OHMAN I, VITOLS S. (1997) Lamotrigine in pregnancy and lactation: a case report. *Epilepsia* 38, 1039-41.
86. OHMAN I, VITOLS S, TOMSON (2000) Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia* 41, 709-713.
87. TRAN TA, LEPPIK IE, BLESI K et al (2002) Lamotrigine clearance during pregnancy. *Neurology* 59, 251-255.
88. PENNELL PB, NEWPORT DJ, STOWE ZN et al (2004) The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology* 62, 292-295.
89. DEHAAN GJ, EDELBROEK P, SEGERS J et al (2004) Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology* 63, 571-573.
90. PENNELL PB, PENG L, NEWPORT DJ, et al (2008) Lamotrigine in pregnancy. Clearance, therapeutic drug monitoring and seizure frequency. *Neurology* 70, 2130-2136.
91. SABERS A, PETRENAITE V (2009) Seizure frequency in pregnant women treated with lamotrigine monotherapy. *Epilepsia* 50, 2163-2166.
92. TERAMO K, HIILESMAA V, BARDY A, SAARIKOSKI S (1979) Fetal heart rate during a maternal grandmal epileptic seizure. *J Perinat Med* 7, 3-6.
93. DEVINSKY O, YERBY MS (1994) Women with epilepsy: reproduction and effects of pregnancy on epilepsy. *Neurologic Clinics* 12, 479-495.

94. GAILY E, GRANSTROM ML, HIILESMAA V, BARDY A (1988) Minor abnormalities in children of mothers with epilepsy. *J Paediatr* 112, 520-529.
95. STEEGERS-THEUNISSEN RP, RENIER WO, BORM GF et al (1994) Factors influencing the risk of abnormal pregnancy outcome in epileptic women: a multicentre prospective study. *Epilepsy Res* 18, 261-269.
96. TERAMO K, HIILESMAA V (1982) Pregnancy and fetal complications in epileptic pregnancies. In: *Epilepsy, Pregnancy and the Child.* Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D (Eds.), Raven Press, New York, USA, 53-59.
97. CHEN Y-H, CHIOU H-Y, LIN H-C, LIN H-L (2009) Effect of seizures during gestation on pregnancy outcomes in women with epilepsy. *Arch Neurol* 66, 979-984.
98. KILIC D, PEDERSEN H, KJAERSGAARD MI et al (2014) Birth outcomes after prenatal exposure to antiepileptic drugs – a population based study. *Epilepsia* 55(11), 1714-1721.
99. VEIBY G, DALTVEIT AK, ENGELSEN BA, GILHUS NE (2014) Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. *J Neurol* 261, 579-588.
100. FARMEN AH, GRUNDT J, TOMSON T et al (2015) Intrauterine growth retardation in foetuses of women with epilepsy. *Seizure* 28, 76-80.
101. SAMREN EB, VAN DUIJN CM, CHRISTIAENS L, HOFMAN A, LINDHOUT D (1999) Antiepileptic drug regimes and major congenital abnormalities in the offspring. *Ann Neurol* 46, 739- 746.
102. DELGADO-ESCUTA AV, JANZ D: (1992) Consensus guidelines: preconception counselling, management, and care of the pregnant woman with epilepsy. *Neurology* 42 (Suppl 5), 149-160.
103. JANZ D (1994) Are antiepileptic drugs harmful when taken during pregnancy? *J Perinat Med* 22, 367-377.
104. HOLMES LB, HARVEY EA, COULL BA et al (2001) The teratogenicity of anticonvulsant drugs. *N Engl J Med* 344, 1132-1138.
105. FINNELL RH, DANSKY LV (1991) Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades; 1: animal studies. *Reprod Toxicol* 5, 281-299.
106. SAMREN EB, VAN DUIJIN C, KOCH S et al (1997) Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 38, 981-990.
107. OLAFSSON E, HALLGRIMSSON JT, HAUSER WA, LUDVIGSSON P, GUDMUNDSSON G (1998) Pregnancies of women with epilepsy: a population-based study in Iceland. *Epilepsia* 39, 887-892.
108. CUNNINGTON MC, WEIL JG, MESSENHEIMER JA, FERBER S, YERBY, M, TENNIS P (2011) Final results from 18 years of the International Lamotrigine Pregnancy Registry. *Neurology* 76, 1817-1823.
109. ARPINO C, BRESCIANINI S, ROBERT E et al (2000) Teratogenic effects of antiepileptic drugs: use of an international database on malformations and drug exposure (MADRE). *Epilepsia* 41, 1436-1443.
110. ANDERSON RC (1976) Cardiac defects in children of mothers receiving anticonvulsant therapy during pregnancy. *J Pediatr* 89, 318-319.
111. HIRSCHBERGER M, KLEINBERG F (1975) Maternal phenytoin ingestion and congenital abnormalities: report of a case. *Am J Dis Child* 129, 984.
112. HANSON JW, SMITH DW (1975) The fetal hydantoin syndrome. *J Pediatr* 87, 285-290.
113. HERNANDEZ-DIAZ S, SMITH CR, SHEN A et al For the North American AED Pregnancy Registry; North American AED (Antiepileptic Drug) Pregnancy Registry; Scientific Advisory Committee; North American AED Pregnancy Registry (2012) Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 78(21), 1692-1699.
114. DIAV-CITRON O, SHECHTMAN S, ARNON J, ORNOY A (2001) Is carbamazepine teratogenic? A prospective controlled study of 210 pregnancies. *Neurology* 57, 321-324.
115. CAMPBELL E, KENNEDY F, RUSSELL A et al (2014) Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neurosurg Psychiatry* 85(9), 1029-1034.
116. GRANSTROM ML, HIILESMAAN VK (1992) Malformations and minor anomalies in children of epileptic mothers: preliminary results of the prospective Helsinki study. In: *Epilepsy, Pregnancy and the Child.* Janz D, Dam M, Richens A, Bossi L, Helge H and Schmidt D (Eds.), Raven Press, New York, USA, 251-258.
117. JENTINIK J, DOLK H, LOANE MA et al For the EUROCAT Antiepileptic Study Working Group (2010) Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study. *BMJ* 341, c6581.
118. KOCH S, LOSCHE G, JAGER-ROMAN E et al (1992) Major birth malformations and antiepileptic drugs. *Neurology* 42(suppl 5):83-88.
119. DILIBERTI JH, FARNDON PA, DENNIS NR, CURRY CJR (1984) The fetal valproate syndrome. *Am J Med Genet* 19, 473-481.
120. DUNCAN S, MERCHO S, LOPES-CENDES I et al (2001) Repeated neural tube defects and valproate monotherapy suggest a pharmacogenetic abnormality. *Epilepsia* 42, 750-753.
121. MALM H, KAJANTIE E, KIVIRIKKO S (2002) Valproate embryopathy in three sets of siblings: Further proof of hereditary susceptibility. *Neurology* 59, 630-633. Report of three families with recurring fetal valproate syndrome.
122. FAIELLA A, WERNIG M, CONSALEZ GC (2000) A mouse model for valproate teratogenicity: parental effects, homeotic transformations, and altered HOX expression. *Hum Molecular Genet* 9, 227-236.
123. NAU H (1985) Teratogenic valproic acid concentrations: infusion by implanted minipumps vs conventional injection regimen in the mouse. *Toxicol Appl Pharmacol* 80, 243-250.
124. VAJDA FJ, GRAHAM JE, HITCHCOCK AA et al (2010) Is lamotrigine a significant human teratogen? Observations from the Australian Pregnancy Register. *Seizure* 19, 558-561.

125. MAWHINNEY E, CAMPBELL J, CRAIG J et al (2012) Valproate and the risk for congenital malformations: Is formulation and dosage regime important? *Seizure* 21, 215-218.
126. MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AUTHORITY (2015) Medicines related to valproate: risk of abnormal pregnancy outcomes. https://www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes#treatment-during-pregnancy
127. HOLMES LB, BALDWIN EJ, SMITH CR et al (2008) Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 70, 2152-2158.
128. MORROW J, RUSSELL A, GUTHRIE E et al (2006) Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 77, 193-198.
129. DOLK H, JENTINK J, LOANE M, MORRIS J, JONG-VAN DEN BERG LT On behalf of the EUROCAT Antiepileptic Drug Working Group (2008) Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? Neurology 71, 706-7.
130. MEISCHENGUISER R, D'GIANO CH, FERRARO SM (2004) Oxcarbazepine in pregnancy: clinical experience in Argentina. *Epilepsy Behavior* 5, 163-167.
131. MONTOURIS G (2005) Safety of the newer antiepileptic drug oxcarbazepine during pregnancy. *Curr Med Res Opin* 21, 693-702.
132. WILTON LV, SHAKIR S (2002) A post-marketing surveillance study of gabapentin as add-on therapy for 3,100 patients in England. *Epilepsia* 43, 951-955.
133. LEPPIK I, GRAM L, DEATON R, SOMMERVILLE K (1999) Safety of tiagabine: summary of 53 trials. *Epilepsy Res* 33, 235-246.
134. OHMAN I, VITOLS S, LUEF G, SODERFELDT B, TOMSON T et al (2002) Topiramate kinetics during delivery, lactation and in the neonate: preliminary observations. *Epilepsia* 43, 1157-1160.
135. HUNT S, RUSSELL A, SMITHSON WH et al (2008) Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 22, 272-276.
136. HOLMES LB, SMITH CR, HERNANDEZ-DIAZ S (2008) Pregnancy Registries: Larger sample sizes essential. *Birth Defects Research (Part A)* 82, 307.
137. MAWHINNEY E, CRAIG J, MORROW J et al (2013) Levetiracetam in pregnancy: results from the UK and Ireland Epilepsy and Pregnancy registers. *Neurology* 80(4), 400-4055.
138. LINDHOUT D, OMTZIGT JGC (1994) Teratogenic effects of antiepileptic drugs: Implications for the management of epilepsy in women of the child bearing age. *Epilepsia* 35 (suppl 4), 19-28.
139. PETRERE JA, ANDERSON JA (1994) Developmental toxicity studies in mice, rats and rabbits with the anticonvulsant gabapentin. *Fund Appl Toxicol* 23, 585-589.
140. NULMAN I, SCOLNIK D, CHITAYAT D, FARKAS L, KOREN G (1997) Findings in children exposed in utero to phenytoin and carbamazepine monotherapy: independent effects of epilepsy and medications. *Am J Med Genet* 68, 18-24.
141. RUDD NL, FREEDOM RM (1979) A possible primidone embryopathy. *J Pediatr* 94, 835-837.
142. JAGER-ROMAN E, DEICHL A et al (1986) Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid. *J Pedriatr* 108, 997-1004.
143. ADAB N, TUDUR SC, VINTEN J et al (2003) Common Antiepileptic Drugs in Pregnancy in Women with Epilepsy (Cochrane review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd; Issue 3.
144. GAILY E, KANTOLA-SCORSA E, GRANSTROM ML (1988) Intelligence of children of epileptic mothers. *J Pediatr* 113, 677-684.
145. SCOLNIK D, NULMAN I, ROVET J et al (1994) Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. *JAMA* 271, 767-770.
146. ADAB N, JACOBY A, SMITH D, CHADWICK D (2001) Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 70, 15-21.
147. ADAB N, KINI U, VINTEN J et al (2004) The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 75, 1575-1583.
148. JONES KLJ, LACRO RV, JOHNSON KA, ADAMS J (1989) Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med* 320, 1661-1666.
149. ORNOY A, COHEN E (1996) Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 75, 517-520.
150. DEAN JCS, HAILEY H, MOORE SJ, LLOYD DJ, TURNPENNY PD, LITTLE J (2002) Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. *J Med Genet* 39, 251-259.
151. ERIKSSON K, VIINIKAINEN K, MONKKONEN A et al (2005) Children exposed to valproate in utero-population based evaluation of risks and confounding factors for long-term neurocognitive development. *Epilepsy Res* 65, 189-200.
152. THOMAS SV, AJAYKUMAR B, SINDHU L, NAIR MK, GEORGE B, SARMA PS (2008) Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy Behav* 13, 229-236.
153. THOMAS SV, SUKUMARAN S, LUKOSE N, GEORGE A, SARMA PS (2007) Intellectual and language functions in children in mothers with epilepsy. *Epilepsia* 48, 2234-40.
154. MCVEARRY KM, GAILLARD WD, VANMETER J, MEADOR KJ (2009) A prospective study of cognitive fluency and originality in children exposed in utero to carbamazepine, lamotrigine, or valproate monotherapy. *Epilepsy Behav* 16, 609-616.
155. BROMLEY RL, MAWER G, LOVE J, et al (2010) Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 51, 2058-2065.
156. NADEBAUM C, ANDERSON VA, VADJA F, REUTENS DC, BARTON S, WOOD AG (2011) Language skills of school-aged children prenatally exposed to antiepileptic drugs. *Neurology* 76, 719-726.

157. BAKER GA, BROMLEY RL, BRIGGS M et al (2015) IQ at 6 years after in utero exposure to antiepileptic drugs. *Neurology* 84, 382-90.
158. BROMLEY RL, WESTON J, ADAB N et al (2014) Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. (Cochrane review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd; Issue 10.
159. BROMLEY RL, MAWER GE, BRIGGS M et al (2013) The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry* 84(6), 637-643.
160. CHRISTENSEN J, GRONBORG TK, SORENSEN MJ et al (2013) Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 309(16), 1696-1703.
161. SHALLCROSS R, BROMLEY RL, CHEYNE CP et al. (2014) In utero exposure to levetiracetam vs valproate: development and language at 3 years of age. *Neurology* 82, 213-221.
162. BARDY A (1982) Epilepsy and Pregnancy. A prospective study of 154 pregnancies in epileptic women. University of Helsinki, Helsinki, Finland.
163. BAR-OZ B, NULMAN I, KOREN G, ITO S (2000) Anticonvulsants and breast feeding: a critical review. *Paediatr Drugs* 2, 113-126.
164. RAMBECK B, KURLEMANN G, STODIECK SRG, MAY TW, JURGENS U (1997) Concentrations of lamotrigine in a mother on lamotrigine treatment and her newborn child. *Eur J Clin Pharmacol* 51, 481-484.
165. TOMSON T, PALM R, KALLEN K et al (2007) Pharmacokinetics of Levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 48, 1111-1116.
166. MEADOR KJ, BAKER GA, BROWNING N, et al on behalf of NEAD Study Group (2014) Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. *JAMA Pediatr* 168(8), 729-736.
167. KUBOTA F, KIFUNE A, SHIBITA N et al (1999) Bone mineral density of epileptic patients on long-term antiepileptic drug therapy: a quantitative digital radiography study. *Epilepsy Res* 33, 93-97.
168. FARHAT G, YAMOUT B, MIKITA MA, DEMIRJIAN S, SAWAYA R, EL-HAJJ FULEIHAN G (2002) Effect of antiepileptic drugs on bone density in ambulatory patients. *Neurology* 58, 1348-1353.
169. PEEBLES, CT, MCAULEY JW, MOORE JL, MALONE HJ, REEVES AL (2000) Hormone replacement therapy in a postmenopausal woman with epilepsy. *Ann Pharmacother* 34, 1028-1031.