Seizure 1999; **8**: 201–217
Article No. seiz.1999.0295, available online at http://www.idealibrary.com on IDEAL®

Best practice guidelines for the management of women with epilepsy

P. CRAWFORD*, R. APPLETON†, T. BETTS‡, J. DUNCAN§, E. GUTHRIE¶, J. MORROW‖, THE WOMEN WITH EPILEPSY GUIDELINES DEVELOPMENT GROUP

**Department of Neurology, York District Hospital, Wigginton Road, York YO3 7HE, UK; †The Roald Dahl EEG Unit, Alder Hey Children's Hospital, Eaton Road, West Derby, Liverpool L12 2AP, UK; ‡Birmingham University Seizure Clinic, Queen Elizabeth Psychiatric Hospital, Edgbaston, Birmingham B15 2QZ, UK; §The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK; ¶The Surgery, 1448 Dumbarton Road, Glasgow G14 9DN, UK ‖Department of Neurology, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, Northern Ireland*

Correspondence to: T. Betts, Birmingham University Seizure Clinic, Queen Elizabeth Psychiatric Hospital, Edgbaston, Birmingham B15 2QZ, UK

Clinical guidelines for the treatment of epilepsy have been published[1,2]. A statement on management issues for women with epilepsy has recently been produced by the American Academy of Neurology[3] which has raised awareness of the issues facing women with epilepsy. The communication presented here aims to review current literature on specific issues relating to women with epilepsy, and proposes graded recommendations for its management within a UK health care framework.

Key words: guidelines; epilepsy; women; fertility; pregnancy; menopause.

INTRODUCTION

Medline searches were performed (from 1966 to 1998) on important issues in the clinical management of women with epilepsy. Searches were limited to the English language and excluded case reports. Additional material was obtained, if necessary, from the personal literature collections of the Panel (i.e. The Women with Epilepsy Guidelines Development Group). Where published evidence was not available, the professional consensus of the Panel was incorporated. These guidelines are both evidence and experience based and the recommendations will require judgement with regard to their applicability in individual circumstances[4].

The current status of each issue relating to the management of women with epilepsy was discussed by the Panel, and statements and recommendations are presented, together with the supporting data. Each statement was assigned a level of evidence (I, II or III) and each recommendation was assigned a strength (A, B or C) according to the level of supporting evidence (Table 1). The criteria were based on a grading system adapted from the Canadian Task Force Classification[5] which was used in existing guidelines for the management of poorly controlled epilepsy[1].

These guidelines are aimed at clinicians who manage women with epilepsy.

MATERIALS AND METHODS

Adolescence and epilepsy

Adolescence is an important time to review the diagnosis of both epilepsy and the epilepsy syndrome, because of the implications and decisions which should be made regarding antiepileptic drug (AED) treatment. Advice on relationships, contraception, the consequences of AED treatment, employment, driving and psychosocial issues needs to be provided at this time[6].

Review of the diagnosis

It is important to recognize that at least 10% of teenagers thought to have epilepsy actually have a non-epileptic disorder[7]. An underlying organic cause for the epilepsy should be sought at this time. Temporal lobe epilepsy (due to hippocampal sclerosis) may present in early adolescence or early adult life, as may a tumour. In rare cases, the development of epilepsy in adolescence may herald the onset of a progressive neurodegenera-

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Table 1: Grading scheme for recommendation strengths and levels of evidence.

Level of evidence
I—Well-designed, randomized, controlled trials, systematic reviews or meta-analyses
II—Well-designed (but non-randomized), prospective- or retrospective-controlled studies *or* other observational studies
III—Uncontrolled trials *or* descriptive studies *or* consensus agreed in reports from expert committees or other respected authorities
Strength of recommendations
A—Based directly on level I evidence
B—Based directly on level II evidence *or* extrapolated from level I evidence
C—Based directly on level III evidence *or* extrapolated recommendation from level I or II evidence

Adapted from reference 1.

tive disorder. Common misdiagnoses include syncope, non-epileptic attack disorder and migraine. A normal computerized tomography (CT) scan undertaken previously should not preclude a repeat scan with magnetic resonance imaging (MRI) in a teenager/young adult with poorly controlled epilepsy[8]. Poorly controlled patients are defined as those who continue to have seizures despite initial assessment and treatment with one or more AED and who continue to feel disabled by their seizures[1].

Puberty is a problematic stage for females due to psychological, social and hormonal changes. Repeated seizures occurring during childhood can affect endocrine systems and growth so that a proportion of girls with epilepsy will not be as tall as their counterparts, will be obese, and will have a delayed menarche. Cosmetic side-effects of AEDs may cause concern in this age group, e.g. the coarsening of facial features, gingivitis, acne and hirsutism occurring with phenytoin, and weight gain occurring with valproate, gabapentin and vigabatrin.

In adolescence, idiopathic generalized and localization-related epilepsies (including temporal lobe epilepsy) are common. Juvenile myoclonic epilepsy may include asymmetrical or symmetrical myoclonic seizures ('jerks') of the upper limbs, particularly in the early morning or following sleep deprivation. Brief absence attacks need to be identified to permit appropriate treatment. Epilepsy, with generalized tonic–clonic seizures on awakening, may also develop at this time[9].

Electroencephalography aids the diagnosis of epilepsy syndromes and should be undertaken in all patients who present with new or changing seizures.

The late childhood to adolescence period is a time when epilepsy is more likely to arise than in any other time of life and it is also a time when pre-existing seizure disorders worsen[10,11]. During adolescence the young woman should be made aware that her condition and the treatment she is taking may affect her future fertility. These issues, taken together with the influence of over-protective parents, may lead to low self-esteem and lack of confidence unless timely and accurate advice and counselling are provided. It is therefore recommended that a full review of the patient be undertaken at this time.

Adolescence and epilepsy—statements and recommendations

- Adolescence is an important time to review the diagnosis of epilepsy (III).
- Advice should be given on the issues relating to the confirmed diagnosis of epilepsy (C).

Epilepsy, menstrual cycle and fertility

The diagnosis of epilepsy and the use of AEDs present women of childbearing age with many problems, as both the disease and its treatment can alter the menstrual cycle and fertility. There are also problems with drug interactions, particularly with oral contraceptives. Furthermore, AEDs are associated with teratogenic effects. The AEDs and the seizure disorder can cause adverse effects during pregnancy, and conversely, the menstrual cycle and pregnancy can affect a seizure disorder due to hormonally induced alteration of the seizure threshold. All women with epilepsy should be counselled about fertility issues at their review consultation.

Effect of epilepsy on fertility

There is decreased fertility amongst women aged 25 to 39 years with treated epilepsy[12]. This has been hypothesized to be due to a reduction in marriage rates for people with epilepsy[13–15]. However, even within marriage, fertility rates are lower than in the general population[12]. There is a higher incidence of menstrual disorders in women with partial seizures of temporal lobe origin (35%) when studied over three cycles, compared with 8% in a control group[16].

Treatment issues and menstrual irregularities. In a study of 65 women with epilepsy, an increased incidence of polycystic ovary syndrome was noted amongst 64% (14/22) women taking valproate monotherapy[17]. In a study of 238 women with epilepsy, 45% on valproate monotherapy (13/29 women) displayed menstrual irregularities (amenorrhoea, oligomenorrhoea, prolonged cycles and irregular menstruation); 60% of these women also displayed polycystic ovaries and 30% had elevated serum testosterone concentrations. These effects were more common in women beginning valproate before the age of 20[18]. Evidence from a group of 12 women with epilepsy suggests that stopping valproate therapy leads to a reversal of hyperinsulinaemia, hyperandrogenism and low serum high-density lipoprotein cholesterol[19].

Luteinizing hormone pulse frequency has been found to be increased[20] or variable in women with epilepsy[21] and this pre-disposes towards the development of polycystic ovary syndrome[22].

The polycystic ovary syndrome includes hyperandrogenism (with raised testosterone levels), multiple ovarian cysts, anovulatory cycles, hirsutism, and in 30–50% of patients, obesity. The prevalence of the polycystic ovary syndrome in women without epilepsy is between 4% and 19%, depending on how the syndrome is defined and assessed[23]. The true prevalence of the condition in women with epilepsy is unknown, but is thought to be higher than in women without epilepsy, even in those not taking AED medication[24]. The condition is thought to be more prevalent in those women taking sodium valproate[17].

The hormonal disturbances of the polycystic ovary syndrome may exacerbate the seizure disorder[22]. Since anovulatory cycles expose the brain to continuous oestrogen without cyclical progesterone, administration of progesterone[25], or the synthetic progestogen, medroxyprogesterone acetate[26], may be helpful.

Fertility—statements and recommendations

- All women with epilepsy should be counselled about their fertility and the possible effects of their AED treatment (C).
- There is decreased fertility amongst women with epilepsy (II).
- There is an increased incidence of anovulatory cycles amongst women with partial seizures (II).
- The true prevalence of polycystic ovary syndrome amongst women with epilepsy, even if they are not taking AEDs, may be higher than in women without epilepsy and the prevalence is higher still in those taking sodium valproate (II).

Catamenial epilepsy

Catamenial seizures refer to an increase in seizures around the time of the menses either just before or during the first few days of menstruation. Catamenial seizures may be uncommon, for example, occurring in 12.5% of 40 women with epilepsy, despite 78% of women claiming that their seizures occurred near the time of menstruation[27]. Anovulatory cycles tend to be associated with an increase in seizure frequency in the second half of the menstrual cycle, whilst ovulatory cycles can have one or two peaks in seizure frequency around the time of menstruation and/or ovulation[28, 29].

Hormonal environment. Catamenial seizure exacerbations may be related to the changing sex hormone concentrations during the menstrual cycle. Oestrogens lowered the seizure threshold in the hippocampus and amygdala, and elicited seizure activity when directly applied to the cortex of animals[30].

Conversely, progestogens and their metabolites appear to have anticonvulsant properties which may be mediated by the type A gamma-aminobutyric acid receptor[31].

Further evidence for the role of alterations in sex hormone concentrations in catamenial epilepsy includes a decreased number of seizures during the luteal phase when progesterone concentrations are highest[32, 33], and the suggestion that a pre-menstrual increase in seizures is related to a reduction in progesterone concentration.

Other factors may be associated with catamenial epilepsy, including changes in AED pharmacokinetics, and menstrually related mood changes. An increased incidence of pre-menstrual tension has been reported amongst women with catamenial seizures (75%) compared to other women with epilepsy (43%)[34].

Treatment issues. Many therapeutic interventions have been evaluated in catamenial epilepsy with varying degrees of success. In the 1950s acetazolamide was advocated[35, 36] and it is still used today in some patients. Over the past decade, there has been some research on hormonal manipulation, with the aim of increasing relative progesterone concentrations or converting anovulatory to ovulatory cycles. In women with catamenial epilepsy, progesterone produced a decrease in seizure frequency[37] but norethisterone failed to show any antiepileptic effect[38].

An alternative treatment for women with epilepsy is a benzodiazepine but continued prescription can lead to tolerance and dependence. This problem can be overcome using an intermittent regimen[39] such as that employed in a double-blind, placebo-controlled crossover assessment of clobazam in women with catamenial seizures[40]. For women already on AEDs, intermittent

use of perimenstrual clobazam or acetazolamide is suggested when a seizure increase is anticipated.

For women with catamenial epilepsy in whom low pre-menstrual progesterone levels may be a factor, an intermittent perimenstrual progesterone supplement is suggested, or a synthetic progestogen during days 10–26 of the menstrual cycle. A combined oral contraceptive pill may be prescribed. If clobazam or a progestogen are unsuccessful, danazol or goserelin may be prescribed for pre-menstrual symptoms but only by those physicians who are experienced in their use. The oestrogen analogue, clomiphene[41], may be useful but should only be used by those experienced in its use, as ovarian hyperstimulation is potentially dangerous.

For those rare women not already taking AEDs, and who have established, isolated catamenial epilepsy, one of the following regimens may be helpful as an alternative to a regular AED regimen: intermittent perimenstrual clobazam (10–30 mg/day); combined oral contraceptive pill, depot progestogen therapy; or perimenstrual progestogen (oral or suppository).

Catamenial epilepsy—statements and recommendations

- Catamenial epilepsy occurs in about 12% of women with epilepsy (II).
- In ovulatory cycles there may be two seizure peaks, perimenstrually and at midcycle (II).
- For women already on AEDs, the currently recommended treatment is intermittent clobazam on days when seizure increase is anticipated (B). Alternative therapies include acetazolamide given perimenstrually or progestogens (C).
- For those rare women not already taking AEDs, the following are alternatives: intermittent perimenstrual clobazam (10–30 mg/day); combined oral contraceptive pill, depot progestogen therapy; or perimenstrual progestogen (III).

Contraception in epilepsy

There are no contraindications to the use of non-hormonal methods of contraception in women with epilepsy.

An interaction between hepatic enzyme-inducing drugs and the combined oral contraceptive pill was first noted when the dose of oestradiol in the oral contraceptive pill was reduced from 100 μg to 50 μg. A higher incidence of breakthrough bleeding and contraceptive failure has been noted amongst women with epilepsy on the oral contraceptive pill[42,43] and this may be due to a relative oestrogen deficiency[44]. The drugs implicated include phenytoin, phenobarbitone, primidone, carbamazepine[42] and more recently, topiramate (Topiramate Summary of Product Characteristics). Clinicians should consider carefully the implications of using these agents in women with child-bearing potential because of their effect on the efficacy of oral contraceptives. Even with higher dose combined oral hormonal contraceptive methods, complete protection from pregnancy is not achievable in women taking hepatic enzyme-inducing AEDs. Non-enzyme inducing AEDs—sodium valproate, benzodiazepines, vigabatrin, gabapentin, lamotrigine and tiagabine—do not show any interactions with the combined oral contraceptive pill. Oxcarbazepine is considered to be a weak enzyme-inducing agent[45].

In women taking phenobarbitone, primidone, phenytoin, carbamazepine and topiramate, the starting dose of ethinyl oestradiol should be 50 μg/day and it may be necessary to increase the ethinyl oestradiol dose to 75–100 μg if breakthrough bleeding occurs. Nausea may occur with these high daily doses. An alternative is to take three packs of a higher dose oral contraceptive pill without a break in between ('tricycling') and then have four days without taking the pill. Women need advising that even on a higher dose combined contraceptive pill and with normal cycles, full efficacy cannot be guaranteed. However, pregnancy rates are lower when oral contraceptives are used in epilepsy (approximately 7 in 100 woman-years) compared with barrier methods (failure rate of 15–20 in 100 woman-years)[42,46].

Medroxyprogesterone injections appear to be effective in women with epilepsy. No adjustment of dosing frequency may be needed in women taking enzyme-inducing AEDs as the rate-limiting step of elimination is hepatic blood flow and not enzyme activity. However, experience of some Panel members suggests that the usual dosing frequency of one medroxyprogesterone injection every 12 weeks could be changed to one injection every 10 weeks in women taking enzyme-inducing AEDs. Levonorgestrel implants are contraindicated in women taking enzyme-inducing AEDs as there is an unacceptably high failure rate[47]. It must be assumed that the efficacy of progesterone-only oral contraceptives is affected by enzyme-inducing AEDs, although it is unknown by how much[24]. Women should be advised not to rely solely on a progesterone-only pill for contraception if they are taking an enzyme-inducing AED, as it may be less effective than the combined oral contraceptive pill.

If appropriate, the morning-after contraceptive pill can be used in women with epilepsy after unprotected sexual intercourse. There are no data on whether a change in dose of the morning-after contraceptive pill is required in women taking AED medication; some practitioners use a slightly higher dose in those women taking enzyme-inducing AEDs.

Contraception—statements and recommendations

- There are no contraindications to the use of non-hormonal methods of contraception in women with epilepsy (III).
- For women on non-enzyme-inducing AEDs (sodium valproate, benzodiazepines, vigabatrin, gabapentin, lamotrigine, tiagabine), all current contraceptive methods are suitable (III).
- Hormonal forms of contraception are affected by enzyme-inducing AEDs. Women taking these forms of contraception should be counselled on their risks and benefits (C).
- For women on enzyme-inducing AEDs (phenytoin, phenobarbitone, primidone, carbamazepine, topiramate) wishing to take the combined oral contraceptive pill:
  - — start with a 50 μg ethinyl oestradiol dosage (C);
  - — if breakthrough bleeding occurs, increase the dose of ethinyl oestradiol to 75 or 100 μg/day or consider giving three packs of the pill without a break ('tricycling') (C).
- Even on a higher dose combined oral contraceptive pill with normal cycles, full oral contraceptive efficacy cannot be guaranteed in women with epilepsy taking enzyme-inducing AEDs (III).
- The progesterone-only pill may be less effective than the combined oral contraceptive pill in women taking enzyme-induced AEDs (III).
- Medroxyprogesterone injections appear to be effective (III).
- Levonorgestrel implants are contraindicated (III).
- If appropriate, the morning-after contraceptive pill can be used in women with epilepsy after unprotected sexual intercourse (C); a slightly higher dose may be needed in women taking enzyme-inducing AEDs (C).

Sexuality

The majority of women with epilepsy appear to have normal sex lives, although in some women with epilepsy both the desire and arousal phases may be inhibited. This is slightly but significantly more likely to occur than in women who do not have epilepsy and will impair quality of life[48].

Psychological factors that can inhibit desire or arousal in women with epilepsy include overprotection in childhood and adolescence, a poor self-image, and the lack of ability to 'let go' during the sexual act for fear of a seizure (or the partner's fear of a seizure).

Research on sexual function in women has concentrated on the influence of AEDs, particularly the enzyme-inducing drugs such as phenobarbitone, which may alter sex hormone binding. Two studies found an association between sexual functioning and sex hormone binding changes: other studies which suggested that this was not an important cause of sexual dysfunction included only a small number of women[48].

Although previous methodological flaws have been largely overcome, recent studies have been mainly conducted on women attending specialist epilepsy clinics, or belonging to epilepsy organizations, thus possibly introducing bias. Direct comparison of sexual responsiveness between women with epilepsy and their unaffected peers has not been carried out.

Epilepsy itself independently affects neuroendocrine functioning in women. In men, epilepsy-related changes in hypothalamic endocrine function have an effect on sexual arousal[48], but it is less clear if this is the case in women since female sexuality may be more dependent on psychological rather than endocrine factors[49].

Sexual feelings occurring as part of a partial seizure are usually feelings of sexual arousal and seem only to have been reported in women[50]. Sexual behaviours can also occur both ictally and post-ictally, are usually inappropriate, and after a seizure, are related to post-ictal confusion.

Many women with epilepsy do not spontaneously complain of sexual difficulty. A short, standard sexual history[49] should form part of the assessment of all women with epilepsy at some point. If a problem is found in addition to psychological assessment, neuroendocrine evaluation may be needed[48], and appropriate referral made for treatment[24].

Sexuality—statements and recommendations

- Sexual desire and sexual arousal may be affected by epilepsy or by the treatment of epilepsy in women (II).
- The majority of women with epilepsy have normal sex lives (II).
- Sexual feelings or behaviours may occur during partial seizures (II).
- Enquiry about sexual feelings and function should be part of the standard assessment of women with epilepsy (C).
- If a disorder of desire or arousal is discovered, expert psychological and neuroendocrine evaluations are recommended (C).

Pre-conception counselling and teratogenicity

Women need to have their epilepsy thoroughly re-assessed before becoming pregnant[51] as some conditions causing epilepsy may be better dealt with before pregnancy, e.g. those for which neurosurgical treatment may be appropriate. Furthermore, formal pre-conception counselling (and re-investigation, if needed) should be available to all women with epilepsy who are considering pregnancy. Counselling should begin at the time of diagnosis of epilepsy and be repeated at intervals throughout its management. Some hospitals offer clinics for teenagers and formal pre-conception clinics but there are few of these and all too often women with epilepsy do not present until a pregnancy has occurred. This situation leaves room for improvement.

Pre-conception counselling involves making women with epilepsy aware of a number of issues relating to future pregnancy, including methods and consequences of prenatal screening, teratogenicity, labour and child-care. The main aim of pre-conception counselling is to ensure that women embark upon pregnancy with a minimum of risk factors, fully aware of any risks and benefits of treatment, and able to make informed decisions about the pregnancy.

Seizure and AED management

Before conception, the continuing need for AED treatment should be reviewed, based on Medical Research Council criteria[52]. Women should enter pregnancy having complete seizure control or as few seizures as possible. If a patient has been seizure-free for at least 2–3 years, consideration may be given to withdrawing AEDs to reduce the potential teratogenic risk. However, many women do not wish to withdraw from drug therapy even when seizure-free as this may affect their eligibility to drive and continue with work and normal activities. The lowest effective dose of the most appropriate AED should be continued, aiming for monotherapy where possible. Currently, the UK Driver and Vehicle Licensing Agency recommend not driving from the commencement of the period of withdrawal and for a period of 6 months after cessation of treatment, even if there are no seizures[53].

Teratogenicity in perspective

As with all women contemplating pregnancy, advice should be given about maintaining good general health in relation to exercise, diet, smoking and alcohol consumption. Although a major concern of women with epilepsy who are contemplating pregnancy is the teratogenic potential of AEDs, it is important to put these risks in perspective. Even women on no medication and with no seizures but who have had epilepsy have a slightly increased risk[54]. The background risk of significant fetal malformation is approximately 3% in developed countries and the consensus from many studies is that this increases to 7% if one AED is taken and to 15% if two or more are taken[43, 55, 56]. Most major malformations develop at an early stage in pregnancy, often before the woman knows she is pregnant. Exposure in the later stages of pregnancy may still lead to minor morphological abnormalities[57–60]. Some AED combinations appear to carry a high risk, e.g. valproate plus carbamazepine plus phenytoin or phenobarbitone has been associated with a 58% malformation rate, possibly due to accumulation of toxic metabolites[61]. The mechanisms whereby AEDs are teratogenic have not been definitely established. Possibilities include the formation of epoxide and arene oxide metabolites, cytotoxic free radicals, and effects on fetal heart rate leading to hypoxia. Folic acid deficiency is also a possible cause.

Is there any difference between the AEDs in terms of teratogenicity?

There is no conclusive evidence for a significantly different teratogenic risk from phenytoin, valproate, carbamazepine or phenobarbitone. There have been suggestions that valproate is more teratogenic than other AEDs[43, 61]. In a prospective study of women who took AEDs during pregnancy (monotherapy and polytherapy), phenobarbitone was associated with the highest relative risk, followed by phenytoin and carbamazepine; there were insufficient numbers of women treated with valproate to assess the risk associated with this drug[62]. Comparison of studies is confounded by patients having different types and severities of epilepsy, by taking different doses and combinations of drugs, and insufficient studies of monotherapy to draw definitive conclusions.

Phenytoin. Phenytoin should be avoided in women with child-bearing potential, particularly in adolescence, as it has a number of undesirable side-effects. Phenytoin is particularly associated with an increased risk of cleft lip and palate as well as dysmorphic features such as nail and distal phalangeal hypoplasia and craniofacial abnormalities[43, 59, 63, 64].

Phenobarbitone. Phenobarbitone has been associated with congenital heart defects, facial clefts, and a specific pattern of minor anomalies and dysmorphic features[55, 65, 66].

Valproate. Doses of valproate greater than 1000 mg/day carry a greater risk of spina bifida than lower doses[67], possibly due to high peak serum concentrations of valproate. Confirmatory studies are required

to assess whether three or four times daily treatment or slow-release preparations minimize this risk by reducing peak plasma levels. A 'fetal valproate syndrome' has been suggested as being associated with dysmorphic features and developmental delay[68]. Valproate in pregnancy has been associated with a 1–2% risk of neural tube defects, particularly an open lumbosacral myelocoele, against a background risk of 0.2–0.5%. There is also an increased incidence of cardiovascular and urogenital malformations[43]. Thus, although valproate may the most suitable drug for some women with epilepsy, the risks and benefits should be carefully considered and discussed with the patient.

Carbamazepine. Carbamazepine was once considered to be the least teratogenic of the older AEDs, but recent studies have shown an association between carbamazepine and congenital malformations in the same order of magnitude as for barbiturates and phenytoin. However, these studies have included small numbers and uncontrolled data and need to be replicated before being regarded as definitive. Furthermore, the types of malformation are different[59]. In one study there was a 0.9% reported risk of neural tube defects in the offspring of mothers who took carbamazepine through pregnancy[69]. There have also been reports of reduced head circumference at birth, of developmental delay in 20% of infants[70] and of dysmorphic features[71].

Dysmorphic features

Dysmorphic features, including epicanthal folds, long philtrum, flat nasal bridge, digital hypoplasia and hypertelorism, are undesirable and cause some disability but they do not result in serious impairment or death. Such abnormalities have been ascribed to syndromes related to specific AEDs, such as the 'fetal hydantoin syndrome'[72], and subsequently revised to recognize a 'fetal AED syndrome'. The extent of the causal relationship with AEDs has been questioned and evidence has been put forward for maternal genetic factors influencing the development of minor abnormalities such as epicanthus and micrognathia[54,73]. Larger prospective studies of women treated with monotherapy are necessary to resolve these issues. Valproate exposure *in utero* is associated with a combination of facial dysmorphic patterns distinct from those associated with phenytoin exposure[74,75].

Digital and craniofacial hypoplasia tend to resolve over the first few years of life[43]. Some investigations have reported that babies exposed to AEDs *in utero* tend to be small at birth and have slow postnatal growth and cognitive development, but controlled data are lacking. Most studies have suggested that there is a very low risk of prenatal AED exposure leading to low intelligence[76]. Other factors affecting a tendency to develop a low intellect include maternal and paternal genetic predisposition and psychosocial influences.

Animal studies

Safety data from limited animal studies suggest that some AEDs appear to show no teratogenic effects. At present there are insufficient monotherapy data in humans to predict the risk of teratogenicity. To date, lamotrigine, gabapentin and tiagabine have not been shown to produce malformations in animal studies[77,78]. Vigabatrin has been associated with cleft anomalies in New Zealand white rabbits[64]. Topiramate is teratogenic in mice, rats and rabbits, and crosses the placental barrier (Topiramate Data Sheet).

Use of folic acid

The UK Medical Research Council study, including women who had previously given birth to an infant with a neural tube defect, found that 4 mg/day of folic acid given prior to conception was associated with a 72% protective effect[79]. Folic acid supplementation has also been shown to have a protective role in the primary prevention of neural tube defects[80–82]. Although there has been no specific study of the effect of folic acid supplementation on the risk of neural tube defects and other congenital malformations in women taking valproate or other AEDs, extrapolations have been made from published studies in the general population and therefore a daily dose of 5 mg of folic acid is recommended before and during pregnancy for all women taking AEDs, starting before conception and continuing until at least the end of the first trimester.

A daily dose of 5 mg of folic acid is probably more than is needed to achieve a maximal reduction of risk. A daily intake of at least 0.4 mg/day has been recommended for the general population[82]. The larger dose, however, does not appear to cause adverse effects, unless the patient has covert pernicious anaemia.

Prospective registers

In clinical evaluations of AEDs, women with childbearing potential are either excluded or encouraged to take adequate contraceptive measures. Therefore, very few pregnancies occur during clinical trials, and those that do, often end in therapeutic abortions.

In the UK, the British Neurological Surveillance Unit has established a prospective pregnancy register for patients taking AEDs. Over the course of 2 years approximately 400 pregnancies have been registered by neurologists, obstetricians and general practitioners. The register has been granted ethical approval and aims to audit the incidence of congenital malformations in the offspring of patients taking AEDs. It should be noted

Table 2: Notification of new AEDs to UK Prospective Register (interim results, March 1998).

Drug (no. of notifications)*	Total outcomes	No malformation			Malformation present			
		Live birth	Abortion		Live birth	Abortion		Intrauterine death
			Spontaneous	Therapeutic		Spontaneous	Therapeutic	
Lamotrigine ($n = 116$)	67	55	7	1	2[a,b]	1[c]	0	1[d]
Vigabatrin ($n = 40$)	27	24	1	0	1[e]	1[f]	0	0
Gabapentin ($n = 35$)	21	15	2	1	3[g,h,i]	0	0	0

[a] Live born infant—mid-gut malrotation and cerebral palsy. [b] Live born infant—hypospadias. [c] Spontaneous abortion—trisomy 21. [d] Inter-uterine death at 24 weeks—thoracic cage abnormality and lung hypoplasia. [e] Live born infant—hypospadias. [f] Spontaneous abortion—trisomy 21. [g] Live born infant—ventricular septal defect. [h] Live born infant—bilateral orofacial clefts. [i] Live born infant—hypospadias. *Includes use in monotherapy and polytherapy: no inferences can be drawn from these figures.

that these data have been obtained on first trimester exposures to AEDs in women receiving monotherapy and polytherapy. Preliminary data are shown in Table 2. It is only with continued support of these prospective registers that the information clinicians require to adequately counsel patients may be obtained (the address of the Register is given in the Appendix).

Genetic predisposition

Many women ask about the risks of passing epilepsy to their children and the majority can be assured that their child is not at risk. In specific cases there may be an underlying genetic cause. For idiopathic generalized epilepsy, the risk of a child developing the condition is 5–20% if there is one affected first degree relative and over 25% if two first degree relatives are affected. Thus the risk of a patient with idiopathic generalized epilepsy having an affected child is about 9–12%, and the risk is 3% in children of patients with cryptogenic localization-related (partial) seizures[83].

Pre-conception counselling and teratogenicity—statements and recommendations

- Pre-conception information should be offered to all females with child-bearing potential (C).
- If changes in AED medication are to be made they should be completed before conception (B).
- If AED treatment is needed, a single agent is preferred (B).
- The risk of fetal malformation is doubled in women receiving treatment for epilepsy compared with the general population (3% in the general population, 7% with one AED, 15% with two or more AEDs) (II). Some combinations of polytherapy are particularly teratogenic (II).
- Most major malformations occur at an early stage in pregnancy, often before the woman knows she is pregnant (I).
- Women with epilepsy who are planning a pregnancy should take folic acid 5 mg daily in the pre-conception period and throughout the pregnancy (B).
- The use of phenytoin, valproate, carbamazepine and phenobarbitone has been associated with an increased risk of major malformations and minor morphological anomalies (II).
- Although valproate may the most suitable drug for some women with epilepsy, the risks and benefits should be carefully considered and discussed with the patient (C).
- It is not known whether vigabatrin, gabapentin, lamotrigine, topiramate and tiagabine are associated with a risk of fetal abnormalities in humans. Gabapentin, lamotrigine and tiagabine are not associated with fetal abnormalities in animal studies (III).
- All pregnancies occurring in women with epilepsy should be reported to the appropriate UK register, regardless of whether or not AEDs are being taken (C).

Management of pregnancy and birth in epilepsy

Effect of pregnancy on epilepsy

Most women with epilepsy do not experience an increase in seizures whilst pregnant[84]. Of those women who do have an increase in seizures (between 8% and 46%)[85], the increase can often be attributed to factors such as poor compliance with prescribed AEDs (sometimes compounded by vomiting), inappropriate reduction of AED therapy, a pregnancy-related fall in plasma drug concentrations, and sleep deprivation[86, 87]. Consequently, the patients' seizures should be monitored and

appropriate AED dosage adjustment made. An increase in seizure frequency is more likely in women with a high pregravid seizure frequency or multiple seizure types. An episode of status epilepticus occurs in less than 1% of pregnancies. The risk of seizures is greatest in the delivery period with tonic–clonic seizures complicating labour in 1–2% of cases and a further 1–2% in the following 24 hours[88].

In contrast, up to 50% of women report that their epilepsy is better controlled during pregnancy, for reasons which include avoidance of excessive fatigue, better compliance and hormonal changes[87, 89].

Effect of epilepsy on pregnancy

Most pregnancies are uneventful in women with epilepsy and most of the babies delivered are healthy[87]. More recent studies have not indicated any increased risk of obstetric complications in women with epilepsy, while other studies report an approximately 1.5–3 times increase in the risk of common complications such as toxaemia, pre-eclampsia, placental bleeding and premature labour and a 1.2–2 times increase in perinatal mortality[90]. Many studies are retrospective or based on registries and are likely to be complicated by ascertainment bias[89].

There is no evidence that simple partial, complex partial, absence and myoclonic seizures adversely affect a pregnancy or developing fetus, other than by the effects of trauma[91]. Prospective studies indicate that there is no association between tonic–clonic seizures during pregnancy and malformations[54, 92]. Anecdotally, tonic–clonic seizures may cause fetal bradycardia in humans[93] or miscarriage[94] but definitive data are lacking.

Management of epilepsy during pregnancy

Having established the patient on optimal monotherapy, if possible, prior to conception, subsequent management of AED treatment during pregnancy is generally straightforward, but requires careful attention. Patients should understand and agree with their prescription and the rationale for any dose change.

Serum AED concentrations often fall during pregnancy, particularly in the first and third trimesters, and a pre-conception baseline value may be helpful[59, 86, 95]. Many factors may contribute to the change in AED pharmacokinetics including: increased hepatic or renal clearance, increased plasma volume and reduced plasma albumin concentration and protein binding. Reduced bioavailability is probably not an important factor.

The value of measuring plasma drug levels routinely during pregnancy is still uncertain. When such measurements are carried out, assessment of the unbound drug fraction is the method of choice[96].

Prenatal diagnosis of malformations

Since epilepsy is associated with an increased risk of fetal malformations, women with epilepsy should be referred by their obstetric/gynaecological consultant to a specialist centre for a high-quality ultrasound scan. They will also usually require more than one scan plus appropriate blood tests and possible amniocentesis. Ultrasound studies from about 18 weeks can identify major cardiac, facial and limb anomalies and recognizing increased nuchal translucency on the scan between weeks 10–14 may give early indication of major cardiac defects[97]. Patients and families need to be advised, however, that even the most sophisticated scans cannot detect 100% of abnormalities.

Management of labour

One to two percent of women with active epilepsy will have a tonic–clonic seizure during labour, and a further 1–2% will have such a seizure in the following 24 hours[88, 89]. Generalized tonic–clonic seizures are likely to result in more profound hypoxia than in the non-gravid state, because of increased maternal oxygen requirements, and this may have deleterious effects on the fetus. Thus it is recommended that the delivery take place in an obstetric unit with facilities for maternal and neonatal resuscitation.

The patient's regular AEDs should be continued throughout labour. If necessary, all drugs may be given by nasogastric tube; phenytoin (as fosphenytoin), valproate, phenobarbitone, diazepam and clonazepam may be given parenterally.

Administration of intramuscular corticosteroids (such as dexamethasone) given to a woman in premature labour can help to prevent respiratory distress syndrome or intraventricular haemorrhage in the infant. An increased corticosteroid dose is necessary in women taking hepatic microsomal enzyme-inducing AEDs (e.g. phenytoin, phenobarbitone, primidone, carbamazepine and topiramate)[98].

Most women with epilepsy have normal vaginal deliveries[93, 99, 100]. Over-breathing, sleep deprivation, pain and emotional stress increase the risk of seizures during labour and it is appropriate to consider epidural anaesthesia early on, to minimize these factors. An elective Caesarean section may be appropriate if frequent tonic–clonic or prolonged complex partial seizures occur in the last weeks of pregnancy. Intravenous lorazepam may be an appropriate acute treatment for serial seizures during labour[93].

Vitamin K_1 deficiency and haemorrhagic disease of the newborn

Vitamin K_1 deficiency bleeding carries a mortality rate of over 30%[101]. It is due to deficiency of factors II, VII, IX and X and is more likely to occur in the offspring of women who have taken hepatic enzyme-inducing drugs during pregnancy[102, 103]. A dose of 20 mg/day of vitamin K_1 given orally in the last month of pregnancy may protect against the problem. Infants born of women with epilepsy should receive 1 mg of vitamin K_1 intramuscularly at birth. The putative association of this treatment with childhood neoplasia is unwarranted[104–110]. Infants should receive intravenous fresh frozen plasma if there is evidence of bleeding or if the concentrations of two or more of factors II, VII, IX or X fall to less than 25% of normal.

The puerperium

If the dose of an AED has been increased during pregnancy, it is usually advisable for it to be gradually reduced to the pre-conception dose over the few weeks following delivery, to reduce the risk of maternal toxicity. However, if the increased dose does not lead to toxic symptoms and there is a sustained improvement in seizure frequency, the regimen should not be altered.

Development of seizures in pregnancy

The annual incidence of new cases of epilepsy in the reproductive years from the teens to the age of 40 is 20–30 per 100 000 per year[111]. Thus, the development of epilepsy during pregnancy is not uncommon. A few specific aetiologies are associated with pregnancy, such as an enlarging meningioma or arteriovenous malformation or other vascular disease. The risk of ischaemic stroke is increased by a factor of 10 in the last 6 months of pregnancy, and approximately 4% of cerebral infarctions may be expected to result in seizures. Other specific vascular disorders occurring in pregnancy and complicated by seizures include cerebral venous thrombosis, subarachnoid haemorrhage and eclamptic hypertensive encephalopathy.

Investigation into causes of epilepsy in pregnant women should follow the same principles as for a non-gravid patient. MRI is favoured over X-ray CT scanning due to its superior resolution and the lack of ionizing radiation. However, the potential effects of a strong magnetic field on a developing fetus are not entirely clear but can be justified if there is a clear clinical indication, whereas lead shielding can protect the uterus during an X-ray CT scan.

The principles of initiating AED treatment in pregnancy are the same as those for the non-pregnant patient. Specific underlying causes for the epilepsy, such as stroke and eclamptic hypertensive encephalopathy, will require their own treatment. Status epilepticus arising as a consequence of eclampsia should be treated initially with an intravenous benzodiazepine, preferably lorazepam, followed, if necessary, by intravenous phenytoin or fosphenytoin. Magnesium sulphate has been shown to prevent tonic–clonic seizures in eclampsia[112, 113], and does not impact on labour, other than to increase the dose of oxytocin that is required[114].

Breast-feeding and AEDs

All women with epilepsy should be strongly encouraged to breast feed their babies. However, drug elimination mechanisms are not fully developed in early infancy, therefore repeated administration of a drug via breast milk may lead to its accumulation in the infant and pharmacological effects may occur[115]. Drug concentrations in milk can substantially differ between the first and last portion of the feed, and between the left and right breast, depending on the fat and protein content [116, 117], although the total amounts of drug transferred to the infant via breast milk are usually much smaller than the amounts transferred via the placenta during pregnancy.

Relatively small amounts of phenytoin are transferred via breast milk (18–20% of plasma concentration)[115] and the serum levels of phenytoin in breast-feeding infants are generally considerably below therapeutic levels. Phenobarbitone, primidone and lamotrigine can accumulate in plasma in the breast-fed baby due to slow elimination. Preliminary data in a small number of cases indicate that lamotrigine passes into breast milk at 40–45% of the level in the plasma; there were no adverse effects in any of the infants[118–120]. It is therefore recommended that the infant is closely monitored and, if appropriate, serum drug levels measured. If the mother is on barbiturates and if the baby is drowsy or sedated, breast- and bottle-feeding can be alternated. Carbamazepine concentrations in breast-fed babies are usually low (breast milk level 39–40% of plasma concentration)[121] and below the level where pharmacological effects might be anticipated. Ethosuximide can be transferred via breast milk in relatively high daily doses (79–100% of the plasma concentration)[115, 122] and plasma concentrations in breast-fed babies can be close to therapeutic levels. Sodium valproate levels in breast-fed babies are low (1–10% of plasma concentration)[115]. Vigabatrin and gabapentin are excreted mainly unchanged in the urine and therefore in infants with fully developed renal function, accumulation of these drugs is unlikely[123]. There are no data relating to topiramate or tiagabine.

Management of pregnancy and birth in women with epilepsy—statements and recommendations

- Most women with epilepsy have normal vaginal deliveries (II).
- Women should be referred by their obstetric/gynaecological consultant to a specialist centre for a high-quality ultrasound scan (C).
- The patient's seizures should be monitored and appropriate adjustments of AED dosage made (C).
- AED exposure (particularly enzyme-inducing AEDs) leads to greater risk of haemorrhagic disease of the newborn, thus vitamin K_1 should be given to the mother in the last month of pregnancy and to the neonate (B).
- Delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation (C).
- The optimal maintenance dose of AEDs should be reviewed after delivery (C).
- All AEDs currently available can be taken whilst breast-feeding (C).
- All women with epilepsy should be encouraged to breast-feed their babies (C).
- If drowsiness occurs in breast-fed babies whose mothers are taking phenobarbitone, breast- and bottle-feeding can be alternated (C).

The care of children of mothers with epilepsy

Although there is much anxiety about the possible risks to a child from the mother's epilepsy there is no published evidence.

The risk of the child being harmed depends on the type of seizure, its severity and frequency, and this risk is probably small if time is taken to train mothers and carers in safety precautions[51]. The women most at risk of injuring young children are those with uncontrolled juvenile myoclonic epilepsy, because children tend to wake early and these mothers are most at risk of myoclonic jerks at that time[51]. Some clinicians recommend that, during the puerperium, mothers whose juvenile myoclonic epilepsy is uncontrolled are advised to have someone else look after the child in the early morning.

Advice about safety precautions should be given to mothers[24, 51], even those who have not had a seizure for some time, because it is possible that seizures may return or their frequency increase due to stress and exhaustion in the puerperium. An experienced epilepsy nurse, together with a health visitor or a midwife, should make a home visit shortly before the birth to advise on safety precautions in the home.

From an early stage, a routine of looking after the baby should be established that maximizes opportunities for bonding but minimizes risk to the child. The partner should be encouraged to assist with feeding the child, especially at night, so that the mother can sleep, e.g. breast milk can be expressed using a breast pump so that it can be given at night by the partner.

There should also be an assessment of the character of the woman's seizures. Seizures in which the mother loses awareness, wanders, has automatisms, convulses, has no warning of the oncoming seizure or has postictal confusion are particularly dangerous.

Table 3 lists practical suggestions for minimizing the risk to the child, whilst providing maximum bonding experience for the mother. The suggestions assume that the mother is of normal intelligence and is not physically disabled.

Cognitive side effects of AEDs

Controversy exists over the differential cognitive side-effects of AEDs because of inadequate study design[124]. When the methodological flaws of studies are taken into consideration, some AEDs (phenobarbitone and benzodiazepines) may have cognitive side-effects[125] and affect the ability to care for children.

Educating the child and family

Children of women with epilepsy will rapidly realize that their mother is special and it is important that they are taught from an early age how to behave if their mother has a seizure. From the age of two many children will be capable of sitting quietly by the mother until the seizure is over, and summoning help if necessary. By the age of five, a child should know what to do if the mother has a seizure while they are outside the home. This approach will ensure that the child will not be taken by surprise or be frightened by what other people do. A child who grows up in a family that copes with the mother's seizures calmly, will also show confidence in dealing with them. After the seizure has ended, it is important that the mother cuddles and comforts the child so that he or she does not feel to blame for the seizure.

Care of children of mothers with epilepsy—statements and recommendations

- The risk of accidentally harming a child is low and depends on the type of seizure, its severity and frequency (III).

Table 3: Practical suggestions for minimizing the risk to children of women with epilepsy.

Activity	Safety precautions
Feeding	• For babies, the mother should breast-, bottle- or spoon-feed the child whilst sitting on the floor or with her back against a wall
	• For older infants, use a low 'highchair' with the mother still sitting on the floor
	• If the mother has automatisms or episodes of confusion, feeding should be supervised by another adult
Bathing	• Care for the child on the floor as much as possible. Bathing should always be supervised by another adult, even when a floor mat and bowl are used. A sponge down may be a suitable alternative to bathing
Travelling or carrying child	• Another person should carry the child up or down stairs or the child should be carried securely strapped in a padded carrycot
	• For babies, use a pram with a dead man's handle to prevent pram running away
	• For toddlers, use reins to stop them wandering away
Around the home	• Place child in a playpen or use safety gates to section off high-risk areas of the home such as the kitchen, stairways, and lock doors leading outside or into the garden

- Stress and exhaustion in the puerperium may make seizures reappear, even in women who have been seizure-free for some time (III).

- Assistance for the mother is particularly important when bathing, carrying or travelling with children. Women with epilepsy who are intellectually and physically challenged need a greater level of assistance (C).

- The child and the child's family need to be educated about managing the mother's seizures calmly and effectively (C).

Epilepsy and the menopause

Female sex hormones alter the expression of epilepsy and the efficacy of AEDs[48]. There is scant literature about the effects of epilepsy on the menopause or the effects of the hormonal changes of the menopause on epilepsy[10]. The few studies that have been carried out have had methodological problems including small numbers and little recognition of the heterogenous nature of epilepsy[126].

The effects of the menopause on epilepsy

Opinion differs on the effect of the menopause on seizure frequency due to the lack of research in the area. Some women may find the menopause has no effect on seizure frequency, others that there is an increase in seizures, or a recurrence of seizures at the time of the menopause, or even a remission of seizures.

Epilepsy and osteoporosis

Women with epilepsy are at increased risk of bone demineralization, since seizures and AEDs affect the hypothalamic-pituitary-adrenal axis and this can have an adverse impact on bone metabolism[48]. The mechanisms of osteoporosis are multiple and incompletely understood. Microsomal enzyme induction by phenobarbitone, phenytoin and carbamazepine accelerates the metabolism of vitamin D and can have profound effects on calcium metabolism, pre-disposing towards osteomalacia.

The reduction in oestrogen levels in the early post-menopausal period may explain the increased frequency of bone fractures at this time[31]. It has been suggested that women on long-term AEDs should have bone density monitored on a regular basis although the optimal frequency has not been assessed.

Hormone replacement therapy (HRT) and epilepsy

The reduction in circulating oestrogen at the time of the menopause results in menopausal symptoms and an increased risk of developing heart disease and bone demineralization. Provided it is clinically indicated, menopausal and post-menopausal women with epilepsy should receive hormone replacements as this therapy appears to have beneficial effects[127]. The HRT regimen should be given in standard doses. Administration of calcium and vitamin D supplements should also be considered for women with epilepsy.

The possibility that treatment with oestrogen increases seizure frequency is supported by the findings of a recent questionnaire survey of members of an epilepsy organization; 620 women who responded to a postal survey were menopausal or post-menopausal and double the number of past HRT users had an increase in seizure frequency compared with those who had not received HRT[128]. It is advisable to add a progestogen to the HRT regimen to counteract the potential proconvulsant effects of oestrogen, even if the woman has no uterus[24]. Addition of progestogen to the HRT regimen does not appear to attenuate the cardioprotective effects of oestrogen[129]. There is no evidence that the route of administration of HRT is important.

Epilepsy and the menopause—statements and recommendations

- The effects of epilepsy on the menopause and the effects of the hormonal changes of the menopause on epilepsy cannot be reliably predicted (III).
- Women with epilepsy are recognized to be at risk of bone demineralization, especially if they are receiving the hepatic enzyme-inducing AEDs, phenobarbitone, primidone, phenytoin and carbamazepine, which can accelerate vitamin D metabolism (III).
- All post-menopausal women with epilepsy should receive HRT (combined oestrogen and progestogen), if it is clinically indicated, even if the woman has no uterus (C).

Multidisciplinary partnership in the general management of epilepsy

The optimal care of women with epilepsy, particularly when pregnant, requires collaboration between a range of professionals from a wide range of backgrounds[2], and will be determined by the needs of the patient and the resources available locally. The voluntary sector also plays an important role. Recognition of the benefits of involving a range of professionals in meeting the needs of any individual person with epilepsy is not new[1, 130, 131]. However, this strategy tends not to take place in practice and is a cause for concern[132].

Good communication is the key to effective multidisciplinary care with good information exchange between primary health care teams and specialists[133]. The clinical nurse specialist in epilepsy has a central role in developing effective partnerships[2, 134, 135].

The integrated care scheme approach has previously been discussed from a national[132] and district[134, 136, 137] perspective.

Key players of the care-giving partnership are the general practitioner and his team, the epilepsy consultant, the epilepsy nurse, the obstetric/gynaecological consultant and the midwife, although they may not see themselves in the team role. The general practice team and the midwives may need specialized education and training. The epilepsy nurse's role should include ensuring that epilepsy care is not compromized and providing information and advice such as pre-conception counselling. By discussing issues relating to their condition with the epilepsy nurse or other health care professional, women with epilepsy will be sufficiently empowered to make decisions about their own treatment.

There should be active liaison between the epilepsy nurse and the hospital/community midwives, and at a later stage of pregnancy, with the health visitor and general practice team. Arguably, the general practitioner should be the team leader[51], but usually the epilepsy consultant and epilepsy liaison nurse lead and liaise. In this scenario, the general practitioner, obstetric/gynaecological consultant and midwife would continue with their traditional roles, with all team members taking into account the specific needs of the woman with epilepsy. For practical purposes, the most appropriate team leader may be the epilepsy liaison nurse, since it is he or she who will keep the lines of communication open between the other members of the team.

Multidisciplinary partnership—statements

- Optimal care for women with epilepsy requires collaboration between a range of professionals from a wide range of backgrounds (III).
- Jointly planned shared care is the preferred model of care for people with epilepsy (III).
- The clinical nurse specialist in epilepsy has a central role in developing effective partnerships (III).

SUMMARY POINTS

- Management of women with epilepsy is multifactorial
- Epilepsy should be rigorously reviewed and women provided with adequate information for them to form their own views on the issues and the management regimen they wish to pursue
- Women with epilepsy should be counselled on reproductive issues, contraception, teratogenicity, pregnancy, labour and child-rearing, and bone health
- If women are receiving AED medication, monotherapy is preferred
- Changes to AED therapy should be made before contraception is stopped
- Women with epilepsy, who decide to embark upon pregnancy, should be seizure-free if possible
- Women with complex needs should be referred to specialist centres for detailed review and assessment

ACKNOWLEDGEMENTS

The Panel gratefully acknowledges the contribution made by Mrs Cathy Fox, RGN, to the discussion of pre-conception counselling and childcare.

The guidelines development group comprised Carole Longson, Technical Director, Complete Medical Communications UK Ltd. and Stephen Lawrence, Business Manager, Complete Medical Communications UK Ltd., in addition to the authors.

Development of the guidelines was funded by an unrestricted grant from Glaxo Wellcome. Travelling expenses, accommodation and time spent by the Panel members away from their normal place of work attending two review meetings was recompensed by Glaxo Wellcome. Panel members received no fees for their written contributions or for reviewing drafts of the guidelines document.

Complete Medical Communications UK Ltd. was responsible for running the group and provided editorial support to the Panel members in obtaining references, drafting the guidelines document and coordinating the review process.

Conflict of interest: none.

REFERENCES

1. Wallace, H., Shorvon, S. D., Hopkins, A. and O'Donoghue, M. *Adults with Poorly Controlled Epilepsy*. London, Royal College of Physicians, 1997.
2. Scottish Intercollegiate Guidelines Network (SIGN), *Diagnosis and Management of Epilepsy in Adults*. Scotland, Scottish Intercollegiate Guidelines Network (SIGN). November 1997: Pilot Edition.
3. Morrell, M. Guidelines for the care of women with epilepsy. *Neurology* 1998; **51** (Suppl. 4): S21–S27.
4. Sackett, D. L., Rosenberg, W. M. C., Gray, J. A. M., Haynes, R. B. and Richardson, W. S. Evidence-based medicine: what it is and what it isn't. *British Medical Journal* 1996; **312**: 71–72.
5. Anon. The periodic health examination. Canadian Task Force on the periodic health examination. *Canadian Medical Association Journal* 1979; **121**: 193–254.
6. Appleton, R. E. Epilepsy and the teenager. *Current Paediatrics* 1996; **6**: 88–91.
7. Appleton, R. E., Chadwick, D. and Sweeney, A. Managing the teenager with epilepsy: paediatric to adult care. *Seizure* 1997; **6**: 27–30.
8. Berkovic, S. F., Duncan, J. S. and Barkovich, A. ILAE neuroimaging commission recommendations for neuroimaging of patients with epilepsy. *Epilepsia* 1997; **38**: 1–2.
9. Aicardi, J. *Epilepsy in Children*. 2nd Edition. New York, Raven Press, 1994.
10. Morrell, M. J. Hormones and epilepsy through the lifetime. *Epilepsia* 1992; **33** (Suppl. 4): S49–S61.
11. Herzog, A. G. Reproductive endocrine considerations and hormonal therapy for women with epilepsy. *Epilepsia* 1991; **32** (Suppl. 6): S27–S33.
12. Wallace, H., Shorvon, S. and Tallis, R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet* 1998; **352**: 1970–1973.
13. Dansky, L. V., Andermann, E. and Andermann, F. Marriage and fertility in epileptic patients. *Epilepsia* 1980; **21**: 261–271.
14. Webber, M. P., Hauser, W. A., Ottman, R. and Annegers, J. F. Fertility in persons with epilepsy: 1935–1974. *Epilepsia* 1986; **27**: 746–752.
15. Schupf, N. and Ottman, R. Likelihood of pregnancy in individuals with idiopathic/cryptogenic epilepsy: social and biologic influences. *Epilepsia* 1994; **35**: 750–756.
16. Herzog, A. G., Seibel, M. M., Schomer, D. L., Vaitukaitis, J. L. and Geschwind, N. Reproductive endocrine disorders in women with partial seizures of temporal lobe origin. *Archives of Neurology* 1986; **43**: 341–346.
17. Isojärvi, J. I. T., Laatikainen, T. J., Knip, M., Pakarinen, A. J., Juntunen, K. T. and Myllyla, V. V. Obesity and endocrine disorders in women taking valproate for epilepsy. *Annals of Neurology* 1996; **39**: 579–584.
18. Isojärvi, J. I. T., Laatikainen, T. J., Pakarinen, A. J., Juntunen, K. T. and Myllyla, V. V. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *New England Journal of Medicine* 1993; **329**: 1383–1388.
19. Isojärvi, J., Rättyä, J., Knip, M., Pakarinen, A., Myllal, V. and Tapanainen, J. Replacing valproate with lamotrigine reduces cardiovascular risks and insulin mediated hyperandrogenism in women with epilepsy. *Epilepsia* 1997; **38** (Suppl. 3): Abstract.
20. Bilo, L., Meo, R., Valentino, R., Buiscaino, G. A., Striano, S. and Nappi, C. Abnormal pattern of luteinising hormone pulsatility in women with epilepsy. *Fertility and Sterility* 1991; **55**: 705–711.
21. Drislane, F. W., Coleman, A. E., Schomer, D. L., Ives, J., Levesque, L. A., Seibel, M. M. and Herzog, A. G. Altered pulsatility secretion of luteinising hormone in women with epilepsy. *Neurology* 1994; **44**: 306–310.
22. Herzog, A. G. Polycystic ovary syndrome in women with epilepsy: epileptic or iatrogenic. *Annals of Neurology* 1996; **39**: 559–560.
23. Lobo, R. A. A disorder without identity: 'HCA', 'PCO', 'PCOD','PCOS', 'SLS'. What are we to call it? *Fertility and Sterility* 1995; **63**: 1158–1160.
24. Betts, T. and Crawford, P. *Women and Epilepsy*. London, Martin Dunitz, 1998: pp. 27–28.
25. Herzog, A. G. Intermittent progesterone therapy and frequency of complex partial seizures in women with menstrual disorders. *Neurology* 1986; **36**: 1607–1610.
26. Mattson, R. H., Cramer, J. A., Caldwell, B. V. and Siconolfi, B. C. Treatment of seizures with medroxyprogesterone acetate: preliminary report. *Neurology (Cleveland)* 1984; **34**: 1255–1258.
27. Duncan, S., Read, C. L. and Brodie, M. J. How common is catamenial epilepsy. *Epilepsia* 1993; **34**: 827–831.
28. Mattson, R. H., Kamer, J. A., Caldwell, B. V. V. and Cramer, J. A. Seizure frequency and the menstrual cycle: a clinical study. *Epilepsia* 1981; **22**: 242.
29. Herzog, A. G., Klein, P. and Ransil, B. J. Three patterns of catamenial epilepsy. *Epilepsia* 1997; **38**: 1082–1088.
30. Mattson, R. A. and Cramer, J. A. Epilepsy, sex hormones and antiepileptic drugs. *Epilepsia* 1985; **26** (Suppl. 1): S40–S51.
31. Bäckstrom, T. Symptoms related to the menopause and sex steroid treatments. *Ciba Foundation Symposium* 1995; **191**: 171–180.
32. Laidlaw, J. Catamenial epilepsy. *Lancet* 1956; **271**: 1235–1237.
33. Bäckstrom, T. Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle. *Acta Neurologica Scandinavica* 1976; **54**: 321–347.
34. Rosciszewska, D., Buntner, B., Guz, I. and Zawisza, L. Ovarian hormones, anticonvulsant drugs and seizures during the menstrual cycle in women with epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry* 1986; **49**: 47–51.
35. Ansell, B. and Clarke, E. Acetazolamide in the treatment of epilepsy. *British Medical Journal* 1956; **1**: 650–654.
36. Livingston, S. *Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence*. Illinois, Thomas Springfield, 1972.
37. Herzog, A. G. Progesterone therapy in women with complex

partial and secondary generalized seizures. *Neurology* 1995; **45**: 1660–1662.
38. Dana-Haeri, J. and Richens, A. Effects of norethisterone on seizures associated with menstruation. *Epilepsia* 1983; **24**: 377–381.
39. Feely, M. and Gibson, J. Intermittent clobazam for catamenial epilepsy: tolerance avoided. *Journal of Neurology, Neurosurgery and Psychiatry* 1984; **47**: 1279–1282.
40. Feely, M., Calvert, R. and Gibson, J. Clobazam in catamenial epilepsy: a model for evaluating anticonvulsants. *Lancet* 1982; **2**: 71–73.
41. Herzog, A. G. Clomiphene therapy in epileptic women with menstrual disorders. *Neurology* 1988; **38**: 432–444.
42. Coulam, C. B. and Annegers, J. F. Do anticonvulsants reduce the efficacy of oral contraceptives? *Epilepsia* 1979; **20**: 519–526.
43. Koch, S., Losche, G. and Jager-Roman, E. *et al.* . Major birth malformations and antiepileptic drugs. *Neurology* 1992; **42** (Suppl. 5): 83–88.
44. Orme, M., Crawford, P., Chadwick, D. and Back, D. Contraception, epilepsy and pharmacokinetics. In: *Women and Epilepsy*. (Ed. M. R. Trimble). Chichester, J. Wiley & Sons, 1991: pp. 145–158.
45. Baruzzi, A., Albani, R. and Riva, R. Oxcarbazepine: pharmacokinetic interactions and their clinical relevance. *Epilepsia* 1994; **35**. (Suppl. 3): S14–S19.
46. Trussell, J. and Kost, K. A guide to interpreting contraceptive efficacy studies. *Obstetrics and Gynecology* 1990; **76**: 558–567.
47. Krauss, G. L., Brandt, J., Campbell, M., Plate, C. and Summerfield, M. Antiepileptic medication and oral contraceptive interactions: a national survey of neurologists and obstetricians. *Neurology* 1996; **46**: 1534–1539.
48. Morrell, M. Sexuality in epilepsy. In: *A Comprehensive Textbook of Epilepsy*. (Eds J. Engel and T. Pedley). Philadelphia, Lippincott-Raven, 1997: pp. 2021–2026.
49. Betts, T. and Kenwood, C. *Practical Psychiatry*. Oxford, Oxford University Press, 1992: pp. 314–332.
50. Toone, B. Epilepsy and sexual life. In: *Epilepsy.* 2nd Edition (Eds A. Hopkins, S. Shorvon and G. Cascino). London, Chapman-Hall, 1995: pp. 557–564.
51. Betts, T. and Fox, C. Evaluation of a preconception clinic for women with epilepsy. *Seizure* 1999; (in press).
52. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Prognostic index for recurrence of seizures after remission of epilepsy. *British Medical Journal* 1993; **306**: 1374–1378.
53. Driver and Vehicle Licensing Agency. *At a Glance Guide to the Current Medical Standards of Fitness to Drive*. Swansea, Drivers Medical Unit, DVLA, March, 1998.
54. Gaily, E., Granstrom, M. L., Hiilesmaa, V. and Bardy, A. Minor abnormalities in children of mothers with epilepsy. *Journal of Pediatrics* 1988; **112**: 520–529.
55. Annegers, J. F., Elveback, L. R., Hauser, W. A., Anderson, V. E. and Kurland, L. I. Congenital malformations and seizure disorders in the offspring of parents with epilepsy. *International Journal of Epidemiology* 1978; **7**: 241–247.
56. Nakane, Y., Okuma, T. and Takahishi, R. *et al.* . Multiinstitutional study on the teratogenicity and fetal toxicity of anticonvulsants: a report of a collaborative study group in Japan. *Epilepsia* 1980; **21**: 663–680.
57. Dansky, L. V. The teratogenic effects of epilepsy and anticonvulsant drugs. In: *Epilepsy.* 2nd Edition (Eds A. Hopkins, S. Shorvon and G. Cascino). London, Chapman and Hall, 1995: pp. 535–536.
58. Dencker, L. Fetal development and sensitivity periods in man. In: *Epilepsy and Pregnancy*. (Eds T. Tomson, L. Gram, M. Sillanpaa and I. S. Johannessen). Chichester, Wrightson Biomedical Publishing Ltd, 1997: pp. 1–9.
59. Samren, E. B., van Duijn, C. M. and Koch, S. *et al.* . 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* 1997; **38**: 981–990.
60. Gaily, E. Minor abnormalities and effects on psychomotor development associated with maternal use of antiepileptic drugs. In: *Epilepsy and Pregnancy*. (Eds T. Tomson, L. Gram, M. Sillanpaa and I. S. Johannessen). Chichester, Wrightson Biomedical Publishing Ltd, 1997: pp. 63–70.
61. Lindhout, D., Hoppener, R. J. E. A. and Meinardi, H. Teratogenicity of antiepileptic drug combinations with special emphasis on epoxidation of carbamazepine. *Epilepsia* 1984; **25**: 77–83.
62. Waters, C. H., Belai, Y., Gott, P. S., Shen, P. and De Giorgio, C. M. Outcomes of pregnancy associated with antiepileptic drugs. *Archives of Neurology* 1994; **51**: 250–253.
63. Hanson, J. W. and Smith, D. W. The fetal hydantoin syndrome. *Journal of Pediatrics* 1975; **87**: 285–290.
64. Lindhout, D. and Omtzigt, J. G. C. Teratogenic effects of antiepileptic drugs: Implication for the management of epilepsy in women of the child bearing age. *Epilepsia* 1994; **35** (Suppl. 4): 19–28.
65. Kallen, B., Robert, E., Mastroiacovo, P., Martinez-Frias, M. L., Castilla, E. E. and Cocchi, G. Anticonvulsant drugs and malformations: is there a drug specificity? *European Journal of Epidemiology* 1989; **5**: 31–36.
66. Anderson, R. C. Cardiac defects in children of mothers receiving anticonvulsant therapy during pregnancy. *Journal of Pediatrics* 1976; **89**: 318–319.
67. Lindhout, D., Omtzigt, J. G. C. and Cornel, M. C. Spectrum of neural-tube defects in 34 infants prenatally exposed to antiepileptic drugs. *Neurology* 1992; **42** (Suppl. 5): 111–118.
68. Nau, H. Toward the mechanism of valproic acid induced neural tube defects. In: *Epilepsy and Pregnancy*. (Eds T. Tomson, L. Gram, M. Sillanpaa and I. S. Johannessen). Chichester, Wrightson Biomedical Publishing, 1997: pp. 35–42.
69. Rosa, F. W. Spina bifida in infants of women treated with carbamazepine during pregnancy. *New England Journal of Medicine* 1991; **324**: 674–677.
70. Jones, K. L., Lacro, R. V., Johnson, K. A. and Adams, J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *New England Journal of Medicine* 1989; **320**: 1661–1666.
71. Ornoy, A. and Cohen, E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Archives of Disease in Childhood* 1996; **75**: 517–520.
72. Hanson, J. W. and Buehler, B. A. Fetal hydantoin syndrome: current status. *Journal of Pediatrics* 1982; **101**: 816–818.
73. Nulman, I., Scolnik, D., Chitayat, D., Farkas, L. D. and Koren, G. Findings in children exposed in utero to phenytoin and carbamazepine monotherapy: independent effects of epilepsy and medications. *American Journal of Medical Genetics* 1997; **68**: 18–24.
74. DiLiberti, J. H., Farndon, P. A., Dennis, N. R. and Curry, C. J. The fetal valproate syndrome. *American Journal of Medical Genetics* 1984; **19**: 473–481.
75. Jager-Roman, E. and Deichl, A. *et al.* Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid. *Journal of Pediatrics* 1986; **108**: 997–1004.
76. Granstrom, M. L. and Gaily, E. Psychomotor development in children of mothers with epilepsy. *Neurology* 1992; **42** (Suppl. 5): 144–148.
77. Morrell, M. The new antiepileptic drugs and women: efficacy, reproductive health, pregnancy and fetal outcome. *Epilepsia* 1996; **37** (Suppl. 6): S34.
78. Petrere, J. A. and Anderson, J. A. Developmental toxicity studies in mice, rats and rabbits with anticonvulsant gabapentin. *Fundamental Applied Toxicology* 1999; **23**: 585–589.

79. Medical Research Council (MRC) Vitamin Study Research Group. Prevention of neural-tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991; **338**: 131–137.
80. Czeizel, A. E. and Dudas, I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *New England Journal of Medicine* 1992; **327**: 1832–1835.
81. Rosenberg, I. H. Folic acid and neural-tube defects—time for action? *New England Journal of Medicine* 1992; **327**: 1875–1876.
82. Department of Health. Chief Medical Officer (letter), 17 December PL/CMO (92) 18 1/CNO (92) 12, 1992.
83. Berkovic, S. F., Howell, R. A., Hay, D. A. and Hopper, J. L. Epilepsies in twins: genetics of the major epilepsy syndromes. *Annals of Neurology* 1998; **43**: 435–445.
84. Schmidt, D. The effect of pregnancy on the natural history of epilepsy: a review of the literature. In: *Epilepsy, Pregnancy and the Child*. (Eds D. Janz, M. Dam and A. Richens *et al.*). New York, Raven Press, 1983: pp. 3–14.
85. Tomson, T. Seizure control during pregnancy and delivery. (Eds T. Tomson, L. Gram, M. Sillanpaa and I. S. Johannessen). Chichester, Wrightson Biomedical Publishing, 1997: pp. 113–123.
86. Tomson, T., Lindbom, U., Ekqvist, B. and Sundqvist, A. Epilepsy and pregnancy: a prospective study of seizure control in relation to free and total plasma concentrations of carbamazepine and phenytoin. *Epilepsia* 1994; **35**: 122–130.
87. Schmidt, D., Canger, R. and Avanzini, G. *et al.* Change of seizure frequency in pregnant epileptic women. *Journal of Neurology Neurosurgery and Psychiatry* 1983; **46**: 751–755.
88. Bardy, A. *Epilepsy and Pregnancy, A Prospective Study of 154 Pregnancies in Epileptic Women*, University of Helsinki, Finland, 1982.
89. Delgado-Escuera, A. V. and Janz, D. Consensus guidelines preconception counselling, management, and care of the pregnant woman with epilepsy. *Neurology* 1992; **42** (Suppl. 5): 149–160.
90. Yerby, M. S. Contraception, pregnancy and lactation in women with epilepsy. *Bailliere's Clinical Neurology* 1996; **5**: 887–908.
91. Devinsky, O. and Yerby, M. S. Women with epilepsy: reproduction and effects of pregnancy on epilepsy. *Neurologic Clinics* 1994; **12**: 479–495.
92. Steegers-Theunissen, R. P., Renier, W. O. and Borm, G. F.*et al.* Factors influencing the risk of abnormal pregnancy outcome in epileptic women: a multi-centre prospective study. *Epilepsy Research* 1994; **18**: 261–269.
93. Yerby, M. S. Problems and management of the pregnant women with epilepsy. *Epilepsia* 1997; **28** (Suppl. 3): 29–36.
94. Beaussant-Defaye, J., Basten, N., Demarca, C. and Beaussart, M. *Epilepsies and Reproduction*. Nord Epilepsy Research and Information Group (Vol. II). Lille, Grine, 1985.
95. Lander, C. M. and Eadie, M. J. Plasma antiepileptic drug concentrations during pregnancy. *Epilepsia* 1991; **32**: 257–266.
96. Yerby, M. S., Friel, P. N. and McCormack, K. Antiepileptic drug disposition during pregnancy. *Neurology* 1992; **42** (Suppl. 5): 12–16.
97. Hyett, J., Perdu, M., Sharland, G., Snijders, R. and Nicolaides, K. Using fetal nuchal translucency to screen for major congenital cardiac defects at 10–14 weeks gestation: population based cohort study. *British Medical Journal* 1999; **318**: 81–85.
98. Patsalos, P. N. and Duncan, J. S. Antiepileptic drugs. A review of clinically significant drug interactions. *Drug Safety* 1993; **9**: 156–186.
99. Anon. ACOG Educational Bulletin. Seizure disorders in pregnancy. Number 231, Dec 1996. Committee on Education. Bulletins of the American College of Obstetricians and Gynecologists. In: *International Journal of Gynaecology and Obstetrics*, Vol. 56. 1997: pp. 279–286.
100. Sabers, A. Complications during pregnancy and delivery. In: *Epilepsy and Pregnancy*. (Eds T. Tomson, L. Gram, M. Sillanpaa and I. S. Johannessen). Chichester, Wrightson Biomedical Publishing Ltd, 1997: pp. 105–111.
101. Lulseged, S. Haemorrhagic disease of the newborn: a review of 127 cases. *Annals of Tropical Paediatrics* 1993; **13**: 331–336.
102. Clarkson, P. and James, A. Parenteral vitamin K: the effective prophylaxis against haemorrhagic disease for all newborn infants. *New Zealand Medical Journal* 1990; **103**: 95–96.
103. Huysman, M. W. and Sauer, P. J. The vitamin K controversy. *Current Opinion in Pediatrics* 1994; **6**: 129–134.
104. VonKries, R. Neonatal vitamin K prophylaxis: the Gordian Knot still awaits untying. *British Medical Journal* 1998; **316**: 161–162.
105. Ekelund, H., Finnstrom, O., Gunnarskog, J., Kallen, B. and Larsson, Y. Administration of vitamin K to newborn infants and childhood cancer. *British Medical Journal* 1993; **307**: 89–91.
106. Anon, Which vitamin K preparation for the newborn? *Drug and Therapeutic Bulletin* 1998; **36**: 17–19.
107. Parker, L., Cole, M., Craft, A. W. and Hey, E. N. Neonatal vitamin K administration and childhood cancer in the North of England. *British Medical Journal* 1998; **316**: 189–193.
108. McKinney, P. A., Juszczak, E., Findlay, E. and Smith, K. Case-control study of childhood leukaemia and cancer in Scotland: findings for neonatal intramuscular vitamin K. *British Medical Journal* 1998; **316**: 173–177.
109. Passmore, S. J., Draper, G., Brownbill, P. and Kroll, M. Ecological studies of relation between hospital policies on neonatal vitamin K administration and subsequent occurrence of childhood cancer. *British Medical Journal* 1998; **316**: 184–189.
110. Passmore, S. J., Draper, G., Brownbill, P. and Kroll, M. Case-control studies of relation between childhood cancer and neonatal vitamin K administration. *British Medical Journal* 1998; **316**: 178–184.
111. Hopkins, A. and Shorvon, S. Definitions and epidemiology of epilepsy. In: *Epilepsy.* 2nd Edition (Eds A. Hopkins, S. Shorvon and F. Cascino). London, Chapman Hall, 1995: pp. 1–24.
112. Chien, P. F., Khan, K. S. and Arnott, N. Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: an overview of the evidence from randomized trials. *British Journal of Obstetrics and Gynaecology* 1996; **103**: 1985–1991.
113. Lewis, R. and Sibai, B. Recent advances in the management of pre-eclampsia. *Journal of Maternal and Fetal Medicine* 1997; **6**: 6–15.
114. Witlin, A. G., Friedman, S. A. and Sibai, B. M. The effect of magnesium sulfate therapy on the duration of labor in women with pre-eclampsia at term: a randomized, double-blind, placebo-controlled trial. *American Journal of Obstetrics and Gynecology* 1997; **176**: 623–627.
115. Nau, H., Kuhnz, W., Egger, H. J., Rating, I. and Helge, H. Anticonvulsants during pregnancy and lactation. Transplacental, maternal and neonatal pharmacokinetics. *Clinical Pharmacokinetics* 1982; **7**: 508–543.
116. Matheson, I. and Skjaeraasen, J. Milk concentrations of flupenthixol, nortriptyline and zuclopenthixol and between breast differences in two patients. *European Journal of Pharmacology* 1988; **35**: 217–220.
117. Fleishaker, J. C., Desai, N. and McNamara, P. J. Factors affecting the milk to plasma drug concentration ratio in lactating women: physical interactions with protein and fat. *Journal of Pharmacological Science* 1987; **76**: 189–193.
118. Tomson, T., Ohman, I. and Vitols, S. Lamotrigine in pregnancy and lactation: a case report. *Epilepsia* 1997; **38**: 1039–1041.

119. Rambeck, B., Kurlemann, G., Stodieck, S. R., May, T. W and Jurgens, U. Concentrations of lamotrigine in a mother on lamotrigine treatment and her newborn child. *European Journal of Clinical Pharmacology* 1997; **51**: 481–484.
120. Ohman, I., Tomson, T. and Vitols, S. Lamotrigine levels in plasma and breast milk in nursing women and their infants. *Epilepsia* 1998; **39** (Suppl. 2): 21.
121. Briggs, G. G., Freeman, R. K. and Yaffe, S. J. *Drugs in Pregnancy and Lactation.* 4th Edition. Baltimore, MD, Williams and Wilkins, 1994.
122. Bennet, P. N. and the WHO Working Group, *Drugs and Human Lactation*. Amsterdam, Elsevier, 1988.
123. Vinge, E. Breast feeding and antiepileptic drugs. In: *Epilepsy and Pregnancy*. (Eds T. Tomson, L. Gram, M. Sillanpaa and I. S. Johannessen). Chichester, Wrightson Biomedical Publishing Ltd, 1997: pp. 93–103.
124. Vermeulen, J. and Aldenkamp, A. P. Cognitive side-effects of chronic antiepileptic drug treatment: a review of 25 years of research. *Epilepsy Research* 1995; **22**: 65–95.
125. Meador, K. J. Cognitive side-effects of antiepileptic drugs. *Canadian Journal of Neurological Science* 1994; **21**: S12–S16.
126. Rosciszewska, D. Epilepsy and the menstrual cycle. *Pol Tyg Lek* 1994; **49**: 99–101.
127. Khaw, K. T. Hormone replacement therapy again. *British Medical Journal* 1998; **316**: 1842–1844.
128. Crawford, P. and Lee, P. Gender difference in the management of epilepsy—what women are hearing. *Seizure* 1999; **8**: 135–139.
129. Grodstein, F., Stampfer, M. J. and Manson, J. *et al.* E. Postmenopausal oestrogen and progestin use and the risk of cardiovascular disease. *New England Journal of Medicine* 1996; **335**: 453–461.
130. Department of Health and Social Security, *Report of the Working Group on Services for People with Epilepsy*. London, HMSO, 1986.
131. Taylor, M. P. Epilepsy in a Doncaster practice: audit and change over eight years. *Journal of the Royal College of General Practitioners* 1987; **37**: 116–119.
132. Brown, S., Betts, T., Crawford, P., Hall, B., Shorvon, S. and Wallace, S. Epilepsy needs revisited: a revised epilepsy needs document for the UK. *Seizure* 1998; **7**: 435–440.
133. Crawford, P. Guide to the withdrawal of antiepileptic drugs. *Prescriber* 1998; **9**: 113–115.
134. Taylor, M., Readman, S., Hague, B., Boulter, V., Hughes, L. and Howell, S. A district epilepsy service, with community-based specialist liaison nurses and guidelines for shared care. *Seizure* 1994; **3**: 121–127.
135. Ridsdale, L. Diagnosis and care of epilepsy. *Practitioner* 1997; **241**: 528–533.
136. Taylor, M. P. *Managing Epilepsy in Primary Care*. Oxford, Blackwell Science, 1996.
137. Hall, B., Martin, E. and Smithson, H. *Epilepsy: A General Practice Problem*. Royal College of General Practitioners, General Practice Series. London, Royal College of General Practitioners, 1997.

APPENDIX

Organizations

Joint Epilepsy Council,
P.O. Box 27027,
Edinburgh EH10 5YN
Tel: (0131) 466 7155
Fax: (0131) 466 7156

National Society for Epilepsy, Chalfont St Peter, Gerrards Cross, Bucks SL9 0RJ
Tel: (01494) 601 300
Fax: (01494) 871 927

British Epilepsy Association, Anstey House, 40 Hanover Square, Leeds, West Yorkshire LS3 1BE
Tel: (0113) 243 9393
Fax: (0113) 242 8804

International League Against Epilepsy (British Branch), Professor S Shorvon (Secretary), c/o National Hospital for Neurology and Neurosurgery, Queen Square, London
Tel: (0171) 837 3611
Fax: (0171) 829 8720

The Epilepsy Association of Scotland,
48 Govan Road, Glasgow G51 1JL
Tel: (0141) 427 4911
Fax: (0141) 427 7414

UK Epilepsy and Pregnancy Register, c/o Dr JI Morrow, Department of Neurology, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA