Scottish Obstetric Guidelines and Audit Project

A Guideline Development Project initiated by the Scottish Executive Committee of the RCOG, funded by the Clinical Resource and Audit Group of the SODoH and working to the methodology of the Scottish Intercollegiate Guidelines Network

The Management of Pregnancy

in

Women with Epilepsy

A clinical Practice Guideline for Professionals Involved in Maternity Care in Scotland

Pilot Edition

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CONTENTS

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1. INTRODUCTION

1.1 WHY A CLINICAL PRACTICE GUIDELINE ON THE MANAGEMENT OF PREGNANCY IN WOMEN WITH EPILEPSY?

Epilepsy is one of the most common chronic illnesses encountered by obstetricians, affecting around 1 in 200 women attending antenatal clinics. Epilepsy itself is associated with a risk of giving birth to a malformed child around 25% higher than for pregnant women generally (in whom the risk is 2-3%) and, for women with epilepsy who are taking anti-epileptic drugs, the increased risk is around three-fold. (Nevertheless, over 90% of babies born to epileptic mothers are normal). The babies of women with epilepsy are also at increased risk of neonatal problems, including haemorrhagic disease of the newborn and 'abstinence syndrome'

In addition to these effects of epilepsy and anti-epileptic medication on the progress of pregnancy, the pregnancy may also influence the progress of epilepsy, with an increase in seizure frequency in around a third of women and altered metabolism of anti-epileptic drugs.

A recent survey of obstetricians in Scotland (Russell et al,)[1] revealed that 20% were dissatisfied with the present level of care received by their patients with epilepsy and over 90% considered guidelines to be important.

Because epilepsy is a common medical condition complicating pregnancy which has important implications for fetal and neonatal well-being, and because of the spirit of support for Guidelines among obstetricians in Scotland, the SOGAP group have included *'Management of Pregnancy in Women with Epilepsy'* among its first four topics for formal obstetric guideline development.

1.2 WHO HAS DEVELOPED THIS GUIDELINE?

This Guideline has been developed by a multi-professional working group representing obstetrics, clinical pharmacology, general practice and midwifery, and including patients nominated by the Epilepsy Association of Scotland. Input from additional clinicians, and a further nominee of the Epilepsy Association was obtained through a peer review appraisal of an advanced draft of the guideline. The group was convened by the grant holders of the Scottish Obstetric Guidelines and Audit Project (SOGAP). The project was originally conceived, and the topics for guideline development chosen by, the Scottish Executive Committee of the RCOG with input from the funding body, the Clinical Resource and Audit Group (CRAG) of the SODoH.

1.3 FOR WHOM IS THIS GUIDELINE INTENDED?

The guideline has been produced under the auspices of the Scottish Executive Committee of the RCOG and is aimed at all healthcare professionals who share in maternity care. In particular, it is hoped that fellows, members and diplomates of the RCOG and their trainees, midwives and general practitioners will find it helpful.

1.4 WHAT METHODS HAVE BEEN USED IN THE DEVELOPMENT OF THIS GUIDELINE?

The development of the guideline has drawn on methodology outlined in the CRAG publication *'Clinical Guidelines'*[2], the SIGN publication '*Clinical Guidelines: Criteria for Appraisal for National Use*'[3] and the NHS Executive's '*Clinical Guidelines*'[3].

In preparing the Guideline, a systematic literature search was undertaken using *CD plus Medline* for the years 1986 - 1996 (principal search terms: pregnancy and epilepsy) and the *Cochrane Pregnancy and Childbirth Database (CPCD)* in order to identify evidence based on randomised controlled trials (RCTs), other forms of clinical study and expert opinion which is appropriate for translation into clinical practice in Scotland. Material identified from the searches was supplemented by references already known to group members and by scrutiny of the reference lists of identified publications for key references from earlier years.

The guideline development group particularly acknowledges the content of the consensus guidelines prepared by Delgado-Escueta and Janz[5] and the Royal College of Midwives publication "*Standards for midwives: the care of mothers with epilepsy*"[6] and has drawn on these in the preparation of this document. Late in the preparation of this guideline, an ACOG Educational Bulletin on Seizure Disorders in Pregnancy (December 1996) became available. The recommendations in the Bulletin largely accord with those in this guideline except for a preference for frequent monitoring of serum anticonvulsant levels in the Bulletin.

The recommendations within this guideline have been graded according to the levels of evidence on which they are based, using the scheme adopted by SIGN[3] which is based on the system proposed by the US Agency for Health Care Policy and Research[7]. The scheme for grading of recommendations is reproduced here (Table I). The literature search undertaken during the preparation of this guideline revealed **no** RCTs relevant to the topic. All recommendations within this guideline are therefore at the Grade B or C level.

The guideline development group met on three occasions and developed successive drafts of the guideline. An advanced draft was then submitted for peer review to a panel of professionals and patient representatives who had not been involved in the development process. The suggestions of the peer reviewers were incorporated in the final version prior to submission to the SIGN editorial board and the Scottish Executive Committee of the RCOG.

Minutes of the guideline development process and copies of all publications quoted in the text are held at the SOGAP offices in Glasgow and Aberdeen.

Table I Grading of recommendations

Grade	**Recommendation** (based on AHCPR 1994)
A	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation
C	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

Throughout the text of the guideline, it has been made explicit which individual recommendations are based on clinical studies (Grade B recommendations) and on the consensus view of the Guideline Development Group (indicating an absence of relevant studies) (Grade C recommendations).

1.5 HOW WILL THIS GUIDELINE BE IMPLEMENTED AND REVIEWED?

This guideline was launched, along with three other guidelines being developed by SOGAP, at a national meeting in March 1997 to which representatives of key disciplines from throughout Scotland were invited. Discussion of the guideline in this forum allowed minor modifications to be made in the light of suggestions from a wider group. A lead clinician from each maternity unit in Scotland will be recruited to initiate the development of local protocols based on the four SOGAP guidelines. Local protocol development and implementation will be supported by site visits by the SOGAP team during the final year of the project timetable.

The impact of the SOGAP guidelines on the process and outcome of care will be monitored through the project's audit component. A profile of pre-guideline practice is currently being prepared based on the results of a questionnaire survey of relevant professional groups (to assess the process of care) and on analysis of relevant data collected by the Information and Statistics Division (ISD) of the NHS in Scotland (to assess the outcome of care). In due course, a similar profile of post-guideline practice will be compiled, using the same methods, in order that any changes can be identified. In addition to this audit component of the SOGAP project, some clinicians may wish to audit the care of pregnant women with epilepsy as part of their local audit programmes. A suggested minimum dataset which might be used for audit at a local level is included in this document (Appendix I).

This guideline is based on evidence and consensus views available at the time of final preparation (December 1997) and will be reviewed under the direction of the Scottish Executive Committee of the RCOG in December 1999, or sooner if changing evidence requires it.

1.6 DECLARATION OF INTERESTS

Declarations of interests (personal, specific and non-specific; non-personal, specific and non-specific) as defined by SIGN[3] have been obtained from all Guideline Development Group members. No conflicts of interest have been identified and copies of all declarations are held at the SOGAP offices in Glasgow and Aberdeen.

2. THE GUIDELINE

2.1 PRE-PREGNANCY CARE AND COUNSELLING

Recommendations

- Pregnancies in women with epilepsy should, whenever possible, be **planned** pregnancies in order that the maximum benefits of peri-conception care can be obtained.
  (GRADE C)

- The avoidance of unplanned pregnancy requires the use of effective contraception. The efficacy of hormonal contraception is reduced in women on enzyme-inducing anticonvulsants (carbamazepine, phenytoin, primidone, phenobarbitone). Combined contraceptive pill regimens containing at least 50µg oestrogen/day or non-hormonal methods should be chosen by such women.
  (GRADE B)

- All women with epilepsy should be provided with the following information from the point of diagnosis onwards, even if not immediately planning pregnancy:
  (GRADE C)

⇒ The majority of babies born to mothers with epilepsy are normal. Nevertheless, women with epilepsy, especially those receiving anti-epileptic drugs, have an increased risk of giving birth to a baby with major malformations, minor anomalies or dysmorphic features compared to women without epilepsy.

⇒ It is possible that some of this risk is caused by a genetic predisposition for birth defects inherent in some families. Both potential parents' family histories should be reviewed.

⇒ Pre-natal screening using serum testing and ultrasound can detect many major malformations and anomalies.

⇒ Tonic-clonic convulsions during pregnancy carry risks for both mother and fetus. Anticonvulsant treatment during pregnancy should be chosen so as to minimise the occurrence of convulsions.

⇒ Anticonvulsant therapy is associated with an increased risk of neural tube defects. Periconceptual folic acid supplementation is therefore of particular importance for women with epilepsy.

⇒ Before and during pregnancy, the aim should be the lowest dose of anticonvulsants that protects against seizures. Pre-pregnancy withdrawal of anticonvulsants could be considered for selected women and a change from poly to monotherapy could be considered for some others.

(These recommendations for counselling of women who may plan pregnancy are adapted from Delgado-Escueta and Janz[5]).

The associations between epilepsy itself and anti-epileptic drugs with fetal malformations, anomalies and dysmorphisms are well established. The evidence for these associations has been extensively reviewed[8] It is also well documented that the incidence of malformations is related to the number of anti-epileptic drugs taken during the first trimester[9].

Clearly therefore, achieving the best possible outcome of pregnancy for women with epilepsy requires that care begins even prior to conception. It has been advised very appropriately[5], that women with epilepsy should be made aware of the known facts about epilepsy and pregnancy outcome from the time of diagnosis, even if they are not immediately planning pregnancy. Equipped with these facts,

women are able to appreciate the importance of pre-conceptual modification of their anticonvulsant regimens and will be motivated to seek pre-conceptual care.

The recommendations prefacing this section of the Guideline are based on those items of information which the Consensus Guideline of Delgado-Escueta and Janz[5] suggests should be made available to all epileptic women of child-bearing age. The SOGAP Group commends the information leaflets for women produced by the Royal College of Midwives/Joint Epilepsy Council of the UK and Ireland, *Guidelines for Women with Epilepsy*[10], and by the Joint Epilepsy Council, *Choices: Women and Epilepsy*[11], and suggests that these be made available to women in General Practice and Specialist Clinic settings from the point of diagnosis of epilepsy onwards.

The full benefits of peri-conceptual care can only be realised if pregnancies in women with epilepsy are planned pregnancies. Women on the enzyme-inducing anticonvulsants (phenobarbitone, phenytoin, primidone, carbamazepine and possibly also topiramate) have particular problems with contraception (and therefore with achieving planned pregnancies) as these drugs increase the rate of metabolism of contraceptive steroids[12]. The intra-uterine device may be a suitable contraceptive method for many women with epilepsy. Those who prefer to use hormonal methods should have treatment modified in line with current recommendations which are summarised below

Hormonal Contraception for Women taking Enzyme-inducing Anticonvulsants (phenobarbitone, phenytoin, primidone, carbamazepine)
This advice comprises Grade C recommendations extracted from the *FPA Contraceptive Handbook*[12] and *Handbook of Family Planning*[13]

Combined oral Contraceptive Pill (COC)
- Use a 50µg oestrogen pill (eg Norinyl-1, Ovran).
- If break through bleeding (BTB) occurs, combine pills to provide 80 or 100 (maximum) µg oestrogen.
- The use of 4 packs of COCs consecutively with a reduced pill-free interval of 4 days after the fourth pack is recommended. Such a regimen provides enhanced contraceptive cover and can reduce the frequency of seizures if hormonally triggered.
- Maintain extra contraceptive cover for 8 weeks if enzyme-inducers withdrawn.

Progestogen-only pill (POP)
- Probably best avoided. If no other method acceptable, doubling the daily dose of POP reported to be effective.

Depot progestogen (Depo-provera)
- Reduce interval between depo-provera injections from 12 weeks to 10.

Progestogen implants (Norplant)
- Currently, not recommended in long-term users of enzyme-inducing drugs.

Clinicians should ensure that women with epilepsy are aware of the support and advice which is available to them through the Epilepsy Association of Scotland (0141 427 4911).

2.2 FOLIC ACID

Recommendation

- All women with epilepsy should be advised to take folic acid 5mg daily while attempting to conceive and for at least 12 weeks after conception.
  (GRADE C)

Neural tube defects are among the malformations which occur more commonly in women on anti-epileptic medication, particularly with sodium valproate[14,15]. It is firmly established that peri-conceptual folic acid (in a dose of 4-5mg/day) is effective in reducing the risk of neural tube defect among mothers at high risk due to having had a previous affected child[16]. Moreover, animal (mouse) studies have shown that high doses of valproate are associated with altered concentrations of specific folate forms in embryonic tissues and increased incidence of neural tube anomalies. However, human studies demonstrating a protective effect of folate supplementation in women with epilepsy are lacking.

Both the UK government[17] and the US Center for Disease Control and Prevention (CDCP)[18] have interpreted available data and reached common recommendations that all women anticipating pregnancy should consume 0.4mg daily of folic acid and that those with a previous pregnancy affected by neural tube defect should consume 4.0mg daily. Despite stronger evidence for the protective effect of 4.0mg (rather than 0.4mg) daily, the higher dose recommendation has not been extended to all women because of the possibility of complicating the diagnosis of vitamin B_{12} deficiency and uncertainties about other possible risks of such doses.

All relevant documents studied in the course of developing this guideline recommend that women with epilepsy receive peri-conceptual folic acid supplements although there is some discord about whether supplementation should be at the 4.0mg, or 0.4mg, level. Recent papers in the HMSO publication *Prescribers' Journal,*[19] and in *British Journal of Hospital Medicine,*[8] advocated supplementation in the higher dose range for all women with epilepsy , whereas a review in *Drug and Therapeutics Bulletin*[20] advocated the 0.4mg dose for women with epilepsy in general and the 4.0mg dose only for those at high risk as a result of a previous affected pregnancy or medication with carbamazepine or valproate specifically. In the interests of simplicity, the SOGAP group concur with those authorities advocating the higher daily dose for **all** women with epilepsy, and have chosen a 5mg, rather than a 4mg dose as this tablet size is more readily available.

2.3 VITAMIN K

Recommendation

- The babies of women treated with enzyme-inducing anticonvulsants (carbamazepine, phenytoin, primidone, phenobarbitone) are at increased risk of haemorrhagic disease of the newborn caused by deficiency of vitamin K-dependent clotting factors. Women on these drugs should be treated prophylactically with vitamin K (Konakion) 20mg orally daily from 36 weeks gestation until delivery and their babies should receive vitamin K 1mg intramuscularly at birth.
  (GRADE B)

A recent reviewer[21] has identified more than 40 case reports of neonatal haemorrhage in infants born to mothers treated with anti-epileptic drugs during pregnancy, and also described a series of 115 neonates born to women taking enzyme-inducing anticonvulsants, of whom 8 experienced severe internal bleeding. Furthermore, a case-control study[22] has confirmed that infants born to mothers taking anticonvulsants have an increased incidence of vitamin K deficiency (as reflected by induction of the protein PIVKA-11) compared to infants of control mothers.

A recent review in *Drugs*[23] has considered the evidence that vitamin K can cross the placenta from maternal to fetal circulation and can improve clotting in the neonate. Studies are quoted which demonstrate that the administration of oral vitamin K 20mg daily for two weeks to the mother is associated with a significant increase in prothrombin levels in the neonate. A case control study[24] showed an absence of PIVKA II (reflecting adequate vitamin K levels) in **all** cord blood samples from infants of mothers on enzyme-inducers treated with antenatal vitamin K, but PIVKA II was measurable (reflecting vitamin K deficiency) in 7 of 20 controls.

Recommendations that mothers with epilepsy receive vitamin K tablets throughout the month before delivery were made as long ago as the 1980's[21], but a recent survey of Scottish obstetricians[1] revealed that 56% never give epileptic women vitamin K; only 7 obstetricians were able to give details of the dosage regimen they would use and a few did not give vitamin K to the newborn infants of epileptic mothers.

Delgado-Escueta and Janz[5] have summarised expert opinions regarding the role of vitamin K in pregnant women with epilepsy. They state that "***all*** *agree that the newborn should receive 1mg of vitamin K intramuscularly at birth*" and "***a majority*** *consider it prudent to administer vitamin K (20mg/ day) prophylactically to the AED*-treated mother during the last month of pregnancy*". These views are reiterated in reviews in *Drugs*[23] and *Prescribers' Journal*[19].

Two oral preparations of vitamin K are currently available, menadiol sodium phosphate (Synkavit) and phytomenadione (Konakion). The former is listed by the manufacturers as contra-indicated in pregnancy. Currently therefore, Konakion is the recommended preparation (Aberdeen Royal Hospitals Trust, Drug Information Service). The standard NHS cost of four weeks treatment is around £10.

2.4 MANAGEMENT OF WOMEN AT RISK OF PRETERM DELIVERY

Recommendations

- Steroid metabolism is potentiated by enzyme-inducing anticonvulsants. Women taking any of these drugs, requiring antenatal steroid therapy because of a perceived risk of preterm delivery, should receive a steroid regimen providing a total of 48mg (rather than the 24mg advocated for other women). This dose may be delivered as two doses of 24mg betamethasone, 12 hours apart. **(GRADE C)**

- If steroid therapy is initiated in a woman on enzyme-inducing anticonvulsants, the perceived risk of preterm delivery also constitutes an indication to commence oral vitamin K therapy at 20mg daily **(GRADE C)**

The companion SOGAP guideline on *Preparation of the Fetus for Preterm Delivery* advocates an increased dose of steroid (with a reduced interval of 12, rather than 24, hours between doses) for women on enzyme-inducing anticonvulsants. This recommendation was made on theoretical grounds and represents the view of the SOGAP *Preterm Delivery* group. The preterm neonate is at particular risk of haemorrhagic disease of the newborn, and it is therefore appropriate to begin maternal vitamin K therapy before the usual 36 weeks gestation if a risk of preterm delivery is perceived.

* Anti-epileptic drug

2.5 ANTICONVULSANT DRUGS BEFORE AND DURING PREGNANCY

Recommendations

- Women with epilepsy who present for pre-conception advice should be referred to a clinician with appropriate expertise for assessment. Such assessment should include full clinical history taking in order that the diagnosis of epilepsy is reviewed and the specific epileptic syndrome present is identified.
  (GRADE C)

- For selected women presenting pre-conceptually who have been seizure-free for at least two years, specialist management may include supervised withdrawal of anticonvulsant medication over a period of 3-6 months.
  (GRADE B)

- For women presenting pre-conceptually and for whom drug withdrawal is inappropriate (those who have not been seizure-free for two years, those whose specific epilepsy syndrome is known to require continual drug treatment and those unwilling to accept a risk of seizure recurrence) consideration should be given to converting multiple drug regimens to single drug regimens.
  (GRADE B)

- The treatment chosen for each woman should be at the lowest dose that protects against seizures.
  (GRADE C)

- Where sodium valproate is the single agent of choice, high plasma levels should be avoided by dividing the required daily dose over at least two administrations or by using a slow release preparation.
  (GRADE B)

- For women who first present for advice when already pregnant, modification of an effective anticonvulsant regimen is not usually warranted as the potential for reducing risks of teratogenesis is minimal.
  (GRADE C)

- There is little clinical experience relating to the effects of anti-epileptic agents in pregnancy. Clinicians managing women on anticonvulsants should contribute to the accumulation of clinical information by notifying all pregnancies to the UK Register of Anti-epileptic Drugs in Pregnancy, contact: Dr Aline Russell (Department of Clinical Neurophysiology, Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF, phone 0141 201 1100, page 2462).
  (GRADE C)

Data are available which demonstrate that the rate of fetal malformations among women on AEDs increases with the number of drugs used (from around 3% in women on single agents up to around 23% in women taking four drugs[9]). Advice to withdraw anti-epileptic medication completely if possible, or to change to a single-agent regimen when complete withdrawal is not possible, is therefore appropriate.

For women who present pre-conceptually and for whom there is, therefore, the opportunity to withdraw anti-epileptic drugs, this should be done gradually over a period of 3-6 months. Such dosage adjustment should be supervised by a neurologist or physician with specialist knowledge of the management of epilepsy.

For those women who first present when already pregnant, particularly those beyond the first trimester when organogenesis is complete, there is probably little to be gained in terms of avoiding teratogenesis by altering treatment[25].

The Consensus Guideline of Delgado-Escueta and Janz[5] quotes evidence from mouse studies suggesting that the teratogenic effects of sodium valproate may result from unpredictably high peak levels. On theoretical grounds therefore, it is recommended that peaks and troughs of valproate levels are avoided by the use of divided daily doses or a slow release preparation.

A number of groups are collaborating in collating data on the outcome of pregnancies occurring in women taking the newer anticonvulsants. Dr Aline Russell is the Scottish Contact for the principal register. The organisers of the UK register have agreed to share data with others interested, including the National Teratology Information Service in Newcastle.

2.6 MONITORING AND ADJUSTMENT OF DOSAGE OF ANTICONVULSANTS DURING PREGNANCY

Recommendations

- Anticonvulsant dosage in pregnancy should be altered on clinical grounds. Increase in seizure frequency is an indication for increased dosage and/or addition of a new anticonvulsant (providing that poor compliance has been excluded).
  (GRADE C)

- Measurement of blood levels of anticonvulsants is not usually indicated. Total plasma levels may be misleading and there is no evidence of a clear-cut relationship between free levels and seizure control. Measurement of plasma levels may be of some use where there is concern about toxicity or compliance or where multiple drug regimens are used.
  (GRADE B)

Opinion is divided about the usefulness of measuring either total or free plasma levels of anti-epileptic drugs (AEDs) during pregnancy. The Consensus guidelines of Delgado-Escueta and Janz[5] state: "*Total serum AED levels, and if possible, free AED fractions, should be measured at regular intervals throughout pregnancy*", whereas the paper in Prescribers Journal[19] says: "*there is no need to check blood concentrations of anticonvulsants during pregnancy.....the results are difficult to interpret....*". Drug and Therapeutics Bulletin[20] says: "...*the seizure frequency does not always correlate with plasma levels, it is often better to adjust dosages according to the woman's clinical condition*".

Several recent publications[26-28] have described observational studies examining the relationships between serum levels of anti-epileptic drugs and seizure control in non-pregnant epileptic patients and have concluded that such measurements are unhelpful. Interpretation of serum levels of anti-epileptic drugs (particularly total serum levels) are further complicated in the situation of pregnancy because of a reduction in the protein-bound fraction. Workers from Brisbane[29] have described their experience with a policy of plasma level monitoring and dosage adjustment and concluded that this policy resulted in no marked improvement in overall seizure control.

A group from Stockholm[30] examined the relationships between seizure control and free and total plasma levels among pregnant women taking carbamazepine and phenytoin. Again, this group could find no clear-cut relationship between seizure control and plasma levels and concluded that total levels could be positively misleading.

The view of the SOGAP group, based on currently available evidence, is that routine measurement of plasma levels of anticonvulsants is unhelpful in pregnancy but that such measurements may have a place in limited circumstances, for example where a multiple drug regimen is used, where there is concern that toxic levels are being reached or where there is doubt about compliance - although such doubt is often better resolved by careful history-taking.

2.7 ANTENATAL CARE

Recommendations

- Shared ante-natal care is appropriate for most pregnant women with epilepsy. Such care should be led by an obstetric consultant with a particular interest in this condition and each obstetric unit should have a mechanism whereby referrals of women with epilepsy are channeled to the interested consultant. The provision of consistent advice and support continuing throughout the ante- and post-natal periods is of particular importance for women with epilepsy. Such support might appropriately be provided by a specialist midwife or health visitor.
  (GRADE C)

- In common with all other pregnant women, those with epilepsy should be offered serum AFP screening. Pre-screening counselling of women with epilepsy should include re-emphasis of the increased risk of neural tube defects. Staff must ensure that couples understand that the implications of such screening may include discussion of termination of the pregnancy should an abnormality be detected.
  (GRADE C)

- All women with epilepsy should be offered a detailed ultrasound scan at 18 - 22 weeks. This scan should be performed by an ultrasonographer with sufficient expertise to identify fetal anomalies. (The ability to reliably identify cardiac lesions might be taken as a suitable level of competence.) Pre-scan counselling should emphasise that ultrasound, even in the most skilled hands, cannot exclude **all** anomalies.
  (GRADE C)

- Prolonged seizures during pregnancy should be managed as in the non-pregnant patient. A suggested regimen comprises diazepam 10 - 20mg IV (the first 10mg as a bolus with slow injection of further 2mg boluses, as required). If necessary, phenytoin IV at 15mg/Kg can be given at a rate no greater than 50mg/minute. If venous access is difficult, the diazepam dose can be given rectally.
  (GRADE C)

The consensus Guideline of Delgado-Escueta and Janz[5] contains a review of the literature on teratogenicity associated with the four principal anti-epileptic drugs (phenytoin, carbamazepine, sodium valproate and phenobarbitone). These authors conclude: *"each of the four major AEDs has been considered more teratogenic than the other three AEDs, depending on the author cited."* The SOGAP Group endorse the further conclusion of these authors that: *"Since no agreement has been reached regarding which AED is the most teratogenic, the present consensus opinion is that the AED that stops seizures in a given patient should be used."*

Thus, all of these anticonvulsants must be regarded as being associated with major malformations (eg. neural tube defects, congenital heart defects, orofacial clefts, intestinal atresias and deformities of the renal system), minor malformations(eg. club foot, equinovarus and hypospadias) and also dysmorphic anomalies (eg. hypertelorism, epicanthal folds and distal digital hypoplasia). Moreover, all women on anticonvulsant medication should be offered the best available 'package' of antenatal screening tests to maximise the pick-up of all these various malformations and anomalies, while being made aware that available techniques cannot hope to detect **all** anomalies.

An appropriate 'package' of antenatal screening would be to offer the same serum screening tests for neural tube defect/Down syndrome at 16 weeks gestation as are offered to all pregnant women plus detailed ultrasound scan (performed by an adequately skilled ultrasonographer)) at 18-22 weeks. The SOGAP Group are of the view that amniocentesis for α-feto protein (AFP) estimation should be reserved for a very few women with raised serum AFP in whom neural tube defect cannot confidently be excluded by scan.

The suggested regimen for prolonged seizures during pregnancy is based on expert opinion (Martin Brodie, personal communication and Cleland[19]).

2.8 LABOUR AND DELIVERY

Recommendations

- The most appropriate place of delivery for women with epilepsy is a labour ward in a consultant-led maternity unit.
  (GRADE C)

- Women with epilepsy should be reassured that most will have a normal, vaginal delivery.
  (GRADE B)

- Each woman's usual anti-epileptic regimen should be continued during labour. Missed doses, and consequent falls in plasma levels of anti-epileptic drugs are to be avoided.
  (GRADE B)

- Tonic-clonic seizures occur in 1 - 2% of women with epilepsy during labour. Fits in labour may be managed with intravenous diazepam 10-20mg (the first 10mg as a bolus with slow injection of further 2mg boluses, as required). Repeated seizures in labour put the fetus at risk of anoxia and constitute an indication for early recourse to Caesarean section under general anaesthetic.
  (GRADE C)

- Women with epilepsy should be offered the same range of methods of pain relief in labour (including epidural analgesia) as is available to other women.
  (GRADE C)

Labour is a time of increased risk for both mother and fetus. Seizures are relatively likely to occur during labour with consequent risk to the fetus due to anoxia. Ideally, each woman's usual anticonvulsant regimen should be continued during labour and postpartum. Where this is not possible (due to nausea or vomiting or after anaesthetic) then an intravenous regimen of phenytoin comprising an initial dose of 10mg/Kg followed 2 hours later by a second dose of 5mg/Kg[31] is recommended.

If seizures do occur in labour, initial treatment should be with intravenous diazepam to a maximum of 20mg (the first 10mg as a bolus and further 2mg boluses injected slowly, as required). Oxygen should be administered. If diazepam fails to control seizures, phenytoin intravenously at 18mg/Kg may be administered and arrangements made for delivery by Caesarean section under general anaesthetic. In circumstances where venous access is difficult, diazepam may be administered rectally, either using Stesolid via a rectal tube or using the intravenous preparation via an ordinary syringe (M Brodie, personal communication).

2.9 CARE OF THE INFANT AND POST-PARTUM CARE

Recommendations

- Epilepsy itself and anticonvulsants are not contra-indications to breast feeding. All women, including those with epilepsy, who wish to breast feed should be offered encouragement and support to do so.
  (GRADE B)

- Parents should be reassured that, although children born to parents with epilepsy have an increased risk of developing epilepsy themselves, this risk is around 3% for most forms of epilepsy, (but significantly higher for women with a familial tendency to epilepsy or with certain specific syndromes).
  (GRADE B)

- Women with epilepsy should be given appropriate advice and support regarding suitable settings for feeding (eg seated on the floor) and for other aspects of infant care in order to minimise danger to the infant should a maternal seizure occur.
  (GRADE C)

- Post-partum care of women with epilepsy should include review of the anticonvulsant regimen, advice about appropriate contraception and re-emphasis of the importance of pre-conceptual care in a subsequent pregnancy.
  (GRADE C)

Most anticonvulsants are excreted in breast milk but concentrations in milk are low in relation to those present in maternal plasma. Reported ratios between breast milk and serum concentrations include 0.1 for valproate, 0.19 for phenytoin, 0.36 for phenobarbitone and 0.41 for carbamazepine[19] In general, however, the resulting dose to the breast fed infant is sub-therapeutic although it is acknowledged that sedative anticonvulsants (phenobarbitone, primidone, benzodiazepines) can cause sedation in the infant. Nevertheless, recent guidance directed at both doctors[5] and midwives[6] advocates that none of these drugs need be regarded as contra-indications to initiating breast feeding, but that if neonatal sedation occurs then alternating the breast and bottle can be a successful strategy when otherwise breast feeding might have to be curtailed.

As a general rule, breast feeding should be encouraged for all the usual reasons. In addition breast feeding may help prevent problems in the neonate resulting from sudden withdrawal of the anticonvulsants to which he was exposed in utero. However, it is essential that the new mother is given adequate opportunity for sleep, as sleep deprivation makes seizures more likely. If the father or another relative is able to take over responsibility for the baby at night this may be in the best interests of the family and in some circumstances breast feeding may not be the best option. Each mother should be given support in her choice of the feeding method which best suits her individual family.

Available sources of guidance for patients and their families[10,11] and for midwives[6] contains sound advice relating to reducing the dangers to the mother with epilepsy and her baby during feeding and child care and are endorsed by the SOGAP group

The impression of SOGAP group members is that only around 10% of women with epilepsy will require modification of their anticonvulsant regimens during pregnancy. For these women, treatment should be re-adjusted to the pre-pregnancy regimen in the immediate postnatal period.

Statement of Intent

This guideline is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns evolve.

These parameters of practice should be considered recommendations only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available.

Significant departures from the local protocol should be fully documented in the patient's case notes at the time the relevant decision is taken.

A background paper on the legal implications of guidelines, prepared by Dr Pamela Abernethy of Simpson and Marwick W.S., is available from the SIGN secretariat.

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APPENDIX I

A suggested minimum dataset for audit of the care of pregnant women with epilepsy

Applicable patient groups: All women with epilepsy diagnosed prior to pregnancy who:

a) deliver a live or stillborn infant
b) undergo induced abortion
c) experience a spontaneous miscarriage

1	Unique identifier (eg hospital no.)	
2	Patient group:	Livebirth/Stillbirth/Induced abortion/miscarriage
3	Was the pregnancy planned?	Yes/No/Not known
4	Folic acid periconceptually?	Yes, at 0.4mg level/Yes, at 4mg level/No/Not known
5	Serum screening?	Yes, low risk result/Yes, high risk result/No
6	Detailed anomaly scan?	Yes/No
7	If yes, enter all gestations between 16 and 24 weeks at which scans performed	.... weeks gestation
8	Antenatal vitamin K supplements?	Yes/No/Not known
9	If yes, no. of weeks of treatment	.....weeks
10	IM vitamin K given to neonate at birth?	Yes/No
11	If no, other form of vitamin K to neonate at birth?	Yes, oral/IV
12	Breast feeding on discharge?	Yes/No/Not applicable