PAPER

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Epilepsy in pregnancy

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ABSTRACT Epilepsy is a domestically intrusive disease which is socially concealed, affects all social classes and ethnic groups, and is common in women of child-bearing age. Excellence in care during pregnancy produces significant benefits for these mothers and their families. There were 13 maternal deaths due to suboptimal management of epilepsy in pregnancy in the latest report of the Confidential Enquiry into Maternal Deaths in the UK (see *Why Mothers Die* by James Drife; http://www.rcpe.ac.uk/fellows/CME/maternal/drife/drife_1.html). One additional death was classified as a head injury but occurred following a seizure.

Correct diagnosis, classification and investigation of epilepsy, contraception advice, preconceptual counselling, use of safest monotherapy, close monitoring of drug side-effects and efficacy in pregnancy, screening for fetal anomalies, high dose folic acid and vitamin K, seizure prevention in labour, and supportive advice for parenting are the mainstays of good maternal medicine.

KEYWORDS Anti-epileptics, congenital abnormality, enzyme-induction, epilepsy, pregnancy

LIST OF ABBREVIATIONS Anti-epileptic drugs (AEDs), Scottish Intercollegiate Guidelines Network (SIGN)

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CME

CONTRACEPTION IN WOMEN TAKING ENZYME-INDUCING DRUGS

Pregnancies in women with epilepsy are frequently unplanned owing to failed contraception, as is the case for non-epileptic women. Planning of pregnancy is, however, all the more important in women with epilepsy in order to optimise drug dosage and the benefits of folic acid. Anti-epileptic drugs that induce liver enzymes (e.g. phenytoin, carbamazepine, topiramate, oxcarbazepine) cause an increase in oestrogen and progestogen metabolism and result in breakthrough bleeding and contraceptive failure. This effect lasts for about four weeks after withdrawal of the enzyme-inducing drug. Most combined pill formulations contain 35 µg ethinylestradiol but a minimum of 50 µg is required in women on enzyme-inducing AEDs. If breakthrough bleeding occurs on this higher dose, then the oestrogen should be increased to 100 µg. In addition, taking pill packets back-to-back for three cycles followed by a four-day (rather than five-day) withdrawal bleed gives better contraception. Even at high doses the oral contraceptive pill is not always as effective in those taking enzyme-inducing AEDs and, ideally, alternative/additional methods of contraception should be considered.

The 'mini pill' (progesterone only) also has reduced efficacy (some authorities use two- to four-fold dose multipliers), and progesterone implants are not effective. Injectable depot progestagens are effective but should be given at shortened intervals (e.g. every 10 weeks rather than every 13 weeks (3 monthly)).

Emergency, post-coital contraception doses also need to be doubled for those on AEDs, i.e. 1·5 mg levonorgestrel, rather than 750 µg, with a repeat dose after no more than 12 hours.

PRE-CONCEPTUAL CARE

Women with epilepsy who are contemplating pregnancy should be made aware of the benefits of taking high dose folic acid (5 mg rather than the 400 µg given to non-epileptic women) in helping to prevent neural tube defects, such as spina bifida, which are associated with AEDs. Scottish Intercollegiate Guidelines Network recommends that high dose folic acid should be taken for three months pre-conceptually and to the end of the first trimester. General opinion is that the baby's brain keeps developing throughout pregnancy and so if the woman is taking folate antagonist drugs there is certainly no evidence of harm in continuing the folate throughout pregnancy. Folate also helps to prevent maternal anaemia. In addition, many women fall pregnant very soon after their first baby (especially when contraceptive choices are limited, as in epilepsy) and so taking folate throughout pregnancy helps to prevent neural tube defects in the next pregnancy. There is even an argument for giving high dose folate to all women with epilepsy of child-bearing age in view of the frequency of unplanned pregnancy.

Most women with epilepsy can expect to have a normal pregnancy and outcome, but they must be aware of the slightly higher incidence of fetal malformation, particularly oro-facial clefts, hypospadias, neural tube defects, and cardiac defects.

Pre-conceptual advice should consider the benefits of optimising seizure control while ensuring safe doses of monotherapy if possible. Routine advice on the benefits of reducing smoking, checking for rubella immunisation, and general health should also be given.

Effective monotherapy should be established before conception if possible. Many women are, however, reluctant to do this because it means avoiding driving again, even if they are currently seizure-free. Lamotrigine and carbamazepine are currently thought to have the lowest major malformation risk, of about 3% (1·5–5·7, 95% confidence), with lamotrigine possibly being a little lower in risk. Valproate has about double this risk and has caused recent controversy as it may have a particular association with impaired childhood intellectual development, as well as an association with maternal obesity and polycystic ovaries. The use of polytherapy can multiply this risk up to eightfold, and there are limited data on the newer drugs such as levitiracetam and topiramate.

About one-third of mothers will experience an increase in seizure frequency during pregnancy (and about one-fifth will experience a decrease in frequency). This has implications for work, ability to drive (if seizure-free before pregnancy, increased frequency will result in a driving licence being revoked), and quality of life, but is less likely if there has been good control prior to pregnancy.

PREGNANCY

Pregnant women with epilepsy should have consultant-led obstetric care in close liaison with their epileptologist and specialist epilepsy nurse. Fetal anomaly scanning at 18–20 weeks can pick up most major anomalies, and fetal echocardiography increases the detection rate for heart defects. High dose folic acid should ideally be continued throughout pregnancy (and between pregnancies). Women who are taking enzyme-inducing AEDs also need vitamin K. We prescribe vitamin K 10 mg orally each day from 35 weeks to delivery, and the baby is given 1 mg vitamin K intramuscularly on delivery. The risk of vitamin K deficiency is postpartum haemorrhage in the mother and haemorrhagic disease in the newborn.

Seizure frequency and severity needs to be assessed carefully throughout pregnancy, and doses of AEDs adjusted appropriately. Most clinicians do not monitor drug levels in pregnancy (other than to assess adherence to therapy or toxicity) as this has not proven to be beneficial in the past. Drug levels usually fall in pregnancy owing to the increased volume of distribution and altered protein binding, but this does not have a clear relationship to drug efficacy. Some clinicians do monitor levels and increase the doses of AEDs to maintain pre-pregnancy levels. This is a controversial area and is currently under investigation through a randomised trial (not yet published).

In premature births, betamethasone is usually given to promote fetal lung maturity. In women on AEDs, the dose is usually doubled, to 24 mg, and repeated after 24 hours.

LABOUR

Pain, fasting, anxiety, hyperventilation, sleep-deprivation, and dehydration are common triggers for seizures and all are common occurrences in normal labour. About 1 in 20 women with epilepsy will have seizures during labour, and these should be treated by routine first aid; airway protection, oxygenation, and intravenous lorazepam if necessary.

Well-meaning, non-obstetric staff sometimes advise women with epilepsy to have a caesarean section, without considering the surgical risks to mother and baby or the considerable implications for future pregnancy, so this should only be done in consultation with the obstetrician. Caesarean section should be considered as an option only after a full assessment of the risks and benefits of each individual case.

PUERPERIUM AND BREASTFEEDING

The paediatric staff should be made aware of the mother's condition and medication so that the baby is examined carefully for minor abnormalities such as digital hypoplasia and epicanthic folds, as well as for major abnormalities. Benzodiazepines are associated with neonatal hypoventilation and withdrawal syndrome, and so babies need careful monitoring.

All mothers with epilepsy should be encouraged to breast feed, even though AEDs are known to be present in breast milk, as long as the baby is born close to term. The baby will already have been exposed to high levels of AEDs *in utero* and breastfeeding may allow gradual weaning.

If doses of AEDs have been increased in pregnancy, toxicity can develop as the body fluid distributions return to normal in the puerperium, so drug doses may need to be weaned back.

The first ovulation after term pregnancy occurs on day 28, with the first period usually occurring on day 42, which marks the end of the puerperium. The combined pill therefore needs to be started on day 21 if contraception is to be effective.

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PARENTING

Sleep deprivation, dehydration, and stress are facts of life for most mothers and are common triggers for seizures. Parents need to consider the risks to the baby from maternal seizures, particularly during carrying and bathing, and appropriate adjustments in lifestyle should be made. The epilepsy specialist nurse and patient's associations can give life-saving advice and support here (e.g. Epilepsy Action)

HIGHLIGHTS

- Epilepsy is common in women in the childbearing years and there were 13 maternal deaths reported in the Confidential Enquiry into Maternal Deaths 2000–2002 associated with suboptimal care.
- Women with epilepsy on enzyme-inducing drugs need higher doses of hormonal contraception and also higher doses of emergency, post-coital contraception.
- Preconceptual drug adjustments, establishing monotherapy if possible, good seizure control, high dose (5 mg) folic acid, and vitamin K make a big difference and improve outcomes.
- Fetal anomaly scanning at 18–20 weeks and fetal echocardiography can detect most significant fetal abnormalities.
- Most women with epilepsy will have normal pregnancy outcomes with good care from an interested obstetrician in close liaison with their epileptologist and specialist nurse.
- The demands of parenting need to be considered and various patient support organisations can give advice.

FURTHER READING

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