CURRENT TOPIC

Anticonvulsants in pregnancy

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Epilepsy and pregnancy

Recurrent seizures affect at least 1% of women who are of childbearing age, but as the fertility of both men and women with epilepsy is slightly reduced,¹ about one in 200 pregnancies occurs in a woman with epilepsy. Most of these women are taking anticonvulsants regularly.

Pregnancy has an unpredictable affect on seizure frequency.²⁻³ For half of the women with epilepsy there is no significant change in the frequency of convulsions when they become pregnant, but a quarter have more seizures than usual. That group includes many women who also tend to have more seizures when menstruating. An increase in the number of seizures during pregnancy is twice as likely if the fetus is male. (There are some women who only have seizures when carrying a male child and none when carrying a female.) Pregnancy itself is not particularly epileptogenic, however by chance epilepsy will sometimes present for the first time during pregnancy; such gestational epilepsy is more likely to be of a focal nature.⁴

Pregnancy affects the metabolism of anticonvulsant drugs in several ways. Those women who suffer severe hyperemesis early in pregnancy may fail to retain the usual dose of oral anticonvulsant, and thereby suffer an increase in seizures. Some drugs are less well absorbed during pregnancy, and for some there is a lower degree of protein binding.⁵ Drug metabolism itself is altered. Pregnancy induces hydroxylating enzymes that lower the level of anticonvulsants such as phenytoin and phenobarbitone.⁶⁻⁷ Fluid retention, and the extra tissues of the fetus and placenta that increase the volume of distribution of the anticonvulsant drug, may lower levels further.

The mother

The maternal mortality, from epilepsy, during pregnancy is low (approximately one fatality per year in England and Wales) but the number has remained steady in the last 50 years and, as other causes of maternal fatality have reduced, that occurring in women with epilepsy has become more prominent. As these fatalities occur as a result of accidents such as asphyxiation at the time of a generalised seizure, those treating pregnant women with epilepsy are likely to continue to seek the best possible control of the seizures with appropriate anticonvulsant therapy and to be wary of any drug reduction (even though it might benefit the fetus).

The pregnant woman with epilepsy is even more likely to become anaemic as a result of

folic acid deficiency than someone who is not taking anticonvulsants; this is because most anticonvulsant drugs act as antagonists to folic acid. Although there is a slight worry that folate supplement may interfere with anticonvulsant metabolism,⁸ for instance by lowering the serum phenytoin concentration, this is neither serious enough nor common enough to contradict the advice that a small folate supplement (in the range 100–1000 µg) be given each day to all women of childbearing age who take anticonvulsants regularly, and that it be continued throughout pregnancy.⁹

Vitamin D deficiency is a potential risk for women, and their fetuses, who are receiving long term phenytoin treatment. Phenytoin induces the production of enzymes that hydrolyse vitamin D, therefore, women receiving regular phenytoin should receive supplementary vitamin D throughout pregnancy.

The risk of complications of pregnancy in a woman with epilepsy is no greater than in a woman without epilepsy, though reports suggest that obstetric intervention, in the form of induction of labour and instrumental delivery, tends to be more prevalent when the mother has epilepsy (without there necessarily being good reason for such intervention).¹⁰ The chance of spontaneous abortion or of multiple birth is not great, nor is there an increased risk of toxæmia.¹¹

The infant

The incidence of babies who are either of low birth weight or who are preterm is similar for both epileptic and non-epileptic women. But the perinatal mortality rate is twice as high among babies of epileptic mothers who have been taking anticonvulsants regularly. This results partly from an increased incidence of spontaneous haemorrhage and partly from a higher incidence of severe congenital abnormality.¹²

Haemorrhage

Anticonvulsant drugs, particularly barbiturates or phenytoin, may depress the vitamin K dependent clotting factors, prothrombin and VII, IX, and X.¹³ Such coagulation deficiencies led to reports of massive haemorrhages occurring in late pregnancy or shortly after birth: they tended to occur suddenly in unusual sites—intrathoracically or retroperitoneally.¹⁴ Once it was realised that the coagulation defect was similar to that found in vitamin K defi-

ciency it became possible to prevent and treat the coagulation abnormality.¹⁵ Providing that the mother is given 10–20 mg of vitamin K during the last month of pregnancy, the occasional severe intrauterine fetal haemorrhage should be prevented, as should neonatal haemorrhage. In addition it is important to give all babies born to epileptic mothers, who are receiving anticonvulsants, an intramuscular injection of vitamin K₁.

Congenital abnormalities

In 1968, six infants with cleft lip and palate were reported who had been born to mothers with epilepsy who had been taking anticonvulsants during pregnancy.¹⁶ The report included the child in the figure and, like that child, several of them had other congenital abnormalities in addition to the cleft lip and palate. All had an unusual facial appearance with a prominent frontal ridge, trigonocephaly, and other minor abnormalities of the face and ears. Minor bone defects of the hands were common. That report led to the notification of many babies believed to have been affected by the teratogenic action of anticonvulsant drugs.¹⁷ In the last 20 years there have been a succession of detailed studies relating to different anticonvulsants, their dose, duration of treatment and their relation to the state of the child.¹⁸

It is certain that there is an increased incidence of congenital malformation in the children born to epileptic women who have taken anticonvulsants during pregnancy. The four large scale prospective studies yield similar find-

ings to those from more than 20 large retrospective studies in showing that children of epileptic mothers have over twice as many major congenital malformations as children of mothers without epilepsy.¹⁸ Therefore if a mother has epilepsy, and is taking anticonvulsant drugs, the chance of her having a child with a major congenital abnormality is just over 6%. Clefts of the lip and palate are particularly likely (10 times more likely than in the general population) and congenital heart disease four times more likely.¹⁹ In addition, minor facial and skeletal abnormalities are common, and there are consistent reports of significant developmental delay in a proportion of children.¹⁸

Relative teratogenicity of anticonvulsants

The early reports reflected the pattern of drug usage at the time of the study thus it was common to incriminate barbiturates, phenytoin, and primidone. Some authors have been keen to identify specific syndromes relating to individual anticonvulsants—for example, the 'hydantoin [phenytoin] syndrome'²⁰ and the 'trimethadione [troxidone] syndrome',²¹ but reviewing the details of those cases, my impression is that the children have features similar to those which were identified in the original early reports and whose mothers sometimes had received other anticonvulsants. Most anticonvulsants predispose to a similar range of abnormality in the fetus. The one anticonvulsant with an outstandingly different pattern of effect is sodium valproate which will be considered later.

In the 25 years since the first recognition of abnormal babies being born to women taking anticonvulsants there have been regular claims, at the time of the introduction of a new anticonvulsant, that the new anticonvulsant will not affect the baby. Thus there was a time when carbamazepine was considered harmless, when benzodiazepines were considered risk free, and when sodium valproate was considered the safest anticonvulsant of all to take during pregnancy. Unfortunately, with time, it has become clear that all anticonvulsants have their problems and that some have more problems than others.

Reviewing the trials and the published case reports the oxazolindione drugs, troxidone (trimethadione) and paramethadione, seem to have been implicated particularly often. These reports were one of the factors leading to their increasingly restricted use for women of child-bearing age. Reviewing all the surveys, phenytoin seems to have been blamed more often for congenital abnormality than most other anticonvulsants. It is difficult to know how much that results from its widespread use at a time when there were fewer effective anticonvulsants available. However, the impression remains that the hydantoin group of drugs may be more damaging than several other anticonvulsants. It should be born in mind that the congenital abnormalities with which hydantoins are associated (clefts of the lip and palate and congenital heart disease) usually are correctable by surgery. Rather more worrying are the isolated reports of

The index child, who was delivered by the author in 1962, and who was reported together with five similar infants in 1968.¹⁶ The mother had severe generalised epilepsy for which she usually received 300 mg of phenytoin and 180 mg of phenobarbitone each day. In early pregnancy she had severe hyperemesis and daily grand mal seizures.

The baby had cleft lip and palate, trigonocephaly, minor abnormalities of the hand bones and nails, and divarication of the rectus abdominal muscles.

neuroblastoma occurring in children who have been exposed to phenytoin in utero.²²⁻²⁴

Of the more recent anticonvulsants, major concern surrounds sodium valproate. Ten years ago it was regarded as completely safe in pregnancy but there is now clear evidence of its association with neural tube defects.²⁵ The International Clearing House for Birth Defects monitoring systems suggest that the risk for a mother with epilepsy, taking sodium valproate during pregnancy, of having a child with spina bifida is approximately 1.2% compared with the risk of 0.06% for a woman who neither has epilepsy nor is receiving anticonvulsants.²⁶⁻²⁷ As, with appropriate counselling and screening for neural tube defects in the first trimester of pregnancy, such abnormal babies may be aborted, there are those who feel that the therapeutic efficacy of sodium valproate for specific patterns of epilepsy, such as juvenile myoclonic seizures, justifies its continued use in women of childbearing age providing that the risks and the options are discussed with the mothers. There are also reports that the offspring of such mothers have long term neurodevelopmental problems. This is a particularly difficult area to evaluate because of the different genetic, social, and environmental factors that contribute to a child's development. It is a sad fact that many children whose parents have severe epilepsy live in a disadvantaged environment.

For many years carbamazepine was considered extremely safe but the report from California last year of children identified both retrospectively and prospectively after exposure to carbamazepine in utero yielded the familiar pattern of minor craniofacial defects, fingernail hypoplasia, and neurodevelopmental delay that has been reported so often in the past with other anticonvulsant drugs.²⁸ Benzodiazepines are less likely to be used as mainstay therapeutic treatment for epilepsy but, when they are taken regularly throughout pregnancy, they too probably increase the chance of a baby with dysmorphic features and developmental delay.²⁹

Several studies suggest that abnormalities are more likely if more than one anticonvulsant is used or if particularly large doses are taken.¹⁸

The teratogenic effect

The many large surveys revealing the increased incidence of congenital abnormalities in the infants of mothers who took anticonvulsants could not include a similar number of mothers with epilepsy who were *not* receiving anticonvulsants. Thus there has always been difficulty in establishing, with certainty, that it is the anticonvulsant drugs that are associated with fetal abnormality rather than epilepsy. Fifteen retrospective comparative studies did not find an increase in the incidence of congenital malformation in epileptic mothers who did not receive anticonvulsant drugs compared with the general population.¹⁸ However, it can be presumed that woman with epilepsy, who are not taking anticonvulsant drugs, have much less severe epilepsy than those receiving anticonvulsant drugs, and therefore there remains the possibility that severe epilepsy itself is associated with congenital abnormality.

People with epilepsy are more prone to certain congenital abnormalities: cleft lip and palate and congenital heart disease, which itself is preferentially associated with clefts.³⁰⁻³¹ However, that association is not strong and cannot account for the more than twofold increase in congenital abnormalities in babies born to mothers with epilepsy.

Moreover, two studies have shown that the children of men with epilepsy do not have an increased rate of severe congenital malformation, or of facial clefts, compared with the children of men in the general population.³²⁻³³ Few will dispute that women with severe epilepsy have a limited choice of husband and, therefore, that their child may be less fortunate in its genetic endowment. Nevertheless, the conclusion is that there are very strong grounds for believing anticonvulsant drugs to be teratogenic. That conclusion is supported by several surveys which have failed to find any link between the severity of epilepsy, the type of epilepsy, or the frequency of seizures during pregnancy and congenital abnormalities in the child. Seizures, *per se*, do not seem to lead to congenital abnormality.²

The teratogenic effect is most likely to occur from 18-56 days after fertilisation, after that, although functional abnormality may occur, structural abnormality is unlikely. It may be relevant that some anticonvulsants have a higher concentration in the fetal bloodstream than in the mother's. The fetus is exposed to a much higher valproic acid concentration than the mother as a result of decreased maternal serum protein binding and raised maternal free fatty acid concentrations.³⁴ Diazepam is also raised preferentially,³⁵ and, as the mother tends to have raised free fatty acid concentrations early in pregnancy, the fetus is particularly likely to be exposed to high concentrations of sodium valproate and diazepam at that time.

The mode of the teratogenic effect is unknown. It has been popular to suggest interference with folate metabolism, as most anticonvulsants lower serum folate and there is much work showing that folic acid antagonists do, and folic acid deficiency probably does, induce congenital defects.³⁶ Nevertheless it may be that particular products of anticonvulsants are themselves toxic. The link with the role of poor nutrition in the aetiology of congenital abnormalities may be relevant, particularly as people who are short of folate are often short of other vitamins and essential nutrients. (The author will never forget the mother of the index case in the figure who came from a most disadvantageous background, and in addition to frequent generalised seizures had the most severe hyperemesis, pronounced anaemia, and undernutrition.) Thus it is understandable that doctors who advise a compound vitamin for women of childbearing age who are planning to have children, will do so even more readily for a woman who has epilepsy and is receiving anticonvulsants.

The puerperium

Anticonvulsants cross the placenta freely. The rate of clearance in the neonate varies according

to the drug and is believed to be in the range of 8–28 hours for carbamazepine, 14–88 hours for sodium valproate, 15–105 hours for phenytoin, and 40–500 hours for phenobarbitone.^{37 38} Such newborn infants may suffer harmful effects from that anticonvulsant level and, as a group, tend to be less efficient at feeding and to gain weight more slowly. A minority will suffer withdrawal symptoms such as tremor, excitability, and seizures (best treated with phenobarbitone). Anticonvulsants pass into the breast milk in relatively small quantities. The ratio between breast milk and serum concentrations is reported to be less than 0.1 for sodium valproate,³⁸ 0.19 for phenytoin, 0.36 for phenobarbitone, and 0.41 for carbamazepine.³⁹ Neither maternal epilepsy nor maternal treatment with anticonvulsant drugs are contraindications to breast feeding.

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