DRUG INFORMATION
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QUESTION:
A woman is planning to get pregnant. What is the safety of carbamazepine in pregnancy?

ANSWER:
BACKGROUND:
Major malformations affect 2-4% of all live births. The cause is not identifiable in most cases and exogenous factors such as drugs may account for only 1-5% of all malformations (ie. affecting < 0.2% of all live births) [1]. However, as drug-induced malformations are often preventable, they remain an important consideration. The risk of foetal malformations is greatest during organogenesis (18 to 55 days post conception) [2,3]. The foetus is reported to have relative resistance to the toxic effects of drugs in the initial few weeks of pregnancy (until about day 17 post-conception) [3]. This is because there is either failed implantation with early abortion, or normal foetal development (ie. an 'all or nothing response'). Drug exposure before the 17th day post-conception would not be expected to pose risk of teratogenicity unless the drug has a long half-life and persists in maternal circulation beyond this period.

EPILEPSY, ANTICONVULSANTS AND PREGNANCY OUTCOMES:
Women with epilepsy appear to have a 2- to 3-fold increased risk of malformations which may be related to the epilepsy itself, the drug therapy or other unidentified confounding issues [4]. All of the older anticonvulsants (carbamazepine, phenytoin, phenobarbitone and valproate) are teratogenic, but there are insufficient data to determine whether one of these agents is better than another. However, some initial studies suggest there might be an advantage for carbamazepine when compared with valproate, although additional study is needed [5]. Data on the newer agents are insufficient to determine safety, although preliminary information on lamotrigine are reassuring (the remainder of this document will refer to the older anticonvulsants only).

MALFORMATIONS: In general, the risk of malformations appears to increase with the number of antiepileptic drugs taken and the dose used (more strictly speaking, it is probably the plasma concentration that is more important than the dose). While all of the older agents are regarded as human teratogens, the particular spectrum of malformations caused by each agent is poorly understood. A recent Cochrane review reported the following in association with anticonvulsants: still births, perinatal and neonatal deaths, major physical defects that cause significant functional disturbance (eg. congenital heart disease, cleft lip and/or palate, limb defects, neural tube defects) and minor anomalies (eg. low set ears, flat nasal bridge, prominent lower lip, nail hypoplasia) [4]. With respect to carbamazepine, it is difficult to be precise about the exact risk of malformations because of limitations of the studies to date, but one recent editorial suggested 2.8 - 7.9% of exposed pregnancies would be associated with a malformation [5]. In another review, cardiac and urinary tract abnormalities, and neural tube defects were among the most frequently reported malformations with carbamazepine, with the risk of neural tube defects estimated to be 5- to 7-fold higher than the general population [6].

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NEUROLOGICAL/COGNITIVE EFFECTS: There are few studies investigating the more subtle effects on neurological and cognitive development in anticonvulsant exposed offspring but some studies have suggested there may be an increased prevalence of developmental delay especially in the first two years of life. Studies in older children have been conflicting with some suggesting antiepileptic-exposed children may have more difficulty with learning, while others have shown a transient impairment with catch-up later in life. It is not clear whether these effects result from seizure activity during pregnancy or drug exposure [3,4]. Some data suggests carbamazepine may offer an advantage over valproate with regard to various intelligence scores, but again the available data are inconclusive [7].

MANAGEMENT OF PREGNANCIES IN EPILEPTIC WOMEN

1) EVALUATE AND MINIMISE EXISTING DRUG THERAPY PRECONCEPTION: Clinicians caring for women with epilepsy who hope to become pregnant should evaluate the existing drug therapy with the view to gradually minimising the number of antiepileptic drugs taken and the doses used. However, while monotherapy with the lowest effective dose is the ideal, it is thought that poor seizure control will have significant maternal and foetal risk (greater than the teratogenic potential of the drugs), especially if the seizures are convulsive in nature. Therefore, in most cases the risks associated with modifying or reducing existing therapy may outweigh the teratogenic potential of the antiepileptics. If maternal drug therapy is deemed necessary it is essential that the mother is reassured that most anticonvulsant-exposed pregnancies (> 90%) result in a pregnancy outcome without apparent problems. Maternal anxiety about foetal risk may result in non-compliance with drug therapy and potentially greater foetal risk (see below).

2) ENSURE COMPLIANCE IF DRUG THERAPY IS NECESSARY: This is particularly important given that seizure control often declines in pregnancy as a result of non-compliance, enhanced anticonvulsant clearance (see below) or other unidentified factors.

3) MONITOR CARBAMAZEPINE CONCENTRATIONS: Increased carbamazepine clearance is expected in pregnancy because of factors such as increased liver blood flow and enzyme induction. Therefore, carbamazepine plasma concentrations must be monitored closely during pregnancy, perhaps with the view to maintaining concentrations similar to those that produced good seizure control prior to conception. Carbamazepine concentrations measured in clinical practice are usually "total" concentrations ie. The reported concentration includes drug that is bound and unbound "free" to plasma proteins. In pregnancy, we advise measuring "free" carbamazepine concentrations as distributional changes (eg. reduced plasma protein binding) may make interpretation of total concentrations difficult. Closer monitoring of carbamazepine plasma concentrations with dose adjustments (if necessary) should continue post-partum until stability which should be achieved by 2 months post-partum [8].

4) FOLIC ACID: There is an increased risk of neural tube defects amongst women on anticonvulsants in pregnancy. The prevalence of spina bifida aperta is estimated to be ~ 0.5% with carbamazepine compared with 1 - 2% for valproate (the exact incidence is difficult to determine with the available studies) [9]. Usual practice in New Zealand would be to prescribe folic acid 5mg daily (rather than 0.8mg daily) to be started at least one month prior to conception and continued through the first trimester. However, there appears to be no information on whether this actually reduces the risks of neural tube defects with anticonvulsants. Consideration should also be made to performing diagnostic detects in the first trimester to rule out neural tube defects.

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5) VITAMIN K: Babies exposed to enzyme inducing anticonvulsants such as carbamazepine are suggested to be more likely to bleed post-partum. This is postulated to be due to reduced availability of vitamin K dependent clotting factors. Some have suggested giving 10 - 20mg vitamin K to mum for a few weeks prior to the expected delivery date. Others have suggested that with carbamazepine monotherapy this approach is unnecessary provided that the baby is administered vitamin K intramuscular post-partum. We advise contacting us or the clinicians at Christchurch Women's regarding the current best practice for vitamin K administration when the patient reaches the third trimester.

6) DELIVERY: There exists a small risk of seizures during the delivery process and the immediate post-partum period. One review suggested the risk of tonic-clonic seizures during delivery in women with epilepsy was 1 - 2%, with a similar percentage having a seizure within 24 hours of delivery [8]. Therefore, delivery should occur in a facility with suitable emergency obstetric services such as Christchurch Women's Hospital.

7) BREASTFEEDING: Carbamazepine is generally regarded as "safe" in breastfeeding because of low transfer into breast milk. The infant dose is low at <1% of the maternal dose, corrected for weight [10]. In addition, in utero exposure will far exceed exposure via breast milk. Note: lamotrigine may not be safe in breastfeeding (although exposure through milk will be far less than in utero exposure) - see enclosed document on lamotrigine in breastfeeding.

CONCLUSION

Pregnancies in women with epilepsy are associated with a 2- to 3-fold increased risk of malformations compared with the general population. However, most pregnancies in women with epilepsy (> 90%) are expected to result in an infant without malformations. Like the other older anticonvulsants, carbamazepine is associated with a spectrum of malformations but it is difficult to be clear on which malformations are specifically associated with this drug. However, the possibility exists of an increase in major and minor malformations (including neural tube defects), and developmental issues. Preliminary studies suggest that carbamazepine may pose lower risk of these effects compared with valproate although further study is needed.

In addition to the general management points outlined above (eg. use the lowest effective dose and monotherapy where possible), we recommend referring this patient to a physician who specialises in management of this sort of pregnancy such as the Obstetric Medicine Clinic at Christchurch Women's Hospital.

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