- 4 **Peters N**, Herzog J, Opherk C, *et al*. A two-year clinical follow-up study in 80 CADASIL subjects. Progression patterns and implications for clinical trials. *Stroke* 2004;**35**:1603–8.
- 5 **Taillia H**, Chabriat H, Kurtz A, *et al*. Cognitive alterations in non-demented

- CADASIL patients. *Cerebrovasc Dis* 1998;**8**:97–101.
- 6 **Amberla K**, Wäljas M, Tuominen S, *et al*. Insidious cognitive decline in CADASIL. *Stroke* 2004;**35**:1598–602.

- 7 **Pantoni L**, Basile AM, Pracucci G, *et al*. Impact of age-related cerebral white matter changes on the transition to disability - the LADIS study: rationale, design and methodology. *Neuroepidemiology* 2005;**24**:51–62.

Teratogenic effects of antiepileptic drugs

Major congenital malformations and antiepileptic drugs: prospective observations

M J Brodie

High dose lamotrigine may be teratogenic

The spectre of teratogenesis has been hanging over young women with epilepsy ever since the association of fetal malformations with antiepileptic drug (AED) exposure was first mooted by Roy Meadow in a letter to *The Lancet* in 1968.¹ There followed a flood of retrospective reports and small prospective studies suggesting that perhaps all of the established drugs could be implicated in this problem. The global licensing of nine new antiepileptic drugs over the past 15 years has added to the confusion. Those agents that did not appear to be teratogenic in rodents have been touted by enthusiasts as “possibly” safe in pregnancy. The most confident claims were made for lamotrigine, and schedules have been devised to switch women of childbearing age from carbamazepine, phenytoin, or sodium valproate to this drug. What was (is) clearly needed was large prospective registries including only women in whom the pregnancy outcome was unknown at recruitment. The UK Epilepsy and Pregnancy Register was established in 1996 and its findings to the end of March 2005 are presented by Jim Morrow and colleagues in this issue of the journal (*see pages 193–8*).²

Data from a total of 3607 completed pregnancies have been analysed to date. The majority of mothers (72%) took a single AED. Importantly, 239 women with epilepsy were untreated throughout pregnancy and the rate of major congenital malformation (MCM) in their babies was no different (3.5%) from that in fetuses exposed to AED monotherapy (3.7%). The greater risk of MCM with polypharmacy (6%) and the likely teratogenic effect of sodium valproate were confirmed.³ The rate of MCM in women taking more than 1000 mg valproate daily (9.1%) was nearly double (5.1%) that in patients established on a lower dose. The MCM rate with carbamazepine was only 2.2%, but it must be remembered that these drugs may be used to treat different forms of epilepsy. Rather disappointingly, no mention is made in the paper of the effect, protective or otherwise, of preconception supplementation with folic acid.

The important new finding from this study² was a significant dose–response relationship for MCMs with lamotrigine with a rate of 5.4% reported in babies born to women taking more than 200 mg lamotrigine daily throughout

their pregnancy. A recent possibly supportive report from the International Lamotrigine Pregnancy Registry suggested a higher rate of MCM in babies exposed to valproate in combination with lamotrigine (12.5%) compared with lamotrigine alone (2.9%) or lamotrigine combined with other AEDs (6.6%).⁴ In the present study, the rate of MCM for valproate with lamotrigine was 9.6%.

Data from pregnancy registries are now coming thick and fast with potentially the biggest, European Pregnancy Registry (EURAP), still to report.⁵ Larger numbers of pregnancies are required to strengthen confidence in the power of these observations. The hope too is that there will be consistency across the different data sets. All this activity has the potential to provide useful guidance for doctors treating young women with epilepsy. This story, however, will run and run.

J Neurol Neurosurg Psychiatry 2006;**77**:145.
doi: 10.1136/jnnp.2005.079376

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Competing interests: The author is a Member of Scientific Advisory Board for the European Pregnancy Registry (EURAP)

REFERENCES

- 1 **Meadow SR**. Antiepileptic drugs and congenital abnormalities. *Lancet* 1968;**2**:196.
- 2 **Morrow JJ**, Russell A, Guthrie E, *et al*. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2005;**77**:193–8.
- 3 **Penovich P**, Gaily E. What can we say to women of reproductive age with epilepsy? *Neurology* 2005;**64**:938–9.
- 4 **Cunnington M**, Tennis P and International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. *Neurology* 2005;**64**:961–5.
- 5 **Tomson T**, Perucca E, Battino D. Navigating toward fetal and maternal health: the challenge of treating epilepsy in pregnancy. *Epilepsia* 2004;**45**:1171–5.