

Women and valproate: what should neurologists do?

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Valproate first received its UK licence for treating epilepsy in 1973; reports of congenital malformations appeared within 10 years¹ and fetal valproate syndrome soon after.² More recently, pregnancy registries have provided information on the risks for major congenital malformations in pregnancies exposed to antiepileptic drugs, consistently showing greater risks to infants exposed to valproate: approximately 10% for monotherapy and dose-related.^{3–5} This is significantly higher than the background rate—pregnancies in women with epilepsy not taking antiepileptic drugs—and the rate with other antiepileptic drugs, including lamotrigine, levetiracetam and carbamazepine (table 1).^{3–5} Studies have defined the types of major congenital malformation associated with valproate, predominantly neural tube defects, clefting abnormalities, cardiovascular defects, genitourinary defects in male and musculoskeletal defects. However, it is the risk of neurodevelopmental disability, including cognitive impairment, autistic spectrum disorder and autism, that has resulted in recommendations to avoid valproate in women of childbearing years and in pregnancy, in particular.⁶ With some studies reporting risks of 30%–40% for certain aspects of neurodevelopment, such caution and plans to mitigate the risks seem justified. However, much is still to be learnt: the true overall risk for neurodevelopmental disability is unknown for valproate, a situation mirrored for all antiepileptic drugs.

Based on current knowledge and recent recommendations, what should neurologists do to support girls and women with epilepsy to make safe choices regarding their use of valproate? While many groups have been targeted to limit valproate exposure, clinicians should not give information on the risks of valproate in isolation, but rather as part of a comprehensive epilepsy assessment.

This has clear implications for neurologists and others providing specialist epilepsy services. In people with newly diagnosed epilepsy, determining the need for antiepileptic drug treatment and the most appropriate drug and its duration, and in those still prescribed valproate their requirement for ongoing medication, the suitability of alternatives, and the risks of its withdrawal with loss of seizure control (including the risks of sudden unexplained death in epilepsy and the psychosocial consequences) cannot be devolved to clinicians who are not fully skilled in managing all aspects of epilepsy care. At the most basic level, not all antiepileptic drugs are suitable for all seizures, and valproate withdrawal or switching to an alternative medication certainly risks the patient losing seizure control. This is also the case during pregnancy, where generalised tonic-clonic seizures were twice as common in those where valproate was withdrawn (33%; n=93), or replaced (29%; n=38) in pregnancy, compared with those who stayed on it (16%; n=1588).⁷

For those women who do require valproate and where alternatives have been considered or tried, are there options to reduce risk? Changing to the prolonged release preparation and fractionating the dose appear beneficial in preclinical studies. While the impact on major congenital malformations in human pregnancies is less clear,⁸ and the effect on neurodevelopment is unknown, in practice, most would advocate such an approach. This is also the case for folate supplementation, where despite the lack of robust evidence of a protective effect against valproate-induced teratogenesis, the prescription of high-dose folate, prescribed before conception and for at least the first 3 months of pregnancy, is presently considered best practice. Minimising the total daily dose has a positive



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Table 1 Major congenital malformation rate for pregnancies exposed to valproate, carbamazepine, lamotrigine and levetiracetam in monotherapy

Registry	Major congenital malformation rate following antiepileptic drug exposure			
	Valproate	Carbamazepine	Lamotrigine	Levetiracetam
UK and Ireland Epilepsy and Pregnancy Registry ³	82/1200 (6.7%, CI 5.5% to 8.3%)	43/1657 (2.6%, CI 1.9% to 3.5%)	49/2098 (2.3%, CI 1.8% to 3.1%)	2/304 (0.7%, CI 0.2% to 2.5%)
European Registry of Antiepileptic Drugs and Pregnancy ⁴	Dose <700 mg: 24/431 (5.6%, CI 3.6% to 8.2%)	Dose <400 mg: 5/148 (3.4%, CI 1.1% to 7.7%)	Dose <300 mg: 17/836 (2.0%, CI 1.2% to 3.2%)	NA
	Dose ≥700 to <1500 mg: 50/480 (10.4%, CI 7.81% to 13.5%)	Dose ≥400 to <1000 mg: 56/1047 (5.3%, CI 4.1% to 6.9%)	Dose ≥300 mg: 20/444 (4.5%, CI 2.8% to 6.9%)	
	Dose ≥1500 mg: 24/99 (24.2%, CI 16.2% to 33.9%)	Dose ≥1000 mg: 18/207 (8.7%, CI 5.2% to 13.4%)		
North American Antiepileptic Drug Pregnancy Registry ⁵	30/323 (9.3%, CI 6.4% to 13.0%)	31/1033 (3.0%, CI 2.1% to 4.2%)	31/1562 (2.0%, CI 1.4% to 2.8%)	11/450 (2.4%, CI 1.2% to 4.3%)

NA, not available.

impact and should be considered in those women where continuation of valproate is felt to be appropriate. Areas requiring further study are whether polytherapy combinations, not containing valproate or combinations containing low-dose valproate in polytherapy, may be safer than medium and high-dose valproate in monotherapy. One study showed that valproate taken as part of polytherapy regimens in total daily doses below 700 mg a day was associated with a major congenital malformation rate of 5.4%, compared with 11.0% for monotherapy doses of 700–1500 mg a day and 24.0% for doses above 1500 mg a day.⁹ We do not know if this applies to neurodevelopmental outcomes.

Another challenge is to identify all women with epilepsy who are still taking valproate, but not under the care of specialist epilepsy services. This is especially relevant for those who were prescribed valproate at a young age for generalised epilepsy syndromes, many of whom will be seizure-free and will have been informed that they need to take antiepileptic medication for life. While neurologists may not be best placed to identify these women, being able to offer timely consultations, repeated regularly, will be difficult in already stretched healthcare systems such as the National Health Service (NHS).

So is there evidence that prescribing practices have changed and that the risks of valproate are being communicated? Pregnancy registries have shown falling valproate registrations,^{10 11} in favour of the safer—but for some women less effective—alternatives lamotrigine and levetiracetam,^{3–5 12} with lower doses being used. Population-based studies have also reported falling exposures. While not directly comparable, results from the UK General Practice Research Database showed the proportion of women with epilepsy aged 15–44 years taking valproate declined from 40.5% in 1999 to 29.5% in 2008.¹³ However, a recent report from NHS England found 18 000 of just over 174 000 prescriptions for valproate were still being given to women with epilepsy of childbearing years.¹⁴ Surveys have also shown that more needs to be done to inform women with epilepsy of the risks of valproate, with one, in over 2000 women with epilepsy in the UK, finding that 18% of women taking

valproate did not know the risks posed during pregnancy, and 28% stating they had not been informed of these.¹⁵

In conclusion, neurologists are best placed to provide a comprehensive assessment of women with epilepsy who are taking valproate. Any discussions should take account of the wishes of individual woman and be responsive to changing desires over time, and be sensitive to those women who do not desire or cannot have children, and to those for whom valproate is required. Ongoing support of pregnancy registries and similar studies on neurodevelopment should also be encouraged (Figure 1).

Do you have epilepsy and are pregnant or planning a pregnancy?

Around 2,500 women with epilepsy will have a baby each year in the UK. If you could be one of these women, find out how you can help improve the health of babies born to pregnant women with epilepsy in the future.

UK epilepsy & pregnancy Register

Pregnancy is an exciting time in a woman's life. For pregnant women with epilepsy, a potential concern may be whether their anti-epileptic treatment will cause harm to their unborn child. There is a major study in the UK investigating which epilepsy treatments show the lowest risk to a baby's health. The aim is to find out which type of epilepsy treatment women are taking while they are pregnant, and to collect information on the health of their babies after delivery. By agreeing to register, your valuable contribution will help doctors give the best advice possible to you and to other women who are thinking of becoming pregnant.

If you wish to register, or would like further information about the pregnancy register, please visit www.epilepsyandpregnancy.co.uk or call:

Freephone 0800 389 1248

All calls will be answered in confidence by experienced healthcare professionals.

Figure 1 Poster advertising the UK (and Ireland) epilepsy and pregnancy register.

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