Ther Adv Drug Saf
(2011) 2(5) 227–234
DOI: 10.1177/2042098611419003



# Long-term consequences after exposure to antiepileptic drugs *in utero*

**Lisa Forsberg and Katarina Wide**

***Abstract*:** Most pregnant women with epilepsy need pharmacological treatment during pregnancy. Children exposed to antiepileptic drugs have an increased risk of being born with major malformations. Some antiepileptic drugs seem to have negative effects on psychomotor or cognitive development in children exposed during foetal life. Neither carbamazepine nor lamotrigine in monotherapy seem to affect the cognition of exposed children. Several studies have shown negative effects on the long-term neurodevelopment of children prenatally exposed to valproic acid or polytherapy (two or more antiepileptic drugs during pregnancy). For most of the newer antiepileptic drugs there are insufficient data regarding long-term outcome.

***Keywords*:** anticonvulsants, child development, cognitive, epilepsy, intelligence, neurodevelopment, pregnancy

## Epilepsy and pregnancy

Pregnant women with epilepsy are a group of patients who challenge the healthcare system. The safety and health of both the woman and the foetus must be taken into consideration. A pregnant woman in good health and with adequate symptom control has a greater chance of giving birth to a healthy baby. However, although pharmacological treatment may be beneficial for both mother and baby, it is also potentially harmful to the developing foetus.

Of all pregnant women, 0.3–0.4% have epilepsy [Olafsson *et al.* 1998]. Women with epilepsy are a heterogeneous group, both with regard to type of seizures, the pathogenesis of the condition, comorbid conditions, and medication before conception. Few studies have observed increased mortality during pregnancy in women with epilepsy, however, a study by Adab and colleagues showed that British women with epilepsy had tenfold increased mortality compared with the general population [Adab *et al.* 2004].

A large number of studies have concluded that first trimester exposure to most of the older types of antiepileptic drugs (AEDs) is associated with an increased risk of congenital malformations [Meador *et al.* 2008]. Valproic acid (VPA) is a well-known teratogen for which is reported an increased risk of several major malformations such as neural tube defects, hypospadia and orofacial cleft [Jentink *et al.* 2010b; Samren *et al.* 1997]. Prenatal folate is recommended to reduce the risk of neural tube defects in women medicating with AEDs during pregnancy [Harden *et al.* 2009b]. Polytherapy is related to an increased risk of congenital malformations compared with monotherapy [Wide *et al.* 2004; Samren *et al.* 1997]. Carbamazepine (CBZ) is associated with an increased risk of malformations, especially spina bifida, compared with the general population, but the risk is lower than that of VPA exposure [Jentink *et al.* 2010a]. Although the relative risk is increased with exposure to CBZ compared with the general population, the absolute risk is still small [Nulman, 2010]. Lamotrigine (LTG) is considered a safer option than VPA with regard to malformations, but symptom control may be less effective [Vajda *et al.* 2010]. Several studies have shown a markedly increased clearance of LTG during pregnancy, leading to decreased plasma levels. It is recommended that drug levels are measured repeatedly in pregnant patients who are medicating with LTG [Harden *et al.* 2009c; Tomson and Battino, 2007]. A Danish population-based cohort study of children exposed to oxcarbazepine, levetiracetam, topiramate, lamotrigine or gabapentin could not find any association between these AEDs and major birth defects. For some of the drugs, the number of exposed

Correspondence to:
**Lisa Forsberg, MD**
Astrid Lindgren Children's Hospital at Karolinska University Hospital Huddinge and Department of Clinical Science, Intervention and Technique (CLINTEC), Karolinska Institutet, Stockholm, Sweden
**lisa.forsberg.1@ki.se**

**Katarina Wide, MD, PhD**
Astrid Lindgren Children's Hospital at Karolinska University Hospital Huddinge and Department of Clinical Science, Intervention and Technique (CLINTEC), Karolinska Institutet, Stockholm, Sweden

infants was low [Mølgaard-Nielsen and Hviid, 2011].

There have been numerous reports of a specific appearance or combination of different minor malformations attributable to intrauterine exposure to AEDs. These include, among others, hypoplasia of the fingers, midface hypoplasia, nail hypoplasia and joint stiffness. Some studies have found a correlation between intelligence quotient (IQ) and minor anomalies in children [Holmes *et al.* 2005], whereas others have not [Wide *et al.* 2000].

## Long-term neurodevelopment in children exposed to maternal epilepsy and antiepileptic drugs

During the 1970s, reports were published on children exposed to anticonvulsants *in utero*, who displayed delayed psychomotor development, minor anomalies and congenital malformations [Hanson and Smith, 1976]. Since then, efforts have been made to establish whether AEDs during pregnancy lead to an increased risk not only of congenital malformations but also of impaired development of neurological and cognitive functions. Long-term neurodevelopment can be assessed in several ways, but IQ measured by a well-known standardized test is a common one. Test results at preschool age may not reflect later cognitive and motor function when tested at school age [Roze *et al.* 2010]. Longitudinal studies that follow children up to school age and beyond are preferred. Other types of outcome have also been studied, for example parental reports of maladaptive behaviour, school performance or neuropsychiatric conditions [Forsberg *et al.* 2011; Bromley *et al.* 2008; Rasalam *et al.* 2005; Adab *et al.* 2001].

Animal studies have shown behavioural deficits in rats or mice prenatally exposed to phenobarbital (PB), phenytoin (PHT) or VPA [Fisher and Vorhees, 1992]. The combination of several AEDs seems to lead to a higher apoptotic response in the immature rat brain [Bittigau *et al.* 2002].

Cognitive and psychomotor development are, of course, very complex processes that are influenced by many internal and external factors such as parental IQ, parental education and socioeconomic status [Meador *et al.* 2011a; Eriksson *et al.* 2005; Losche *et al.* 1994]. Factors related to the child's health, such as gestational age at birth, perinatal complications and subsequent health, are also of importance for the mental development.

There may be negative effects of maternal epilepsy that are not related to prenatal exposure to AEDs but to some genetic or environmental effect of the disease [Karouni *et al.* 2010]. Holmes and colleagues found no significant IQ difference between 57 children born to women with epilepsy who had not been medicating with AEDs during pregnancy and matched controls [Holmes *et al.* 2000]. A German group investigated possible genetic effects by comparing children born to women with epilepsy not taking AEDs during pregnancy, children exposed to AEDs during pregnancy and children who had fathers with epilepsy. They found more speech difficulties in the group of children exposed to AEDs than in the two other groups [Steinhausen *et al.* 1994].

There is also a possibility that generalized tonic–clonic seizures can have a negative effect on neurodevelopment. Most studies have failed to find such a correlation [Bromley *et al.* 2010; Meador *et al.* 2009; Titze *et al.* 2008; Gaily *et al.* 1988], but Adab and colleagues showed a negative association between five or more tonic–clonic seizures during pregnancy and cognitive outcome [Adab *et al.* 2004].

## Long-term neurodevelopment following exposure to specific antiepileptic drugs during pregnancy

### *Phenobarbital*

A Danish study investigated adult men prenatally exposed to PB. These men were born between 1959 and 1961 and their mothers had been treated for other reasons than epilepsy. Men exposed to PB *in utero* had lower verbal IQ scores than their matched controls. Third trimester exposure affected the results more than exposure earlier in the pregnancy. The strengths of this study are long follow-up time and consistent results between a group of men tested with the Wechsler intelligence scale and a more simplified test performed at conscription. The diversity of underlying diseases in the mothers makes the results of this study difficult to interpret [Reinisch *et al.* 1995].

A follow-up study of children born to women who received a single prenatal dose of PB to

prevent intracranial haemorrhage in the infant revealed no significant differences between children prenatally exposed to PB and a control group [Shankaran *et al.* 2002].

### *Phenytoin*

Hanson and Smith first reported foetal hydantoin syndrome. Five children exposed to PHT *in utero* displayed a similar pattern of abnormalities: craniofacial anomalies, nail and digit hypoplasia, prenatal onset growth deficiency, and mental deficiency. However, four out of five children reported were also exposed to other AEDs *in utero* [Hanson and Smith, 1976].

Several studies have shown lower scores in various cognitive or psychomotor tests in children exposed to PHT *in utero*. Vanoverloop and colleagues showed that 20 children exposed to PHT (polytherapy or monotherapy) scored significantly lower in the Wechsler Preschool and Primary Scale of Intelligence (WPSSI) or the Wechsler Intelligence Scale for Children (WISC) compared with children whose mothers did not have epilepsy. This study was not population based, information on maternal medication was collected *post partum* and there was no information on parental IQ, only on socioeconomic status [Vanoverloop *et al.* 1992]. However, similar results were seen in a prospective cohort study with higher methodological quality, in 34 PHT-exposed toddlers who were compared with children exposed to nonteratogens, such as penicillins, during pregnancy. The mean IQ in the exposed group was about 10 points lower than in the unexposed group [Scolnik *et al.* 1994]. Significantly lower scores in the locomotor subtest of the Griffiths' Mental Development Scale (GMDS) in a prospective cohort of AED-exposed children were found in 16 children exposed to PHT monotherapy. No differences were seen in the total score in this small but population-based cohort [Wide *et al.* 2002].

None of these small cohort studies showed an increased risk of mental retardation in children exposed to PHT *in utero*. A large, register-based study did not reveal an increased risk of not receiving a final grade from compulsory school in children exposed to PHT in monotherapy [Forsberg *et al.* 2011]. Several other studies have reported no differences between children exposed to PHT in monotherapy and children without AED exposure [Adab *et al.* 2004; Gaily *et al.* 1988].

### *Carbamazepine*

CBZ has, in most studies, shown no negative effects on neurodevelopment. A well-designed Finnish prospective cohort study, a Canadian study of preschool children and a recent British study of toddlers exposed to CBZ all concluded that children prenatally exposed to CBZ in monotherapy displayed no significant differences in cognitive or psychomotor testing compared with nonexposed peers [Bromley *et al.* 2010; Gaily *et al.* 2004; Scolnik *et al.* 1994]. In our register-based study of children born to women with epilepsy, CBZ-exposed children did not have an increased risk of not receiving a final grade at age 16 compared with the general population. We found that children exposed to CBZ monotherapy had a significantly increased risk of not receiving a high grade in mathematics, English and Swedish. However, these results are difficult to interpret in a register study with limited access to data regarding confounders [Forsberg *et al.* 2011]. Meador and colleagues found a significant negative association between dose of CBZ during pregnancy and verbal index when prenatally exposed children were tested at 3 years of age [Meador *et al.* 2011b].

### *Valproic acid*

Recent studies have increasingly focused on the effects of VPA on the developing brain. Adab and colleagues found, in a retrospective cohort study, that 22% of school-aged children exposed to VPA *in utero* had exceptionally low verbal IQ (69 or below), compared with 2% in a group of children unexposed to maternal epilepsy and AEDs, and 8% in children prenatally exposed to CBZ [Adab *et al.* 2004]. The same cohort study also showed more additional educational needs in the VPA-exposed group [Adab *et al.* 2001] and a correlation between lower verbal IQ and dysmorphic facial features [Kini *et al.* 2006]. A Finnish prospective cohort study that included 13 children prenatally exposed to VPA also found a significantly lower verbal IQ compared with children exposed to other AEDs or children born to women without epilepsy [Gaily *et al.* 2004].

In 2009, a large prospective multicenter study from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study group compared four groups of children prenatally exposed to monotherapy: CBZ, VPA, PHT or LTG.

The children were tested at age 2–3 years and large amounts of data were gathered regarding the mother, the course of pregnancy, and the child. Children exposed to VPA had a significantly lower full-scale IQ at age 3 years. However, no significant differences were seen between the therapy groups when the analyses were restricted to children exposed to doses below the median, in the case of VPA meaning doses below 1000 mg/day. In children exposed to LTG, CBZ or PHT there was a significant correlation between maternal IQ and the child's IQ. This correlation was not seen in children exposed to VPA [Meador *et al.* 2011a; Meador *et al.* 2009]. A recently published paper from the same study reported a number of other neuropsychological tests on the same study population. Children exposed to VPA had significantly lower verbal scores than children exposed to other monotherapies. There was a negative association between dose of AED and verbal and nonverbal scores [Meador *et al.* 2011b]. An Australian register-based study also reported dose-dependent negative effects on verbal abilities in school-aged children prenatally exposed to VPA. This small study contained prospectively gathered data on maternal epilepsy, health history and socioeconomic status, but maternal or paternal IQ was not tested [Nadebaum *et al.* 2010].

Valproic acid has also been suspected of increasing the risk of autism spectrum disorders (ASD) [Williams *et al.* 2001]. A population-based cohort study from the UK found a significantly higher prevalence of ASD in children prenatally exposed to AEDs. Of children exposed to VPA, 8.9% (95% CI 1.3–16.5%) had been diagnosed with autistic spectrum disorder or Asperger's syndrome, compared with a prevalence of 0.25% in a UK survey of the population [Rasalam *et al.* 2005]. Preliminary data from a British cohort study reported that 6.3% of children exposed to VPA *in utero* had been diagnosed with ASD. This prevalence was higher than expected, compared with both a control group and the general population [Bromley *et al.* 2008]. Another study from the same group reported an increased risk of delayed early development in children exposed to VPA *in utero* [Bromley *et al.* 2010].

### Lamotrigine

In a study that prospectively followed a group of preschool children, those exposed to LTG or CBZ showed no significant difference compared with control children when tested with the GMDS. A drawback of this study is the young age at testing (mean age 10 months) but it was otherwise well performed [Bromley *et al.* 2010]. There were no significant differences in psychomotor and cognitive testing at age 3 years between children exposed to LTG, CBZ or PHT reported in the paper from the NEAD study group [Meador *et al.* 2009].

### Polytherapy

There are several studies reporting that polytherapy during pregnancy has more harmful effects on neurodevelopment than monotherapy [Forsberg *et al.* 2011; Thomas *et al.* 2008; Titze *et al.* 2008; Gaily *et al.* 2004; Losche *et al.* 1994]. However, an observational study of pregnant women with epilepsy may include women taking a large number of different drug combinations. The conclusions drawn from a 'polytherapy group' may be accurate for some of these drug combinations, but not necessarily for all of them. Women who need to medicate with two or more AEDs during pregnancy may have a more severe form of epilepsy than women who become seizure free from taking just one drug. This may have an impact on the cognitive and psychomotor outcome of the child.

A population-based Finnish cohort study found a lower verbal IQ (WPPSI-R or WISC) in children exposed to polytherapy *in utero* compared with children born to women without epilepsy and children exposed to monotherapy. These results were adjusted for maternal education but not maternal IQ [Gaily *et al.* 2004]. Dessens and colleagues retrospectively studied school performance and tested intelligence in 147 adults prenatally exposed to AEDs (PB, PHT and combinations, also including amphetamine) and found significantly lower scores in the polytherapy group, compared with matched controls. Retrospective design and the inclusion of amphetamine-exposed subjects are drawbacks of this study [Dessens *et al.* 2000]. In our register-based study of children exposed to maternal epilepsy with and without AEDs during pregnancy, we found that children exposed to two or more drugs had a higher risk (odds ratio 2.99, 95% CI 2.14–4.17) of not receiving a final grade from compulsory school than the overall population. No information on type of maternal epilepsy or seizures during pregnancy was available [Forsberg *et al.* 2011].

A recent well-performed prospective cohort study found no statistical differences in early overall development between young children exposed to polytherapy compared with monotherapy or polytherapy, compared with controls [Bromley *et al.* 2010].

### *Newer antiepileptic drugs*

Most of the newer AEDs, such as topiramate, levetiracetam (LEV) or zonisamide, have not been systematically studied with regard to long-term neurodevelopment. A recently published study from the Liverpool Manchester Neurodevelopment Group assessed 51 children exposed to LEV during pregnancy. The children were tested with the GMDS at 3–24 months of age. Children exposed to LEV showed significantly higher developmental scores than children exposed to VPA *in utero*. There were no significant differences between children exposed to LEV and control children born to mothers without epilepsy [Shallcross *et al.* 2011]. This study was well designed, prospective and adjusted for many important confounders such as maternal IQ. Testing at an older age would, however, have provided more information.

## Discussion

There are many factors that contribute to the quality of a study on prenatal risk factors and neurodevelopment. Population-based studies are generally considered to have a higher external validity. Some of the above-mentioned studies are population based [Forsberg *et al.* 2011; Rasalam *et al.* 2005; Gaily *et al.* 2004], whereas others have recruited patients from tertiary centres [Meador *et al.* 2009; Adab *et al.* 2004; Steinhausen *et al.* 1994] or from teratology information centres and tertiary units [Scolnik *et al.* 1994]. Retrospective studies may overestimate the risks attributable to intrauterine drug exposure, mainly due to recall bias. Some well-performed retrospective studies in this field have been very important in addressing the risks attributed to, for example, VPA [Adab *et al.* 2004]. However, prospective studies are generally considered to have a higher scientific value.

Randomized studies are not ethically possible in this field of research. Confounders must therefore be taken into consideration when studies are designed. There are many potential confounding factors, such as parental IQ or parental education, that may influence the outcome of children prenatally exposed to maternal epilepsy and AEDs. Some of the earlier studies [Wide *et al.* 2000; Losche *et al.* 1994] have not adjusted for maternal IQ but most of the larger, more recent ones have. Register studies have natural limitations when it comes to accessing certain baseline data and adjusting for them, for example maternal IQ. However, in our register-based study on school performance, information on maternal education was available. The NEAD study group has made a very ambitious effort to control and adjust for a large number of potential confounders [Meador *et al.* 2009]. Some information, such as paternal IQ, was not obtained and the authors received some criticism on this matter [Battino, 2009].

Most women with epilepsy have an uncomplicated pregnancy and give birth to a healthy child. However, a woman with epilepsy needs specialized care during pregnancy and there are certain considerations that need to be taken with regard to the child. One of the most important recommendations to women of childbearing age with epilepsy is that their pregnancies should be planned. A woman who is seizure free 9 months before pregnancy has a high chance of staying seizure free throughout pregnancy [Harden *et al.* 2009a]. Physicians who treat women with epilepsy should discuss the most efficient and safe treatment plan for the patient before pregnancy. It is also important that paediatricians who treat adolescents raise the issues of pregnancy and contraception. Depending on the type of epilepsy and the likelihood of recurrence while off treatment, an attempt to stop medication before a planned pregnancy in women who have been free from seizures during a long period of time may be considered. For certain types of epilepsy, such as epilepsy resulting from a structural lesion, or juvenile myoclonic epilepsy, this is not advisable. Since many pregnancies are, in reality, unplanned [Finer and Henshaw, 2006], pharmacological recommendations regarding pregnant women have strong implications for how epilepsy in women of childbearing age is managed.

An expert committee assembled by the American Academy of Neurology in 2009 published a systematic review along with recommendations regarding the care of women with epilepsy during pregnancy. The committee recommended that ‘avoidance of VPA and antiepileptic polytherapy throughout pregnancy should be considered and avoidance of PHT and PB may be

considered to prevent reduced cognitive outcomes' [Harden *et al.* 2009b].

The NEAD study added further information on the negative effects of VPA on neurodevelopment. In this paper, the authors conclude that 'valproic acid should not be used as a first-line antiepileptic drug in pregnant women' [Meador *et al.* 2009]. There are, however, different opinions on how to interpret the results, and voices are raised partly in the defence of VPA, stating that in lower doses it may be as safe as other AEDs [Battino, 2009].

It is a difficult task to balance the health of the mother against the possibly teratogenic effects of pharmacotherapy or uncontrolled seizures. Prenatal exposure to certain AEDs may be a rare, but preventable, cause of developmental delay in children. To adopt a principle of caution and make strong efforts to avoid VPA and polytherapy during pregnancy seems, to us, to be the most reasonable way to approach this problem.

Newer AEDs must be thoroughly evaluated with regard to the long-term outcome of exposed children before it can be established that they are safe to use in pregnant women. Women with psychiatric conditions may also be considered for treatment with AEDs during pregnancy. These groups need to be further investigated.

## Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

## Conflict of interest statement

The authors declare no conflict of interest in preparing this manuscript.

## References

Adab, N., Jacoby, A., Smith, D. and Chadwick, D. (2001) Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatr* 70: 15–21.

Adab, N., Kini, U., Vinten, J., Ayres, J., Baker, G., Clayton-Smith, J. *et al.* (2004) The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatr* 75: 1575–1583.

Battino, D. (2009) Cognitive outcome after exposure to antiepileptic drugs in utero. *Lancet Neurol* 8: 600–601.

Bittigau, P., Sifringer, M., Genz, K., Reith, E., Pospischil, D. and Govindarajalu, S. (2002) Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci U S A* 99: 15089–15094.

Bromley, R.L., Mawer, G., Clayton-Smith, J. and Baker, G.A. (2008) Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology* 71: 1923–1924.

Bromley, R.L., Mawer, G., Love, J., Kelly, J., Purdy, L., McEwan, L. *et al.* (2010) Early cognitive development in children born to women with epilepsy: A prospective report. *Epilepsia* 51: 2058–2065.

Dessens, A.B., Cohen-Kettenis, P.T., Mellenbergh, G.J., Koppe, J.G., Van de Poll, N.E. and Boer, K. (2000) Association of prenatal phenobarbital and phenytoin exposure with small head size at birth and with learning problems. *Acta Paediatr* 89: 533–541.

Eriksson, K., Viinikainen, K., Monkkonen, A., Aikia, M., Nieminen, P., Heinonen, S. *et al.* (2005) Children exposed to valproate in utero—Population based evaluation of risks and confounding factors for long-term neurocognitive development. *Epilepsy Research* 65: 189–200.

Finer, L.B. and Henshaw, S.K. (2006) Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. *Perspect Sex Reprod Health* 38: 90–96.

Fisher, J.E. and Vorhees, C.V. (1992) Developmental toxicity of antiepileptic drugs: relationship to postnatal dysfunction. *Pharmacol Res* 26: 207–221.

Forsberg, L., Wide, K. and Kallen, B. (2011) School performance at age 16 in children exposed to antiepileptic drugs in utero—a population-based study. *Epilepsia* 52: 364–369.

Gaily, E., Kantola-Sorsa, E. and Granstrom, M.L. (1988) Intelligence of children of epileptic mothers. *J Pediatr* 113: 677–684.

Gaily, E., Kantola-Sorsa, E., Hiilesmaa, V., Isoaho, M., Matila, R., Kotila, M. *et al.* (2004) Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology* 62: 28–32.

Hanson, J.W. and Smith, D.W. (1976) Fetal hydantoin syndrome. *Lancet* 1: 692.

Harden, C.L., Hopp, J., Ting, T.Y., Pennell, P.B., French, J.A., Hauser, W.A. *et al.* (2009a) Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 73: 126–132.

Harden, C.L., Meador, K.J., Pennell, P.B., Hauser, W.A., Gronseth, G.S., French, J.A. *et al.* (2009b) Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): II.

Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 50: 1237–1246.

Harden, C.L., Pennell, P.B., Koppel, B.S., Hovinga, C.A., Gidal, B., Meador, K.J. *et al.* (2009c) Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 50: 1247–1255.

Holmes, L.B., Coull, B.A., Dorfman, J. and Rosenberger, P.B. (2005) The correlation of deficits in IQ with midface and digit hypoplasia in children exposed in utero to anticonvulsant drugs. *J Pediatr* 146: 118–122.

Holmes, L.B., Rosenberger, P.B., Harvey, E.A., Khoshbin, S. and Ryan, L. (2000) Intelligence and physical features of children of women with epilepsy. *Teratology* 61: 196–202.

Jentink, J., Dolk, H., Loane, M.A., Morris, J.K., Wellesley, D., Garne, E. *et al.* (2010a) Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study. *BMJ* 341: c6581.

Jentink, J., Loane, M.A., Dolk, H., Barisic, I., Garne, E., Morris, J.K. *et al.* (2010b) Valproic acid monotherapy in pregnancy and major congenital malformations. *N Engl J Med* 362: 2185–2193.

Karouni, M., Arulthas, S., Larsson, P.G., Rytter, E., Johannessen, S.I. and Landmark, C.J. (2010) Psychiatric comorbidity in patients with epilepsy: a population-based study. *Eur J Clin Pharmacol* 66: 1151–1160.

Kini, U., Adab, N., Vinten, J., Fryer, A. and Clayton-Smith, J. (2006) Dysmorphic features: an important clue to the diagnosis and severity of fetal anticonvulsant syndromes. *Arch Dis Child Fetal Neonatal Ed* 91: F90–F95.

Losche, G., Steinhausen, H.C., Koch, S. and Helge, H. (1994) The psychological development of children of epileptic parents. II. The differential impact of intrauterine exposure to anticonvulsant drugs and further influential factors. *Acta Paediatr* 83: 961–966.

Meador, K.J., Baker, G.A., Browning, N., Clayton-Smith, J., Cohen, M.J., Kalayjian, L.A. *et al.* (2011a) Relationship of child IQ to parental IQ and education in children with fetal antiepileptic drug exposure. *Epilepsy Behav* 21: 147–152.

Meador, K.J., Baker, G.A., Browning, N., Clayton-Smith, J., Combs-Cantrell, D.T., Cohen, M. *et al.* (2009) Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 360: 1597–1605.

Meador, K.J., Baker, G.A., Browning, N., Cohen, M.J., Clayton-Smith, J., Kalayjian, L.A. *et al.* (2011b) Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. *Brain* 134: 396–404.

Meador, K.J., Pennell, P.B., Harden, C.L., Gordon, J.C., Tomson, T., Kaplan, P.W. *et al.* (2008) Pregnancy registries in epilepsy: a consensus statement on health outcomes. *Neurology* 71: 1109–1117.

Mølgaard-Nielsen, D. and Hviid, A. (2011) Newer-generation antiepileptic drugs and the risk of major birth defects. *JAMA* 305: 1996–2002.

Nadebaum, C., Anderson, V., Vajda, F., Reutens, D., Barton, S. and Wood, A. (2010) The Australian Brain and Cognition and Antiepileptic Drugs Study: IQ in School-Aged Children Exposed to Sodium Valproate and Polytherapy. *J Int Neuropsychol Soc* 17: 133–142.

Nulman, I. (2010) Carbamazepine in pregnancy. *BMJ* 341: c6582.

Olafsson, E., Hallgrimsson, J.T., Hauser, W.A., Ludvigsson, P. and Gudmundsson, G. (1998) Pregnancies of women with epilepsy: a population-based study in Iceland. *Epilepsia* 39: 887–892.

Rasalam, A.D., Hailey, H., Williams, J.H., Moore, S.J., Turnpenny, P.D., Lloyd, D.J. *et al.* (2005) Characteristics of fetal anticonvulsant syndrome associated autistic disorder. *Dev Med Child Neurol* 47: 551–555.

Reinisch, J.M., Sanders, S.A., Mortensen, E.L. and Rubin, D.B. (1995) In utero exposure to phenobarbital and intelligence deficits in adult men. *JAMA* 274: 1518–1525.

Roze, E., Meijer, L., Van Braeckel, K.N., Ruiter, S.A., Bruggink, J.L. and Bos, A.F. (2010) Developmental trajectories from birth to school age in healthy term-born children. *Pediatrics* 126: e1134–e1142.

Samren, E.B., Van Duijn, C.M., Koch, S., Hiilesmaa, V.K., Klepel, H., Bardy, A.H. *et al.* (1997) Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 38: 981–990.

Scolnik, D., Nulman, I., Rovet, J., Gladstone, D., Czuchta, D., Gardner, H.A. *et al.* (1994) Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. *JAMA* 271: 767–770.

Shallcross, R., Bromley, R.L., Irwin, B., Bonnett, L.J., Morrow, J. and Baker, G.A. (2011) Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology* 76: 383–389.

Shankaran, S., Papile, L.A., Wright, L.L., Ehrenkranz, R.A., Mele, L., Lemons, J.A. *et al.* (2002) Neurodevelopmental outcome of premature infants after antenatal phenobarbital exposure. *Am J Obstet Gynecol* 187: 171–177.

Steinhausen, H.C., Losche, G., Koch, S. and Helge, H. (1994) The psychological development of children of epileptic parents. *I. Study design and comparative findings.* Acta Paediatr 83: 955–960.

Thomas, S.V., Ajaykumar, B., Sindhu, K., Nair, M.K., George, B. and Sarma, P.S. (2008) Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy Behav* 13: 229–236.

Titze, K., Koch, S., Helge, H., Lehmkuhl, U., Rauh, H. and Steinhausen, H.-C. (2008) Prenatal and family risks of children born to mothers with epilepsy: effects on cognitive development. *Dev Med Child Neurol* 50: 117–122.

Tomson, T. and Battino, D. (2007) Pharmacokinetics and therapeutic drug monitoring of newer antiepileptic drugs during pregnancy and the puerperium. *Clin Pharmacokinet* 46: 209–219.

Vajda, F.J., Graham, J.E., Hitchcock, A.A., O'Brien, T.J., Lander, C.M. and Eadie, M.J. (2010) Is lamotrigine a significant human teratogen? Observations from the Australian Pregnancy Register. *Seizure* 19: 558–561.



Vanoverloop, D., Schnell, R.R., Harvey, E.A. and Holmes, L.B. (1992) The effects of prenatal exposure to phenytoin and other anticonvulsants on intellectual function at 4 to 8 years of age. *Neurotoxicol Teratol* 14: 329–335.

Wide, K., Henning, E., Tomson, T. and Winbladh, B. (2002) Psychomotor development in preschool children exposed to antiepileptic drugs in utero. *Acta Paediatr* 91: 409–414.

Wide, K., Winbladh, B. and Kallen, B. (2004) Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid: a nation-wide, population-based register study. *Acta Paediatr* 93: 174–176.

Wide, K., Winbladh, B., Tomson, T., Sars-Zimmer, K. and Berggren, E. (2000) Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study. *Dev Med Child Neurol* 42: 87–92.

Williams, G., King, J., Cunningham, M., Stephan, M., Kerr, B. and Hersh, J.H. (2001) Fetal valproate syndrome and autism: additional evidence of an association. *Dev Med Child Neurol* 43: 202–206.