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K. J. Meador, P. B. Pennell, C. L. Harden, et al.

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# Pregnancy registries in epilepsy

A consensus statement on health outcomes



K.J. Meador, MD  
 P.B. Pennell, MD  
 C.L. Harden, MD  
 J.C. Gordon, PhD  
 T. Tomson, MD, PhD  
 P.W. Kaplan, MB,  
 FRCP  
 G.L. Holmes, MD  
 J.A. French, MD  
 W.A. Hauser, MD  
 P.G. Wells, PhD  
 J.A. Cramer, BS  
 For the HOPE Work  
 Group\*

Address correspondence and  
 reprint requests to Dr. Kimford J.  
 Meador, Department of  
 Neurology, Emory University,  
 Woodruff Memorial Research  
 Building, 101 Woodruff Circle,  
 Suite 6000, Atlanta, GA 30322  
 Kimford.meador@emory.edu

## ABSTRACT

Most pregnant women with epilepsy require antiepileptic drug (AED) therapy. Present guidelines recommend optimizing treatment prior to conception, choosing the most effective AED for seizure type and syndrome, using monotherapy and lowest effective dose, and supplementing with folate. The Epilepsy Therapy Project established the international Health Outcomes in Pregnancy and Epilepsy (HOPE) forum to learn more about the impact of AEDs on the developing fetus, particularly the role of pregnancy registries in studying AED teratogenicity. The primary outcome of interest in these registries is the occurrence of major congenital malformations, with some data collected on minor malformations. Cognitive and behavioral outcomes are often beyond the time-frame for follow-up of these registries and require independent study. The HOPE consensus report describes the current state of knowledge and the limitations to interpretations of information from the various sources. Data regarding specific risks for both older and newer AEDs need to be analyzed carefully, considering study designs and confounding factors. There is a critical need for investigations to delineate the underlying mechanisms and explain the variance seen in outcomes across AEDs and within a single AED. *Neurology*® 2008;71:1109–1117

## GLOSSARY

**AED** = antiepileptic drug; **EURAP** = European and International Registry of Antiepileptic Drugs in Pregnancy; **FDA** = Food and Drug Administration; **HOPE** = Health Outcomes in Pregnancy and Epilepsy; **NEAD** = Neurodevelopmental Effects of Antiepileptic Drugs; **WWE** = women with epilepsy.

Approximately 25,000 children are born each year in the United States to women with epilepsy (WWE), most requiring antiepileptic drugs (AED). An urgent need to understand the impact of AEDs on the developing fetus has led to the establishment of several pregnancy registries. The Epilepsy Therapy Project established the Health Outcomes in Pregnancy and Epilepsy (HOPE) forum with nine international working groups outlining current state of knowledge and pointing the way toward future research. We report on their consensus view.

**EPIDEMIOLOGY, EPILEPSY, AND REPRODUCTION** Childbearing rates are lowered in both men and women with epilepsy.<sup>1</sup> Childbearing rates are 16.9–22.5 per 1,000 in WWE compared to 67.6 per 1,000 in women without epilepsy.<sup>2,3</sup> Lower marriage rate in WWE does not fully explain this difference.<sup>2,4</sup> One survey found that women with idiopathic/cryptogenic epilepsy were only 37% as likely to become pregnant as female siblings without epilepsy. In contrast, population-based studies from Iceland suggest no difference in childbearing rates between WWE and the general population. Studies from Rochester, Minnesota, suggest little difference, but possible reduction in high birth periods (1950s). Risk of spontaneous abortion is significantly increased for pregnancies of women with localization-related epilepsy, and risk is greatest in women with family history of epilepsy (OR = 2.12,  $p < 0.05$ ).<sup>5</sup>

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\*Members of the HOPE Work Group are listed in the appendix.

From the Department of Neurology (K.J.M.), University of Florida, Gainesville; Emory Epilepsy Program (P.B.P.), Emory University School of Medicine, Atlanta, GA; Department of Neurology (C.L.H.), Weill Cornell Medical College, New York, NY; Epilepsy Therapy Project (J.C.G.), Reston, VA; Department of Clinical Neuroscience (T.T.), Karolinska Institutet, Stockholm, Sweden; Johns Hopkins University School of Medicine (P.W.K.), Baltimore, MD; Neuroscience Center at Dartmouth (G.L.H.), Dartmouth Medical School, Lebanon, NH; New York University (J.A.F.), New York; Columbia University College of Physicians and Surgeons (W.A.H.), New York, NY; University of Toronto (P.G.W.), Ontario, Canada; and Department of Psychiatry (J.A.C.), Yale University School of Medicine, New Haven, CT.

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Although the majority of children born to WWE are normal, these children are at increased risk for both poor anatomic and behavioral outcomes. Major malformation frequency in the general population is 1.6–2.1% at birth.<sup>6,7</sup> Estimates of risk vary, but a recent study indicates 4.5% (OR 2.6) frequency for AED monotherapy in utero exposure and 8.6% (OR 5.1) for AED polytherapy.<sup>6</sup> The most common major congenital malformations associated with AEDs are heart malformations (e.g., ventricular septal defect), orofacial defects (e.g., cleft lip with or without cleft palate), urologic defects (e.g., hypospadias), skeletal abnormalities (e.g., radial ray defects, phalangeal hypoplasia), and neural tube defects (e.g., spina bifida).

Although some women can safely discontinue AEDs prior to pregnancy, most WWE require AEDs to control seizures. Current therapeutic strategies typically employ monotherapy and lowest dose to control tonic-clonic seizures, which can result in fetal intracranial hemorrhage,<sup>8</sup> cause transient fetal bradycardia, and heartbeat variability.<sup>9</sup> Isolated cases have reported changes in fetal heart rate during partial seizures.<sup>10,11</sup> One review found no evidence that non-convulsive seizures during pregnancy adversely affect outcome apart from trauma.<sup>12</sup> Status epilepticus resulted in 30% maternal mortality and 50% infant mortality in prior reports,<sup>13</sup> but more favorable outcomes with status epilepticus were seen in the prospective European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) registry.<sup>14</sup>

Older studies showed that AED polytherapy (mostly with phenobarbital and hydantoins) was associated with increased rates of major and minor malformations.<sup>15,16</sup> Few old or recent reports differentiate between major and minor abnormalities. Preliminary data on WWE suggest increased obstetric complications.<sup>9,17,18</sup> Preterm birth and small for gestational age infants occur in 12.5% of US deliveries, and are increased for WWE (OR 2.5–2.8),<sup>9,19</sup> even after controlling for multiple factors.<sup>18</sup> A population-based study from Iceland, however, found no significant differences in mean birthweight or perinatal mortality.<sup>7</sup>

**RESEARCH METHODOLOGIES** For descriptive research, the sample being representative vis à vis a population of interest is the key concern. For analytic research, comparability of samples being contrasted is the key concern. Observational studies do not involve randomization. Thus they must emphasize sources of sampling and measurement bias, maximizing response rate and avoiding selective refusal, and

consider biologic basis of disease and potential associations.

Measurement bias and data collection timing are important. Assessment of exposure should preferably be done prior to outcome, or at least without knowledge of outcome. Assessment must be sensitive, specific, and may require a trained specialist. Information is needed on AED dosages (separately for trimesters), other drug exposures (including drugs of abuse and vitamins/supplements, particularly folic acid), maternal demographics, previous pregnancy outcomes, prior fertility problems, family history, and maternal seizure type, frequency, and severity, etiology, and syndrome. DNA from child and mother is desirable.

Several AED pregnancy registries have been established to provide a more rational approach to management of WWE of childbearing potential. These prospective observational studies aim to enroll large numbers of AED exposed pregnancies employing systematic assessment of outcomes. There are also national birth registries that have examined AEDs.<sup>20,21</sup> The primary outcome of interest in these registries is the occurrence of major congenital malformations. Definition of major vs minor malformations vs deformations should be clear. Timing of assessment can affect reported rates. Some malformations (e.g., congenital heart defects) may be missed at birth and require re-examination. For minor congenital malformations, a trained teratologist blinded to drug exposure and family history should assess the children. When cognition or behavior outcomes are of interest, evaluations should continue to approximately age 6 years and be performed by blinded trained personnel. Information on abortions and stillbirths should be collected with chromosomal and anatomic assessments if possible.

Based on prior reports, it is estimated that approximately 500 monotherapy cases are necessary to determine AED differences in the occurrence of a major malformation at birth. Larger numbers may be needed for stratification, control of confounders, and selective malformations with low frequency.

**ETHICS, SCIENTIFIC INTEGRITY, REGULATORY CONTROL** Meaningful human data on a drug's teratogenic effects seldom are available at initial marketing. The Food and Drug Administration (FDA) evaluates and considers many factors before recommending a postmarketing change in drug labeling, including data reliability, seriousness of events, maternal benefit of the drug vs potential risks to the fetus, number of reports, plausibility of causal relationship, and public health impact. Research involving pregnant women and their children raises

**Table 1** North American registry prospective outcome data

AED in monotherapy	MM/n	% MM	95% CI	RR; 95% CI
<b>Phenobarbital</b>	5/77	6.5%	2.1-14.5%	4.2; 1.5-9.4*
<b>Valproate</b>	16/149	10.7%	6.3-16.9%	7.3; 4.4-12.2†
<b>Lamotrigine</b>	15/564	2.7%‡	1.5-4.3%	1.7; 1.0-2.7
<b>Carbamazepine</b>	22/873	2.5%§	1.6-3.7%	1.6; 0.9-2.8

\*RR 2.0; 95% CI 0.9–4.5 compared with three other AEDs combined in monotherapy.

†OR compared with an internal comparison group (infants exposed to all other AEDs as monotherapy) 4.0 (95% CI: 2.1–7.4).

‡Five exposed to lamotrigine had oral clefts, RR compared with background rate 32.8 (95% CI: 10.6–101.3).

§Five exposed to carbamazepine had oral clefts, RR compared with background rate 24 (95% CI: 7.9–74.4).

AED = antiepileptic drug; MM = major malformations; RR = relative risk compared with external background rate.

special ethical concerns. The FDA provides Guidance on Pregnancy Registries,<sup>22</sup> which collect data with no planned intervention upon registered subjects. Data collection presents negligible risk to mother and child, while potential benefits for disclosing risks from exposures can be significant.

Registry enrollment technique can alter enrollment. For example, the IRB overseeing the North American AED Pregnancy Registry requires that women call the registry after leaving the doctor's office to eliminate possible coercion, despite negligible risks. As a consequence, enrollment is clearly diminished compared to other registries such as EURAP, which allows physicians to enroll pregnant patients after informed consent. Further, enrollment techniques affect how representative the study sample is to the entire exposed population. We presently have significant findings for only a few AEDs, and clinicians are unable to provide patients with evidence on other AEDs. Strongest signals will exist across multiple registries or studies. If an AED consistently exhibits low teratogenesis across multiple registries, should this information be withheld until a statistical finding is assured for each registry separately?

### TERATOGENESIS: ANATOMIC AND COGNITIVE/BEHAVIORAL EFFECTS OF AEDS

**Anatomic teratogenesis.** Older generation AEDs have two- to sixfold increased risks for birth defects,<sup>23</sup> but many studies lack power to demonstrate differences between AEDs. The teratogenic potential of most individual AEDs remains unclear.

Existing pregnancy registries have been able to enroll larger numbers of prospective pregnancies than previous studies and have generated new important information. Three of the four independent registries and the Finnish and Swedish Medical Birth Registries have released outcome data on different AEDs.

The North American registry with over 3,000 women enrolled while on AEDs during pregnancy has reported that phenobarbital (6.5%) and valproate (10.7%) have increased rates for major mal-

formations (table 1).<sup>24,25</sup> Dose effect was not assessed for phenobarbital and was not significant for valproate. Two recent preliminary reports from the same group noted specific risks of cleft lip/palate (0.89%) for lamotrigine<sup>26</sup> and carbamazepine (0.57%).<sup>27</sup> The UK register with 3,607 pregnancy outcomes (table 2) found highest major malformation rate for valproate (6.2%), and increased risk for lamotrigine at higher doses.<sup>28</sup> Levetiracetam was associated with major malformations in 3/117 pregnancies, 2.7% (95% CI: 0.9%–7.7%).<sup>29</sup> All malformations were with polytherapy, but there were only 39 monotherapy exposures, so a larger sample is needed.

The Australian Registry with 555 outcomes (485 prospective) reported malformations in 5% of live births and additional 1% in induced abortions (table 3).<sup>30</sup> Valproate monotherapy (first trimester) at doses above 1,100 mg/day was associated with significantly higher risk (38.5%) of malformations than other AEDs, which were 6/155 (3.8%) carbamazepine, 0/61 (0%) lamotrigine, 1/17 (5.9%) phenytoin, and 19/113 (16.8%) valproate. Both the Swedish Medical (9.7%) and Finnish (10.7%) Birth Registries reported higher malformation rates for valproate (table 4).<sup>20,21</sup> Valproate's effect was dose dependent in the Finnish study.

**Table 2** United Kingdom pregnancy registry outcome data

AED	No.	% MM	95% CI
All AEDs	3,607	4.2	3.6-5.0
All AEDs polytherapy		6.0	4.5-8.0
All AEDs monotherapy		3.7	3.0-4.5
No AED		3.5	1.8-6.8
Valproate monotherapy	715	6.2	4.6-8.2
Carbamazepine monotherapy	900	2.2	1.4-3.4
Lamotrigine monotherapy	647	3.2	2.1-4.9

AED = antiepileptic drug; MM = major malformations.

**Table 3** Australian register prospective outcome data

AED in monotherapy	MM/n	% MM	95% CI	OR; 95% CI*
Valproate	22/166	13.3	8.5-19.4	4.1; 1.2-14.0
Carbamazepine	7/234	3.0	1.2-6.1	0.82; 0.21-3.26
Lamotrigine	146	1.4	1.7-4.9	0.37; 0.06-2.26

\*vs untreated.

AED = antiepileptic drug; MM = major malformations.

EURAP has published data on seizure control but has not released data on teratogenic outcome for specific AEDs.<sup>14</sup> Although not a registry, the ongoing prospective multicenter Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study in the United Kingdom and United States examining behavioral outcomes found increased serious adverse outcomes (i.e., fetal death or major malformations) in children (n = 333) exposed to monotherapy with valproate (20%; 95% CI: 12, 32) vs carbamazepine (8%; 4, 15), lamotrigine (1%; 0, 6), or phenytoin (11%; 4, 22).<sup>31</sup> Valproate's effect was dose dependent.

The International Lamotrigine Pregnancy Registry (table 5)<sup>32</sup> reported 2.9% risk of malformations for lamotrigine, which was not dose dependent.<sup>33</sup> The value of company driven single AED registries is limited, especially without internal comparison groups. Overall malformation rates for lamotrigine were similar for the company registry, UK registry, and North American registry, although only the United Kingdom found a dose effect. Additional studies are needed to clarify lamotrigine risks.

A common finding in these reports has been a significantly higher malformation rate associated with exposure to valproate than different comparators. Although valproate has a long known specific risk for neural tube defects, the observed malformations from recent studies involved multiple body sys-

tems. The study design and methodology of eight registries are summarized in tables e-1 and e-2 on the *Neurology*® Web site at [www.neurology.org](http://www.neurology.org). It is clear that there are significant methodologic differences, which may explain some divergence in outcomes. Tables 6 and e-3 provide summary updates from the registries. It appears that overall malformation rates are higher in the Australian Registry and EURAP than UK Register. Different methods for enrollment, variable ascertainment rates, dissimilar exclusion criteria, definitions of outcome, and differences in duration of follow-up could all contribute. So far, most comparisons of malformation rates have been for all birth defects taken together. Separate risk assessments for different types of malformations are highly desirable. Further analyses are needed to include potential confounding factors, e.g., seizures during pregnancy, type of epilepsy, and family history of birth defects. Malformation rates for different AEDs need to be compared at different doses. None of the present registries collects serum AED levels. Given the changes in AED pharmacokinetics during pregnancy, future studies would be well advised to incorporate serum levels.

**Cognitive/behavioral teratogenesis.** Animal studies have demonstrated that in utero AED exposure

**Table 4** Swedish and Finnish birth registries outcome data

	MM/n	% MM	95% CI	OR; 95% CI
<b>Swedish</b>				
All AEDs monotherapy	68/1,256	5.4	4.2-6.8	1.61; 1.18-2.19*
Valproate monotherapy	26/268	9.7	6.4-13.9	2.51; 1.43-4.68†
Carbamazepine monotherapy	28/703	4.0	2.7-5.7	
<b>Finnish</b>				
All AEDs monotherapy	52/1,231	4.2	3.2-5.5	
All AEDs polytherapy	13/180	7.2	3.9-12.0	
Valproate monotherapy	28/263	10.7	7.2-15.0	4.18; 2.31-7.57‡
Carbamazepine monotherapy	22/805	2.7	1.7-4.1	

\*vs the expected estimate from all infants born.

†vs carbamazepine monotherapy.

‡vs offspring of untreated patients (n = 939).

MM = major malformations; AED = antiepileptic drug.

**Table 5** International lamotrigine pregnancy registry outcome data

Lamotrigine therapy	MM/n	% MM	95% CI
Monotherapy	26/908	2.9	1.9-4.2
Polytherapy with valproate	15/133	11.3	6.7-18.2
Polytherapy without valproate	8/307	2.6	1.2-5.3

MM = major malformations.

can produce behavioral defects at dosages lower than those required to produce somatic malformations.<sup>34</sup> Cognitive studies in humans are less clear.

**Carbamazepine.** Two prospective controlled population-based studies reported objective cognitive outcomes for carbamazepine monotherapy.<sup>35,36</sup> No IQ impairment was found in the 121 children exposed to carbamazepine monotherapy compared to nonexposed children of WWE or controls. A retrospective population-based study found no increase in autistic spectrum disorder in children exposed to carbamazepine.<sup>37</sup>

**Phenobarbital.** A prospective controlled study of 305 children of WWE exposed to phenobarbital monotherapy and 4,705 children of mothers without epilepsy exposed to phenobarbital did not differ from control children for IQ measured at 4 years, but maternal IQ was not assessed.<sup>38</sup> In contrast, 114 men exposed in utero to phenobarbital had approximately half SD lower IQ scores than expected after control of confounding factors.<sup>39</sup> Impairment was greatest after third trimester exposure. Phenobarbital exposure for toddlers with

febrile seizures resulted in lowered IQ and impairment of language/verbal skills.<sup>39</sup>

**Phenytoin.** Prospective IQ data after prenatal phenytoin exposure have been reported in two controlled population-based studies.<sup>38,40</sup> Children (n = 205) exposed to phenytoin (81 monotherapy) were compared to 40 nonexposed children of WWE and over 27,000 control children of mothers without epilepsy, controlling for socioeconomic class and maternal educational level. Both studies reported lower IQ values in children of WWE compared to controls but no significant associations to phenytoin or other drug exposure. Another cohort from the same database consisting of 83 children with phenytoin exposure (25% monotherapy) had significantly lower (5 points) age 7 IQ than control children of mothers without epilepsy, controlled for socioeconomic status.<sup>41</sup>

**Valproate.** Prospective IQ data on prenatal valproate monotherapy exposure are limited to 26 children from two population-based evaluator-blinded studies.<sup>36,42</sup> Verbal IQ was 11–13 points lower for valproate monotherapy than children with no AED exposure or carbamazepine monotherapy. Valproate's effect was dose dependent.<sup>36</sup> Pooled data from these studies showed 3/34 (8.8%) children exposed to valproate monotherapy had mental deficiency compared to 1/94 (1.1%) children exposed to other monotherapies. Valproate's effect remained significant after accounting for maternal educational level in one study,<sup>36</sup> but not after covarying for maternal IQ in the other study.<sup>42</sup>

**Table 6** Updates from five international AED and pregnancy registries

Registry	North American	United Kingdom	Australia	EURAP	Swedish Medical Birth Registry	Finnish Birth Registry
Enrolled pregnancies (n)	5,525	5,406	966	8,885	NA	NA
Pure prospective (% of enrolled)	61%	100%	76%	79%	NA	NA
Completed prospective pregnancies (n)	3,916 (including not only pure prospective)	4,405	848 (including also retrospective)	3,749	2,444	2,350
Dropouts/lost to follow-up (%)	NA	8%	1%	12%	NA	NA
Malformation rate all exposed (%)	NA	4.2% (of AED exposed)	6.3% (including also retrospective)	6.7%	NA	4.6%
Malformation rate polytherapy (%)	NA	6.0%	NA	9.8%	NA	7.2%
Malformation rate monotherapy (%)	NA	3.7%	6.6%	6.0%	8.0% (5.4% "severe")	4.2%
AEDs with >500 exposures in monotherapy	LTG, others NA	CBZ, VPA, LTG	None	CBZ, VPA, LTG	CBZ	CBZ

AED = antiepileptic drug; CBZ = carbamazepine; VPA = valproate; LTG = lamotrigine; EURAP = European and International Registry of Antiepileptic Drugs in Pregnancy.

A retrospective study with the largest number of valproate monotherapy exposures ( $n = 41$ ) found verbal IQ to be significantly lower compared to unexposed and other monotherapies.<sup>43</sup> Valproate's effect was dose dependent, and the magnitude (10 points lower) was approximately the same as the prospective studies. Maternal IQs did not differ between valproate and other groups, but other factors were not controlled. A related study reported increased educational needs in children exposed to valproate monotherapy.<sup>44</sup> Recent preliminary results based on blinded cognitive assessments at age 2 from an ongoing multicenter prospective study in the United States and United Kingdom found lower cognitive outcomes for children exposed in utero to valproate monotherapy.<sup>31</sup>

Social or behavioral difficulties were reported in 26/260 children of WWE (42% of the population) in a retrospective population-based study.<sup>37</sup> Autism spectrum disorder (Diagnostic and Statistical Manual of Mental Disorders–IV criteria) was diagnosed in 12/26 children (9 valproate exposures). Autism was diagnosed in 5/56 (8.9%) of valproate monotherapy exposed children. Estimated minimum prevalence of autism in children of WWE (1.9%) was significantly higher than in the general population.

Recent studies replicate earlier reports that polytherapy exposure results in increased risks.<sup>36,45</sup> There is no information to suggest whether some combinations would be safer or more hazardous than others, except that polytherapies with valproate appear to be at higher risk. Effects of brief maternal generalized tonic-clonic seizures are controversial,<sup>40,43</sup> but prolonged seizures and status epilepticus can be a serious hazard for both mother and fetus.<sup>9</sup>

Prospective population-based studies give no definite evidence that carbamazepine or phenytoin fetal exposure impair intelligence. Data on fetal phenobarbital are insufficient. Published results of small prospective and retrospective studies, although not conclusive, raise concern that valproate may impair cognitive/behavioral development.

**LIMITATIONS OF EXISTING REGISTRIES** Registry results at present can only evaluate a few of many existing treatment options. Nevertheless, prospective pregnancy registries appear to be the most efficient way to assess clinical teratogenic potential of AEDs. Although methodologies of most registries appear sound, there are problems inherent to their nature and methodology. While all of the registries provide some helpful information, most current epilepsy registries are not representative of the entire population of WWE; thus findings may not be applicable to all WWE. Many registries collect data regardless of time in pregnancy although most analyses

have been limited to mothers identified in first trimester and before outcome has been assessed. Some registries do not allow accurate assessment of WWE on several important factors: 1) epilepsy seizure type, syndrome, etiology, or severity; 2) AED dose and plasma levels; 3) information on potential confounders (other illnesses, smoking, alcohol, and other medications). Outcome assessments differ between registries, and may not be blinded to exposure. Malformations differ in impact severity; thus, assessments for different types of malformations are highly desirable, but may require more exposures.

It might be useful to pool data from the different registries to increase statistical power, but many registries are too different to allow pooling. Alternatively, it is advantageous to have independent registries with somewhat different methodologies to allow observations to be confirmed by independent studies. A potential problem with several active registries is that the same pregnancy might be enrolled in more than one and counted as two independent exposures. It is important that mechanisms are developed to identify such pregnancies while maintaining patient privacy.

Cognitive and behavioral determinations require sufficiently long and complete follow-up of offspring to allow accurate assessments (e.g., age 6 years). Further, there is seldom a concurrent comparison group, and comparability is a concern when a comparison group is present.

**MECHANISMS UNDERLYING ADVERSE AED EFFECTS ON DEVELOPMENT** Substantial variability exists in the nature/severity of birth defects and neurodevelopmental deficits across individual children with similar in utero exposure and other risk factors. Pregnancy registries have not addressed the crucial question of why only a fraction of the exposed develop abnormalities. Mechanisms underlying adverse effects of fetal AED exposure are uncertain. Differences in mechanisms may be manifest in different AEDs, different developing tissues, and different developmental stages. Multiple mechanisms likely contribute.

Teratogens interact with genotype to produce both anatomic and behavioral defects. Whether a defect occurs depends on susceptible genotype and may involve interaction of multiple-liability genes.<sup>46</sup> Proposed mechanisms underlying teratogenicity of AEDs include folate, ischemia, neuronal suppression, reactive intermediates (e.g., epoxides or free radicals), and AED-induced neuronal apoptosis.<sup>47</sup> Neuronal dysfunction short of apoptosis or migration disorders may also contribute. Mechanisms of anatomic and behavioral teratogenesis may well dif-

fer since it appears that anatomic defects result from first trimester AED exposure while behavioral defects arise from third trimester exposure. A leading hypothesis of anatomic teratogenesis involves oxidative macromolecular damage from free radicals formed as reactive intermediates of AED metabolism.<sup>48</sup>

AED-induced apoptosis has been proposed as a possible mechanism for the behavioral deficits. Widespread neuronal apoptosis in animals occurs as a result of exposure to clonazepam, diazepam, phenobarital, phenytoin, vigabatrin, or valproate in neonatal rats.<sup>49</sup> The effect is dose dependent, occurs at therapeutically relevant blood levels, requires only a relatively brief exposure, and can be synergistic suggesting possible increased polytherapy risk. Similar apoptotic effects were not seen at therapeutic dosages for carbamazepine, levetiracetam, lamotrigine, or topiramate in monotherapy.<sup>50-53</sup> Further, fetal exposure to GABAergic AEDs such as valproate and vigabatrin can result in hippocampal and cortical dysplasias secondary to impaired migration and neuronal death.<sup>54</sup>

**PHARMACOLOGY** Pharmacokinetics of AEDs undergo significant changes during pregnancy and puerperium, but precise time course of these changes and their potential relevance for fetal and maternal well-being have not been fully explored.<sup>55-59</sup> An analysis of EURAP registry data indicated that monotherapies with lamotrigine or oxcarbazepine are more often associated with a need to increase dose during pregnancy,<sup>14</sup> an observation which might be explained by pharmacokinetic alterations. Potential changes in pharmacokinetics in many new AEDs during pregnancy and puerperium have not been investigated.

Effect of AED exposure through breastfeeding is uncertain. The amount of medication exposure through breast milk is invariably lower and shorter than in utero exposure. Additional research is needed since there are known benefits of breastfeeding, but potential long-term risks on the developing brain are raised by findings of AED-induced apoptosis in the neonatal rat brain.

**CONCLUSIONS** Evaluation and comparison of reports on AED teratogenicity are difficult, limiting an evidence-based approach to care of WWE. While there has been considerable progress recently in developing pregnancy registries to provide more insight, outcome data are incomplete. Registries are variable, deal with different cultures, have different definitions, and have variable follow-up times. Lack of information about mothers (and fathers) as well as lack of follow-up restricts usefulness of registry data.

Risk of fetal malformation with newer AEDs is largely unknown, and consequences to individual offspring could be severe and lifelong.

Risks of fetal AED exposure on the developing nervous system in humans remains uncertain, but recent discovery of AED-induced neuronal apoptosis in immature animal brain raises concerns. It remains unclear whether similar apoptotic changes occur in humans. Future studies with blinded neuropsychological testing and volumetric MRI studies in humans are needed.

Present guidelines recommend optimizing treatment prior to conception, choosing the most effective AED to control seizures, using monotherapy and lowest effective dose if possible, and supplementing with folate.<sup>60</sup> Discontinuing AEDs prior to pregnancy may be an option in women with seizures that would not put her or her fetus at risk. However, sudden cessation or lowering of AEDs should not be done by a WWE without consultation with her physician. Seizure control must be maintained, and most mothers with epilepsy are not able to safely stop AEDs; thus, their fetus must be exposed.

Each of the individual registries has weaknesses, ranging from missing data on key variables to low numbers for specific AEDs. Nevertheless, the finding of worse anatomic and neurodevelopmental outcomes following fetal valproate exposure in multiple studies suggests that it poses a special risk. Thus, it seems prudent not to use valproate as a first choice AED in WWE of childbearing age. When valproate is employed in women of childbearing potential, dosage should be kept as low as possible since its effect appears to be dose dependent. Although present data are more limited, it appears that phenobarital poses an overall increased risk. Lamotrigine and carbamazepine may have a specific risk for cleft lip/palate but with an overall modest risk for major malformations. Additional studies are required to confirm these risks. Further, there is a critical need for investigations to delineate the underlying mechanisms and explain the variance seen in outcomes across AEDs and within a single AED.

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## DISCLOSURE

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## APPENDIX

HOPE international working group members include Richardae Araojo, PharmD; Gus Baker, MSc, PhD; Dina Battino, MD; Elinor Ben-Menachem, MD, PhD; Anne Berg, PhD; Tuuli Cnaan, PhD; Morris Cohen, MD; Jill Conway, MD, PhD; Maurice Druzin, MD; Karen Feibus, MD; Eija Gaily, MD, PhD; Karen Gale, PhD; Barry Gidal, PharmD; Frank Gilliam, MD, MPH; Denis Grant, PhD; Dale Hesdorffer, PhD; Lewis Holmes, MD; Joyce Liporace, MD; Jim Morrow, MD; Errol Norwitz, MD; Alison Pack, MD; Emilio Perucca, MD, PhD; David Portman, MD; Elisabeth Robert-Gnansia, MD; Julian Robinson, MD; Anne Sabers, MD; Angela Scheuerle, MD; David Thurman, MD; Frank Vajda, MD; Michael Westerveld, PhD; Katarina Wide, MD.

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K. J. Meador, P. B. Pennell, C. L. Harden, et al.

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