ORIGINAL ARTICLE

Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations

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ABSTRACT

BACKGROUND

The use of valproic acid in the first trimester of pregnancy is associated with an increased risk of spina bifida, but data on the risks of other congenital malformations are limited.

METHODS

We first combined data from eight published cohort studies (1565 pregnancies in which the women were exposed to valproic acid, among which 118 major malformations were observed) and identified 14 malformations that were significantly more common among the offspring of women who had received valproic acid during the first trimester. We then assessed the associations between use of valproic acid during the first trimester and these 14 malformations by performing a case–control study with the use of the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database, which is derived from population-based congenital-anomaly registries. Registrations (i.e., pregnancy outcomes with malformations included in EUROCAT) with any of these 14 malformations were compared with two control groups, one consisting of infants with malformations not previously linked to valproic acid use (control group 1), and one consisting of infants with chromosomal abnormalities (control group 2). The data set included 98,075 live births, stillbirths, or terminations with malformations among 3.8 million births in 14 European countries from 1995 through 2005.

RESULTS

Exposure to valproic acid monotherapy was recorded for a total of 180 registrations, with 122 registrations in the case group, 45 in control group 1, and 13 in control group 2. As compared with no use of an antiepileptic drug during the first trimester (control group 1), use of valproic acid monotherapy was associated with significantly increased risks for 6 of the 14 malformations under consideration; the adjusted odds ratios were as follows: spina bifida, 12.7 (95% confidence interval [CI], 7.7 to 20.7); atrial septal defect, 2.5 (95% CI, 1.4 to 4.4); cleft palate, 5.2 (95% CI, 2.8 to 9.9); hypospadias, 4.8 (95% CI, 2.9 to 8.1); polydactyly, 2.2 (95% CI, 1.0 to 4.5); and craniosynostosis, 6.8 (95% CI, 1.8 to 18.8). Results for exposure to valproic acid were similar to results for exposure to other antiepileptic drugs.

CONCLUSIONS

The use of valproic acid monotherapy in the first trimester was associated with significantly increased risks of several congenital malformations, as compared with no use of antiepileptic drugs or with use of other antiepileptic drugs.

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Valproic acid, which has been used for the treatment of seizure for more than 30 years, has long been recognized as a teratogen. Maternal exposure to valproic acid monotherapy during the first trimester was first linked to an increased risk of congenital spina bifida in the 1980s[1-6]; subsequent studies confirmed this increased risk and also suggested increased risks of other major congenital malformations.[7,8] Recently, the American Academy of Neurology recommended avoidance of valproic acid during pregnancy if possible.[9] However, if treatment with valproic acid has been providing good seizure control, it can be difficult to change the drug before or during pregnancy.[10,11]

Although a number of cohort studies of women exposed to valproic acid in pregnancy have shown an association with a range of malformations,[12-17] these studies have had limited power individually to detect excess risks of specific malformations. For rare outcomes, such as these specific malformations, large population-based case–control studies are more appropriate.[18]

We combined the data from cohort studies to identify indications that malformations were occurring at greater frequency than expected among offspring exposed to valproic acid during the first trimester of pregnancy. We then conducted a population-based, case–control study to test our hypotheses, using the antiepileptic-study database established by European Surveillance of Congenital Anomalies (EUROCAT).

METHODS

EUROCAT DATABASE

We used the EUROCAT antiepileptic-study databases, which included data on affected live births, stillbirths, fetal deaths after 20 or more weeks of gestation, and terminations of pregnancy after prenatal diagnosis for the years 1995 through 2005 from 19 population-based EUROCAT registries in 14 countries (for more information, see Section 1 of the Supplementary Appendix, available with the full text of this article at NEJM .org).[19] The study sample consisted of 3,881,592 live births and stillbirths, of which 98,075 involved a major congenital malformation.

The standard data recorded for each registration are described in EUROCAT Guide 1.3.[20] Multiple sources are used to ascertain pregnancy outcomes with malformations (registrations).[21] Data are managed in a standard software program that is used by all registries and includes error checks.[20] Infants or fetuses having only malformations categorized as minor according to EUROCAT definitions were excluded.[20] One syndrome and up to eight malformations are coded with *International Classification of Diseases, Ninth Revision* (ICD-9) or *International Classification of Diseases, Tenth Revision* (ICD-10) codes, with British Pediatric Association (BPA) one-digit extensions. These codes are regrouped into the standard EUROCAT malformation subgroups.[20] Maternal illness before and during pregnancy (ICD-9 or ICD-10 code plus descriptive information) and drug exposure in the first trimester of pregnancy (descriptive information or Anatomical Therapeutic Chemical [ATC] code[22]) are recorded. The first trimester is defined as the period from the first day of the last menstrual period through the 12th week of gestation.

ASCERTAINMENT OF EXPOSURE

Information on maternal antiepileptic-drug exposure is mainly obtained from medical hospital records generated during pregnancy (for all 19 registries). Five registries also use other prospectively recorded sources of information (records from general practitioners, pharmacy records, and medical records held by the patient), and three registries use a structured interview or questionnaire after birth to acquire additional information on drug exposure. The persons who recorded information in registries were not aware of the specific hypothesis of the study. Antiepileptic drugs are available by prescription only and are typically supplied for long-term use; thus, medical records were considered to be a good source of data for ascertainment of exposure.

To be included in the EUROCAT antiepileptic-study database, a registry must have recorded a diagnosis of maternal epilepsy or antiepileptic-drug exposure for at least 3 registrations per 1000 (to exclude registries with low rates of exposure ascertainment) and must have recorded a complete drug name or ATC code for at least 80% of all pregnancies exposed to antiepileptic drugs throughout the study period (to exclude registries with incomplete data on exposure to antiepileptic drugs).

STUDY DESIGN

We searched PubMed, Web of Science, and Embase for studies addressing exposure to valproic

acid in pregnancy. Eight cohort studies met the inclusion criteria and were included in the review (see Section 2 in the Supplementary Appendix for a description of the inclusion criteria).[12-17,23,24] These eight studies included 1565 pregnancy outcomes in which there was exposure to valproic acid monotherapy during the first trimester; in 118 of these outcomes there was a major congenital malformation as defined by EUROCAT. The overall rate of major congenital malformations was 7.5% (95% confidence interval [CI], 6.3 to 9.0) (Table 1).

All 14 malformations with prevalences that were significantly higher in the studies of maternal exposure to valproic acid than in the EUROCAT reference group (of 3.8 million) ($P<0.05$) were included in the case–control study. The number of cases with each of these 14 malformations is detailed in Section 2 in the Supplementary Appendix.

To minimize the chances that we missed a group that warranted inclusion by looking only at cohort studies in the literature review, we also searched case–control studies. The one additional group we found — limb-reduction malformations[25,26] — was excluded to avoid a possible underestimation in the case–control analyses; we examined the group with limb-reduction malformations separately.

We used the EUROCAT antiepileptic-study database to compare the odds of exposure to valproic acid monotherapy among cases (for each of the 14 malformations identified from the literature review) with the odds of exposure in two groups of controls — a group with major malformations other than those under study and a group with malformations associated with chromosomal abnormalities. Exposure to valproic acid monotherapy during the first trimester was compared with the absence of exposure to antiepileptic drugs and with exposure to an antiepileptic-drug monotherapy other than valproic acid.

Cases were defined as all live births, fetal deaths after at least 20 weeks of gestation, and terminations of pregnancy after prenatal diagnosis with at least one of the following malformations: spina bifida, microcephaly, ventricular septal defect, atrial septal defect, tetralogy of Fallot, pulmonary-valve atresia, hypoplastic right heart, cleft palate (without associated cleft lip), diaphragmatic hernia, gastroschisis, hypospadias, clubfoot, polydactyly, and craniosynostosis. All

Table 1. Overview of Studies Included in the Analysis.

Study	Country	Birth Years Included	First-Trimester Exposure to Valproic Acid Monotherapy		
			Exposed Pregnancies	Births with Malformation	Malformation Rate
			number		*% (95% CI)*
Samrén et al.[14]	Germany, Finland, and the Netherlands	1972–1990	184	16	8.7 (5.4–13.7)
Kaaja et al.[24]	Finland	Jan. 1980–Sept. 1998	61	4	6.6 (2.6–15.7)
Sabers et al.[23]	Denmark	Sept. 1996–May 2000	30	2	6.7 (1.9–21.3)
Vajda et al.[15]	Australia	July 1999–Oct. 2002	89	15	16.9 (10.5–26.0)
Wide et al.[16]	Sweden	July 1995–Dec. 2001	268	26	9.7 (6.7–13.8)
Wyszynski et al.[17]	United States	Feb. 1997–Nov. 2003	149	16	10.7 (6.3–16.8)
Meador et al.[12]	United Kingdom and United States	Oct. 1999–Feb. 2004	69	12	17.4 (10.2–28.0)
Morrow et al.[13]	United Kingdom	Dec. 1996–March 2005	715	44	6.2 (4.6–8.2)
All studies		1972–2005	1565	135	8.6 (7.3–10.1)
All studies, excluding minor malformations*		1972–2005	1565	118	7.5 (6.3–9.0)

* According to the classification of major congenital malformations in the European Surveillance of Congenital Anomalies (EUROCAT) registry, based on the *International Classification of Diseases, 10th Edition*, 17 malformations were minor and were therefore excluded from the analysis.

cases with a diagnosed chromosomal or monogenic syndrome were excluded.

Control group 1 included live births, fetal deaths after 20 weeks or more of gestation, and pregnancy terminations after prenatal diagnosis that involved major malformations other than the 14 malformations under study. We excluded chromosomal disorders (the disorders in control group 2), as well as identified syndromes (1806 registrations); cleft lip, cleft lip and palate, or the Pierre Robin sequence without a reported cleft palate (3382); limb-reduction defects (1704); and anencephaly or encephalocele (1759). We also excluded five controls for which type of birth was unknown. Control group 2 comprised live births, fetal deaths after 20 weeks or more of gestation, and pregnancy terminations after prenatal diagnosis that involved malformations associated with chromosomal abnormalities. We excluded two of the entries in this group because type of birth was unknown.

All registrations with recorded maternal antiepileptic-drug use or maternal epilepsy were selected, verified by the registry, and coded according to the name of the antiepileptic drug. After verification, 99.9% of the antiepileptic drugs to which mothers were exposed in the first trimester of pregnancy had been identified. To minimize the risk of misclassification, we excluded all registrations for which there had been a previous diagnosis of maternal epilepsy but for which there was no history of maternal antiepileptic-drug use in the first trimester (a total of 96 cases, 122 controls in group 1, and 19 controls in group 2).

STATISTICAL ANALYSIS

Logistic-regression analysis was used to calculate odds ratios with Stata software, version 10. Crude odds ratios were calculated for all registries, including those without records of valproic acid exposure. Odds ratios were adjusted for maternal age (categorized as less than 25 years, 25 to 29 years, 30 to 34 years, or more than 34 years) and the child's year of birth (categorized as being between 1995 and 1998, between 1999 and 2001, or between 2002 and 2005). Odds ratios were also adjusted for the individual registry (registries with no entries for valproic acid exposure were excluded) in the comparison of exposure to valproic acid monotherapy with no exposure to antiepileptic drugs; there were too few controls to make this adjustment in other comparisons. For anomalies for which there were fewer than six cases with exposure to valproic acid, no adjustments were made and the exact confidence intervals are presented.

RESULTS

A total of 37,154 cases, 39,472 controls without chromosomal abnormalities (control group 1), and 11,763 controls with chromosomal abnormalities (control group 2) were included in the study. The frequency of maternal use of antiepileptic drugs overall in the first trimester of pregnancy was 5.7 per 1000 registrations, and the frequency of maternal use of valproic acid specifically was 2.0 per 1000. The frequency of exposure to valproic acid was three times as high among cases (3.3 per 1000 registrations) as among controls in both groups (1.1 per 1000) (Table 2).

In analyses of cases and the controls in group 1, exposure to valproic acid monotherapy during the first trimester as compared with no exposure to antiepileptic drugs during that period was associated with significant increases in the risks of spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis but not in the risks of microcephaly, tetralogy of Fallot, pulmonary-valve atresia, diaphragmatic hernia, ventricular septal defect, hypoplastic right heart (no exposed cases), gastroschisis, or clubfoot (Table 3). Adjustment for reporting registry, birth year of the registration, and maternal age did not substantively affect the results (see Section 3 in the Supplementary Appendix for details).

Using the same control group, we found generally similar associations between valproic acid exposure and malformations when valproic acid monotherapy was compared with monotherapy with another antiepileptic drug — with two exceptions. When compared with use of another antiepileptic drug, valproic acid use was not associated with a significantly increased risk of craniosynostosis but was associated with a significantly increased risk of ventricular septal defect.

In corresponding analyses comparing cases with the controls in group 2 (those with chromosomal abnormalities), the results were generally similar. Separate analyses of the suggested association between valproic acid exposure and limb reduction showed a significantly increased risk

Table 2. Exposure to Antiepileptic Drugs in the First Trimester of Pregnancy among Cases and Controls with Congenital Malformations.*

Exposure	Cases (N=37,154)		Control Group 1 (N=39,472)		Control Group 2 (N=11,763)	
	no.	*no./1000 registrations*	*no.*	*no./1000 registrations*	*no.*	*no./1000 registrations*
No exposure to antiepileptic drugs	36,869	—	39,290	—	11,725	—
Any antiepileptic-drug monotherapy or polytherapy	285	7.7	182	4.6	38	3.2
Any antiepileptic-drug monotherapy	223	6.0	155	3.9	32	2.7
Valproic acid monotherapy	122	3.3	45	1.1	13	1.1
Other monotherapy	101†	2.7	110‡	2.8	19§	1.6

* Malformations included spina bifida, microcephaly, ventricular septal defect, atrial septal defect, tetralogy of Fallot, pulmonary-valve atresia, hypoplastic right heart, cleft palate, diaphragmatic hernia, gastroschisis, hypospadias, clubfoot, polydactyly, and craniosynostosis.

† Among these patients, 58 received carbamazepine, 21 received lamotrigine, 8 received phenobarbital, 4 received oxcarbazepine, 3 received clonazepam, 2 received phenytoin, 1 received methylphenobarbital, 1 received topiramate, and 3 received unspecified medications.

‡ Among these patients, 65 received carbamazepine, 18 received lamotrigine, 9 received phenobarbital, 7 received oxcarbazepine, 3 received phenytoin, 3 received primidone, 2 received clonazepam, 1 received ethosuximide, 1 received methylphenobarbital, and 1 received topiramate.

§ Among these patients, 10 received carbamazepine, 4 received phenobarbital, 2 received lamotrigine, 1 received clonazepam, 1 received oxcarbazepine, and 1 received phenytoin.

of limb reduction (crude odds ratio, 3.4; 95% CI, 1.6 to 7.2) as compared with the absence of exposure to antiepileptic drugs.

In control group 1, we also compared the distribution of malformations among controls exposed to valproic acid with the distribution among controls without exposure to antiepileptic drugs and found no significant differences (data not shown). We found no malformations other than those reported in the literature that had a significant association with valproic acid exposure in this group.

DISCUSSION

In a review of published cohort studies, we identified 14 major congenital malformations for which the risk appeared to be significantly increased in association with exposure to valproic acid monotherapy during the first trimester of pregnancy as compared with no exposure to antiepileptic drugs during the first trimester. We then tested these indications in a large population-based case–control study and found significant associations between exposure to valproic acid monotherapy in the first trimester (as compared with no exposure to antiepileptic drugs) and six of these conditions: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis. Risks for five of these conditions were 2 to 7 times as high for exposed fetuses, and the risk for the sixth condition, spina bifida, was 12 or 16 times as high, depending on the control group used. We also found an association between limb defects and exposure to valproic acid monotherapy as compared with no exposure to antiepileptic drugs, as suggested in previous case–control studies.

Significant associations with valproic acid exposure were noted for five of the six specific malformations in analyses comparing exposure to valproic acid monotherapy with other antiepileptic-drug monotherapy; an association with craniosynostosis was not found. A significant association with ventricular septal defect was detected, but only for the comparison of cases with controls in the group that had malformations not associated with a chromosomal abnormality — not for the comparison of cases with the other control group. Although the observational nature of this study precludes a conclusion about cause and effect, these findings support a relationship of these malformations to valproic acid specifically rather than to antiepileptic drugs

generally or to underlying epilepsy. Valproic acid is used for various indications in European countries, which means that its use is unlikely to be very strongly related to a particular type or severity of epilepsy. However, we do not have information on the type or severity of epilepsy and therefore cannot rule out the possibility of confounding by indication.

Studies evaluating the risk of general malformations after in utero exposure to an antiepilep-

Table 3. Odds Ratios for Malformations with Exposure to Valproic Acid Monotherapy as Compared with No Antiepileptic-Drug (AED) Exposure and with Exposure to Monotherapy with Other Antiepileptic Drugs in Control Groups 1 and 2.*

Type of Malformation	No. with Malformation†	No. with Malformation Exposed to Valproic Acid Monotherapy	Adjusted Odds Ratio for Valproic Acid Monotherapy vs. No AED (95% CI)‡	Adjusted Odds Ratio for Valproic Acid Monotherapy vs. Other AED Monotherapy (95% CI)‡
Nervous system				
Spina bifida	2,046	27		
Control group 1			12.7 (7.7–20.7)	5.7 (2.6–12.3)§
Control group 2			16.3 (8.0–33.4)	3.5 (1.2–10.0)§
Microcephaly¶	696	2		
Control group 1			2.5 (0.3–9.7)‖	1.6 (0.1–14.7)‖
Control group 2			2.6 (0.3–11.6)‖	1.0 (0.1–9.8)‖
Heart				
Ventricular septal defect	11,711	19		
Control group 1			1.6 (0.9–2.7)	2.2 (1.1–4.4)§
Control group 2			1.8 (0.8–3.9)	1.5 (0.6–4.2)§
Atrial septal defect	8,267	19		
Control group 1			2.5 (1.4–4.4)	3.2 (1.5–7.0)§
Control group 2			3.3 (1.4–7.4)	2.4 (0.8–7.0)§
Tetralogy of Fallot	960	3		
Control group 1			2.8 (0.6–8.6)‖	1.5 (0.2–7.9)‖
Control group 2			2.8 (0.5–10.4)‖	0.9 (0.1–5.5)‖
Pulmonary-valve atresia	311	1		
Control group 1			2.8 (0.1–16.7)‖	2.4 (0.0–193.6)‖
Control group 2			2.9 (0.1–19.5)‖	1.5 (0.0–120.7)‖
Hypoplastic right heart	85	0		
Control group 1			—	—
Control group 2			—	—
Cleft palate	2,244	13		
Control group 1			5.2 (2.8–9.9)	3.0 (1.2–7.4)§
Control group 2			5.2 (2.2–12.3)	1.9 (0.6–5.9)§
Diaphragmatic hernia	754	2		
Control group 1			2.3 (0.3–9.0)‖	1.2 (0.1–8.9)‖
Control group 2			2.4 (0.3–10.7)‖	0.7 (0.1–6.1)‖
Gastroschisis	798	1		
Control group 1			1.1 (0.0–6.5)‖	1.2 (0.0–24.0)‖
Control group 2			1.1 (0.0–7.6)‖	0.7 (0.0–15.6)‖
Hypospadias (male outcome only)	5,395	32		
Control group 1			4.8 (2.9–8.1)	6.7 (2.9–15.2)§
Control group 2			6.3 (2.6–15.2)	4.1 (1.1–15.0)§

Table 3. (Continued.)

Type of Malformation	No. with Malformation†	No. with Malformation Exposed to Valproic Acid Monotherapy	Adjusted Odds Ratio for Valproic Acid Monotherapy vs. No AED (95% CI)‡	Adjusted Odds Ratio for Valproic Acid Monotherapy vs. Other AED Monotherapy (95% CI)‡
Limb				
Clubfoot¶	3,676	6		
Control group 1			1.6 (0.7–3.7)	1.3 (0.5–3.9)§
Control group 2			2.2 (0.8–6.7)	1.2 (0.3–4.7)§
Polydactyly	3,500	9		
Control group 1			2.2 (1.0–4.5)	7.1 (1.8–28.4)§
Control group 2			2.4 (0.9–6.4)	4.4 (0.8–22.6)§
Craniosynostosis	520	4		
Control group 1			6.8 (1.8–18.8)‖	4.9 (0.7–55.2)‖
Control group 2			7.0 (1.7–22.9)‖	2.9 (0.4–35.8)‖

* Control group 1 included registrations without chromosomal abnormalities, and control group 2 registrations with chromosomal abnormalities. For the number of cases with no exposure to valproic acid, see Section 3 in the Supplementary Appendix, available with the full text of this article at NEJM.org.
† A case or control may have been counted in more than one subgroup.
‡ Odds ratios were adjusted for reporting registry, birth year, and maternal age unless otherwise indicated.
§ Odds ratios were adjusted for birth year and maternal age only.
¶ Microcephaly and clubfoot occurred without spina bifida.
‖ Odds ratios were not adjusted because of the small number of exposed cases.

tic drug as compared with no such exposure have shown that the risk is significantly higher with exposure to valproic acid than with exposure to other antiepileptic drugs. Furthermore, these studies have suggested increased risks of malformations in general in association with higher doses of valproic acid as compared with lower doses.[13,15-17] Since our data set does not include dose information, we were not able to address this question.

Previous studies of valproic acid monotherapy during the first trimester and the risk of specific malformations, other than spina bifida,[27,28] have generally been limited by relatively small samples or potential selection bias, since they have not been population-based.[11,13,15,17] Our results are in line with those of another large, population-based, case–control registry study of congenital malformations in which the control group had malformations; specific associations were reported between valproic acid exposure and spina bifida, hypospadias, malformations of the brain and heart, and limb-reduction malformations.[26]

A recent study showed that children exposed to valproic acid in utero were more likely to have impaired cognitive function at 3 years of age than children exposed in utero to other antiepileptic drugs.[29] The American Academy of Neurology has recommended avoiding valproic acid in pregnancy, if possible, on the basis of evidence that exposure to valproic acid is associated with an increased risk of major congenital malformations and poor cognitive outcomes and confers a higher risk than that associated with exposure to other antiepileptic drugs.[9]

For malformations seen less frequently, our study was able to rule out very large risks but not smaller risks. The confidence limits were wide, showing that even a study of nearly 4 million pregnancies is not enough to address a potentially moderate association between rare malformations and relatively rare drug exposures.

A limitation of our study, as discussed above, is the lack of information on potential confounders. Furthermore, we used controls with malformations instead of those without malformations, since EUROCAT does not include detailed population-based data on pregnancy outcomes without malformations. An advantage of using controls with malformations is that it minimizes the potential for recall bias and other possible sources of differential exposure ascertainment, although such biases would be unlikely to influence the results, since most drug information was recorded before the outcome of pregnancy was known. Use of controls with malformations

for comparison could lead to a conservative estimation of the risk associated with valproic acid exposure if some of the malformations present in the control group were also associated with this exposure; however, by design we excluded from the control groups malformations previously associated with valproic acid exposure. The rate of valproic acid exposure was similar in the two control groups (1.1 per 1000), and the point estimates for the control group with chromosomal abnormalities were similar but slightly higher than those for the control group without chromosomal abnormalities in comparisons of exposure to an antiepileptic drug with no such exposure. We therefore concluded that there was likely to be little or no contamination of our control groups with malformation types associated with valproic acid exposure and that underestimation of odds ratios because of this bias was unlikely.

Although the relative risks of several malformations were increased in association with exposure to valproic acid during the first trimester, it should be recognized that the absolute rates of specific malformations are low, and the majority of children born to mothers who take valproic acid do not have malformations. For example, the baseline prevalence of spina bifida is about 0.5 cases per 1000 (see Section 2 in the Supplementary Appendix). We calculated an adjusted odds ratio of 12.7 for the risk of spina bifida when comparing exposure to valproic acid with no exposure to an antiepileptic drug (Table 3); the absolute risk of having a child with spina bifida is approximately 0.6% in cases of exposure to valproic acid monotherapy during the first trimester. The estimated absolute risks for the other five malformations after exposure are as follows: atrial septal defect, 0.5%; cleft palate, 0.3%; hypospadias, 0.7%; polydactyly, 0.2%; and craniosynostosis, 0.1%. In determining whether to prescribe antiepileptic drugs, as well as which drug to prescribe, several factors must be taken into account, among them the goal of optimizing seizure control in the individual patient. The decision should be made by the patient and her clinician after consideration of the benefits and risks of various agents.

In summary, we found that exposure to valproic acid during the first trimester was associated with increased risks of six specific malformations, as compared with no exposure to antiepileptic drugs, and the risks of five of these six malformations remained significantly increased when we compared valproic acid exposure with exposure to other antiepileptic drugs. Our findings provide further support for the recommendation of the American Academy of Neurology to avoid the use of valproic acid, if possible, in pregnant women.[9] Since switching drugs during or just before pregnancy is difficult, the risks associated with valproic acid use should be routinely considered in choosing therapy for women with childbearing potential.

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APPENDIX

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