Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy

L.B. Holmes, MD
E.J. Baldwin, MPH
C.R. Smith, MPH
E. Habecker
L. Glassman
S.L. Wong
D.F. Wyszynski, MD, PhD

Address correspondence and reprint requests to Dr. L.B. Holmes, Genetics Unit, MassGeneral Hospital for Children, CPZS-504, 175 Cambridge Street, Boston, MA 02114
holmes.lewis@mgh.harvard.edu

ABSTRACT

Background: Pregnancy registries for women taking anticonvulsant drugs have been developed to determine more efficiently the fetal risks of each drug. A total of 722 drug-exposed pregnancies are needed to identify a sevenfold increase in the rate of occurrence of a specific abnormality, such as spina bifida, with a frequency of 1 in 1,000.

Methods: The infants with major malformations born to the 791 women who had taken lamotrigine as monotherapy and had enrolled in the North American AED Pregnancy Registry were identified. Medical records were obtained from the affected infants' doctors. A total of 107 of the 791 infants or pregnancies were excluded.

Results: A total of 16 (2.3%) of 684 infants exposed to lamotrigine had major malformations that were identified at birth. Five infants (7.3/1,000) had oral clefts: isolated cleft palate (3), isolated cleft lip (1), and cleft lip and palate (1). The rate among the lamotrigine-exposed infants showed a 10.4-fold increase (95% CI: 4.3–24.9) in comparison to 206,224 unexposed infants surveyed at birth at Brigham and Women's Hospital in Boston, where the prevalence of isolated oral clefts was 0.7/1,000. A comparison was made also to 1,623 infants exposed to lamotrigine, as monotherapy, who had enrolled in five other registries. There were four infants with oral clefts: prevalence 2.5/1,000 (RR: 3.8, 95% CI: 1.4–10.0).

Conclusions: The infant exposed in the first trimester of pregnancy to the anticonvulsant drug lamotrigine has an increased risk to have an isolated cleft palate or cleft lip deformity.
***Neurology*® 2008;70:2152–2158**

GLOSSARY

AED = antiepileptic drug; **BWH** = Brigham and Women's Hospital; **CL** = cleft lip without cleft palate; **CLP** = cleft lip and palate; **CP** = cleft palate; **LMP** = last menstrual period.

Every anticonvulsant drug studied in human pregnancies, to date, including phenobarbital, phenytoin, carbamazepine, and valproate,[1-3] has been shown to be teratogenic. The magnitude of the risks and the associated effects on physical features, learning skills, and intelligence have varied for each drug. However, for many "new" anticonvulsant drugs marketed in the 1990s[4] there is no information on the potential fetal risks from their use during pregnancy. The Pregnancy Categories A, B, C, D, and X, developed to provide estimates of fetal risk, have been found to be inaccurate.[5,6] Pregnancy registries[7-9] have been proposed as a method of postmarketing surveillance to determine over a few years time the frequency of one potential outcome: major malformations. These findings can be used to provide narrative summaries which have been proposed to replace the Pregnancy Categories.

The North American AED Pregnancy Registry was established in 1997 with financial support from several pharmaceutical companies.[10,11] Lamotrigine (LTG) is a phenyltria-

e-Pub ahead of print on April 30, 2008, at www.neurology.org.

From the North American AED Pregnancy Registry (L.B.H., E.J.B., C.R.S., E.H., L.G., S.L.W.), Genetics and Teratology Unit, MassGeneral Hospital for Children, Boston; and Genetics Program (D.F.W.), Department of Medicine, Boston University School of Medicine, MA.

The North American AED Pregnancy Registry is supported by funds provided by Abbott, Eisai, GlaxoSmithKline, Novartis, Ortho-McNeil, and Pfizer Pharmaceuticals.

Disclosure: Each of the authors received salary support from funds provided since 1997 by the six sponsors of the Registry. At the time this manuscript was written, the sponsors were Abbott, Eisai, GlaxoSmithKline, Novartis, Ortho-McNeil, and Pfizer.

Copyright © 2008 by AAN Enterprises, Inc.
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

zine, which inhibits the release of glutamate, an excitatory amino acid, and inhibits voltage-sensitive sodium channels.[12] The drug differs structurally from the other anticonvulsant drugs available currently. Clinical trials with LTG were under way in 1992[13]; Food and Drug Administration approval was granted in 1994.

In two recent published articles,[14,15] the prevalence rates of all malformations in LTG-exposed pregnancies were 2.9% and 3.2%, respectively, but no increase in any specific malformations was noted. This report is the first to demonstrate an increased prevalence of a specific malformation, isolated cleft palate, and possibly cleft lip and palate, in infants exposed during the first trimester of pregnancy to LTG.

METHODS To enroll in the North American AED Pregnancy Registry, the eligible woman called its toll-free telephone number (1-888-233-2334). After informed consent was obtained, she was interviewed three times: 1) at enrollment, 2) at 7 months gestation, and 3) 8 to 12 weeks after the expected date of delivery. Using a computer-assisted telephone interview, the enrollee was asked about the dose, frequency, and medical indication of each anticonvulsant drug taken, the signs and symptoms of epilepsy (or a mood disorder), the apparent causes of her epilepsy, demographic characteristics, habits (such as alcohol use, cigarette smoking, use of illicit drugs), other potential teratogenic exposures (such as maternal diabetes or taking the acne medication Accutane), other prescribed and over-the-counter medications taken, and family history of epilepsy (or mood disorders) and of birth defects. She was asked if she was taking a multivitamin supplement, and a folic acid supplement in particular, at conception.

Enrolled women were classified as "pure" prospective enrollees if they did not know, at the time of enrollment, whether the fetus had a malformation. The "traditional" prospective enrollees had some knowledge of the status of the fetus, typically after having prenatal screening by ultrasound at 16 to 20 weeks of gestation. The term "undetermined" was used if in the initial interview several years ago the information recorded was not sufficient to determine whether she was a "pure" prospective enrollee. Women were not enrolled after the pregnancy had ended.

Only women exposed to an anticonvulsant drug as monotherapy during the first 16 weeks of gestation were analyzed. Monotherapy was defined as exposure to only one anticonvulsant drug at any time during pregnancy. If a second anticonvulsant drug was added after 16 weeks of gestation, that woman's pregnancy was considered monotherapy-exposed.

The informed consent document had been reviewed and approved annually, since 1996, by the Human Studies Committee of the Massachusetts General Hospital and Partners HealthCare in Boston. Each enrolled mother was identified only by a study number to protect the confidentiality of the information compiled.

Release forms were mailed to the mothers to be signed and returned. These signed requests were sent to the woman's neurologist (or other treating physicians) and her infant's physicians. The information from the interviews and from the medical records was entered into an Oracle database. Relative risks and their 95% CIs were calculated with the software Stata, version 9.1 (Stata Corp., College Station, TX).

When mothers did not sign medical record release forms, they were re-contacted to encourage them to provide this written permission. The parents of all infants with major malformations were interviewed, whenever possible, to confirm the information provided about family history, doses of medications reported, and to ask if a specific syndromic diagnosis had been established.

A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance. The physical features excluded were 1) minor anomalies (transverse palmar crease); 2) deformations or positional deformities (torticollis); 3) features due to prematurity (undescended testes) in an infant born at less than 37 weeks gestational age; 4) birthmarks (hemangiomas); 5) genetic disorders (albinism and Down syndrome; and 6) any finding by prenatal sonography (or at surgery or autopsy), such as absence of one kidney, that was not identified by an examining pediatrician. The written descriptions in the pediatricians' examinations were reviewed separately by the clinical teratologist (L.B.H.), blinded to exposure status, to determine inclusion or exclusion. The examination by a physician at birth was used as the gold standard for the detection of all malformations. Anomalies detected only by prenatal ultrasonography (and not by the pediatrician) were excluded because all infants did not have such examinations and among those who did, there was no uniformity of the timing, the equipment used, and the experience of the sonologists.

The findings in the Active Malformations Surveillance Program at Brigham and Women's Hospital (BWH) in Boston were used as the comparison group of unexposed newborn infants.[16,17] This Surveillance Program, directed since 1972 by one of the authors (L.B.H.), uses the same inclusion and exclusion criteria as the AED Pregnancy Registry. The prevalence rates of cleft palate (CP), cleft lip without cleft palate (CL), and cleft lip and palate (CLP) were determined from the entire population (206,224 infants and elective terminations for fetal anomalies) surveyed between 1972 and 1974 and between 1979 and 2000. Since the time period for identification of major malformations in this comparison group was between birth and 5 days of age, the time period for the identification of malformations in the LTG-exposed group was limited to birth to 5 days of age.

Two risk factors in the occurrence of CL, CLP, and CP are the use of a folic acid supplement at the time of conception[18] and cigarette smoking by the mother during pregnancy.[19] The answers to the questions about each of these factors were tabulated for each malformed infant.

With regard to the role of the sponsoring companies, each has one or two representatives on the Steering Committee of the Registry. However, the members of the Scientific Advisory Committee (members listed in Acknowledgment) and the staff of the Registry meet separately, where decisions are made about the release of any findings. The findings for infants exposed to specific drugs are discussed anonymously;

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Table 1 Participants exposed to lamotrigine monotherapy during the first trimester of gestation

	"Pure" prospective, n = 511	"Traditional" prospective, n = 230	Undetermined, n = 50
Analyzable data			
Liveborn	425	202	43
Elective terminations	7	0	0
Stillborn	2	1	0
Neonatal death	3	1	0
Total used in the analysis	437	204	43
Insufficient data			
Spontaneous abortions	31	0	1
Lost to follow-up/withdrawn	25	9	5
Unknown/still pregnant	18	17	1
Total not used in the analysis	74	26	7

Table 2 All infants with major malformations

Malformations	No. (total = 19)
Identified before fifth day of life (n = 16)	
Oral clefts	5 (3 P, 2 T)
Limb defects*	3 (2 P, 1 T)
Heart defects	2 (2 P)
Anencephaly	1 (P)
Choanal atresia	1 (P)
Craniosynostosis	1 (P)
Holoprosencephaly	1 (P)
Hydrocephalus, ? etiology	1 (T)
Urethral obstruction	1 (P)
Prune belly syndrome	16
Identified after fifth day	
Inguinal hernia	3

*Limb defects: terminal transverse limb defect below elbow (1); nubbins at M-P joint; missing fingers 2–4 (1); one toenail growing laterally (1).
P = pure prospective; T = traditional prospective.

that is, without identifying the drug. After a decision is made by the Scientific Advisory Committee, the members of the Steering Committee (representatives of the sponsors) are informed of the decision, but not the identity of the drug. The company which manufactures the drug being evaluated is informed of the finding. The company has the option, for a period of 30 days, of obtaining additional information from the Registry. After this period, all members of the Scientific Advisory and Steering Committees are informed about the identity of the drug whose findings are being released.

RESULTS From February 1, 1997, through March 1, 2006, a total of 4,688 antiepileptic drug (AED)–exposed women were enrolled in the North American AED Pregnancy Registry. A total of 62%, or 2,902, of these women reported taking an anticonvulsant as monotherapy and had a liveborn, a stillborn infant, or a pregnancy terminated because of a fetal abnormality. A total of 791 women, including 511 in the "pure" and 230 in the "traditional" prospective groups, had taken LTG as monotherapy during the first trimester of pregnancy (table 1). The "pure" prospective women enrolled, on average, 2.5 months after their last menstrual period (LMP) and the "traditional" prospective women, 6 months after their LMP. These two groups were reduced by 107 pregnancies for these reasons: spontaneous abortions (less than 20 weeks gestational age with no examination for malformations; n = 32), withdrawals from the Registry and being lost to follow-up (in spite of intense efforts to locate; n = 39), and still pregnant (n = 36).

Nineteen infants with major malformations were born to the 684 mothers (proportion, 2.8%; 95% CI: 1.7–4.3) (table 2). The additional interviews with many of the mothers of the malformed infants did not change the diagnosis for any infant. The malformations in three infants were identified after 5 days of age, reducing the rate to 16/684 = 2.3% (95% CI: 1.3–3.8). In comparison to the baseline rate of 1.62% in unexposed newborn infants,[16] the relative risk in the LTG-exposed infants was not significant statistically at alpha <0.05 (RR 1.4; 95% CI: 0.9–2.3).

Among the 16 infants with malformations, three had an isolated CP (1:228 or 4.4/1,000), one had an isolated CL, and one had a bilateral CLP. The prevalence of all oral clefts was 5 in 684 infants or 1:137 or 7.3/1,000. The findings in both the "pure" and "traditional" prospective groups were combined, as cleft palate is not very likely to be identified by prenatal screening by ultrasound. The cleft lip deformity in one infant (#5638) was identified by prenatal ultrasound screening after his mother's enrollment; at birth, he was found to have a cleft palate, as well.

The total prevalence of CL alone, CLP, and CP alone, including both isolated and syndromic forms, was 1.23/1,000 among the 206,224 births, including stillbirths and elective terminations surveyed for anomalies, at BWH in Boston for 1972–1974, 1979–2000[16,17] (table 3). Because the LTG-exposed infants with oral clefts appeared to have only "isolated" or nonsyndromic deformities, the frequency of each phenotype, i.e., CL, CLP, and CP, as an isolated deformity was also determined. The relative risk of isolated CP in the LTG-exposed

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Table 3 Prevalence rate of oral clefts in lamotrigine monotherapy–exposed pregnancies in comparison to unexposed infants

	Lamotrigine-exposed: AED Pregnancy Registry (n = 684)	Comparison group BWH Hospital (n = 206,224)	Relative risk (95% CI) (isolated clefts)
Cleft palate alone			
Total	3	94	21.0 (6.8–65.1)
Isolated	3	43 (46%)	
Rate isolated	4.4/1,000	0.21/1,000	
Rate total		0.46/1,000	
Cleft lip alone			
Total	1	65	5.8
Isolated	1	52 (80%)	(0.8–41.1)
Rate isolated	1.5/1,000	0.24/1,000	
Rate total		0.31/1,000	
Cleft lip and palate			
Total	1	95	6.0
Isolated	1	50 (53%)	(0.9–42.8)
Rate isolated	1.5/1,000	0.24/1,000	
Rate total		0.46/1,000	
All			
Total	5/684 isolated	254/206,224	10.4
Rate isolated	7.3/1,000	0.7/1,000	(4.3–24.9)
Rate total		1.23/1,000	

AED = antiepileptic drug; BWH = Brigham and Women's Hospital.

infants (4.4/1,000) compared to unexposed infants (0.21/1,000) was 21.0 (95% CI: 6.8–65.1).

The relative risk of isolated CLP and CL (2 of 684 infants or 2.9/1,000) in LTG-exposed infants compared to the unexposed comparison group was 5.8 (95% CI: 0.8–41.1).

Combining the types of oral clefts (7.3/1,000), the relative risk of isolated CP and isolated CL and CLP in LTG-exposed newborn infants in comparison to unexposed controls (0.7/1,000) was 10.4 (95% CI: 4.3–24.9).

A total of 305 (45%) of the enrolled mothers have been unwilling to provide the written permission needed to obtain written copies of the medical records of their infants. We compared the mother's verbal report with the doctors' records for the other 379 (55%) infants whose mothers had provided written permission and whose infants' records had been obtained. There was agreement for 378/379 (99%) of the reports. The one exception was a mother who reported that her infant was healthy, after he had a surgical repair of an inguinal hernia.

Fifteen (73%) of the 19 mothers of the malformed infants, including all 5 infants with CP or CL, reported having taken a multivitamin with folic acid supplement (1 to 3 mg/day) at the time of conception (table 2).

Two (13.3%) of the 19 mothers of the malformed infants reported having smoked to 1 pack of cigarettes per day in the first trimester (table 2).

The mean daily dose of LTG at the time of the woman's last menstrual period was 344.7 mg for the 19 mothers with malformed infants and 319.3 mg for the 665 mothers whose infants were not malformed, a difference which was not significant ($p = 0.52$).

DISCUSSION The frequency of CP or CLP was determined in five other studies of infants exposed during pregnancy to LTG as monotherapy (table 4). There were four affected infants among the 1,623 infants[14,15,20-23] (J. Morrow and K. Wide, personal communications) for a prevalence of 1:406 or 2.5/1,000; each was an isolated deformity that is nonsyndromic. The relative risk of CP, CL, and CLP in the LTG-exposed infants in these five other registries was 3.5 (95% CI: 1.3–9.3) compared to the unexposed newborns at BWH (0.7/1,000).

The family studies of Fogh-Andersen[24] suggested different genetic etiologies for isolated cleft lip and isolated cleft palate, because the rate of occurrence of isolated cleft palate was not increased among the relatives of individuals with isolated CL, while the rate of CL was increased. However, two environmental exposures, cigarette smoking and phenobarbital,[19,23,25] have been shown to be associated with an increased rate of occurrence of both CL and CP. This suggests that teratogenic exposures can increase the frequency of both CP and CL.

Initially for this Registry, the criterion for releasing findings was when the frequency of all malformations was increased to the point that the lower of the 95% CIs was 2.0 or higher. Using these criteria, the findings in phenobarbital-exposed[10] and valproate-exposed[11] pregnancies were released. For this release, a new criterion, the "rule of three," was used. This "rate" refers to the fact that the identification of three infants with a specific defect (e.g., isolated CP) in a cohort of 600, [26] when the true rate of occurrence in the general population is 1 in 700, is very unlikely to occur by chance. By these criteria, identifying two infants with either CL or CLP in a cohort of 600 would not justify the release of these findings.

Common malformations, like CP or CL, have many recognized etiologies, including chromosome abnormalities, genetic disorders, and specific malformation syndromes.[27] With age,

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Table 4 Findings of published studies that evaluated the fetal effects of maternal exposure to lamotrigine monotherapy

	No. of women exposed to lamotrigine monotherapy	Prevalence of all major malformations (95% CI)	Infants with oral clefts
GSK International Lamotrigine Registry[14,20]*	707	2.8% (1.6–5.1%)	1 cleft palate; 1 cleft lip and palate
UK Epilepsy and Pregnancy Register[15]†; J. Morrow, personal communication	647	3.2% (2.1–4.9%)	1 cleft lip and palate
Swedish Medical Birth Registry[21]‡; K. Wide, personal communication	90	4.4%	1 cleft palate
Australian Pregnancy Registry[22]*	128	0%	None
Danish Multicentre Registry[23]*	51	2% (0.1–10.7)	None
Total	1,623		4 (2.5/1,000)

*Pregnancy registry; women enrolled primarily by their physicians.
†Women enrolled by their physicians while pregnant; reports on health status of infant from primary care physician of mother and infant.
‡Information from a national malformation surveillance program which enrolls all infants born each year.

additional physical features can be identified in the infant with an apparent "isolated" CP or CL that leads to the diagnosis of a specific syndrome, such as Stickler syndrome (Mendelian Inheritance in Man #108300) or the velocardiofacial syndrome with the associated chromosome 22q11.2 deletion.[28] (Only one of the five families of LTG-exposed children with oral clefts has been willing to have these studies carried out, even at no cost to them. No 22q11.2 deletion was identified.)

Taking supplements of multivitamins, and folic acid in particular, has been associated with a decreased rate of occurrence of CL and CP in some,[18] but not all,[29] studies. These vitamin supplements have also been associated with a decrease in the rate of spina bifida in carbamazepine-exposed pregnancies,[30] but not in valproate-exposed pregnancies.[11] Lamotrigine is a mild inhibitor of dihydrofolate reductase,[12] but LTG therapy has not been associated with significant changes in serum or red blood cell folate concentrations.[31] In this study, 15 (73%) of the 19 mothers of the malformed infants, including all 5 whose infants had oral clefts, reported having been taking a multivitamin with a folic acid supplement at the time of conception.

A dose-response relationship is an expected characteristic of a human teratogen. In a study of 647 LTG-exposed pregnancies in the UK Epilepsy and Pregnancy Registry, the mean daily dose of the mothers of children with a major malformation was higher than for those without a major malformation (352.4 vs. 250.6 mg; $p = 0.005$),[15] but no significant differences were found in this study. However, there was no evidence of a dose-response relationship in the recent analysis[32] of either the Lamotrigine International Pregnancy Registry or in this study.

There are several limitations to this report. First, the prevalence rate of CL, CP, and CLP in the comparison population is not from this Registry, but is a population of newborn infants at a major university hospital, BWH, in Boston. The information on the presence of CL, CP, and CLP was obtained from reading the doctors' findings between birth and 5 days of age in their medical records.[16] These infants were identified in the Active Malformations Surveillance Program. The same inclusion and exclusion criteria were used. The Director of the Registry (Holmes) also directs this Malformations Surveillance Program. A concurrent control group is now being recruited by the Registry. While 313 infants have been enrolled, the sample is not adequate for the comparisons needed.

A second limitation is the theoretical possibility that maternal epilepsy, unrelated to the anticonvulsant drug, is teratogenic. However, 10 studies have shown that the mother with a history of epilepsy, but taking no anticonvulsant drug, did not have an increased risk of having children with major malformations.[33] A third limitation is the fact that the enrollment of eligible women in a pregnancy registry is not systematic or random, which could lead theoretically to spurious associations. A fourth potential limitation is the possibility that women who enrolled in the North American AED Pregnancy Registry enrolled also in the GlaxoSmithKline (GSK) International Lamotrigine Registry. None of the mothers of the five infants with oral clefts reported in personal interviews that they had enrolled in both registries. However, in a comparison of the characteristics of 359 women enrolled in the GSK Registry

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

and the enrollees in this Registry, 27 women appeared to have enrolled in both registries, including three whose infants had major malformations. A fifth limitation is the fact that the medical records of the 305 infants that were not obtained could have identified additional major malformations not reported by these mothers in the postpartum interviews. However, we were reassured by the fact that there was a 99% (378/379) agreement between the mothers' reports and their infants' medical records.

A sixth limitation is the fact that the prevalence rate of isolated cleft palate in routine examinations of newborn infants in the comparison population at BWH could be low. Almost all published reports of the prevalence of CP (and CL and CLP)[34] include postnatal detection through age 1 year or older and are higher than the BWH rate. For CP, there is the added concern that the deformity might not be detected at birth. In one follow-up study,[35] 25% of the infants with CP were not identified at birth. We are aware of one other malformations surveillance program that has identified infants with CP at birth. M.L. Martinez-Frias (personal communication) established a prevalence rate of 0.29/1,000 for isolated CP among 382,340 infants born between 1980 and 1985, before elective termination for fetal anomalies was legal. This rate is 38% higher than the rate of 0.21/1,000 for isolated CP in the comparison population at BWH in Boston (table 3). If this higher prevalence rate for isolated CP of 0.29/1,000 was used for comparison, the relative risk in the lamotrigine-exposed infants would be 15.0 (95% CI: 4.8–46.3), instead of the RR of 21.0 (95% CI: 6.8–65.1) when compared to the BWH population (table 3).

The prevalence rate of isolated, nonsyndromic CP, CL, and CLP among newborn infants in Spain was 0.85/1,000 in comparison to 0.7/1,000 at BWH in Boston, a rate that is 21% higher. If this higher prevalence rate for isolated CP, CL, and CLP is used for comparison, the relative risk in the lamotrigine-exposed infants would be 8.6 (95% CI: 3.6–20.5), instead of 10.4 (95% CI: 4.3–24.9) when compared to the BWH population (table 3).

ACKNOWLEDGMENT

The authors thank the pregnant women who enrolled and assisted in obtaining medical information on them and their infants. The authors thank the members of the Scientific Advisory Committee for their contributions to the development of this study and this analysis: Janet Cragan, MD, Atlanta, GA; Allen Hauser, MD, New York, NY; Margaret Jacobs, Bethesda, MD; Robert Mittendorf, MD, DrPH, Chicago, IL; Mark Yerby, MD (Chair), Portland, OR.

Received April 4, 2007. Accepted in final form November 19, 2007.

REFERENCES

1. Holmes LB, Harvey EA, Coull BA, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med 2001;344:1132–1138.
2. Matalon S, Schechtman S, Goldzweig G, Ornoy A. The teratogenic effect of carbamazepine: a meta-analysis of 1255 exposures. Reprod Toxicol 2002;16:9–17.
3. Mawer G, Clayton-Smith J, Coyle H, Kiri U. Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher dose of sodium valproate. Seizure 2002;11:512–518.
4. Sabers A, Gram L. Newer anticonvulsants: comparative review of drug interactions and adverse effects. Drugs 2000;60:23–33.
5. Lo WY, Friedman JM. Teratogenicity of recently introduced medications in human pregnancy. Obstet Gynecol 2002;100:465–473.
6. Kweder SL.. Progress report on the pregnancy labeling revision. Teratology 2001;63–70.
7. White A, Eldridge R, Andrews E. Birth outcomes following zidovudine exposure in pregnant women: the Antiretroviral Pregnancy Registry. Acta Paediatr Suppl 1997;421:86–88.
8. Honein MA, Paulozzi LJ, Cragan JD, Correa A. Evaluation of selected characteristics of pregnancy drug registries. Teratology 1999;60:356–364.
9. Shields KE, Galil KI, Seward J, Shanar RG, Cordero JF, Slater E. Varicella vaccine exposure during pregnancy: data from the first 5 years of the pregnancy registry. Obstet Gynecol 2001;98:14–19.
10. Holmes LB, Wyszynski DF, Lieberman E. The AED (antiepileptic drug) Pregnancy Registry: a 6-year experience. Arch Neurol 2004;61:673–678.
11. Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology 2005;64:961–965.
12. Leach MJ, Marden CM, Miller AA. Pharmacological studies on lamotrigine; a novel antiepileptic drug: II: neurochemical studies on the mechanism of action. Epilepsia 1986;27:490–497.
13. Richens A. Safety of Lamotrigine. Epilepsia 1994; 35(suppl 5):S37–240.
14. Cunnington M, Tennis P, the International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. Neurology 2005;64:955–960.
15. Morrow J, Russell A, Guthrie E, Parsons L, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psych 2006;77:193–198.
16. Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. N Engl J Med 1989;320:19–23.
17. Peller AJ, Westgate M-N, Holmes LB. Trends in congenital malformations, 1974–1999: effect of prenatal diagnosis and elective termination. Obstet Gynecol 2004;104:957–964.
18. Itikala PR, Watkins ML, Mulinare J, Moore CA, Liu Y. Maternal multivitamin use and orofacial clefts in offspring. Teratology 2001;63:79–86.

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

19. Wyszynski DF, Duffy DL, Beaty TH. Maternal cigarette smoking and oral clefts: a meta-analysis. Cleft Palate Craniofac J 1997;34:206–210.
20. Lamotrigine Pregnancy Registry: Interim Report (9-1-92 through 9-30-05). Project of GlaxoSmithKline.
21. Wide K, Winbladh B, Källén B. 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 2004;93:174–176.
22. Vajda FJE, Eadie MJ. Maternal valproate dosage and fetal malformations. Acta Neurol Scand 2005;112:137–143.
23. Sabers A, Dam M, a-Rogvi-Hansen B. Epilepsy and pregnancy: lamotrigine as main drug used. Acta Neurol Scand 2004;109:9–13.
24. Fogh-Andersen P. Inheritance of Harelip and Cleft Palate. Copenhagen: Arnold Busck; 1942.
25. Samrén EB, van Duijn CM, Christiaens GCM, Hofman A, Lindhout D. Antiepileptic drug regimens and major congenital abnormalities in the offspring. Ann Neurol 1999;46:739–749.
26. Covington DL, Tilson H, Elder J, Doi P. Assessing teratogenicity of antiretroviral drugs: monitoring and analysis plan of the Antiretroviral Pregnancy Registry. Pharmacoepidemiol Drug Saf 2004;13:537–545.
27. Jones MC. Etiology of facial clefts: prospective evaluation of 428 patients. Cleft Palate J 1988;25:16–20.
28. Gothelf D, Presburger G, Levy D, et al. Genetic, developmental, and physical factors associated with attention deficit hyperactivity disorder in patients with velocardiofacial syndrome. Am J Med Genet Part B 2004;126B:116–121.
29. Czeizel AE. Prevention of congenital abnormalities by periconceptional multivitamin supplementation. BMJ 1993;306:1645–1648.
30. Hernández-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. Am J Epidemiol 2001; 153:961–968.
31. Sander JWAS, Patsalos PN. An assessment of serum and red blood cell folate concentrations in patients with epilepsy on lamotrigine therapy. Epilepsy Res 1992;13:89–92.
32. Cunnington M, Ferber S, Quartey G. Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. Epilepsia 2007;48:1207–1210.
33. Fried S, Kozer E, Nulman I, Einarson TR, Koren G. Malformation rates in children of women with untreated epilepsy: a meta-analysis. Drug Safety 2004;27: 197–202.
34. Tolarová MM, Cervenka J. Classification and birth prevalence of orofacial clefts. Am J Med Genet 1998; 75:126–137.
35. Habel A, Elhadi N, Sommerlad B, Powell J. Delayed detection of cleft palate: an audit of newborn examination. Arch Dis Child 2005;91:238–240.

New Categories of Resident & Fellow Section

Clinical Reasoning: Case presentations to aid in developing clinical reasoning skills.

Right Brain: Neurology and the medical humanities — history, literature, and arts.

Child Neurology: Patient case with detailed discussion about topic of focus.

Pearls and Oy-sters: Clinical insights (pearls) and advice for avoiding mistakes (oysters).

International: Educational exchanges, experiences in low and middle income countries.

Emerging Subspecialities: History of fields such as Pain Medicine and Headache.

Continue to submit articles about education research and educational topics, training videos, and teaching Neuro*Images*!

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.