Published in final edited form as:

JAMA. 2010 August 25; 304(8): 905–906. doi:10.1001/jama.2010.1214.

Acyclovir Exposure and Birth Defects:

An Important Advance, But More Are Needed

James L. Mills, MD, MS and Tonia C. Carter, PhD

Division of Epidemiology, Statistics & Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

Twenty-two percent of pregnant women are seropositive for herpes simplex virus¹ and 2% of susceptible pregnant women acquire a primary herpes simplex virus infection.² Data on the use of acyclovir and valacyclovir to treat infected women are extremely scarce. The Slone Epidemiology Center, Boston, Massachusetts, statistics on normal pregnancies indicate that approximately 2 per 1000 pregnancies are exposed to each drug during organogenesis (A. Mitchell and C. Louik, Slone Epidemiology Center at Boston University, written communication, July 14, 2010). Thus, each year in the United States approximately 15 000 conceptuses are potentially exposed to these drugs, yet little information is available on their teratogenicity. Until now, only relatively small studies had evaluated the potential teratogenicity of acyclovir and related drugs.^{3–6} Although these studies generally showed no teratogenic effects, they were underpowered to answer the question definitively.

In this issue of *JAMA*, the article by Pasternak and Hviid⁷ on exposure to acyclovir, valacyclovir, and famciclovir and the risk of birth defects addresses the important concern—are acyclovir and related drugs associated with birth defects? This article merits discussion for 3 reasons: the authors present important new information on the safety of these drugs; the study leaves an important question unanswered; and the report illustrates the paradox that a study requiring a large number of pregnancies, as this study does, cannot be performed in the United States, which has 4 million live births per year, but can be done in Denmark, which has only 63 000.

The study by Pasternak and Hviid⁷ included 837 795 live births in Denmark between 1996 and September 2008, of which 1804 pregnancies were exposed to acyclovir, valacyclovir, or famciclovir in the first trimester. Major birth defects were detected in 2.2% of infants exposed to the antivirals and 2.4% of the unexposed (adjusted prevalence odds ratio [POR], 0.89; 95% confidence interval [CI], 0.65–1.22). A major birth defect was diagnosed in 2.0% of infants exposed to acyclovir (adjusted POR, 0.82; 95% CI, 0.57–1.17) and in 3.1% of infants exposed to valacyclovir (adjusted POR, 1.21; 95% CI, 0.56–2.62). Few infants were exposed to famciclovir.

©2010 American Medical Association. All rights reserved.

Corresponding Author: James L. Mills, MD, MS, Epidemiology Branch, Division of Epidemiology, Statistics & Prevention Research, National Institute of Child Health and Human Development, National Institutes of Health, 6100 Executive Blvd, Room 7B03, Bethesda, MD 20892 (jamesmills@nih.gov).

Financial Disclosure: None reported.

Given how many exposures occur during organogenesis, the finding that these drugs are not associated with an increased risk of malformations overall is good news. From a public health perspective, this study provides fairly strong reassurance that acyclovir is not a major cause of birth defects.

However, this study leaves a key question unanswered—is acyclovir a teratogen? Even a large cohort study is unlikely to have a sufficient number of exposures to provide data on individual defects. The authors note they are not able to exclude an increased risk for any individual defect because of the small number of exposed cases in each defect group. This is a critical limitation because no teratogen produces an increase in all malformations. Instead, each produces a characteristic pattern of malformations, almost a distinctive signature. The Danish data reported by Pasternak and Hviid⁷ have too few birth defects to examine even common defects individually to look for such a pattern. Case-control studies are used to study rare events such as individual birth defects, but the data on individual defects in this study are too sparse even to provide guidance as to which defects are worth more exploration.

Several other limitations of this study are worth noting. Data on exposure were obtained from records of prescriptions filled, but this information provides no direct evidence that the drug was used, when it was used, or how much was used. In fact some data indicate that prescribed drugs are often not taken for reasons that include doubts about the benefit of treatment, medication adverse effects, complexity of the treatment regimen, and medication costs.⁸ Some birth defects could remain undiagnosed in the first year of life (the period covered by the registry) and would not have been included among the outcomes in this study. Although using a birth defects registry has the advantage that the cases are representative of all cases, it has the disadvantage that it is difficult to examine cases with multiple malformations to identify patterns. Moreover, only 229 women were exposed to valacyclovir, and only 26 were exposed to famciclovir. Birth defects occurred in 7 valacyclovir-exposed infants and 1 famciclovir-exposed infant, too few to draw any conclusions about the association of these drugs with birth defects. Despite these limitations, this study has provided important reassurance regarding the safety of acyclovir.

Why has such a study not been performed in the United States? The Nordic countries have an integrated health care system in which data from multiple sources can readily be merged to answer medical questions. In contrast, the United States has a fragmented system that makes it extremely difficult to address these questions. Yet the situation is not hopeless. Pharmacy records and birth defects registry data in the United States are computerized. The Health Information Technology for Economic and Clinical Health Act (2009) was enacted to stimulate universal use of electronic medical records in the United States and the formation of a nationally linked network that will provide access to data in these records.⁹ Ideally, these efforts will increase the amount of information that could be used to determine, for instance, whether or not acyclovir is a teratogen, and to answer a great many other important medical questions.

However, important issues need to be addressed before the potential of such a system can be realized. Privacy must be protected whenever identifiers are used to link data from multiple

sources. The quality of the data must be reviewed critically for each application. For example, vaccines may be obtained from sources such as grocery or discount stores that do not keep detailed records. Ignoring these sources of exposure would lead investigators to misclassify some individuals as unvaccinated. Data on prescriptions filled have inherent limitations in that it is not clear when, or even if, the medication was actually used, leading to possible exposure misclassification. These and other similar issues must be and are being¹⁰ addressed to make it feasible to use electronic health information to monitor drug safety and assess drug benefits.

The study by Pasternak and Hviid⁷ is helpful in demonstrating the safety of acyclovir in pregnancy, but additional strategies must be developed to resolve the remaining issues. At a time when the health care system in the United States is facing enormous financial challenges, it is important not to ignore any sources of data that could answer critical medical questions.

Acknowledgments

Funding/Support: This work was funded by the Intramural Research Program of the National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Role of the Sponsor: The Intramural Research Program of the National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development had no role in the preparation, review, or approval of the manuscript.

References

1. Xu F, Markowitz LE, Gottlieb SL, Berman SM. Seroprevalence of herpes simplex virus types 1 and 2 in pregnant women in the United States. *Am J Obstet Gynecol*. 2007; 196(1):43.e1–43.e6. [PubMed: 17240228]
2. Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med*. 1997; 337(8):509–515. [PubMed: 9262493]
3. Wilton LV, Pearce GL, Martin RM, Mackay FJ, Mann RD. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. *Br J Obstet Gynaecol*. 1998; 105(8):882–889. [PubMed: 9746382]
4. Reiff-Eldridge R, Heffner CR, Ephross SA, Tennis PS, White AD, Andrews EB. Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: a pharmaceutical company commitment. *Am J Obstet Gynecol*. 2000; 182(1 pt 1):159–163. [PubMed: 10649172]
5. Ratanajamit C, Vinther Skriver M, Jepsen P, Chongsuvivatwong V, Olsen J, Sørensen HT. Adverse pregnancy outcome in women exposed to acyclovir during pregnancy: a population-based observational study. *Scand J Infect Dis*. 2003; 35(4):255–259. [PubMed: 12839155]
6. Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the international acyclovir pregnancy registry, 1984–1999. *Birth Defects Res A Clin Mol Teratol*. 2004; 70(4):201–207. [PubMed: 15108247]
7. Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. *JAMA*. 2010; 304(8):859–866. [PubMed: 20736469]
8. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005; 353(5):487–497. [PubMed: 16079372]
9. Health Information Technology for Economic and Clinical Health Act of 2009, 42 USC §201 (2009).
10. Foundation for the National Institutes of Health. [Accessed July 23, 2010] Observational medical outcomes partnership. <http://omop.fnih.org/>