RESEARCH LETTERS

Atovaquone-Proguanil Use in Early Pregnancy and the Risk of Birth Defects

Malaria infection in pregnancy is associated with increased risk of complications for the mother and fetus,[1] particularly in individuals not previously exposed to malaria, eg, travelers. Pregnant women are advised to avoid travel to countries where there is elevated risk of contracting malaria.[2,3] For pregnant individuals who still choose to or must travel to malaria-endemic areas where there is chloroquine resistance, currently none of the available prophylactic drugs are recommended in early pregnancy. This is either owing to adverse fetal effects (doxycycline), paucity of safety data (mefloquine), or absence of such (atovaquone-proguanil).[2-4]

We conducted a registry-based cohort study to investigate whether exposure to atovaquone-proguanil in early pregnancy was associated with increased risk of any major birth defect.

Methods. On the basis of the Danish Medical Birth Register, which registers all deliveries by women living in the country, we established a cohort of all live-born infants (birth date, January 2000–September 2008). Individual-level data were linked between nationwide registries to ascertain information on dispensed atovaquone-proguanil prescriptions to cohort mothers (Prescription Drug Register), birth defect diagnoses among infants (National Patient Register), and potential confounders. We evaluated the association between exposure to atovaquone-proguanil in the period of maximal susceptibility to teratogenic agents (weeks 3 through 8 after conception) and the risk of major birth defects diagnosed within the first year of life. Any filling of an atovaquone-proguanil prescription was considered as exposure and timing of exposure was defined by the date of filling the prescription. All methods used in this study have been described in detail previously.[5] The study was approved by the Danish Data Protection Agency.

The majority of exposed mothers were likely travelers receiving atovaquone-proguanil on prophylactic indications. Because mothers diagnosed as having malaria may have received other treatment, potentially confounding the studied association, they were excluded from the cohort (n = 10).

Logistic regression was used to estimate prevalence odds ratios with 95% confidence intervals comparing prevalence odds of any major birth defect in infants from pregnancies exposed to atovaquone-proguanil and in infants from unexposed pregnancies. Multivariate models included those potential confounders that were significant ($P < .05$) risk factors for birth defects in univariate analyses. Multiple imputation was used for variables with missing values.

Results. Among 570 877 live births included in the cohort, 13 995 (2.5%) were diagnosed as having a major birth defect within the first year of life. Atovaquone-proguanil exposure at any time in weeks 3 through 8 after conception was not significantly associated with increased risk of any major birth defect (**Table**). A sensitivity analysis that tested the robustness of the exposure definition by including pregnancies exposed at any time in the first trimester produced similar estimates (Table).

Table. Association Between Atovaquone-Proguanil Use in Early Pregnancy and Major Birth Defects in a Cohort of 580 877 Live Births in Denmark (January 2000–September 2008)

Atovaquone-Proguanil Exposure	No. of Live Births	Birth Defects, No. (%)[a]	POR (95% CI)	
			Crude	Adjusted[b]
3-8 Weeks after conception				
Exposed	93	1 (1.1)	0.43 (0.06-3.10)	0.43 (0.06-3.11)
Unexposed	570 784	13 994 (2.5)	1 [Reference]	1 [Reference]
First trimester				
Exposed	149	2 (1.3)	0.54 (0.13-2.19)	0.55 (0.14-2.21)
Unexposed	570 728	13 993 (2.5)	1 [Reference]	1 [Reference]

Abbreviations: CI, confidence interval; POR, prevalence odds ratio.

[a] Birth defects were classified according to standardized classification scheme (EUROCAT),[6] as described previously.[5] Infants were followed up for a maximum of 1 year for the first registered diagnosis of a major birth defect.

[b] Adjusted for maternal age, parity, origin (Denmark, Europe, and North America or rest of the world), place of living, socioeconomic class, educational level, smoking, antibiotic use in first trimester, and hospital contact for infectious disease in first trimester, as well as the infant's birth year and history of birth defects in siblings.

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Comment. This study of a large nationwide cohort study found no significant association between exposure to atovaquone-proguanil in early pregnancy and the risk of any major birth defect. To our knowledge, these are the first safety data ever reported on early pregnancy exposure to atovaquone-proguanil.

Although based on a limited number of exposed pregnancies and cases, the findings provide some reassurance that atovaquone-proguanil is not a major teratogen. However, the analysis could only exclude more than a 3-times higher risk of birth defects associated with atovaquone-proguanil exposure.

Main strengths of this study include its registry-based design, providing the opportunity to investigate an uncommon drug exposure in pregnancy among women living in an industrialized country and allowing independent ascertainment of dispensed prescriptions and birth defect diagnoses. However, a main limitation is that after filling prescriptions for atovaquone-proguanil, some participants may have found out that they were pregnant. Therefore, some of them may have cancelled their trip and never taken the drug. Any noncompliance to the dispensed drugs would bias estimates toward the null.

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1. Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis.* 2007;7(2):93-104.
2. World Health Organization. *Malaria: International Travel and Health.* Geneva, Switzerland: World Health Organization; 2010:142-164.
3. Arguin PM, Steele SF. Malaria. In: Brunette GW, Kozarsky PE, Magill AJ, Shlim DR, eds. *Health Information for International Travel 2010.* Atlanta, GA: Centers for Disease Control and Prevention; 2009.
4. Ward SA, Sevene EJ, Hastings IM, Nosten F, McGready R. Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance. *Lancet Infect Dis.* 2007;7(2):136-144.
5. 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.
6. Epidemiologic Surveillance of Congenital Anomalies (EUROCAT). Coding of EUROCAT subgroups of congenital anomalies (issued on 01-03-2007). In: *Eurocat Guide 1.3 and Reference Documents: Instructions for the Registration and Surveillance of Congenital Anomalies.* Revised May 2009:chapter 3.3. http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf. Accessed March 3, 2010.

Use of Neuroimaging in US Emergency Departments

Advanced diagnostic imaging use is increasing, raising concerns about patient safety and cost.[1] Recent estimates indicate that 4000 future cancers may result from the head computed tomographic (CT) examinations performed nationwide in 2007[2] and that costs of CT and magnetic resonance imaging (MRI) doubled between 1997 and 2006.[3] In US emergency departments (EDs), the greatest increase has been in neuroimaging (head CT and MRI).[4] Nevertheless, there are no national benchmarks against which health care providers and hospitals can measure their use of ED neuroimaging. We aimed to calculate head CT and MRI use in US EDs and to examine patient and hospital factors associated with use.

Methods. We performed a cross-sectional analysis of neuroimaging in US EDs by analyzing the 2007 National Hospital Ambulatory Medical Care Survey (NHAMCS) ED component with a primary outcome of head CT use and a secondary outcome of head MRI use. We coded patient and hospital covariates a priori to identify predictors of neuroimaging and calculated the percentage of visits (with 95% confidence intervals [CIs]) associated with neuroimaging. We conducted multivariate logistic regression to estimate the adjusted association of covariates on the primary outcome. The regression model had good fit, with a

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C statistic of 0.71. Among visits in which head CT was performed, we calculated the leading reasons for visit[5] and discharge diagnoses by grouping primary *International Classification of Diseases, Ninth Revision, Clinical Modification* discharge diagnoses into the 285 clinical categories of the Clinical Classification System.[6] We performed all statistical analyses using SAS 9.1.3 (SAS Institute Inc, Cary, North Carolina).

Results. There were approximately 117 million visits to 4891 US EDs in 2007, based on 35 490 ED visits in the NHAMCS sample. Head CT scans were performed during 6.7% (95% CI, 6.1%-7.3%) of visits, while head MRIs were performed during 0.26% (95% CI, 0.18%-0.35%) of visits. Patient and hospital characteristics associated with neuroimaging are presented in the **Table**. Patient characteristics independently associated with lower use of head CT use were decreasing age and non-Hispanic black race and ethnicity (vs non-Hispanic whites). Hospital characteristics associated with lower CT use included rural setting (vs urban) and hospitals owned by state or local governments (vs nonprofit hospitals).

The 3 leading reasons for visits among patients receiving head CTs in the ED were trauma (18.1%; 95% CI, 12.8%-23.5%), headache (13.0%; 95% CI, 10.8%-15.2%), and dizziness (6.1%, 95% CI, 4.6%-7.6%). The 3 leading discharge diagnosis categories were trauma (20.5%; 95% CI, 15.8%-25.3%), headache (9.2%; 95% CI, 7.4%-11.0%), and epilepsy/convulsions (5.2%; 95% CI, 3.8%-6.6%).

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