TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media LLC

INSIDE

Volume 20, No. 9
September 2010

Antibiotic Use During Pregnancy and Risk of Birth Defects

ABSTRACT & COMMENTARY

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Dr. Jensen receives research support from, is a consultant to, and serves on the speaker's bureau of Bayer Healthcare/Bayer Schering; he also receives research support from Wyeth and Warner-Chilcott, and is a consultant to Schering Plough. Peer reviewer Catherine LeClair, MD, Associate Professor, Oregon Health & Science University, reports no financial relationships relevant to this field of study.

Synopsis: First trimester exposure to nitrofurantoin and sulfonamides was associated with an increase in the risk of several birth defects including cleft lip and palate in the National Birth Defects Prevention Study.

Source: Crider KS, et al. Antibacterial medication use during pregnancy and risk of birth defects: National Birth Defects Prevention Study. *Arch Pediatr Adolesc Med* 2009;163:978-985.

This article originally appeared in the July 2010 issue of *OB/GYN Clinical Alert*.

THE PURPOSE OF THIS STUDY WAS TO ESTIMATE THE ASSOCIATION BETWEEN ANTIbacterial medications and selected birth defects. The authors conducted a population-based, multisite, case-control study of women who had pregnancies affected by 1 of more than 30 eligible major birth defects identified via birth defect surveillance programs. The study population included 13,155 cases of women with affected pregnancies and 4941 control women with unaffected pregnancies randomly selected from the same geographical regions (10 states). The main exposure was reported maternal use of antibacterials (1 month before pregnancy through the end of the first trimester), and odds ratios (ORs) measuring the association between antibacterial use and selected birth defects were constructed and adjusted for potential confounders. The reported use of antibacterials increased during pregnancy, peaking during the third month.

Sulfonamides were associated with anencephaly (adjusted OR [AOR] = 3.4; 95% confidence interval [CI], 1.3-8.8), hypoplastic left heart syndrome (AOR = 3.2; 95% CI, 1.3-7.6), coarctation of the aorta (AOR = 2.7; 95% CI, 1.3-5.6), choanal atresia (AOR = 8.0; 95% CI, 2.7-23.5), transverse limb deficiency (AOR = 2.5; 95% CI, 1.0-5.9), and diaphragmatic hernia (AOR = 2.4; 95% CI, 1.1-5.4).

Nitrofurantoins were associated with anophthalmia or microphthalmos (AOR = 3.7; 95% CI, 1.1-12.2), hypoplastic left heart syndrome (AOR = 4.2;

95% CI, 1.9-9.1), atrial septal defects (AOR = 1.9; 95% CI, 1.1-3.4), and cleft lip with cleft palate (AOR = 2.1; 95% CI, 1.2-3.9).

Other antibacterial agents were not associated with a significant increase in the AOR of these birth defects. The authors concluded that sulfonamides and nitrofurantoins were associated with several birth defects, indicating a need for additional scrutiny. In contrast, penicillins, erythromycins, and cephalosporins appeared to be safer alternatives.

■ COMMENTARY

The National Birth Defects Prevention Study (NBPS) is conducted by investigators at the Centers for Disease Control and Prevention. This large representative multistate database is about as good as we get in the current United States health care system to assess exposure and rare outcomes in a large population-based classic case-control study. While case-control studies cannot demonstrate a causal relationship, they can suggest important relationships worthy of additional consideration. For the assessment of rare outcomes where prospective randomized studies are impractical, they provide the best evidence for clinical guidance.

Case-control studies are always subject to confounding. Common events such as urinary tract infections (UTIs) will lead to multiple exposures, and common drugs will be widely used. Recall bias further complicates studies of exposure, as those women who experience an abnormal pregnancy may have a greater tendency to report exposure or to recall the drug they were treated with.

More than 2% of women in this study were treated for a UTI in the first trimester. The authors designed their assessment to critical exposure during the period of early fetal development. Still, many of the abnormalities are restricted to an even more limited time of exposure, with most structural anomalies occurring before 6 weeks of gestation.[1] The majority of subjects in the NBPS were treated between 8-13 weeks, well after the expected developmental critical windows for the listed anomalies.

However, the most commonly used antibiotics — penicillins, erythromycins, and cephalosporins (all FDA pregnancy category B) — were not associated with an increased risk of anomalies in this study, while both nitrofurantoin and sulfonamides were associated with significant increased AOR of risk for a variety of anomalies. Sulfonamides (FDA pregnancy category C or D) have been shown to be teratogenic in animal studies, although it is unclear whether sulfonamides without trimethoprim pose a significant risk.[2] The two drugs act synergistically to block two steps in the biosynthesis of reduced folates, and other case-control studies have demonstrated an increased risk of anomalies with first trimester exposure.[3] These drugs can also affect bilirubin metabolism and should not be used in the third trimester and while breast feeding. The observed increase in risk with nitrofurantoin (Category B) is more surprising. The drug primarily concentrates in the urinary tract and has not previously been associated with fetal harm. It is well tolerated, easy to take, and highly effective against most pathogens.

Taken together, the results from this study are far from conclusive. Since there are alternatives to use of nitrofurantoins and sulfa/trimethoprim in the first trimester, it is wise to do so even if the evidence is limited. Avoid

Travel Medicine Advisor (ISSN # 1930-8067) is published monthly by AHC Media LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Travel Medicine Advisor,*** PO Box 740059, Atlanta, GA 30374-9815.

Subscription Information: Customer Service: (800) 688-2421 or fax (800) 284-3291. Hours of operation: 8:30am-6pm Monday-Thursday; 8:30am-4:30pm Friday ET. Email: customerservice @ahcmedia.com Website: www.ahcmedia.com. Subscription rates: USA, one year (12 issues) $449. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

sulfonamides in the third trimester to avoid the known association with hyperbilirubinemia.

A more important consideration is the reproductive age non-pregnant patient who presents or calls with UTI symptoms. Is it safe to use nitrofurantoin or sulfa drugs in these women? In contrast to the patient at 8 weeks, these are exactly the individuals in whom an early fetal exposure is possible. Consider carefully the drug resistance patterns in your community and the contraceptive status of your patient when considering therapy. If she is at high risk for pregnancy, best to avoid these drugs. ■

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Bacterial Enteritis and Intussusception

ABSTRACT & COMMENTARY

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Dr. Jenson reports no financial relationships relevant to this field of study.

Peer reviewer Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado, Denver, Denver Health Medical Center, reports no financial relationships relevant to this field of study.

Synopsis: Bacterial enteritis in children significantly increased the risk for intussusception, with a relative risk of 40.6 (95% CI = 28.6-57.5; p < 0.0001).

Source: Nyland CM, Denson LA, Noel JM. Bacterial enteritis as a risk factor for childhood intussusception: A retrospective cohort study. *J Pediatr.* 2010;156:761-765.

This article originally appeared in the July 2010 issue of Infectious Disease Alert.

A RETROSPECTIVE COHORT STUDY WAS CONDUCTED OF ALL children age birth to five years enrolled at a Department of Defense treatment facility between January 1998 and December 2005, who were diagnosed with bacterial enteritis. Their medical records were reviewed for the ensuing six months for a diagnosis code (DRG code 560.0) or procedure code consistent with intussusception.

A total of 387,514 children were enrolled in a treatment facility, yielding a total of 293 cases of intussusception and an incidence of 15.1 cases/10,000 children/year. Of the 1,412 cases of bacterial enteritis, intussusception ensued in 37 cases (13 in females and 24 in males), representing 12.6% of all cases of intussusception. The overall relative risk for intussusception in the six months following bacterial enteritis was 40.6 (95% CI = 28.6-57.5; $p < 0.0001$). The relative risk was greater in children 1-5 years of age (56.2 [95% CI = 36.0-87.8]) compared to children < 1 year of age (16.0 [95% CI = 9.1-28.2]). The absolute risk for intussusception following enteritis was 2.3% for children < 1 year of age and 3.3% for children 1-5 years of age.

The relative risk of intussusception was increased for all four major causes of bacterial enteritis: *Salmonella* (16 cases; 28.7 [95% CI = 7.2-113.4]); *Escherichia coli,* including enteropathogenic, enterotoxigenic, enteroinvasive, and enterohemorrhagic (13 cases; 25.0 [95% CI = 5.62-111.6]); *Shigella,* including *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei* (six cases; 23.6 [95% CI = 3.6-156.0]); and *Campylobacter* (two cases; 32.9 [95% CI = 3.48-310.7]). No cases of intussusception followed *Yersinia enterocolitica* enteritis, likely resulting from the low rate (1%) of *Yersinia* enteritis among this cohort.

The median interval between the episode of enteritis and development of intussusception was 58 days, with a range from 1 to 175 days. Using negative binomial regression for 30-day time periods while controlling for age, the relative risk for intussusception after bacterial enteritis was significantly increased for the first 30-day period (9.5 [95% CI = 2.5-35.8]; $p < 0.0009$). After the first 30 days, the risk decreased and did not reach significance, with the exception of the interval of 120-150 days.

■ COMMENTARY

Many studies have suggested an association between enteritis and intussusception, which is the prolapse of one part of the intestine into the lumen of an adjoining part, most frequently ileocolic. Lymphoid hyperplasia, or hypertrophy of Peyer's patches, is a common finding in intussusception that is felt to predispose to intussusception by serving as a mechanical lead point.

This retrospective study, using a large population cohort, showed a statistically significant increased risk of intussusception among children with bacterial enteritis within the previous six months. These results show the highest risk of intussusception in the first 30 days after enteritis, followed by a lower but continued

risk through the subsequent six months. Physicians and parents should appreciate the increased risk, and should facilitate earlier recognition and prompt treatment of intussusception following bacterial enteritis. This study did not address the potential impact of antibiotic treatment on the risk for intussusception, which might be favorable. ■

Anthrax in Heroin Users

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This article originally appeared in the July 2010 issue of Infectious Disease Alert.

A CRITICALLY ILL PATIENT, WHO WAS A HEROIN USER, WAS admitted to a hospital in Scotland in December 2009 and was found to be infected with *Bacillus anthracis*.[1] He was not the last such patient and, as of June 11, 2010, Scottish health authorities had identified 45 confirmed cases of anthrax in heroin users; 13 of these cases were fatal. Cases were also identified in England and Germany.

Most of the affected cases injected their heroin, either intravenously, subcutaneously, or into muscle, but some also smoked or snorted it. Of the patients described to date, none have presented with classical presentations of anthrax cutaneous infection with a painless black eschar, inhalational disease with hemorrhagic mediastinal lymphadenopathy, or typical gastrointestinal disease.[2] Rather than the expected cutaneous ulcer, skin and soft-tissue infections in this outbreak have, instead, been quite variable in appearance, with the exception of the apparently universal presence of marked edema that appears to be in excess of the degree of induration. The induration, as well as any associated erythema is, in fact, often minimal. Systemic symptoms are variable and depend upon the stage of disease, but many patients have a normal temperature at presentation. Also commonly normal are the white blood cell count, CRP, and serum lactate concentration. In some patients, the illness has been biphasic, with an initial response to therapy, especially fluid infusion, followed by rapid deterioration with hypotension, third-spacing, and coagulopathy.

While classical inhalational anthrax has not been observed, pleural effusions are common. At presentation, some patients have abdominal symptoms, including nausea, vomiting, and abdominal pain, but the gastrointestinal mucosal ulcerations and associated hemorrhagic lymphadenopathy have not been seen. Ascites may occur. Some patients, not all of whom had evident soft tissue infection, presented with meningoencephalitis, with evidence of intracranial bleeding with features of a subarachnoid hemorrhage—a syndrome which has been universally fatal.

Management involves infusion of large volumes of fluid, antibiotics, and surgical debridement. The Health Protection Agency of Scotland recommends administration of ciprofloxacin together with an antibiotic with "CNS penetration," such as penicillin, ampicillin, meropenem, rifampin, or vancomycin, together with clindamycin, with the hope of reducing toxin production. The Scottish authorities recommend excision of affected skin with a margin greater than 2 cm, excision of needle tracks within muscle, and decompression in the presence of compartment syndrome. Debridement, which may have to be repeated one or more times, is complicated by the fact that, in contrast to findings in necrotizing fasciitis, the margins between normal and affected tissue may be indistinguishable. They state that pleural and ascitic fluid should be drained because it contains toxin. In addition to these measures, the Scottish authorities also recommend consideration of the use of Anthrax Immune Globulin Intravenous, an investigational preparation derived from vaccinated human volunteers that was made available to them by agreement with the U.S. CDC and FDA.

Contaminated heroin also has been the source of infection or intoxications by other spore-forming organisms in injection-drug users. There was, for example, a marked increase in such illnesses in the United Kingdom from 2000 to May 2004, during which the following were etiologic: *Clostridium novyi* (68 cases), *Clostridium histolyticum* (9), *Clostridium sordelli* (1), *Bacillus cereus* (1), together with 20 cases of tetanus and 57 of wound botulism.[3] ■

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