OBSTETRICS

Safety of macrolides during pregnancy

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OBJECTIVE: Prior studies have reported increased risks of congenital heart defects (CHD) and pyloric stenosis (PS) after prenatal exposure to macrolide antibiotics. We sought to assess the association between maternal use of erythromycin and nonerythromycin macrolides and the risks of CHD and PS.

STUDY DESIGN: Among participants in the Slone Epidemiology Center Birth Defects Study from 1994 through 2008, we identified 4132 infants with CHD and 735 with PS as cases, and 6952 infants without any malformation as controls. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) associated with use of erythromycin or nonerythromycin macrolides in each trimester using conditional logistic regression and adjusting for risk factors for CHD and PS, fever, specific types of infections, and their associated treatments.

RESULTS: During the first trimester, 0.4% and 0.7% of control women had used erythromycin and nonerythromycin macrolides, respectively. Compared to non-use during pregnancy, first-trimester exposure to erythromycin was not associated with an increased risk of CHD (OR, 1.3; 95% CI, 0.6−2.6) or PS (OR, 0.9; 95% CI, 0.3−3.0). The corresponding ORs for nonerythromycin macrolides were 0.7 (95% CI, 0.4−1.3) for CHD and 1.7 (95% CI, 0.6−4.6) for PS. We found no association between third-trimester exposure to erythromycin or nonerythromycin macrolides and the risk of PS. Hypothesis generation analyses did not identify appreciable associations between maternal use of macrolides and other common specific birth defects.

CONCLUSION: We found no meaningful associations between the risks of CHD, PS, and other common malformations in relation to use of macrolides in pregnancy.

Key words: azithromycin, clarithromycin, congenital malformations, erythromycin, macrolides

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Macrolide antibiotics are frequently used for presumed or documented gram-positive lower and upper respiratory infections, soft tissue infections, and *Helicobacter pylori*−related peptic ulcer. Moreover, for the treatment of *Chlamydia* and other selected infections in pregnancy, erythromycin has been specifically recommended because other effective antibiotics for such infections are contraindicated for pregnant women.[1] Because these indications are common and azithromycin and erythromycin are classified as Food and Drug Administration category B, macrolide antibiotics are the second most frequently used antibacterial class during pregnancy in the United States.[2,3] Macrolide antibiotics are often subdivided into erythromycin, the first-introduced macrolide, and nonerythromycin drugs, including clarithromycin and azithromycin, which have fewer effects on gastrointestinal motility than erythromycin.[4]

Exposure to erythromycin in early pregnancy has been associated with an increased risk of congenital heart defects (CHD) (odds ratio [OR], 1.84; 95% confidence interval [CI], 1.29−2.62); the association was largely attributed to unspecified CHD (OR, 3.57; 95% CI, 1.70−6.12).[5] However, Cooper et al[6] did not find an increase in the risk of CHD after exposure to either erythromycin or nonerythromycin macrolides. The National Birth Defects Prevention Study also published null findings for macrolides overall in relation to CHD, but they did not differentiate erythromycin from nonerythromycin macrolides.[3]

In 1999, infantile hypertrophic pyloric stenosis (PS) was linked to exposure to macrolide antibiotics in postnatal days 2-17,[7] a finding confirmed in 2001.[8] Kallen et al[5] reported an elevated risk of PS among the offspring of women who took erythromycin in early pregnancy (risk ratio, 3.03; 95% CI, 1.08−8.50). Cooper et al[9] did not replicate this association, but found an elevated risk of PS associated with exposure to nonerythromycin macrolides prescribed any time during pregnancy (OR, 2.77; 95% CI, 1.22−6.30). Using data from the Slone Birth Defects Study (BDS) (1976 through 1998), Louik et al[10,11] found no association between PS and exposure to either type of macrolide antibiotics >32nd gestational week (OR, 0.7; 95% CI, 0.3−1.8 for erythromycin and OR, 1.1; 95% CI, 0.3−3.6 for nonerythromycin macrolides), but there were very few subjects exposed to nonerythromycin macrolides in this study. These findings have raised con-

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cerns regarding maternal use of macrolide antibiotics in either early or late pregnancy.

Despite being commonly prescribed during pregnancy, the safety profile of macrolide antibiotics is yet to be determined, not only with regard to the hypothesized risks of CHD and PS, but also with regard to the range of other specific major birth defects. We therefore sought to test the hypotheses that the risks of CHD and PS are elevated among infants or fetuses exposed to erythromycin and/or nonerythromycin macrolides during pregnancy and, in exploratory analyses, to identify possible associations with other specific defects. The analyses utilized data from the BDS, an ongoing program of case-control surveillance of medications in relation to birth defects.

Materials and Methods

Study population

The BDS was established in 1976,[12] and since that time has interviewed mothers of malformed infants ascertained through review of admissions and discharges at major referral hospitals and clinics in the greater metropolitan areas of Boston, Philadelphia, Toronto, and San Diego, and through statewide birth defects registries in New York State (since 2004) and Massachusetts (since 1998). For hospital-based surveillance, the subjects' physicians are asked to confirm the diagnosis and mothers are asked to provide medical record releases to permit confirmation of the infant's condition. Infants with isolated minor defects are excluded. Beginning in 1992, the BDS also enrolled a sample of mothers of nonmalformed infants as controls: initially these infants were identified exclusively at study hospitals but, since 1998, the BDS also includes a population-based random sample of newborns in Massachusetts. The study has been approved by the Boston University Institutional Review Board and the institutional review boards of all relevant participating institutions. It is fully compliant with the requirements of the Health Insurance Portability and Accountability Act. The current analysis was restricted to women interviewed from 1994 through 2008 because full ascertainment of our control group, nonmalformed infants, was not underway until 1994. Among eligible subjects in the last decade, the mothers of 73% of malformed infants and 68% of nonmalformed controls contacted agreed to an interview and provided informed consent.

Cases

Hypothesis testing

Cases consisted of 4132 infants and fetuses with a diagnosis of CHD and 735 infants with PS. We excluded from analysis infants with chromosomal defects, known mendelian inherited disorders, syndromes, DiGeorge sequence (associated with 22q deletion), and metabolic and functional disorders. CHD or PS complicated with other defects (but not as part of an identified chromosomal or mendelian inherited syndrome) were included in the general analysis and studied separately in a secondary analysis.

Exploratory analyses

Other major defects examined included the following categories: 1348 oral clefts, 1138 central nervous system defects, 308 respiratory system defects, 1825 gastrointestinal system defects, 1099 genital system defects, 1511 urinary system defects, 1948 musculoskeletal system defects, and 385 others. Where there were sufficient numbers of subjects with specific defects, those were considered as well. The same exclusion criteria described above also applied to these case groups.

Controls

Our control group consisted of 6952 infants without any malformation.

Interviews

Within 6 months of the subject's delivery, trained study nurses unaware of study hypotheses interview mothers of study subjects. The 45- to 60-minute interview is detailed and structured and includes questions on maternal demographic characteristics, mothers' medical histories, obstetric histories, maternal health behaviors and occupation, and a detailed history of the use of medication (including prescription, over-the-counter, and vitamin and herbal products) from 2 months before the date of the last menstrual period (LMP) through the entire pregnancy. Recall of medication exposures is enhanced by questions regarding indications for use (eg, infections), and a list of specifically named medications,[13] which includes, among other antibiotics, erythromycin and nonerythromycin macrolides.

Mothers who report taking a particular medication are further asked to identify, as accurately as possible, the dates when use began and ended. Recall of the timing of medication use is enhanced by the use of a calendar that highlights the mother's reported LMP date and her delivery date. Further, subjects are asked how certain they are about each of these dates. Interviewers record the certainty of each reported date as follows: (1) exact, if the exact date is reported, (2) estimated, if a date is stated as an estimate, or (3) sometime in a given month, if the day within a month is unknown. Mothers who cannot recall the month are considered to have unknown dates of exposure. Mothers are also asked details about their pattern of use of the particular medication, including duration (days of treatment), frequency of use (eg, days per week or month), and specific doses. We defined exposure as systemic use of erythromycin or nonerythromycin macrolides.

Algorithm to classify timing of exposure

We developed an exposure classification algorithm taking into account recall uncertainty in reported timing of medication exposure.[14] For uncertain start/stop dates reported as being sometime in a month, we considered the possible exposure period to be the widest interval consistent with that report (eg, if a mother reported medication use sometime in May, we assigned May 1 as her start date and May 31 as her stop date). When a mother is not certain about the exact exposure date, assuming different start dates consistent with the reported range, the exposure period may overlap with the window of interest or not. If the exposure period includes window of interest with any possible start dates of the exposure, we classified the mother as "likely exposed." Details about all possible scenarios were previously pub-