OBSTETRICS

Case-control analysis of maternal prenatal analgesic use and cardiovascular malformations: Baltimore–Washington Infant Study

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OBJECTIVE: We sought to assess maternal prenatal use of analgesics and risk of cardiovascular malformations (CVM) in the offspring.

STUDY DESIGN: Data from the Baltimore–Washington Infant Study, a population-based case-control investigation of CVM, were used to examine selected isolated CVM diagnoses and maternal analgesic use during the periconceptional period (3 months before and after conception). We compared case and control infants on frequency of maternal use of analgesics and estimated adjusted odds ratios (adjORs) and 95% confidence intervals (CI) with logistic regression models for specific CVM phenotypes.

RESULTS: Frequency of periconceptional use of any analgesic was 52% among control mothers and 53% among case mothers. Analyses by CVM diagnoses identified an association of tetralogy of Fallot with maternal acetaminophen use (adjOR, 1.6; 95% CI, 1.1–2.3) and dextrotransposition of the great arteries with intact ventricular septum with maternal nonsteroidal antiinflammatory drug use (adjOR, 3.2; 95% CI, 1.2–8.7).

CONCLUSION: Analgesic use during the periconceptional period was not associated with CVM in the aggregate or with most phenotypes of CVM examined. Associations with 2 phenotypes of CVM may have occurred by chance. These findings warrant corroboration and further study, including further evaluation of the observed associations, the dose of analgesic taken, more specific timing of analgesic use, and indications for use.

Key words: analgesics, birth defects, cardiovascular malformations, congenital heart defects, pregnancy

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Analgesic medications are commonly used during pregnancy. Estimates of the prevalence of maternal analgesic use during pregnancy have reached ≥70%.[1,2] Indications for analgesic use are varied and include pain, fever, flu, preterm labor, and certain rheumatologic conditions. Analgesics are easily accessed either through prescription or over-the-counter purchase. They freely cross the placental barrier, which theoretically could pose potential risk to the developing fetus.[3] However, while maternal use of analgesics is high, the safety of analgesic use during pregnancy has not been well established.

Cardiac morphogenesis is complex and dependent on the expression of multiple genes and on many molecular pathways.[4] Maternal use of certain medications during fetal development, such as anticonvulsants and antihypertensives, has been associated with some types of cardiovascular malformations (CVM).[5,6]

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Whether use of analgesics may pose a risk is unclear. Many nonopioid analgesics, including salicylates and some other nonsteroidal antiinflammatory drugs (NSAIDs), exert their analgesic and antiinflammatory effects through inhibition of cyclooxygenase (COX) 1 and 2. It has been hypothesized that COX inhibition during the sensitive window of cardiogenesis may be involved in the disruption of heart development.[7-9] However, epidemiologic studies of the possible association between maternal analgesic use and CVM have had varied results.

Given the prevalence of analgesic use during pregnancy, the limited data on the safety of analgesic use during pregnancy, and the varied results from existing studies, additional evaluation of the possible association between maternal use of the more common analgesics and CVM is needed. In this analysis, we used data from the Baltimore–Washington Infant Study (BWIS) to examine associations between maternal analgesic use during the periconceptional period and CVM phenotypes.

Materials and Methods

The BWIS population consisted of infants born to residents of Maryland, the District of Columbia, and 6 adjacent counties of northern Virginia from April 1981 through December 1989. The methods of this study have been previously described in detail.[10,11] All data used in our study were deidentified and analyses were performed with an exemption from the Institutional Review Board of the Centers for Disease Control and Prevention.

Cases

Cases were infants with any type of CVM ascertained from searches of community hospitals, 6 pediatric cardiology centers serving the study region, and the medical examiner's logbooks from Maryland. CVM noted at registration were confirmed by echocardiography, cardiac catheterization, surgery, or autopsy. CVM were coded by pediatric cardiologists. Updated information about CVM diagnoses at 1 year of age obtained for all registered cases resulted in a change in only 7.8% of the initial diagnoses. Infants of gestational age <38 weeks with patent ductus arteriosus as the only CVM were not included. Also, because of improvements in diagnostic capability over the study period and the resultant rapid rise in the population prevalence among young infants, only a random sample of the infants with small ventricular septal defects (VSD) were included in BWIS. Infants with >1 cardiac defect were assigned 1 anatomic diagnosis using a hierarchical classification approach developed for BWIS based on the presumed embryonic timing of the defects. These diagnoses were then placed into categories based on their developmental mechanism.[10,12] Cases were further classified based on the presence of other anomalies as isolated (ie, no noncardiac defects); chromosomal disorders (eg, Down syndrome, other trisomies); recognizable syndromes (eg, Ivemark, DiGeorge, Noonan, Williams, fetal alcohol, congenital rubella); or multiple defects (ie, with noncardiac anomalies of unknown cause).

From all identified CVM cases (n = 4390), we excluded all cases with ≥1 of the following factors: maternal reports of pregestational diabetes since this condition is a known risk factor for CVM (n = 87); recognized syndromes or chromosomal abnormalities with the exception that we included infants with Down syndrome who had atrioventricular septal defect (AVSD) (n = 947 excluded); infants who were 1 of a set of twins, triplets, or other multiple births (n = 156); and those for whom no maternal interview was obtained (n = 1013). We then evaluated singleton infants with isolated CVM whose mothers did not have pregestational diabetes and did complete interviews (final n = 2525).

Controls

Controls (n = 3572) were a random sample of all liveborn infants without CVM from the same birth cohort who were delivered in participating hospitals, stratified by month, year, and hospital of birth. Controls were similar to all area births during the study period by infant sex, race, birth weight, plurality, season of birth, and maternal age.[13] For this analysis, we included interviewed, singleton controls with no CVM, chromosomal anomalies, syndromes, or maternal reports of pregestational diabetes (final n = 3435).

Data collection

Home interviews with the parents of case and control infants were conducted within 18 months of birth of the study subjects. A structured, standardized questionnaire was administered by trained interviewers to obtain information on sociodemographic factors, family history, maternal medical conditions, and environmental factors. The latter included reports on medication use during the periconceptional period (3 months before the last menstrual period through the first trimester of pregnancy).

Analgesic use

For this analysis, we defined exposure as maternal use of an analgesic-containing medication at any time during the periconceptional period to ensure that all relevant exposures were included regardless of errors in recall of the last menstrual period or in recall of the exact timing of medication use. Maternal reports of use of prescription and nonprescription analgesics during the periconceptional period were grouped into pharmacologic classes: salicylates, acetaminophen, other NSAIDs, and opioids.

Statistical analysis

First, we compared the frequency of selected maternal and infant demographic and clinical characteristics among cases and controls using the χ^2 statistic. A χ^2 statistic was not calculated if the proportion of subjects with missing values was >5% of the total. Then, because the presence of maternal fever or flu symptoms has been associated with an increased risk of CVM in the infant in previous analyses of BWIS data, we examined the frequency of maternal analgesic use among case and control infants by pharmacologic class stratified by the presence of fever or maternal flu symptoms during the periconceptional period.[5,10] Finally, we used multiple logistic regression models to evaluate possible associations of