

Monday, February 5, 10:00AM-12:00PM
Plenary Session

Findings and Future of the National Birth Defects Prevention Study

Moderator: Peggy Honein, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA

Overview of the NBDPS and Update on Current Research Agenda

Jennita Reefhuis, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA

Antihypertensive Medication Use and Congenital Heart Defects

Alissa R. Caton (NY), Erin M. Bell, Charlotte M. Druschel, Martha M. Werler, Marilyn L. Browne, Paul A. Romitti, Allen A. Mitchell, Angela E. Lin, Richard S. Olney, Adolfo Correa, and the National Birth Defects Prevention Study

Background: Chronic hypertension is present in 1-5% of pregnancies, but there is limited information on the relationship between use of antihypertensive medications during pregnancy and birth defects. We investigated the relationship between antihypertensive medication use and congenital heart defects in the National Birth Defects Prevention Study, a population-based, multicenter, case-control study of birth defects.

Objective: Are women taking antihypertensive medications during early pregnancy at a higher risk of having an infant with a congenital heart defect?

Methods: Estimates of adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated by logistic regression for the associations between maternal self-reported exposures to antihypertensive medications from one month pre-conception through three months post-conception and conotruncal, left obstructive, right obstructive, and septal heart defects. Analyses were restricted to simple, isolated CHDs. Women with pre-existing diabetes and multiple births were excluded. Adjustment factors included study center, maternal age, race/ethnicity, parity, smoking, and folic acid use.

Results: Mothers of 37 (1.4%) case infants and 25 (0.6%) control infants reported antihypertensive medication use during one month preconception through pregnancy month three, while mothers of 32 (1.2%) case infants and 28 (0.7%) control infants reported initiating treatment after the first trimester. After adjustment, there was an almost twofold increase in risk for CHDs (aOR 1.8, CI 1.1-3.1) in women reporting medication use during early pregnancy. Elevated adjusted OR were detected for RVOTO (aOR 3.0; CI 1.4-6.6) and septal defects (aOR 2.3; CI 1.2-4.3) in early users. Risks were approximately doubled in women initiating use in late pregnancy for RVOTO and septal defects. Some women reported use of contraindicated medications.

Conclusions: Use of antihypertensive medications during pregnancy is rare, limiting the ability to examine specific classes of medications or more specific subgroups of heart defects. Although there was some evidence of associations of early pregnancy use with an increased risk of right obstructive and septal defects, further research is needed to examine the possibility of confounding or effect modification by indication.

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Genitourinary Infections and the Risk of Gastroschisis

Marcia L. Feldkamp (UT), Lorenzo D. Botto, Jennita Reefhuis, Jim Kucik, Sergey Krikov, Andy Wilson, Cynthia Moore, John C. Carey

Background and Objective: Several studies suggest gastroschisis is increasing in prevalence around the world, particularly among young women. The pathogenesis and etiology of gastroschisis are not understood but young maternal age is the strongest and most consistent risk factor. Genitourinary (GU) infections, which include both urinary tract infections (UTIs) and sexually transmitted diseases (STDs), are common among sexually active young women. Two common pathogens, *Chlamydia trachomatis* and human papillomavirus (HPV) are increasing, also among young women, with almost two thirds of all STDs occurring among women 15 to 24 years of age. To date, no previous investigations have identified GU infections as a potential risk factor for gastroschisis. The objective of this study was to assess whether GU infections increase the risk for gastroschisis among participants in the National Birth Defects Prevention Study (NBDPS).

Methods: NBDPS is a multi-center, population-based case-control study of risk factors for major birth defects. Case-families are ascertained through selected birth defect registries, and families of healthy live born controls are selected through birth certificates. Mothers are interviewed between 6 weeks and 24 months postpartum. Records of 538 potential cases of gastroschisis were reviewed by one clinician (CM). Of these, we excluded 22 cases because of features of limb-body wall complex, amniotic band sequence, ruptured omphalocele, and Cantrell pentalogy and another 7 cases because of incomplete interviews. The final case group therefore included 509 cases. We excluded 41 of 5,008 controls because of incomplete interviews, leaving 4,967 controls included in the analysis. A woman was considered exposed if she reported a GU infection from one month prior to conception through 3 months after conception. We examined several exposure categories, including exposure to any STD, UTI, STD without UTI, UTI without STD, and the combination of STD with UTI.

Results: 17 (3.5%) cases and 81 (1.7%) controls reported an STD, and 18 (3.6%) cases and 89 (1.8%) controls reported a UTI. Crude odds ratios (cOR) (95% CI) were 2.1 (1.2, 3.6) for STD, 2.0 (1.2, 3.3) for UTI, 1.6 (0.9, 3.0) for STD without UTI, 1.6 (0.9, 2.8) for UTI without STD, and 7.0 (2.2, 22.1) for STD with UTI. Estimated risks appeared to vary by maternal age. Among women 30 years of age or older reporting an STD, the cOR for gastroschisis was 4.6 (1.1, 20.4). Among women under 20 and 20 to 24 age who reported an STD with UTI the cOR for gastroschisis was 2.7 (0.4, 19.1) and 8.3 (1.4, 50.1), respectively. Maternal age-adjusted ORs were 1.5 (0.9, 2.6) for STD, 1.5 (0.9, 2.7) for UTI, and 4.3 (1.2, 15.2) for STD with UTI. The OR for STD with UTI remained elevated after controlling for multiple covariates.

Conclusions: Reported exposure to STD from one month before conception through the first trimester of pregnancy was associated with an increased risk for gastroschisis in NBDPS. The association was strongest for women less than 25 years of age, and among women reporting exposure to both an STD and UTI during this same time period.

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Maternal Corticosteroid Use and Risk of Orofacial Clefts

Suzan L. Carmichael (CA), Gary M. Shaw, Chen Ma, Martha M. Werler, Sonja A. Rasmussen, Edward J. Lammer, and the National Birth Defects Prevention Study

Background: Corticosteroids are useful in treating various conditions, e.g., asthma, arthritis, and eczema. Corticosteroids administered to experimental animals cause orofacial clefts. Evidence for their teratogenicity in humans is limited and has resulted in inconsistent recommendations regarding use during early pregnancy. This study examined whether maternal corticosteroid intake was associated with risk of cleft lip with or without cleft palate (CLP) or cleft palate alone (CP) among offspring.

Methods: This study used data from the National Birth Defects Prevention Study, a multi-state, population-based case-control study of infants with estimated dates of delivery from 1997-2002. Non-malformed, liveborn controls were selected randomly from birth certificates or birth hospitals. Data from maternal telephone interviews were available for 1141 CLP cases, 628 CP cases, and 4143 controls. Corticosteroid exposures were derived from several questions about medication use for various health conditions.

Results: In total, 33 CLP case mothers (2.9%), 6 CP case mothers (1.0%) and 72 control mothers (1.7%) reported any corticosteroid use during the four weeks before or 12 weeks after conception. Univariate logistic regression models indicated that the odds ratio (OR) for any versus no corticosteroid intake was 1.7 (95% confidence interval (CI) 1.1-2.6) for CLP and 0.6 (95% CI 0.2-1.3) for CP. ORs for systemic corticosteroid intake were 2.1 (0.9-4.7) for CLP and 0.8 (0.2-3.6) for CP; numbers of exposed for these comparisons were 9 for CLP, 2 for CP and 16 for controls. ORs for nasal spray/inhaled corticosteroids were 1.5 (0.9-2.5) for CLP and 0.7 (0.3-1.8) for CP; numbers of exposed were 19 for CLP, 5 for CP, and 47 for controls. Results were similar after adjustment for maternal race-ethnicity, education, smoking, intake of folic acid supplements and study center.

Conclusions: These results suggest that corticosteroid intake may be associated with increased risk of CLP, but not CP.

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Spectrum of birth defects associated with maternal diabetes

Suzanne Gilboa, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA

Background: There is a substantial body of epidemiologic literature consistently indicating the increased risk for several types of structural birth defects in relation to maternal pregestational diabetes, particularly cardiovascular and central nervous system defects but also with rarer defects such as sacral agenesis and caudal dysgenesis. The mechanisms underlying these associations are not well delineated; however, hyperglycemia during embryogenesis has been shown clinically to be associated with congenital malformations among infants of diabetic mothers. Experimentally, hyperglycemia has been shown to induce malformations and is considered to be teratogenic. Most previous studies have been limited by small sample sizes and unable to explore a wide spectrum of birth defects.

Methods: We used data from the National Birth Defects Prevention Study (1997-2002), a multi-center, population-based, case-control study to examine associations with diabetes for a total of 39 mutually exclusive categories of birth defects. Restricting our analysis to mothers with a completed telephone interview and a known diabetes status, our sample included a total of 9,929 cases and 4,086 controls. All diabetes and covariate data were ascertained through a maternal computer-assisted telephone interview. Crude and adjusted associations between pregestational or gestational diabetes and birth defects were estimated using logistic regression.

Results: Pregestational diabetes was associated with a significant increase in risk for 27 of the 39 categories of birth defects examined (adjusted odds ratios ranging from 2.53 to 118.99) and a non significant increase in risk (odds ratio ≥ 2.0) for 7 additional categories of birth defects. New associations were identified between pregestational diabetes and specific categories of heart defects, oral clefts and limb defects. We found a few associations of specific birth defect phenotypes with gestational diabetes; these associations were weak and inconsistent.

Conclusions: The primary study limitation is that diabetes status is self-reported. Despite this limitation, however, several previous findings in the literature of strong positive associations between pregestational diabetes and birth defects were confirmed. Specific associations with early embryonic cardiovascular malformations have also been confirmed. As expected there were fewer and weaker associations with gestational diabetes, consistent with the fact that “true” gestational diabetes does not develop until after the critical period of embryonic organogenesis.