Wednesday, January 21, 10:00AM-12:00PM

Plenary Session

National Birth Defects Prevention Study (NBDPS),

Centers for Birth Defects Research and Prevention

Moderator: Larry Edmonds, Centers for Disease Control and Prevention, Atlanta, GA

Status and Demographics of the NBDPS

Jennita Reefhuis, Centers for Disease Control and Prevention, Atlanta, GA

Objective: To present the current status of the National Birth Defects Prevention Study (NBDPS) and to assess the representativeness of the NBDPS by comparing the demographics of the interviewed cases and controls to all births in the United States.

Methods: The NBDPS is a large multi-center case control study collecting data from medical records, maternal telephone interviews and buccal swabs. The NBDPS began with births occurring on October 1, 1997 and is an ongoing study. Using data from the NBDPS for all births with an estimated date of delivery (EDD) before July 1, 2001 and Vital Statistics data from 2000 live births, we compared the distributions of several demographic and exposure variables.

Results: While data collection remains ongoing in the NBDPS, the study has also entered its analytic phase, and numerous epidemiologic analyses are underway to identify risk factors for major birth defects. A total of 11,121 NBDPS interviews had an EDD prior to July 1, 2001 and are included in these analyses: 8,151 mothers of children with major birth defects (cases) and 2,970 mothers of children without major birth defects (controls). Mothers enrolled in the study are slightly older than the general population, more often non-Hispanic White or Hispanic, and more highly educated. Because there is tremendous variation in the prevalence of different types of birth defects, the number of interviewed cases varies from 54 infants with choanal atresia to 876 infants with cleft lip with or without cleft palate. There are also differences in the prevalence of numerous exposure variables, as would be expected because some of these exposure variables may be risk factors for birth defects.

Conclusions and implications: The NBDPS is a large multi-site study that provides the opportunity to study associations between birth defects and many risk factors. The demographic distribution of the subjects in the NBDPS is comparable to that of the general US population with respect to maternal age, race/ethnicity, and educational level.

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Case classification in the NBDPS

Sonja Rasmussen, Centers for Disease Control and Prevention, Atlanta, GA

Background: Previous studies have suggested that etiologic heterogeneity may complicate epidemiologic analyses designed to identify risk factors for birth defects. Case classification uses knowledge of embryologic and pathogenetic mechanisms to make case groups more homogeneous and is important to the success of birth defects studies.

Methods: The goal of the National Birth Defects Prevention Study (NBDPS), an ongoing multi-site casecontrol study, is to identify environmental and genetic risk factors for birth defects. Clinical data on infants are reviewed by clinical geneticists to ensure they meet the detailed case definitions developed specifically for the study. To standardize the methods of case classification for the study, an algorithm has been developed to guide NBDPS clinical geneticists in this process.

Results: Methods for case classification into isolated, multiple, and syndrome categories will be described. Defects considered to be minor for the purposes of case classification have been defined. Differences in the approach to case classification for studies of specific defects and of specific exposures will be discussed.

Conclusions: The case classification schema developed for the NBDPS may be of value to other clinicians working on epidemiologic studies of birth defects etiology. Consideration of these guidelines will lead to more comparable case groups, an important element of careful studies aimed at identifying risk factors for birth defects.

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Maternal Caffeine Consumption and Risk of Cardiovascular Malformations in the NBDPS

Marilyn Browne, Charlotte Druschel, Allen Mitchell, Paul Romitti, Angela Lin, Adolfo Correa Speaker: Marilyn Browne, New York State Department of Health, Troy, NY

Background: Evidence from animal studies suggests that maternal prenatal exposure to high dose caffeine may cause cardiovascular malformations (CVMs) and other birth defects and at lower doses may enhance the teratogenicity of other substances such as nicotine, alcohol, bronchodilators, and phenytoin. Most epidemiologic studies have failed to show an association between maternal caffeine use and risk of CVMs. It is possible that any increase in risk occurs mainly in interaction with other factors and only for certain types of CVMs. Since pregnant women commonly consume caffeine, even a small increase in the risk of malformations, possibly restricted to subgroups exposed to "co-teratogens," would be an important public health concern.

Objectives: 1) To examine whether caffeine ingestion is associated with an increased risk of cardiovascular malformations; if so, at what level. 2) To examine the "co-teratogen" effect of caffeine in combination with smoking and alcohol.

Methods: Using data from the NBDPS, we will examine whether maternal caffeine consumption during the first trimester increases the risk of CVMs and whether caffeine acts as a "co-teratogen" in combination with alcohol and smoking. Approximately 2880 cases and 2600 controls will be included in the analysis.

Conclusions: The number of CVM cases in the NBDPS is much larger than in most other epidemiologic studies to date, providing power to detect relatively small increases in risk of malformations. Preliminary results of our analysis of the association between caffeine intake and risk of CVMs will be presented.

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Hypospadias and Maternal Exposures to Cigarette Smoke

Suzan L. Carmichael, Gary M. Shaw, Cecile Laurent, Ed Lammer, Richard Olney Speaker: Suzan Carmichael, California Birth Defects Monitoring Program, Berkeley, CA

Objective: Several lines of evidence suggest that hypospadias may be associated with maternal smoking. Only a few previous studies have addressed this research question, and most had important methodologic limitations.

Methods: This study uses data from the National Birth Defects Prevention Study, a multi-state, populationbased case-control study. This study includes data on hypospadias cases that were considered severe (i.e., the urethra opens onto the penile shaft, scrotum or perineum), and that were delivered from 1997-2000. Nonmalformed, liveborn controls were selected randomly from birth certificates or from birth hospitals. Maternal interviews were completed by telephone, within 24 months after delivery, with 449 case mothers and 1255 control mothers.

Results: Maternal smoking was not associated with hypospadias risk. For example, during the first month of pregnancy, smoking <1/2 pack/day had an odds ratio (OR) of 0.9 (95% CI 0.6-1.5); $\frac{1}{2}$ pack/day, 1.0 (0.7-1.5); and >1/2 pack/day, 0.7 (0.4-1.1). Exposure to any secondhand smoke at home during the 1st month of pregnancy showed an OR of 0.6 (95% CI 0.4-1.0), and exposure at work or school, an OR of 0.7 (0.5-1.2). Similar associations were observed for other months during the periconceptional period, and adjustment for several potential confounders did not substantially alter results.

Conclusions and Implications: This analysis confirms previous reports that maternal smoking during pregnancy is not associated with an increased risk of having offspring with hypospadias.

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Integrating a local study of congenital heart defects with the NBDPS

Charlotte A. Hobbs, Mario A. Cleves, S. Jill James, and Stepan B. Melnyk Speaker: Charlotte Hobbs, Arkansas Center for Birth Defects Research and Prevention, Little Rock, AR

Objective: Epidemiologic evidence suggests that folic acid-containing multivitamins reduce the risk of pregnancies affected by congenital heart defects (CHDs). The metabolic and molecular basis for this protective effect is unknown. Using data from Arkansas participants of the National Birth Defects Prevention Study (NBDPS), we conducted a local study to better understand alterations in folate metabolism among women with pregnancies affected by CHDs.

Methods: Women who had a pregnancy affected by a CHD (n=213) and control women (n=90) were recruited for this local study. Participating women provided a sample of blood for metabolic analyses for biomarkers of folate metabolism including folate, homocysteine, methionine, and cysteine.

Results: Significant differences were found between case and control women for all biomarkers analyzed. Among women with CHD-affected pregnancies, serum levels of folate and methionine were lower, and homocysteine and cysteine levels were higher, as compared with control women.

Serum Biomarkers	CHD	Case	Control	p-value
	women		women	
Folate (nM)	10.10		12.15	0.032
Homocysteine (µM)	9.58		7.90	< 0.0001
Methionine (µM)	25.13		26.79	0.013
Cysteine (µM)	240.02		233.26	0.002

Conclusions: The goal of this study was to demonstrate an association between variations in biomarkers of the folate metabolic pathway among women with pregnancies affected by CHDs, compared with control women. Further analyses will determine if the observed alterations in folate metabolism among women with CHD-affected pregnancies are associated with genetic polymorphisms in the folate metabolic pathway.

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A New Study of Spina Bifida Risk Factors

Gary M. Shaw, Suzan L. Carmichael, John A. Harris, Edward J. Lammer, Richard H. Finnell Speaker: California Birth Defects Monitoring Program, Berkeley, CA

The underlying mechanisms by which folic acid contributes to reduced risks for spina bifida are unknown. Also unknown is why a substantial proportion of women who take folic acid supplements in the periconceptional period deliver offspring who are affected with NTDs. Thus, further investigation of folic acid, and of other etiologic factors in folate- and nonfolate- supplemented women, will tremendously inform future spina bifida prevention strategies. We were recently awarded funding under CDC Supplement to PA 02081. Our research program will focus on various etiologies of spina bifida by: 1) studying new genetic polymorphisms related to the folate pathway; 2) studying new genetic polymorphisms that are outside the folate pathway; 3) exploring dietary intake of other important nutrients, controlling for folate intake; 4) estimating the population attributable fraction of numerous risk factors among non-folate preventable spina bifida cases; 5) measuring the midpregnancy nutritional status in sera from women who deliver fetuses/infants with spina bifida compared to those who do not; and 6) measuring midpregnancy serum lead from women who deliver fetuses/infants with spina bifida compared to those who do not. Our research program will use state-of-the-art laboratory genotyping methods of human DNA derived from population-based collection activities involving buccal cells and newborn blood specimens. It will draw upon data from two large population-based epidemiologic datasets of spina bifida cases and their controls, i.e., the NBDPS and one of our local studies in California, uniquely providing an internal comparison and simultaneous replication of findings. It includes a novel approach to measuring the nutritional status of women and lead concentrations in mid-pregnancy serum specimens. These specimens will be available from a serum bank from approximately 250,000 pregnant women we will assemble in California. The aims and proposed methods of this research program will be described.