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The National Birth Defects Prevention Study

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SYNOPSIS

The National Birth Defects Prevention Study was designed to identify infants with major birth defects and evaluate genetic and environmental factors associated with the occurrence of birth defects. The ongoing case-control study covers an annual birth population of 482,000 and includes cases identified from birth defect surveillance registries in eight states. Infants used as controls are randomly selected from birth certificates or birth hospital records. Mothers of case and control infants are interviewed and parents are asked to collect buccal cells from themselves and their infants for DNA testing. Information gathered from the interviews and the DNA specimens will be used to study independent genetic and environmental factors and gene-environment interactions for a broad range of birth defects.

As of December 2000, 7470 cases and 3821 controls had been ascertained in the eight states. Interviews had been completed with 70% of the eligible case and control mothers, buccal cell collection had begun in all of the study sites, and researchers were developing analysis plans for the compiled data.

This study is the largest and broadest collaborative effort ever conducted among the nation's leading birth defect researchers.

The unprecedented statistical power that will result from this study will enable scientists to study the epidemiology of some rare birth defects for the first time. The compiled interview data and banked DNA of approximately 35 categories of birth defects will facilitate future research as new hypotheses and improved technologies emerge.

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Birth defects are the leading cause of infant mortality in the United States, accounting for more than 20% of all infant deaths.[1] Birth defects also contribute substantially to morbidity and long-term disability. Although several human teratogens such as Thalidomide and rubella virus have been identified, the causes of more than 70% of all birth defects are still unknown.[2] In 1996, Congress directed the Centers for Disease Control and Prevention (CDC) to establish Centers for Birth Defects Research and Prevention to help reduce birth defects in the US. The next year, CDC awarded 5-year grants to establish Centers in seven states: Arkansas, California, Iowa, Massachusetts, New Jersey, New York, and Texas. The Centers are based in two universities, four health departments, and one publicly funded research organization. Each Center is a collaboration among state health departments, local hospitals, universities, and the state chapter of the March of Dimes Birth Defects Foundation.[3] A main activity of each Center is to participate in the National Birth Defects Prevention Study (NBDPS), a case-control study of major structural birth defects that began in 1997. The CDC Birth Defects and Pediatric Genetics Branch in Atlanta participates in the NBDPS as the eighth study site and coordinates the Centers' collaborative activities.

From an epidemiologic perspective, birth defects are difficult to study. Individual conditions are relatively rare, the fetus is exposed to an array of unknown genetic and environmental factors, the biologic mechanisms that cause most birth defects are unknown, and the defects identified at birth represent only the birth prevalence, not the true incidence of the condition. Several lines of evidence support the belief that a combination of genetic and environmental factors is important in the etiology of many birth defects. These include a higher recurrence risk of birth defects in some families than in the general population, but not as high as expected if caused by a single gene disorder. There is also a higher concordance of defects in monozygotic (genetically identical) twins than in dizygotic (fraternal) twins, but less than the 100% expected if the etiology were entirely genetic.[4] The specific genetic and environmental factors involved in the etiology of birth defects have, for the most part, eluded identification.

A few large case-control studies of birth defects have included assessments of multiple exposures.[5-11] Some of these studies were limited by small numbers of affected infants; an inability to distinguish the occurrence of isolated defects from multiple malformations and syndromes of known etiology; and the lack of biologic specimens from which to study genetic causes. In addition, lack of consideration of gene-environment interactions may have concealed the effects of environmental factors on disease risk.[12] For example, in a study of cleft palate, maternal smoking was not associated with cleft palate when all cases of cleft palate were studied. Yet, when cases with a specific genetic polymorphism in the gene for transforming growth factor alpha (TGF) were examined, a sevenfold risk for cleft palate was observed in infants of mothers who smoked.[13] This and other examples[14-16] illustrate the importance of considering gene-environment interactions in birth defects epidemiology.

The National Birth Defects Prevention Study, as the largest collaborative birth defect study in the US, seeks to improve the study of birth defects by including (*a*) a large ethnically and geographically diverse birth population that provides unprecedented statistical power to evaluate potential risk factors for birth defects, (*b*) more etiologically and pathogenetically homogeneous case definitions for specific birth defects, (*c*) an interview instrument that includes a broad range of potential exposures and confounders, and (*d*) the collection of DNA from which to study genetic susceptibility and gene-environment interactions.

METHODS

Study population. The eight states participating in the NBDPS have ongoing population-based birth defects surveillance systems. Details about each of the surveillance systems, including legislative authority, population size, outcomes covered, data sources, and data collected, have been reported elsewhere.[17] The New Jersey and New York surveillance systems include only liveborn infants; the other six states include both stillborn infants (fetal deaths at greater than 20 weeks gestation) and liveborn infants in whom at least one major birth defect is diagnosed within the first year of life. Arkansas, California, Georgia, Iowa, and Texas also include pregnancies that are diagnosed prenatally and electively terminated.

Case infants for the study are identified from each state's birth defect surveillance system. Arkansas, Iowa, and Massachusetts ascertain eligible cases statewide. California, Georgia, New York, and Texas ascertain eligible cases from selected areas of the state. New Jersey ascertains cases statewide but due to its large number of births, takes a systematic random sample of the five most common birth defects included in the NBDPS study and determines the size of the sampling fraction by the birth prevalence of those five defects. The annual birth popula-

tion covered in the eight states is approximately 482,000, or 10% of births in the United States. Participant enrollment in the study began with birth dates or estimated dates of delivery (for terminations) of October 1, 1997. A termination date for the study has not been decided.

Table 1 lists the birth defects eligible to be included in the NBDPS. Several factors were considered in the selection of defects. To help improve recall, an initial goal was set to interview mothers within six months of the infants' date of birth. Thus, most of the defects had to be apparent and accurately identified by six weeks of age. Defects of public health significance were given high priority, as well as those with specific hypotheses regarding etiology. Some defects of low prevalence were also included because the large population base provided a unique opportunity to study them. Because the goal of the study is to identify causes of birth defects, defects of known etiology (such as single-gene conditions and chromosome abnormalities) were excluded. However, defects associated with conditions presumed to be related to maternal exposure to a teratogen (such as maternal diabetes or anticonvulsant exposure) were included in order to study genetic factors that potentially modify teratogenic effects.[18]

Table 1. Birth defects eligible to be included in the National Birth Defects Prevention Study, grouped by organ system, and number of cases ascertained from October 1, 1997, to December 31, 2000 (N = 7470)[a]

Birth defects	Cases n
Anencephaly, craniorachischisis	194
Spina bifida	315
Encephalocele, cranial meningocele, encephalomyelocele	68
Holoprosencephaly	71
Hydrocephalus	240
Dandy-Walker malformation	54
Anophthalmia, microphthalmia	71
Cataracts, glaucoma and related eye defects[b]	21
Anotia, microtia	185
Conotruncal heart defects	706
Single ventricle	64
Septal heart defects (atrial septal defects, ventricular septal defects)	1968
Atrioventricular septal heart defects	186
Ebstein malformation	57
Obstructive heart defects (right and left ventricular outflow tract defects)	1119
Anomalous pulmonary venous return	126
Heterotaxia	107
Choanal atresia	43
Cleft lip, with and without palate	849
Cleft palate	463
Esophageal atresia, with and without tracheoesophageal fistula	177
Intestinal atresia/stenosis	537
Biliary atresia	46
Hypospadias, second- or third degree	451
Renal agenesis/hypoplasia	86
Limb deficiency, intercalary	19
Limb deficiency, longitudinal	157
Limb deficiency, transverse	254
Limb deficiency, not elsewhere classified	22
Craniosynostosis	249
Diaphragmatic hernia	217
Sacral agenesis	26
Omphalocele	147
Exstrophy, bladder	21
Exstrophy, cloacal	17
Gastroschisis	308
Amnion rupture sequence	125

[a]An infant with more than one eligible birth defect is counted in each eligible category. Controls = 3821

[b]Included in the study as of January 1, 2000

Specific case definition criteria were developed by the Centers' clinicians for each of the eligible defects. These criteria include: definitions of defects; required confirmatory diagnostic procedures (for example, echocardiography, cardiac catheterization, surgery, or autopsy are required for diagnosis of congenital heart defects); conditions where prenatal diagnosis is acceptable for case eligibility; and specific exclusions (hydrocephalus associated with another brain lesion, for example, is excluded unless the primary lesion is an eligible diagnosis). Case information obtained from hospital reports and medical records is entered into a standardized database. The information includes demographic data, growth parameters, verbatim diagnoses, diagnostic codes, methods of diagnosis, and eligibility status. These entries are reviewed by a clinical geneticist at each Center to ensure that the defects meet the case definition, as well as to standardize the coding and evaluate the case for a possible syndrome of known etiology. Cases in which a syndrome is suspected by the Center's geneticist but not diagnosed by the physician who clinically evaluated the child are included in the study but may be excluded by investigators during analysis. Inter-reviewer reliability studies are performed periodically among the clinical reviewers to ensure consistent review of the cases. Clinical review methods for this study will be reported elsewhere.

Controls for the NBDPS are liveborn infants with no major birth defects who are randomly selected from birth certificates in three states (Iowa, Massachusetts, New Jersey) and from birth hospitals in five states (Arkansas, California, Georgia, New York, Texas). States that select controls from hospitals use a systematic random sampling scheme that selects infants in proportion to the number of births in each hospital in the geographic area. Each Center is meeting the study's goal of contributing approximately 300 cases and 100 controls per year to the study.

Contacting mothers. Standard procedures are used for contacting mothers of case and control infants and enrolling them in the NBDPS. The mothers are mailed a packet that includes an introductory letter describing the NBDPS, a pamphlet that addresses frequently asked questions, a "Rights of Research Subjects" fact sheet, a $20 money order, a response list for several items included in the interview, and a calendar that covers the duration of her pregnancy. This packet, available in both English and Spanish, is mailed to the mothers no earlier than six weeks after the infant's estimated date of delivery (EDD).

Approximately 10 days after the packet is mailed, an interviewer calls the mother to answer any questions she may have and to either conduct the interview or schedule a more convenient time. Standard procedures are used to trace mothers whose contact information is incorrect or to contact mothers who do not respond to phone calls or letters. Extensive efforts are made to speak with each mother.

Maternal interview. As with all aspects of the NBDPS, the data collection processes and instruments were developed by a committee with representatives from each Center. The basis for the maternal interview came from the instrument used for the Birth Defects Risk Factor Study, a case-control study of birth defects conducted by CDC, the California Birth Defects Monitoring Program, and the Iowa Birth Defects Registry from 1993 through 1996. For the current study, several sections of the previous questionnaire were eliminated (for example, pesticide use and family history of birth defects) because of sparse or unreliable data, and several sections were added (for example, diet and drinking water). The interview covers a wide range of environmental factors broadly defined to include infectious, chemical, physical, nutritional, and behavioral factors (Table 2). The topics included in the interview were selected based on hypotheses about what causes birth defects. Some of the topics, such as drug use, have been studied for years, while others have received more recent attention, such as dietary minerals and assisted reproductive techniques.

The interviews take about one hour and are conducted in English or Spanish by female interviewers using a computer-assisted telephone interview. Before the interview begins, the interviewer reads a script to the mother and obtains verbal informed consent for her participation in the study. The interview includes detailed questions about exposures that occurred from three months before conception through the end of the pregnancy of interest. Most of the questions are structured with pre-coded response lists. A few questions are open-ended, such as those about occupation that allow the mother to describe the chemicals or substances to which she may have been exposed.

A pregnancy calendar allows the mother to respond to questions about the timing of exposures in the way that she best remembers—by date, month of pregnancy, or trimester. The interview is completed in one or several sessions at the mother's request. Interviews are targeted for completion within six months of the EDD but must be completed no earlier than 6 weeks and no later than 24 months of the EDD.

Table 2. Question topics in the National Birth Defects Prevention Study maternal interview

- Maternal health
  - Diabetes
  - High blood pressure
  - Seizures
  - Respiratory illness
  - Fever
  - Bladder, kidney, urinary tract infections
  - Other diseases or illnesses
  - Injuries
  - Surgery
  - X-rays
  - Medications
- Pregnancy
  - Pregnancy history
  - Contraception
  - Assisted reproductive techniques
  - Morning sickness
  - Prenatal care
- Diet/Substance use
  - Vitamins
  - Food supplements
  - Dietary assessment
  - Caffeine
  - Tobacco
  - Alcohol
  - Street drugs
- Home/Work
  - Residence
  - Hot tub/sauna
  - Occupation
  - Military service
- Family demographics
  - Race/ethnicity
  - Income
  - Education
- Water use
  - Drinking water sources
  - Bathing
  - Swimming pool
  - Other uses of water

Buccal cell collection. After the interview is completed, a buccal (cheek) cell collection kit is sent to the mother to take a sample on her child (if living) and both parents. The collection kits include informed consent forms, simple instructions, an additional $20 money order, materials for completing the specimen collection, and prepaid US mail packets for specimen return. Centers utilize a cytologic brush for buccal cell collection.[19] Routine DNA extraction is performed and all samples undergo a standardized quality control procedure that consists of polymerase chain reaction (PCR) analysis of two anonymous genetic markers. A portion of each sample that meets the quality control criteria (successful PCR amplification after at least two attempts with at least one marker and alleles consistent with the reported family relationship) are sent to a biologic specimen storage facility at CDC. Centralized storage is intended to make samples easily available for current and future Centers-wide studies. A tracking system developed using Microsoft Access provides a centralized data source to Centers on all specimens. Its linkage to the clinical database allows investigators to rapidly determine the number of specimens available for a specific defect type.

Data management. CDC's Birth Defects and Pediatric Genetics Branch coordinates the NBDPS and maintains a copy of all data collected in the study. Each month, each Center electronically transmits a copy of its clinical, interview, and biologic tracking data to CDC. The transmitted data do not contain any personally identifiable information. The Microsoft Access replication process used to transfer and store data for the NBDPS ensures the integrity and security of the data and allows each Center to have timely access to the compiled database. A paper on the informatics of this study will be available elsewhere.

A Data Sharing Committee has been established to ensure equitable access to the pooled data among the Centers' scientists, promote accurate and scientifically sound research, and establish guidelines for collaboration and authorship. Before NBDPS data are released to an investigator, this committee must review and approve a detailed research proposal. The committee also reviews all manuscripts generated by the study and ensures that authorship follows the guidelines developed by the International Committee of Medical Journal Editors.[20] Investigators outside the Centers may conduct research using NBDPS data only if a Centers' scientist is a collaborator in the research.

All of the Centers participating in the NBDPS have obtained a Certificate of Confidentiality from CDC that protects the privacy of the research subjects by withholding from anyone not connected with the study any personally identifying characteristics of the research subjects. The CDC Institutional Review Board (IRB) has approved the NBDPS, as have the IRBs for each participating Center.

Several lines of evidence support the belief that a combination of genetic and environmental factors is important in the etiology of many birth defects.

Data analysis. Interview and genetic data will be used to evaluate risk factors for birth defects. In some cases, this evaluation will provide additional understanding of previously recognized risk factors. In other cases, the data will be used to generate new hypotheses about the causes of birth defects. Univariate analyses will be used to look for individual risk factors for specific defects. Multivariate logistic regression will be the major analytic tool used to evaluate confounding and interactions and to look for best-fit models to explain the observed outcomes. Analysis of genetic material will focus on candidate genes known or suspected to play a role in the development of different organ systems or in the metabolism of suspected teratogenic agents. Relative risks for specific birth defects will be estimated using odds ratios for the exposures alone, genotypes alone, and for the joint effect of the exposure and genotype.

RESULTS

These data provide a preliminary description of the cases and controls included in the study from October 1, 1997, through December 31, 2000. The eight Centers combined ascertained 7470 cases and 3821 controls during that period. Interviews had been completed for approximately 74% of the cases and 63% of the controls. A recent evaluation of each Center revealed that participation rates to date range from 58% to 77% for case interviews and from 63% to 73% for control interviews.

Cases of the common defects such as cleft lip and palate, spina bifida, and selected heart defects, are accumulating rapidly (see Table 1). Cases of more rare defects such as biliary atresia, bladder exstrophy, and some limb deficiencies, will require several years of data collection before enough cases are accrued for descriptive or analytical studies. Approximately 76% of the cases in the study have only one birth defect that is eligible for the study; 14% have two eligible birth defects, and 9% have three or more eligible birth defects. Males constitute 58% of the cases and 50% of the controls.

The interviews require 55 minutes on average, and 80% are completed in one session. The average length of time from birth (or EDD) to interview of the mother varies by type of birth defect. For example, the average length of time for cases with anencephaly is about 8 months and the average length of time for cases with craniosynostosis is about 12 months. The average length of time from birth (or EDD) to interview also varies by state because of differences in case identification and abstraction and the time necessary to locate and contact the mothers. The average age of control infants at the time of interview is about 8 months. Preliminary analysis of the interview data provides information about the demographic characteristics of the mothers of the case and control infants in the study (Table 3). Mothers of case and control infants are approximately the same age on average (28 years) and have had the same average number of pregnancies (1.6). The distribution of mothers by race or ethnicity is similar for case and control mothers, as is the proportion of mothers born in the United States. A slightly greater proportion of control than case mothers had some degree of education beyond high school and household incomes in the highest category. Approximately 74% of all mothers were employed either full- or part-time.

DISCUSSION

Conducting a multi-state study is an efficient way to study uncommon conditions such as birth defects, but it can be a challenge to implement and coordinate. More than 12 IRBs reviewed and approved the NBDPS protocol (some states had more than one IRB review). The process is repeated each time substantial changes are made to the study. Standardizing study methodology has also been difficult because of variations in state laws regarding issues such as genetic testing, informed consent, and protection of identifiable data. On the other hand, the heterogeneity of the study populations in the eight states contributes enormously to the value of the data collected, and the

Table 3. Demographic characteristics of mothers of infants with and without birth defects based on 5538 case and 2403 control interviews completed through December 31, 2000[a]

Characteristic	*Case (N = 5538)*		*Control (N = 2403)*	
Maternal mean age at infant's birth—years (range)	27.6 (12 – 50)		28.2 (13 – 50)	
Number of prior pregnancies—mean (range)	1.6 (0 – 15)		1.6 (0 –12)	
	Number	*Percent*	*Number*	*Percent*
Maternal "race"/ethnicity				
White	3430	63	1488	63
Hispanic	1131	21	448	19
Black/African American	553	10	286	12
Asian/Pacific Islander	105	2	49	2
American Indian/Alaskan Native	21	<1	9	<1
Other	212	4	82	3
Mother born in US	4525	83	1960	83
Maternal education—highest grade completed at time of birth				
No formal schooling	24	<1	5	<1
1–11 years	1007	18	380	16
High school or equivalent	1461	27	606	26
Some college	1465	27	659	28
4-year college or Bachelor's degree	1153	21	528	22
Advanced degree	347	6	184	8
Maternal employment during pregnancy				
Not employed	1266	23	474	20
Student	215	4	93	4
Full or part-time job	4032	73	1827	76
Household income in the year before infant's birth				
Did not know or refused	307	6	143	7
Less than $10,000	923	19	341	17
$10,000–$20,000	714	14	263	13
$20,000–$30,000	724	15	271	14
$30,000–$40,000	496	10	207	10
$40,000–$50,000	385	8	108	5
Greater than $50,000	1428	29	669	33

[a]Totals for each characteristic may not equal 5538 cases and 2403 controls because some mothers did not answer some of the questions.

combined expertise of the Centers' scientists is critical for the consistent monitoring and evaluation necessary for a study of this complexity and size.

The multiyear duration of the NBDPS affords the opportunity to review and fine-tune the study design and methodology. For example, within the first year of the study, a large number of muscular ventricular septal defects (VSDs) and VSDs "not otherwise specified" were collected. After one year of ascertainment these two defects represented more than one-sixth of the total cases. In consideration of the goals of the NBDPS, ascertainment of these defects has been suspended until a preliminary analysis of risk factors can be performed on the data already collected. Beginning in January 2000, cataracts, glaucoma and related eye defects were added as eligible defects in response to advances in the molecu-

lar genetics of congenital eye defects.[21] Additionally, a few changes have been made to the maternal interview. Some questions have been modified, and several new questions have been added, including a new section about drinking water. None of the changes to the case definition or interview instrument are likely to bias the study results. A few defects and environmental factors will have fewer years of data collection, but this will be taken into account when the data are analyzed.

As a result of examining the preliminary participation rates, a number of factors emerged that required modification. Feedback from the mothers revealed that the initial contact materials were overwhelming. As a response, the introductory letter describing the study, and the confidentiality assurances, have been simplified. Mothers are told more clearly that they can do the interview in more than one session and can choose to participate in the interview only, without having to do the buccal collection. In an effort to reduce the time from case identification to interview, Centers have modified how they abstract and clinically review cases and new tracing procedures, such as the use of commercial tracing services, have been implemented to locate hard-to-find mothers.

Additional phone calls to families after they receive the buccal cell collection kits have also been implemented to answer any questions and encourage them to complete the kits. Finally, $20 money orders for both the interview and the buccal cell collection are now being provided to the families to compensate them for their time. (Originally only the buccal cell collection was compensated.) All of these changes have resulted in increased participation in the study. Preliminary analyses of the impact of the changes show that participation rates in all Centers now exceed 65%, up from an early start of about 55%. The differences among mothers who participated before and after the changes were made will be studied carefully.

The NBDPS relies heavily on mothers' ability to recall exposures. Mothers are asked to recall not only specific types of exposures, but also the dosage and timing of gestational exposure. It has been suggested that mothers of affected children may be more likely to report exposures than mothers of healthy children. However, few studies have documented the existence of recall bias in case-control studies of reproductive outcomes. Analysis of a case-control study of birth defects that included a postpartum maternal interview showed that recall bias may be present for some exposures but not for others.[22] One method that has been used to address the issue of recall bias is to use "affected" control infants (that is, infants with birth defects other than the ones of interest). Studies have shown, however, that even when recall bias exists, the observed association can be closer to the true association when population controls are used than when affected controls are used.[23,24] Researchers using the NBDPS will have the opportunity to use both population controls and affected controls and can more carefully study the potential effects of differential recall of specific exposures during pregnancy.

Although the NBDPS is population based, only five Centers are able to include cases that were diagnosed prenatally and electively terminated. In several Centers, state law prevents the release of information pertaining to elective terminations. In other Centers, ascertainment of prenatally diagnosed cases is difficult because there are multiple locations where diagnoses are made, and information about subsequent elective terminations is often lacking. Incomplete ascertainment of prenatally diagnosed cases will be particularly relevant for the study of some birth defects in the NBDPS, such as neural tube defects.[25] The exception of two of the eight centers to inclusion of stillbirths in case ascertainment also will be taken into account when the data are analyzed.

Because the study of genetic susceptibility and gene-environment interaction is an important goal of the NBDPS, careful consideration is given to the collection of genetic samples. To maximize subject participation in this part of the study, collection of buccal samples was selected instead of blood specimens. Collecting buccal samples from both the child and parents enables study of candidate genes in both the child and mother, because both the maternal and infant genotypes may contribute to the etiology of certain defects.[26] In addition, the availability of specimens from parents allows the use of analytical techniques that decrease the chance of spurious associations that may occur in case-control studies.[27-30] However, the amount of DNA available from buccal samples is limited.[31] Therefore, proposals for studies using genetic material will be scrutinized by the Centers to ensure that the study is an optimal use of the available material. Future advances in technology, which may allow genomic amplification of small amounts of DNA,[32] may make this less of a concern. Study participants are informed that their samples will be stored for future research but that they will be used only to study birth defects and for no other purpose. As discussed earlier, the Data Sharing Committee must review and approve all research proposals.

The National Birth Defects Prevention Study is a unique collaborative effort that can serve as a model for

studies of other rare health conditions. The information gathered from the interviews, combined with the availability of DNA specimens, will provide an invaluable resource for the study of genetic susceptibility to environmental exposures for a broad range of birth defects.

The NBDPS also will provide opportunities to study the validity of survey research methods and can be used to describe the prevalence of selected behaviors among women of reproductive age in the United States.

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