HHS Public Access

Author manuscript

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

Birth Defects Res A Clin Mol Teratol. 2015 August ; 103(8): 733–740. doi:10.1002/bdra.23373.

Next steps for birth defects research and prevention: The Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS)

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Abstract

Background—The Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) is a population-based, multi-Center case-control study of modifiable risk factors for selected birth defects in the United States. BD-STEPS is the second major research effort of the Centers for Birth Defects Research and Prevention, which extends and expands the initial research effort, the National Birth Defects Prevention Study (NBDPS).

Methods—BD-STEPS focuses on 17 categories of structural birth defects selected based on severity, prevalence, consistent ascertainment, and previous findings that warrant additional research. Cases are identified through existing birth defects surveillance programs; controls are from vital records or birth hospital logs from the same catchment area. BD-STEPS usess a standardized computer-assisted telephone interview to collect information from case and control mothers on topics including demographics, health conditions, and medication use. Following the maternal interview, selected Centers request permission to sample residual newborn screening

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CDC Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The authors declare that they have no conflicts of interest.

blood spots from state repositories for genetic analyses. New components planned for BD-STEPS include linkages with external datasets and use of online questionnaires to collect in-depth information on selected exposures.

Results—BD-STEPS extends NBDPS by continuing to collect data on many exposures that were assessed in NBDPS, allowing data from both studies to be combined and providing an unprecedented sample size to analyze rare exposures. BD-STEPS expands upon NBDPS by collecting more detailed information on existing exposures as well as new exposures.

Conclusions—The goal of BD-STEPS is to provide women and healthcare providers with information they need to make decisions to promote the healthiest pregnancy possible.

Keywords

birth defects; congenital anomalies; case-control; epidemiology; pregnancy

INTRODUCTION

Birth defects are common, costly, and critical. Although some birth defects are caused by known genetic disorders (e.g., Trisomy 21) or environmental (i.e., non-genetic) exposures (e.g., thalidomide), the etiology is unknown for an estimated two-thirds of birth defects (Nelson and Holmes, 1989). Identifying modifiable risk factors for birth defects allows women, their partners, and health care providers to take preventive action.

The Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) is a population-based, multi-Center case-control study in the United States that focuses on understanding the role of modifiable risk factors for selected structural birth defects. BD-STEPS is a collaborative activity of the Centers for Birth Defects Research and Prevention (CBDRP), which were established in response to the Birth Defects Prevention Act of 1998. The first collaborative activity of the CBDRP was the National Birth Defects Prevention Study (NBDPS), a population-based, multi-Center case-control study of environmental and genetic risk factors for selected structural birth defects that interviewed nearly 44,000 women about their pregnancies in 10 CBDRP Centers across the United States (Yoon and others, 2001) [add Reefhuis et al., this issue].

Over 200 NBDPS manuscripts were published between 2001 and 2014 on a wide range of topics [add Dawson et al., this issue]. Although the study sample size of NBDPS was unprecedented and allowed for examination of a wide variety of risk factors for birth defects, several research areas could benefit from additional study. BD-STEPS was designed to advance knowledge about specific modifiable risk factors for birth defects by extending and expanding the activities of NBDPS.

In September 2013, six CBDRP study Centers located in Arkansas (AR), California (CA), Iowa (IA), Massachusetts (MA), New York (NY), and North Carolina (NC), were funded to collaborate on BD-STEPS. As with NBDPS, the Centers for Disease Control and Prevention (CDC) contributes data from Georgia and serves as a seventh study Center. BD-STEPS benefits from a multidisciplinary team comprised of epidemiologists, biostatisticians,

clinicians (including clinical geneticists, pediatricians, pediatric cardiologists, and perinatologists), geneticists, study coordinators, data managers, and interviewers.

The purpose of this paper is to provide an overview of the BD-STEPS rationale and design.

METHODS OVERVIEW

Study design

BD-STEPS is a population-based, multi-Center case-control study. All English or Spanish speaking women who reside within defined ascertainment areas and experienced a pregnancy for which at least one eligible birth defect was reported in an active, population-based birth defects surveillance system are recruited for inclusion in the study. All Centers include cases that are live births, fetal deaths (stillbirths), or pregnancies ending in terminations (to the extent possible). Population-based controls are live born infants without a diagnosis of any major birth defects and are identified through vital records (AR, IA, MA, GA, NC Centers) or hospital records (CA and NY Centers).

The birth population encompassed within each of the participating BD-STEPS Centers ranges from 35,000 to 70,000 (Table 1). We estimate that approximately 1,400 case pregnancies with eligible defects will be identified study-wide per year. Each Center will identify approximately 100 to 125 eligible control infants per year. Based on the experience of NBDPS, we estimate the participation rate will be close to 70%, resulting in completed interviews for approximately 1,000 cases and 500 controls per year. BD-STEPS data collection began with births on or after January 1, 2014.

The population-based, multi-Center design of BD-STEPS, combined with the geographic and racial/ethnic diversity of the BD-STEPS study population, is important for minimizing potential bias and improving generalizability of the results from this study to other populations. A comparison of the maternal demographic characteristics of NBDPS control mothers with those of all U.S. births supports the scientific merits of this approach with respect to the representativeness and generalizability of the study findings (Cogswell and others, 2009).

Critical partnerships with BD surveillance programs: The foundation for case-finding

BD-STEPS builds upon key partnerships between the CDC, academic institutions, and state health departments established for NBDPS. An essential component of these partnerships is the population-based birth defect surveillance programs within each of the study Centers. These surveillance programs provide the basis for clinical data collection at each of the seven Centers. Some BD-STEPS Centers are housed within or closely collaborate with the state health department that manages the birth defects surveillance program (MA, NY, NC), while other Centers are housed within a university or federal agency that has arrangements with the state health department to conduct birth defects surveillance activities (AR, CA, GA, IA). Each of the surveillance programs has statutory authority from their respective states to review and abstract maternal and infant medical records in order to collect birth defects data, and has authority to use that information for public health research with appropriate approvals. Local agreements within each participating Center provide for the use

of birth defect surveillance and vital records data to recruit study participants for BD-STEPS. Use of existing population-based surveillance systems is an expedient and highly cost-effective approach for the conduct of large, multi-Center epidemiologic studies such as BD-STEPS.

Clinical methods

The clinical methods of BD-STEPS are similar to those of the NBDPS (Rasmussen and others, 2003), but with a more limited number of birth defects. Medical record data abstracted by the birth defects surveillance programs are searched using a list of eligible ICD-codes. Identified records are then reviewed by a clinical geneticist at each study Center to determine whether each case meets diagnostic criteria for inclusion. The primary inclusion criterion is the presence of at least one of the 17 categories of eligible structural defects (Table 2). These defects were chosen for BD-STEPS based on severity (i.e., associated with infant deaths, disabilities, comorbidities, or high healthcare costs), prevalence (i.e., retained more common NBDPS defects), or high public health importance (e.g., all seven types of critical congenital heart defects that are primary targets for newborn screening using pulse oximetry (Kemper and others, 2011)); consistent ascertainment (enabling more homogeneous and complete case groups); and results from previous findings that supported further research (e.g., NBDPS data helped document the existence of a new teratogen - mycophenolate mofetil – and its association with anotia/microtia (Anderka and others, 2009)). Defects that did not have these characteristics were not selected for this study. For example, anencephaly is lethal, relatively common, and has been the intense focus of previous public health research and prevention programs; however, ascertainment varied across NBDPS due to the relative infrequency of live births among pregnancies with anencephaly (Cragan and Gilboa, 2009) and varying sources of prenatal data with inconsistent ascertainment of terminated pregnancies. Therefore, anencephaly was not included as an eligible birth defect in BD-STEPS. The combined prevalence of the 17 birth defect categories included in BD-STEPS is estimated to be approximately 39.2 cases per 10,000 live births.

Like NBDPS, BD-STEPS excludes infants with recognized or strongly-suspected chromosomal or single-gene disorders. Case definitions with defect-specific inclusion and exclusion criteria are used by clinicians at each study Center to determine eligibility of individual cases. Once data are compiled across Centers, each case is subjected to a second level of clinical review, in which a single clinician will review and classify all cases within a particular category of defects. This classification process includes a review for consistency of coding and inclusion among the various study Centers, as well as further categorization into homogeneous analysis groups based on the presence or absence of multiple major defects and defect patterns.

Recruitment

The recruitment process for BD-STEPS is similar to that of the NBDPS. Contact information is identified through the abstracted medical or vital record, and when necessary, a commercial tracing service is used. An introductory packet is mailed to prospective study participants by staff located at the individual study Centers no earlier than six weeks after

the estimated date of delivery (EDD). The introductory packet, with all documents in English and Spanish, includes a letter of introduction, a fact sheet on rights of human subjects, a question and answer sheet, a $20 gift card, and materials to assist with recall during the interview (a calendar covering the period of the pregnancy and a chart for summarizing medication information).

Interviewers begin placing calls 4 to 10 days after the introductory packets are mailed. An interview can be initiated up to 18 months after EDD. This eligibility period allows sufficient time for complete diagnosis of the defects and ascertainment by the birth defects surveillance programs. Trained study interviewers use approved standardized telephone scripts for all study communications. Comprehensive tracing methods are used to maximize participation rates and include several follow-up calls, letters, and emails to locate hard-to-reach women.

Interview

The BD-STEPS maternal interviews are conducted in English and Spanish by a centralized interview contractor to maximize efficiency and standardization of data collection and provide bilingual interviewers during all call hours. For all Centers, maternal verbal informed consent is obtained at the beginning of the interview with the exception of two Centers. One Center's state requires that informed consent be obtained locally for all births and another Center's state requires local written consent for women whose pregnancy ended in an elective termination.

Interviewers are all female and receive intensive initial and on-going training on the use of the BD-STEPS computer-assisted telephone interview (CATI) instrument. Interviewers are monitored, initially on all interviews, and then randomly after they have gained experience. Women can complete interviews during the day or in the evening, and on weekdays or weekends at their convenience. The topics included in the BD-STEPS CATI are listed in Table 3.

The BD-STEPS interview was designed to be shorter in duration than the NBDPS interview, taking approximately 45 minutes to complete (versus approximately 60 minutes for NBDPS), to reduce subject burden and increase the likelihood of completing the interview in one session (although women have the option to complete the interview in multiple sessions). Several topic areas that were included in the NBDPS interview were removed, either because sufficient data were available from NBDPS (e.g., dietary data from a food frequency questionnaire) or future study was not deemed to have the same potential for additional discovery.

The BD-STEPS interview was also designed such that some data could be combined with data from NBDPS for increased power. For some rarer exposures (e.g., use of venlafaxine (Polen and others, 2013)), data can be combined to produce more stable estimates of association. Where possible, we maintained exact or similar wording for questions covering topics also included in the NBDPS interview (e.g., questions on race, education, acculturation, and some of the disease and medication questions). NBDPS questions about physical activity, stress, and social support were introduced later during the study and were

retained in BD-STEPS in order to accumulate data. In the BD-STEPS interview, we also chose to expand on topics that had a limited number of questions in the NBDPS interview. These topics include fertility treatments, details of multiple gestation (i.e., twins and higher order pregnancies), and chronic diseases and health conditions (e.g., obesity, thyroid disease, asthma, cancer, migraines, autoimmune disease, depression, anxiety, and attention deficit hyperactivity disorder [ADHD]). New topic areas in the BD-STEPS questionnaire include maternal dental procedures and insurance status.

The time period for which we ask women to report their exposures and experiences is shortened in BD-STEPS. Because structural birth defects primarily occur during the first trimester of pregnancy, most of the BD-STEPS questions focus on the one month before through the third month of pregnancy. Advantages of shortening the exposure period are that women have a shorter time period for which to recall and possibly fewer exposures to report due to the elimination of exposures that may have only occurred later in pregnancy. A limitation of the shortened exposure period is that we will not be able to describe exposure prevalence during the entire pregnancy; analyses of the prevalence of exposure patterns among our population-based controls will be able to focus on early pregnancy.

New and expanded focus areas

Chronic maternal medical conditions: One key topic area expanded in BD-STEPS is chronic maternal medical conditions, for which more detailed information is being collected about specific conditions during pregnancy, including when women were diagnosed, whether women spoke to their healthcare providers about management of their condition during pregnancy, the medications or other treatments used to treat her condition, and symptoms experienced during pregnancy. There are several reasons for this intensified focus on chronic maternal medical conditions. Certain serious conditions previously thought to preclude pregnancy are now more easily managed so that women of childbearing age have increased survival and opportunity for pregnancy. For example, cancer is diagnosed in 1 in every 1,000 pregnancies and 160,000 to 240,000 women of childbearing age (<45 years) received a cancer diagnosis in 2013 (Salani and others, 2014). As another example, transplant receipt typically requires lifetime immunosuppression maintenance and one well-known antirejection medication, mycophenolate mofetil, has been recently identified as a human teratogen (Anderka and others, 2009).

Other chronic conditions show increasing prevalence over time among women of childbearing age, making it even more important that we understand the implications of diagnosis and management of these conditions during pregnancy. Asthma prevalence increased steadily over the previous decade and is common among women (9%) (Akinbami and others, 2012). NBDPS analyses showed a possible association between asthma medication use and increased risk for specific birth defects (Lin and others, 2008; Lin and others, 2012; Munsie and others, 2011); however, confounding by indication could not be ruled out in these analyses due to a lack of detailed information on asthma status and severity; BD-STEPS will collect this additional information. Depression has also shown an increasing prevalence over time, from 3% in 1991 (Compton and others, 2006) to 9% in 2006 – 2008 (Centers for Disease and Prevention, 2010) and is common among women

(10%) (Centers for Disease and Prevention, 2010). Depression may influence risk for birth defects through stress or other physiological response; use of medications, which have previously been associated with risk for certain birth defects (Alwan and others, 2007; Polen and others, 2013); or coping behaviors, such as smoking, drinking, or illicit drug use. In the NBDPS interview, women were asked about the use of medications that could be used to treat depression. The interview questions, however, did not ask women about the reason for use; as a result, depression could not be distinguished from other possible indications for use (e.g., anxiety, post-traumatic stress disorder, or obsessive compulsive disorder). The BD-STEPS interview includes questions designed to make this distinction, and to obtain information on symptoms and duration of the condition. Other chronic conditions about which detailed questions are asked in the BD-STEPS interview are: thyroid disease, autoimmune disease, migraines, cardiac arrhythmias and other heart conditions, anxiety, and attention deficit hyperactivity disorder ADHD.

Diabetes, obesity, physical activity, and bariatric surgery: Maternal pregestational diabetes and obesity are known risk factors for specific types of birth defects (Correa and others, 2008; Stothard and others, 2009) and the prevalence of both conditions are increasing in the United States (4; Flegal and others, 2012). Obesity and diabetes are distinct, but interrelated conditions. Few data are published on whether or not physical activity reduces the risk for birth defects attributable to diabetes or obesity (Flak and others, 2012). Although bariatric (weight loss) surgery is effective in improving certain health outcomes related to obesity, it is also associated with increased risk for certain pregnancy complications and adverse birth outcomes (Belogolovkin and others, 2012); furthermore, it is unknown whether it modifies the association between obesity and birth defects. BD-STEPS data will help us to explore the complexities of these health conditions and their associations with birth defects.

Medications: Medications are a common exposure during pregnancy, with approximately one-half of pregnant women reporting use of at least one prescription medication during the first trimester (Mitchell and others, 2011); even more women report use of over-the-counter medication during pregnancy (Werler and others, 2005). New medications are constantly being introduced to the market, but pregnant women are almost always excluded from clinical trials due to concerns about potential harm to the fetus. In addition to new medications, women are using existing medications for new indications, often at different dosages. For example, medications traditionally considered as antiepileptics are increasingly being used to treat migraines (Rogawski and Loscher, 2004) and to aid in weight loss (Garvey and others, 2012).

Although the NBDPS interview collected considerable information about medication use, the BD-STEPS interview will collect even more detailed data, including additional information on dose and indication for use and by expanding the list of chronic conditions for which medications are taken, with follow-up questions about medications used to treat those conditions.

Genetics

In contrast to buccal (cheek) cell swabs collected in NBDPS, residual samples from newborn metabolic screening blood spots will be used to evaluate genetic susceptibility and biologic markers of exposure among live births in BD-STEPS. The collection of newborn metabolic screening blood spots is completed by collecting blood from infant heel sticks on filter paper soon after the infant's birth.

Newborn blood spots have several advantages over buccal swabs: specimen collection is not required, reducing the burden on participants and potential errors/contamination during sample collection as well as reducing the cost. In addition, biomarkers present at the time of birth can be measured, allowing for evaluation of inflammatory cytokines (Keustermans and others, 2013), biochemical parameters (Paglia and others, 2010), DNA methylation (Wong and others, 2008), and environmental exposures such as heavy metals and persistent compounds (Chaudhuri and others, 2009). Disadvantages of this method are that samples are only available for liveborn infants in states that retain the newborn bloodspots and the lack of parental DNA samples.

For the Centers that require parental consent to obtain identified newborn blood spots, a written consent form requesting access to their infant's residual newborn blood spots and a newborn blood spot question and answer sheet are included with the interview thank-you letter along with a $10 gift card. For parents of multiples (e.g. twins or triplets), the interview thank-you letter and the written consent forms will ask for access to residual blood spots from the case or control infant included in BD-STEPS and the index infant's multiple sibling(s) who are not study participants.

Because individual defects are rare, many years of data collection are required to obtain enough samples to complete a valid etiologic study for a specific birth defect. Residual newborn blood spot specimens will be retained locally either by the Center or at the state health department. Each Center is responsible for processing and completing quality control analyses on the specimens before use. To ensure that each laboratory conducting genetic and epigenetic analyses of the newborn blood spot specimens is proficient in their respective laboratory techniques, an external quality assessment will be used for laboratories planning to conduct such research.

New components

Data linkages—We plan to link BD-STEPS data with selected existing environmental, surveillance, healthcare claims and clinical data to enhance the utility of the study data to explore important public health questions about birth defects. Such linkages can be used to validate self-reported data, evaluate associations of birth defects with additional exposures (e.g. environmental data), and conduct health services and outcomes research. For example, data from NBDPS have been successfully linked to environmental data on air pollution (Stingone and others, 2014) and water quality. For the water quality studies, NBDPS geocoded residence data were linked to water source maps for which water quality measures were available. Analyses to date have focused on nitrate exposure and selected birth defects (Brender and others, 2013), and work is currently underway to examine associations

between exposure to water disinfection byproducts and orofacial clefts, and other birth defects. Additionally, linkage to longitudinal datasets can provide a picture of the impact of birth defects across the lifespan as well as the changing met and unmet needs of those living with birth defects.

In addition, selected linkages between maternal responses in the BD-STEPS interview and other clinical data sources will allow validation of these self-reports by estimating bias and, if present, adjusting for bias, thus improving confidence in study findings. For examples, the Massachusetts Center led a project that linked NBDPS maternal reports of artificial reproductive therapy to clinical data from the Society for Assisted Reproductive Technologies (Liberman and others, 2014) and the Utah Center led a project that linked self-reported NBDPS smoking data to data from other sources (Srisukhumbowornchai and others, 2012).

Online questionnaires—Online questionnaires are increasingly being used in studies of pregnancy and health outcomes (Boston University Slone Epidemiology Center; Huybrechts and others, 2010). BD-STEPS plans to implement the use of supplemental online questionnaires (paper questionnaires will be made available upon request). In the BD-STEPS telephone interview, women are asked about their willingness to participate in future online questionnaires and to provide their email address. Those women willing to participate in this supplemental part of the study are eligible to receive periodic online surveys from BD-STEPS. The initial online questionnaire module, which will be released after the start of the study, will focus on occupational exposures. All women who reported working during early pregnancy in certain occupations and who indicated their willingness to participate in future online questionnaires will receive an email invitation to participate in the online survey and will be asked detailed questions about their potential exposures specific to that occupation. This first online questionnaire will serve as a pilot project to assess participation and the potential for selection bias, and associated costs. If this method yields useable information at an acceptable cost, online questionnaires on a variety of topics will be developed and periodically released throughout the course of the study.

NEED FOR BD-STEPS

Various approaches are used to improve our current understanding of the etiology and prevention of birth defects. Existing birth defects surveillance systems can be used to examine descriptive epidemiology on a population level and tend to have excellent diagnostic information, especially if based on active ascertainment. In some states, surveillance data can be linked to other data resources to explore more specific questions, such as the association of residential proximity to environmental exposures or neighborhood-level socioeconomic level with birth defects risks. Teratogen Information Services (TIS) typically collect information on pregnant women who contact TIS regarding concerns about various exposures, especially medications. Although not population-based, TIS data can address specific exposures of concern, especially newly emerging ones, and potentially generate important leads for etiologic analyses. Existing administrative databases (e.g., Healthcare Cost and Utilization Project data, proprietary health insurance claims databases, or Medicaid data) often contain detailed information about treatments and

outcomes within relatively large populations. Although the diagnostic specificity and accuracy of the birth defects diagnosis in administrative data sources may be problematic, linkage with population-based birth defects surveillance systems, which often use rigorous clinical diagnostic procedures, can minimize this limitation. However, the underlying population that these data sources represent may be ill-defined, and often are not representative of the general public. Thus additional approaches to studying etiology and prevention are needed.

BD-STEPS has several unique features that enhance its ability to contribute to our understanding of the causes of birth defects – with the ultimate goal of prevention. The study includes abstraction of detailed and standardized diagnostic data on specific birth defects, which is rarely available from existing administrative data sources. The methods of case and control selection are population-based. Exposure assessment is based on primary data collection (telephone interviews) rather than administrative datasets or aggregate information, which enables collection of detailed information on investigator-selected exposures, as opposed to secondary analysis of data available from existing systems that may not have been designed for etiologic research.

Each research approach has its own set of strengths and weaknesses. For retrospective case-control studies such as BD-STEPS these include for instance selection bias and reliance on self-reported exposure data. In the end, the strength of epidemiological findings often rests on their coherence across different study populations and study designs.

CONCLUSIONS

The goal of BD-STEPS is to identify modifiable risk factors for selected structural birth defects. BD-STEPS aims to extend and expand beyond the strong foundation established by NBDPS. The longevity of the collaborative efforts of the CBDRP provides a unique opportunity to combine data across studies, a major strength of BD-STEPS that will allow for unprecedented statistical power for analyses of less common exposures. The design of BD-STEPS was based largely on the knowledge gained and lessons learned from NBDPS. Results from BD-STEPS will provide women, their partners, and healthcare providers with information they need to make decisions that will promote the healthiest pregnancies possible.

Acknowledgments

Funding: This work was supported through a cooperative agreement under FOA DD-13-003 from the Centers for Disease Control and Prevention to the Centers for Birth Defects Research and Prevention for participation in the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS).

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Table 1

Description of catchment areas for the Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS) study sites

BD-STEPS study site	Description of catchment area	Approximate annual birth population of catchment area
Arkansas	Entire state	37,000
California	San Joaquin Valley counties (Fresno, Kern, Kings, Madera, Merced, San Joaquin, Stanislaus, and Tulare)	65,000
Georgia	Metropolitan Atlanta counties (DeKalb, Fulton, and Gwinnett)	35,000
Iowa	Entire state	40,000
Massachusetts	Central and Eastern counties (Barnstable, Essex, Middlesex, Norfolk, Plymouth, Suffolk, and Worcester)	58,000
North Carolina	Perinatal Care Regions II and IV counties (Alamance, Alexander, Allegheny, Ashe, Avery, Burke, Caldwell, Caswell, Catawba, Chatham, Davidson, Davie, Durham, Forsyth, Franklin, Granville, Guilford, Iredell, Johnston, Lee, Orange, Person, Randolph, Rockingham, Rowan, Stokes, Surry, Vance, Wake, Warren, Watauga, Wilkes, and Yadkin)	51,000
New York	Selected Western and Downstate counties (Allegany, Bronx, Cattaraugus, Chautauqua, Erie, Genesee, Monroe, Niagara, Orange, Orleans, Putnam, Rockland, Westchester, and Wyoming)	66,000

Table 2

Birth defects included in the Birth Defects Study to Evaluate Pregnancy exposures (BD-STEPS)

Defect category	Estimated annual number of eligible cases across all study sites[1]
Spina bifida	135
Anophthalmia / microphthalmia	15
Anotia / microtia	20
Congenital heart defects	
Transposition of the great arteries (TGA)	80
Tetralogy of Fallot	115
Truncus arteriosus	20
Pulmonary atresia	40
Tricuspid atresia	20
Coarctation of the aorta	130
Hypoplastic left heart syndrome	40
Anomalous pulmonary venous return	60
Cleft lip with or without cleft palate	230
Cleft palate	130
Esophageal atresia	60
Transverse limb deficiency	60
Diaphragmatic hernia	80
Gastroschisis	140

[1] Based on 2005 – 2009 prevalence data from the Metropolitan Atlanta Congenital Defects Program

Table 3

Topic areas included in the Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS) computer-assisted telephone interview

Pregnancy history
Multiple gestation
Family history
Fertility treatments
Maternal health conditions
Diabetes
Cancer
Heart problems
Obesity
Thyroid disease
Asthma
Epilepsy
Migraine
Autoimmune disease
Transplant receipt
Depression/anxiety
Attention deficit hyperactivity disorder
Genitourinary infections
Fever
Medications
Herbals
Vitamins
Stress
Physical activity
Dental procedures
Smoking
Alcohol use
Residential history
Maternal occupation
Race/acculturation
Education
Insurance status