nbdps
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NEWS

NBDPS News is distributed from the Centers for Disease Control and Prevention (CDC)-funded Centers for Birth Defects Research and Prevention.

The purpose of this newsletter is to inform study participants and the public of the Centers' activities and current news about birth defects.

In this issue

NBDPS Next Steps

Thank you for participating in the National Birth Defects Prevention Study (NBDPS). As NBDPS interviewing has come to a close, we will continue to analyze NBDPS data for years to come. We are excited to have launched a new study to continue the effort to learn more about the causes of birth defects. This new study is called the Birth Defects Study To Evaluate Pregnancy exposureS, or BD-STEPS. BD-STEPS furthers the work of other studies, like the NBDPS, that have been going on for more than 25 years.

About BD-STEPS

BD-STEPS began conducting phone interviews with women living in seven states—Arkansas, California, Georgia, Iowa, Massachusetts, New York, and North Carolina. BD-STEPS participants include women who have had a pregnancy affected by a birth defect as well as mothers of babies who do not have a birth defect.

The BD-STEPS interview focuses on a variety of topics. A main area of focus is modifiable risk factors, which are risk factors for birth defects that might be changed to reduce the chance of having a child born with a birth defect. For example, BD-STEPS interviewers ask women detailed questions about medicines they take for longstanding diseases like asthma and high blood pressure. We know many women must take medicine to treat these diseases. However, a woman may be able to take a different medicine with a lower risk for causing birth defects. In this case, taking a different medicine is an example of a modifiable risk factor that she can change before and during pregnancy. BD-STEPS hopes to learn which medicines could pose fewer risks for birth defects.

BD-STEPS builds on knowledge from previous studies like NBDPS. NBDPS researchers identified some birth defect risks that need more research. For instance, NBDPS researchers learned that obesity and diabetes can increase a woman's risk of having a child with certain types of birth defects. With BD-STEPS, researchers will further explore obesity and diabetes, and focus on behaviors women can change. This new research will give women more information about how they can reduce their risks for having a child with a birth defect.

Currently, BD-STEPS primarily uses phone interviews to collect information. However, BD-STEPS is looking for better and easier ways for women to take part in the study. Some women may be asked to complete BD-STEPS surveys online to help us develop new ways for doing birth defects research.

Learning about birth defects takes time and involves many people. We learn something from every interview, but there is still more work to do. BD-STEPS is part of a strong and continued commitment by researchers to learn even more about the causes of birth defects.

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Recent Findings from the NBDPS

NBDPS is no longer interviewing participants. Over the course of 14 years of interviews, 43,000 women from 10 states took part in the study. We also have cheek cell kits (genetic samples) from more than 25,000 families that will be used to understand how genetics play a role in birth defects.

Although NBDPS data collection is complete, we will continue to analyze this rich source of information for years to come. More than 200 scientific and medical papers using NBDPS data have already been published. Here are some of the recent research findings.

Polycyclic Aromatic Hydrocarbons and Oral Clefts

Polycyclic aromatic hydrocarbons (PAHs) are chemicals formed during the burning of coal, oil, gas, garbage, or from smoking cigarettes, cigars, or pipes, or from charbroiling meat. There are many ways to come in contact with PAHs at home or at work. NBDPS researchers looked for evidence of a link between PAHs in a woman's workplace and oral clefts (clefts of the lip and palate) in their babies.

Among women interviewed for the NBDPS, researchers found that it was not very common for women to work in places with PAHs. PAH exposure occurred most often among women working in food preparation and serving. Pregnant women who worked in places with any PAHs were more likely to have babies with cleft lip with or without a cleft palate. Pregnant women who worked in places with higher PAH levels were even more likely to have babies with cleft lip than women who worked in areas with lower PAH levels. Since this was the first study to show this link, more research is needed to understand it fully.

Langlois PH, Hoyt AT, Lupo PJ, et al. Maternal occupational exposure to polycyclic aromatic hydrocarbons and risk of oral cleft-affected pregnancies. The Cleft Palate-Craniofacial Journal. 2013;50(3): 337-46.

Butalbital Use and Birth Defects

Butalbital (byoo-TAL-bi-tal) is an ingredient in some medicines (for example, Fioricet®, Fiorinal®) prescribed for the treatment of migraine and tension-type headaches. Little is known about the safety or risk of using butalbital while pregnant. NBDPS researchers looked to see if there is a link between butalbital use and birth defects.

Researchers found that butalbital use is rare among women in NBDPS. Researchers also found a link between using butalbital while pregnant and certain congenital heart defects. The heart defects in the study with this link include tetralogy of Fallot, pulmonary valve stenosis, and atrial septal defects. This study is the first to show these links. More research is needed to learn more about the risks and benefits of butalbital use among pregnant women.

Browne ML, Van Zutphen AR, Botto LD, et al. Maternal butalbital use and selected defects in the National Birth Defects Prevention Study. Headache. 2014;54(1):54–66.

Antiherpetic Medication and Gastroschisis

Gastroschisis is a birth defect of the abdominal (belly) wall. The baby's intestines are outside of the baby's body through a hole beside the belly button. The causes of gastroschisis are not known, but it is thought that exposures in early pregnancy might play a key role.

Herpes infections can occur during pregnancy, and to treat these infections antiherpetic medicines are sometimes used. Researchers used NBDPS data to see if antiherpetic medicine use in early pregnancy is linked to the risk of gastroschisis. This study found that the risk of gastroschisis could be higher in children born to women with herpes infection who used antiherpetic medicine.

More research is needed to determine the risks of herpes and antiherpetic medications in pregnancy.

Ahrens KA, Anderka MT, Feldkamp ML, et al. Antiherpetic medication use and the risk of gastroschisis: findings from the National Birth Defects Prevention Study, 1997-2007. Pediatric and Perinatal Epidemiology. 2013 Jul; 27:340-5.

Genetics and Congenital Heart Defects

Genetics and congenital heart defects (CHDs) are the most common type of birth defect, affecting about one in every 100 babies born in the United States. Scientists are working hard to learn the causes of CHDs. Most CHDs are due to a complex relationship among environment, lifestyle, and genetic factors.

Using the genetic samples that NBDPS families provided, NBDPS researchers identified changes (sometimes called variants) in several genes that were linked with CHDs. Variants in four genes were found to increase the risk of heart defects. More research is needed to understand the functions of these genes and to confirm the study findings among different groups. This study is one of the first in NBDPS to study genes from babies and their mothers.

Li M, Cleves MA, Mallick H, et al. A genetic association study detects haplotypes associated with obstructive heart defects. Human Genetics. Sep 2014;133(9):1127-38.

Fever in Pregnancy and Congenital Heart Defects

Fever in early pregnancy is common. It is reported by 5% to 10% of women during the first trimester. Congenital heart defects (CHDs) are the most common birth defect. NBDPS researchers looked to see if there is a link between fever during pregnancy and CHDs.

Among mothers of a baby without a birth defect, one out of 13 had a fever in early pregnancy. For mothers of a baby with a CHD, about one in 12 had a fever in early pregnancy. Researchers found that the risk for CHDs was higher if the fever was from a urinary tract infection or pelvic inflammatory disease than if it was from a respiratory, flu-like disease. The increased risk was seen for certain CHD types, such as heterotaxy and some obstructive heart defects. Results of this study suggest the risk for these heart defects might be lower in women who were taking multivitamins before their pregnancy.

Botto LD, Panichello JD, Browne ML, et al. Congenital heart defects after maternal fever. American Journal of Obstetrics and Gynecology. 2014 Apr;210(4):359.e1-359.e11.

Air Pollution and Congenital Heart Defects

Many pregnant women, especially those who live in urban areas, are exposed to different air pollutants. Although the Environmental Protection Agency sets air quality standards to limit the amount of pollution in our air, we still do not know whether the amounts of pollution women are exposed to can affect their unborn babies.

NBDPS researchers found that higher exposure to air pollutants related to car traffic, specifically nitrogen dioxide, was more common among mothers of babies born with certain types of congenital heart defects (CHDs). More research is needed to learn what levels of air pollution affect an unborn baby.

Stingone JA, Luben TJ, Daniels JL, et al. Maternal exposure to criteria air pollutants and congenital heart defects in offspring: results from the National Birth Defects Prevention Study. Environmental Health Perspectives. 2014 Aug;122(8):863-72.

The Potential Impact of Newborn Pulse Oximetry Screening

In the United States, about 7,200 babies born each year have critical congenital heart disease, also known as CCHD. CCHDs are the most serious types of CHDs. CCHDs often lead to low levels of oxygen in a newborn. A low oxygen level in a baby can be found by testing oxygen levels 24 hours after birth.

NBDPS researchers found that about 30% of the babies with CCHDs were diagnosed more than three days after birth. The percentage of babies with more than three days delay in diagnosis varied based on CCHD type—ranging from about 8% for babies with pulmonary atresia to 62% for babies with coarctation of the aorta. If these babies had been tested for CCHD within 24–48 hours of birth, as is now mandated in many state newborn screening programs, some of them might have been diagnosed sooner, leading to earlier treatment.

Peterson C, Ailes E, Riehle-Colarusso T, et al. Late detection of critical congenital heart disease among US infants: estimation of the potential impact of proposed universal screening using pulse oximetry. Journal of the American Medical Association (JAMA) Pediatrics 2014;168(4):361-70.

Risk Factors for Choanal Atresia in the NBDPS

Choanal atresia is a narrowing of the nasal airway and can cause severe breathing problems in newborns. It is one of the leading causes of nasal surgery. Choanal atresia is rare, and not much is known about its risk factors. NBDPS researchers looked for reasons that might increase the risk for having a baby with choanal atresia.

Researchers found that the risk of choanal atresia was higher when women smoked cigarettes, had three or more cups of coffee with caffeine every day, or used thyroid medications early in their pregnancy. This study is one of the first to look at risk factors for choanal atresia, so more research is needed to confirm these findings.

Kancherla V, Romitti PA, Sun L, et al. Descriptive and risk factor analysis for choanal atresia: the National Birth Defects Prevention Study, 1997-2007. European Journal of Medical Genetics. 2014;57(5):220-9.

Participation in the Genetic Component of NBDPS

Most women (63%) who finished an NBDPS phone interview also gave NBDPS genetic samples by providing swabs of their cheek cells. NBDPS researchers found that taking part in the genetics part of the study differed by Center. The participation ranged from 50% to 74% across different sites.

Participation also differed by race/ethnicity. Among white and Hispanic women, those with a higher education and had a baby with a birth defect were more likely to complete the cheek cell collection than women of other races. Among all racial/ethnic groups, an extra $20 incentive and a shorter time between the baby's due date and the phone interview were linked with women being more likely to participate. Researchers can use this feedback to increase participation in similar studies in the future.

Glidewell J, Reefhuis J, Rasmussen S, et al. Factors affecting maternal participation in the genetic component of the National Birth Defects Prevention Study—United States, 1997–2007. Genetics in Medicine. 2014 Apr;16(4):329-37.

Exploring the Relationship Between Medication and Birth Defects

Many women take medicines during pregnancy. In fact, we have learned from the NBDPS and other studies that nearly 90% of women in the United States take one or more medicines during their pregnancies, including a large number who take prescription medicines. Even more women take medicines that are available without a prescription, called "over-the-counter", or OTC, products. Reasons for taking medicine range from treating longstanding illnesses such as diabetes, high blood pressure, and asthma, to treating more short-term problems such as a urinary tract infection or a cold.

With so many women taking medicines while pregnant, it is very important to learn as much as we can about whether these products might harm (or help) a pregnancy. We know now that some medicines may cause birth defects if a woman takes them while pregnant. For example, thalidomide, isotretinoin (Accutane), and methotrexate may harm the developing baby. At the same time, we have learned that some vitamins can reduce the risk of certain birth defects. For example, folic acid has been shown to reduce the risk of severe birth defects of the spine and brain. However, for most medicines, we know very little about their possible effects when taken during pregnancy. Women and their healthcare providers need to know which medicines to try to avoid and which are the safest to take during pregnancy.

Our new study, BD-STEPS, studies medicines by asking questions during the interview about any medicine use during the first trimester of pregnancy. Our focus is on the first trimester because it is when most birth defects occur. We ask women to tell us about all the medicines they took, including prescription and OTC products, vitamins, supplements, and herbals. We want to know about pills and liquids as well as shots, suppositories, and inhaled medicines. Then we ask women to tell us when during pregnancy they took these products and how often they took them. We ask women to try to report as accurately as they can by looking at calendars and prescription bottles.

Because most birth defects are quite rare, we must gather data from many women. We will combine the medications information already obtained from the NBDPS interviews with the new BD-STEPS medications information; this will greatly strengthen the birth defects data. Once we have studied these data carefully, BD-STEPS researchers will be able to help women and their healthcare providers make better choices about the medicines women decide to take in pregnancy.

Spotlight on NBDPS Research Centers and the Principal Investigators

Did you know that all of the NBDPS Research Centers work together to continue analyzing data, but each Center is unique? Many of these Centers will continue their work in researching birth defects in BD-STEPS. Read below for more information about the NBDPS Centers and the Principal Investigators at these Centers.

ARKANSAS

Each year in Arkansas, around 1,300 babies are born with a birth defect and more than 100 babies will die because of them. The Arkansas Center for Birth Defects Research and Prevention seeks to reduce the occurrence of birth defects in Arkansas and the nation. The Center collects its data through the Arkansas Reproductive Health Monitoring System (ARHMS), one of the oldest active birth defects surveillance systems.

Research at the Arkansas Center looks at genetic factors that might increase the risk for birth defects. Its participation in NBDPS and BD-STEPS provides the opportunity to look more closely at genes, a woman's lifestyle, and the interaction between genes and exposures in the woman's surroundings that might lead to birth defects. The goal of the research is to find exposures in early pregnancy that may be prevented.

The Arkansas Center's Principal Investigator is **Charlotte Hobbs, MD, PhD**. Since 1997, Dr. Hobbs has been the PI for the Arkansas Center (during NBDPS and now in BD-STEPS) and the Medical Director of ARHMS. Dr. Hobbs oversees study analyses, presents findings at meetings and in scientific journals, and takes a lead role in mentoring new birth defects researchers. Dr. Hobbs has devoted her career to the study and prevention of birth defects.

CALIFORNIA

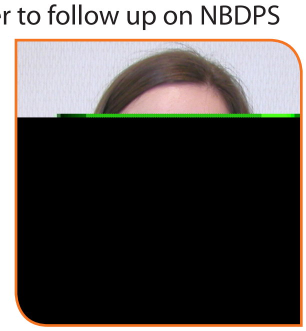
Fifteen percent of all U.S. births occur in California. Each year, 17,000 babies are born with birth defects in California, and as many as 2,000 of these babies will die in their first year of life. The California Center of Excellence is a partnership with Stanford University School of Medicine and the California Birth Defects Monitoring Program in the Department of Public Health. The Center collects data from women who live in eight counties in the Central Valley. The Center has been part of the CDC-funded Centers for Birth Defects Research and Prevention since 1997. The California Center focuses its research on the impact of nutrition, environmental exposures, and genetics on risks of birth defects.

Gary Shaw, DrPH, and **Suzan Carmichael, PhD**, are the Principal Investigators for the California Center. Dr. Shaw has conducted birth defects r esearch for over 25 years. Dr. Carmichael has focused on birth defects research for the past 15 years. Together, Drs. Shaw and Carmichael are leaders in birth defects research and have written hundreds of scientific papers on the topic. They have researched causes related to diet, obesity, drugs, alcohol, stress, pollution, jobs, and genes.

GEORGIA CDC

CDC coordinates NBDPS data-management and analyses and BD-STEPS study activities and serves as the Georgia study site. CDC brings a lot of experience, like studying medication use among pregnant women and finding new ways to look at the data. In addition, CDC keeps track of birth defects in Atlanta through the Metropolitan Atlanta Congenital Defects Program (MACDP). MACDP has collected data in Atlanta since 1968 and serves as a model for other state birth defects tracking systems.

More than 3,000 women from Georgia have helped us understand the causes of birth defects by taking part in the NBDPS. The Georgia Center is eager to follow up on NBDPS research findings with BD-STEPS.



The Principal Investigator for the Georgia Center is **Sarah Tinker, PhD**. Dr. Tinker focuses on collecting high-quality data from local study subjects. She works with those involved in the