2003 Annual Report

Birth defects in Arkansas:
Taking steps in the right direction

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Arkansas Center for Birth Defects Research and Prevention
Arkansas Reproductive Health Monitoring System
From Our Director

On behalf of the Arkansas Center for Birth Defects Research and Prevention, I am delighted to present this report on surveillance, research and prevention of birth defects in Arkansas. For most of us, our structural architecture develops perfectly and we are born with our organs and tissues present, complete, and in their correct places. But for babies with birth defects, something does not come together quite right. Although some defects are minor and surgically correctable, others impose a devastating burden of health problems, financial expense, and impaired quality of life. Birth defects are the leading cause of death among infants.

Throughout our research, we are working to solve the mystery of structural birth defects. By learning why problems occur early in development, we believe we will be able to prevent the problems from occurring. We know that the causes of birth defects are very complex. In most cases, birth defects result from interactions among multiple maternal environmental exposures and behaviors, and the parental and fetal genes. The complexity of exploring the relevant hypoth-
eses makes a team approach to our research essential. We have assembled a multidisciplinary group of experts to address the questions and search for answers. The Arkansas Center for Birth Defects Research and Prevention, is a collaborative organization representing Arkansas Children’s Hospital, the University of Arkansas for Medical Sciences, and the Arkansas Dpartment of Health. The Center was established in 1997 by the Centers for Disease Control and Prevention.

Through the continued support of our sponsors and study participants, our sustained growth and contribution to birth defects research will help to diminish the consequences of birth defects for families in Arkansas and the nation.

Charlotte A. Hobbs, MD, PhD, Director

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For Scientists, Clinicians, Families, and the Media

Important Note: The information and resources listed here are intended for educational use only. The information provided through this section should not be used for diagnosing or treating a health problem or disease. It is not a substitute for professional care.

The Arkansas Center for Birth Defects Research and Prevention
http://www.h.uams.edu/forbirthdefectsresearch.uams.edu

The Arkansas Folic Acid Coalition
http://www.folicacid.org

National Human Genome Research Institute
http://www.genome.gov

Online Mendelian Inheritance in Man

The Center for Human Genetics at Duke University
http://www.bupa.duke.edu

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention
http://www.cdc.gov/ncbddd/bd/

National Birth Defects Prevention Network
http://www.nbdpn.org

National Healthy Mothers, Healthy Babies Coalition
http://www.hmbh.org

Spina Bifida Association of America
http://www.sbaa.org

International Clearinghouse for Birth Defects Monitoring Systems
http://www.earlycase.org

University of Kansas Medical Center Genetics and Rare Conditions Site
http://www.ukm.edu/go/support/index

National Clearinghouse for Birth Defects & Health Promotion: Maternal and Infant Health
http://www.cdc.gov/ncbddd/mip.html

National Birth Defects Prevention Network
http://www.nbdpn.org

CDC National Center for Chronic Disease Prevention & Health Promotion: Maternal and Infant Health
http://www.cdc.gov/mip.html

Online Mendelian Inheritance in Man

National Human Genome Research Institute
http://www.genome.gov

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25. Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other NTDs. MMWR 41:1-7. 1992

Who we are / What we do

OUR MISSION
The mission of the Arkansas Center for Birth Defects Research and Prevention is to reduce the prevalence of birth defects in Arkansas and the nation, as well to decrease the economic, social, and psychological impact of birth defects. To accomplish our goal, we obtain data through the birth defects surveillance system in Arkansas, participate in national research on the causes and consequences of birth defects, and develop programs to prevent birth defects.

HOW WE ARE FUNDED
The Birth Defects Prevention Act of the U.S. Congress authorized funding through the Centers for Disease Control and Prevention (CDC) to support regional centers for applied epidemiologic research on the prevention of birth defects. In 1997, a competitive grant award from the CDC established the Arkansas Center for Birth Defects Research and Prevention in Little Rock. Currently, additional Centers are located in California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah.

PUBLIC EDUCATION THAT MAKES A DIFFERENCE
The Arkansas Center for Birth Defects Research and Prevention is the lead organization of the Arkansas Folic Acid Coalition, which encourages Arkansans women to consume folic acid to prevent neural tube defects such as spina bifida. In order for folic acid to be effective, it must be taken very early in pregnancy, often before a woman knows that she is pregnant. Because of this, all women of childbearing age are urged to take a multivitamin containing 400 micrograms (mcg) of folic acid daily. The Folic Acid Coalition communicates this important message to Arkansans through various public media and consistent involvement in folic acid awareness activities organized by the Arkansas chapter of the March of Dimes.

2003 Report of the Arkansas Center for Birth Defects Research and Prevention

Every year in the United States, about 150,000 babies are born with birth defects, affecting 3 to 4 percent of all live births.
Every baby is born with a birth defect. Arkansas’ birth defects surveillance program led the way of development of registries in 7 states during the early 1980s.

In 1985, the Arkansas General Assembly officially established the state’s birth defect registry, the Arkansas Reproductive Health Monitoring System (ARHMS). ARHMS monitored birth defects primarily among residents of central Arkansas between 1985 and 1992, and received additional funding from the Centers for Disease Control and Prevention in the mid-1990s to expand the population coverage to all residents in the state. Since 1993, ARHMS has monitored birth defects diagnosed among residents of Arkansas statewide.

OUR PURPOSE

The purpose of ARHMS is to collect and analyze data on children, infants, and fetuses affected by birth defects. ARHMS enables researchers to identify trends in the prevalence of birth defects and provides the basis for studying their causes. The causes of most birth defects are multifactorial including, such factors as genetics, demographic, or behavioral changes, maternal intake of pharmaceutical products, and environmental agents. Through public health surveillance, ARHMS provides essential data needed to discover the causes of birth defects.

ACTIVE SURVEILLANCE METHODS

ARHMS uses population-based, active surveillance methods to monitor birth defects diagnosed prenatally and among children less than 2 years old. Staff members travel throughout the state and review discharge records from 83 Arkansas hospitals that provide obstetrical or pediatric care.

CONFIDENTIALITY

When the Arkansas General Assembly established ARHMS, it also charged the program with maintaining the confidentiality of all records with personal identifying information. All information gathered by ARHMS, including personal and hospital identifiers, are used only for statistical and research purposes. All identifying information is strictly safeguarded and is protected by state law from unauthorized release. In addition, ARHMS adheres to all federal laws protecting the confidentiality of information gathered for public health surveillance purposes. ARHMS is committed to protecting the confidentiality of the citizens it serves. Multiple precautions are in place at the Center to ensure that confidential information will not be used in ways that might harm the individuals to which it pertains.

WHAT TO AVOID DURING PREGNANCY

- Exposure to toxic substances and chemicals such as cleaning solvents, lead and mercury, some insecticides, and paint
- Eating undercooked meat and handling cat litter: These increase the risk of Toxoplasmosis, an infection caused by a parasite that can seriously harm a fetus.
- X-rays: If dental work or diagnostic tests are necessary, the dentist or physician must be informed about the pregnancy so that extra care can be taken.
- Saunas, hot tubs, and steam rooms: Excessive high heat may be harmful during pregnancy.
- Illegal, or “street” drugs: Women who use illegal drugs can have babies who are small, premature, or have birth defects.
- Alcohol: There is no scientific evidence to identify a safe amount of alcohol a woman can drink while pregnant. Fetal alcohol syndrome causes growth retardation, facial defects, and central nervous system dysfunction.
- Tobacco: Cigarette smoking during pregnancy can result in low birth weight and prematurity. It has also been associated with infertility, miscarriages, tubal pregnancies, certain birth defects, infant mortality, and childhood learning disabilities.

MEDICATIONS AND PREGNANCY

For most over-the-counter and prescribed medications, there are no studies conducted among pregnant women to determine how they affect human pregnancy. If a woman finds out that she is pregnant while she is taking any medication, she should talk to her doctor as soon as possible to determine whether she should continue the medication. Some common over-the-counter medicines contain alcohol or other ingredients that should be avoided by pregnant women.

For women with certain conditions, some medications may be necessary for a healthy pregnancy. Medical conditions such as diabetes, epilepsy, and high blood pressure should be treated before pregnancy, and monitored carefully through regular prenatal care.

Some prescription drugs are known to cause birth defects and should never be taken if there is any chance that a woman is pregnant or could become pregnant while taking the drug.

Arkansas consistently ranks among the least healthy states for maternal risk behaviors, such as smoking during pregnancy and inadequate prenatal care, and for poor pregnancy outcomes, such as infant mortality, low birth weight, and birth defects.
The exact causes of most birth defects are still unknown. Birth defects are not always caused by something the parents can control. Sometimes the causes of birth defects can be determined after the baby is born, but most of the time, a causal factor cannot be identified. That is why studies of birth defects require very large numbers of pregnancies to determine the significance of single risk factors. Nevertheless, it is important to know what can be done to improve the chances of having a healthy baby.

**BEFORE PREGNANCY**

Many birth defects happen very early in pregnancy, sometimes before a woman even knows that she is pregnant. Nearly half of all pregnancies in the United States are not planned. That is why planning pregnancy and preparing for a healthy pregnancy is one of the most important things women can do for the health of their babies. Prenatal care can help find some problems early in pregnancy so that they can be monitored or treated before birth. Also, it is recommended that women get needed vaccines before pregnancy.

Women are also encouraged to take 400 micrograms (mcg) of folic acid in the form of a multivitamin daily before pregnancy and to increase to 800 micrograms (mcg) daily during pregnancy, to reduce the risk of neural tube defects, serious birth defects of the brain and spine. All women who can physically become pregnant should take a vitamin with folic acid every day. In addition, dietary sources of folic acid include enriched grain products (cereals, rice, breads, and pastas) and foods naturally high in folate (orange juice, green leafy vegetables, beans, peanuts, broccoli, asparagus, peas, and lentils). However, most women do not get the recommended daily amount of folic acid in their diet alone, so daily supplementation of folic acid in a pill form is recommended.

**BIRTH DEFECTS PREVENTION IN ARKANSAS**

The Arkansas Center for Birth Defects Research and Prevention is the lead organization for the Arkansas Folic Acid Coalition, which encourages Arkansas women of child-bearing age to take folic acid supplements daily to prevent neural tube defects such as spina bifida, anencephaly, and encephalocele.

The Center works with dedicated individuals and member agencies of the Folic Acid Coalition to communicate this important message to Arkansans, through newspaper articles, radio and television interviews, and the Internet. Additional activities of the Folic Acid Coalition include participating in annual March of Dimes WalkAmerica fundraising events, staffing of community education tables throughout the state, and conducting folic acid educational programs for students at the University of Arkansas for Medical Sciences.

The Center is also working with women who have had a previous pregnancy affected by a neural tube defect to educate them about the benefits of taking folic acid and to help them identify and overcome any barriers that may be preventing them from taking the vitamin. This is an especially important project because a woman who has had one affected pregnancy has a 10-fold higher risk than the general population for neural tube defects affecting their future pregnancies.

**OUR RECOGNITION**

ARHMS ranks as one of the best birth defects surveillance programs in the country. Since 2001, both the Pew Environmental Health Commission at Johns Hopkins School of Public Health and the Trust for America’s Health, independent agencies concerned with environmental exposures and health outcomes, have evaluated each state’s birth defects surveillance program. ARHMS has been awarded an “A” grade by both of these agencies, joining only seven other state surveillance programs to receive this high grade.

**OUR PARTNERSHIPS**

Most state birth defects surveillance systems operate solely from the state departments of health. ARHMS is operated by the University of Arkansas for Medical Sciences and the state’s only pediatric specialty hospital, Arkansas Children’s Hospital, in close collaboration with the Arkansas Department of Health (ADH). ADH has been instrumental in the development and the success that ARHMS has experienced throughout the years. ADH leaders serve as advisors for ARHMS. When appropriate, ARHMS personnel assist ADH with public health activities related to birth defects or other adverse reproductive outcomes. The working relationship between ARHMS and the ADH Center for Health Statistics is crucial to providing the state with quality data on the impact of birth defects in Arkansas.

**USING SURVEILLANCE DATA**

Birth defects surveillance for the United States is a patchwork of state systems across the country where various methods are used to identify cases and operate these systems. Thus, comparisons between states or systems are limited by a lack of standardized surveillance methods.

ARHMS was modeled after the Centers for Disease Control and Prevention surveillance system in Atlanta, Georgia, to provide the most comparable data. The figure below shows the rates of selected birth defects in Arkansas and Atlanta. Differences in rates may result from differences between the frequency of or exposure to the causes of birth defects in these populations, or slight differences in surveillance methods between the two systems.

In Arkansas every year, about 1500 babies are diagnosed with a birth defect, and more than 100 will die because of birth defects.

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**Birth Defect Rates in Arkansas and Atlanta, 1995-1999**

<table>
<thead>
<tr>
<th></th>
<th>Birth Defect Rates in Arkansas and Atlanta, 1995-1999</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NTD</td>
</tr>
<tr>
<td>NTD</td>
<td>0</td>
</tr>
<tr>
<td>TF</td>
<td>0</td>
</tr>
<tr>
<td>TGA</td>
<td>3.0</td>
</tr>
<tr>
<td>Clefts</td>
<td>1.5</td>
</tr>
<tr>
<td>Ab wall</td>
<td>0.10</td>
</tr>
<tr>
<td>Limbs</td>
<td>0.05</td>
</tr>
<tr>
<td>Down</td>
<td>0.01</td>
</tr>
</tbody>
</table>

NTD = neural tube defects; TF = tetralogy of Fallot; TGA = transposition of great arteries; Cleft = cleft lip, palate, or both; Ab wall = gastroschisis or omphalocele; Limbs = upper or lower limb reduction; Down = Down syndrome.

<table>
<thead>
<tr>
<th>Birth Defect</th>
<th>Total diagnosed cases*</th>
<th>Live born Survival to 1st Birthday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephalus</td>
<td>86</td>
<td>22 (25.6%)</td>
</tr>
<tr>
<td>Bilateral renal agenesis</td>
<td>35</td>
<td>20 (57.1%)</td>
</tr>
<tr>
<td>Trisomy 13 or 18</td>
<td>53</td>
<td>34 (64.2%)</td>
</tr>
<tr>
<td>Hydropsplastic left heart syndrome</td>
<td>63</td>
<td>62 (98.4%)</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>51</td>
<td>50 (98.0%)</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>74</td>
<td>71 (95.9%)</td>
</tr>
<tr>
<td>Encephalocele</td>
<td>46</td>
<td>32 (69.6%)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>70</td>
<td>70 (100%)</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>55</td>
<td>36 (65.5%)</td>
</tr>
<tr>
<td>Transposition of great arteries</td>
<td>84</td>
<td>83 (98.8%)</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>259</td>
<td>233 (90.0%)</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>161</td>
<td>110 (68.3%)</td>
</tr>
</tbody>
</table>

* Includes prenatal and postnatal diagnoses

Cases with anencephalus, bilateral renal agenesis, or trisomy 13 or 18 were excluded from the remainder of the defect categories.

Preventive Health Behaviors of Reproductive-aged Women

A second study, “Influence of physician counseling on preventive health behaviors of women of reproductive age,” assessed the impact of physician advice on women’s regular intake of folic acid. Many women report that they are aware of the benefits of folic acid, but they are hesitant to take folic acid supplements unless told to do so by a physician. This randomized trial tested the efficacy of a brief consultation by a physician or nurse about the benefits of folic acid. The goal of this project was to determine whether a very brief amount of provider time can result in behavioral changes that could considerably reduce the risk of a preventable birth defect. Analyses are underway to assess the results of these interventions.
Although birth defects account for 15-30 percent of all pediatric hospitalizations, they exact a proportionally higher health care cost than other hospitalizations. Approximately $8 billion is spent annually to provide medical and rehabilitative care for affected children in the United States. In addition to medical care expenses, the losses incurred among families affected by birth defects include overall diminished quality of life and caregiver time or loss of income. Thus, birth defects impart a significant burden to families and society.

ECONOMIC IMPACT OF BIRTH DEFECTS

Although studies have documented difficulties associated with caring for children with birth defects, estimates of the impact on the caregiver that can be used in economic studies are lacking. Dr. J. Mick Tilford led a recent study to assess caregiver time costs and health utilities for children and families affected by spina bifida, a seriously disabling birth defect.

For this study, families of children with spina bifida and control families completed a survey that measured health preferences for the caregivers using the Quality of Well-Being scale and health utilities for children using the Health Utilities Index. Findings from this study will be used to improve estimates of the costs of spina bifida by allowing for inclusion of non-medical costs of the defect. Improved estimates of cost are used to support resource allocation, public health policy, and evaluation of prevention programs.

HEALTH CARE QUALITY AND UTILIZATION STUDIES

The Health Services Research and Prevention Group at the Arkansas Center for Birth Defects Research and Prevention facilitated the creation of a powerful new database that can be used to study birth defects. Under the direction of Dr. Joseph Thompson, researchers at the Center demonstrated that the Health Care Quality and Utilization Project database used in many studies of adults did not have sufficient power to study rare pediatric hospitalizations.

In response to the urging of Dr. Thompson, the Agency for Health Care Research and Quality released the Kids’ Inpatient Database (KID) in the fall of 2001. The KID contains 80 percent of the pediatric hospital discharges from 22 states for a given year, and was developed specifically to enable analyses of hospital utilization by children with rare conditions.

Studies currently underway describe national characteristics of hospitalizations for all birth defects, and specifically hospitalizations for hypoplastic left heart syndrome. This new source of data will enhance the determination of the health-related impact of birth defects on families and society.

GENETIC EPIDEMIOLOGY OF BIRTH DEFECTS

Abnormalities in a single gene or chromosome are known to cause some birth defects. However, about 75 percent of birth defects are caused by undetermined factors that might be genetic, environmental, or behavior-related. In addition, these factors might interact with each other to cause a birth defect.

Although the causes of most birth defects remain unknown, the Human Genome Project promises to contribute greatly to our understanding of the pathophysiology and etiology of many congenital malformations. Current biomedical research being conducted at the Arkansas Center for Birth Defects Research and Prevention combines epidemiology, genomics, and biochemistry to help unravel the complex mysteries of birth defects.

THE NATIONAL BIRTH DEFECTS PREVENTION STUDY

Funded by the Centers for Disease Control and Prevention, the Centers for Birth Defects Research and Prevention are located in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. These Centers work together on the National Birth Defects Prevention Study (NBDPS). The purpose of this study is to collect information about environmental and genetic risk factors for 30 major structural birth defects. Specific activities include interviews with women having recent pregnancies either affected by birth defects (cases) or not affected by birth defects (controls). Both groups of women provide information concerning their pregnancy, medical history, diet, and other environmental exposures. In addition to the maternal interview, cheek cell samples from children and their parents are used for genetic analyses. This allows the obtain information from both the interview and the cheek cell samples is especially important for identifying complex gene-environment interactions that might be responsible for birth defects.

Each of the Centers contributes data from interviews and cheek cell samples from 300 case families and 100 control families per year. When this study is complete, it will be one of the largest sources of information ever collected about factors that may increase the risk for, or protect against, birth defects.
THE NATIONAL BIRTH DEFECTS PREVENTION STUDY

This unique collaborative study provides unprecedented power to test hypotheses posed by investigators from each Center regarding the etiology of birth defects. A recent study initiated by the Arkansas Center for Birth Defects Research and Prevention involves evaluating the risk of ventricular septal defects (a common type of heart defect) among the offspring of women who have used common over-the-counter medications during pregnancy. Other locally directed studies using NBDPS data include evaluating key risk factors for neural tube defects, heart defects, limb defects, and diaphragmatic hernia. Exploration of the relationship between dietary and genetic influences on folate metabolism and the risk for birth defects is an area of intense research effort at the Arkansas Center for Birth Defects Research and Prevention.

FOLATE METABOLISM AND BIRTH DEFECTS

In 2000, the Center received funding from the National Institute of Child Health and Human Development to study genetic susceptibilities and environmental causes of birth defects. This five-year study, "Genes, micronutrients and homeobox-related malformations," led by Dr. C.A. Hobbs, utilizes the infrastructure of the NBDPS, focusing specifically on neural tube defects and congenital heart defects.

Experimental data support the hypothesis that disturbances in normal folate metabolism during critical phases of early embryogenesis promote errors in gene expression and cell differentiation that result in tissue-specific malformations. The aims of this study are to define: (a) the gene-nutrient interactions that may increase susceptibility to neural tube and congenital heart defects; (b) specific biochemical and molecular biomarkers of maternal micronutrients and their interactions with genetic polymorphisms involved in the folate metabolic pathway; and (c) genetic alterations in homeobox genes associated with these defects and their interaction with maternal genetic and micronutrient status.

This study uses maternal interview data and DNA collected through the NBDPS, as well as dietary intake information and maternal blood samples. Obtaining funding for this study was a critical step in the recent development of the Center, advancing the technical capabilities, faculty composition, and contributions to key knowledge about how certain genetic and metabolic factors influence the risk of birth defects.

It is well established that 6-10 percent of women with diabetes give birth to infants with birth defects. This rate is approximately two to three times higher than that among non-diabetic women and accounts for about half of the perinatal morbidity and mortality in diabetes-affected pregnancies. Despite major advances in diabetes management, the rate of birth defects remains unacceptably high and the knowledge of the biochemical and molecular basis for malformation remains unacceptably low. The understanding of the pathogenic mechanisms and the eventual resolution of this clinical dilemma will depend upon knowledge gained from experimental and clinical models of diabetic embryopathy (malformation). Human genetic studies are also being developed to further define the inherited vulnerability to diabetic embryopathy.

GENETIC VULNERABILITY TO OXIDATIVE STRESS

An excess of oxygen free radicals in the non-pregnant diabetic patient has implicated the phenomenon has been published. Data from animal studies has shown that hyperglycemia harms the membranes surrounding embryos during development. However, dietary supplementation of inositol, safflower oil, or vitamin E, to diabetic pregnant rats can reduce the risk of diabetes-induced birth defects. This rate is approximately two to three times higher than that among non-diabetic women and accounts for about half of the perinatal morbidity and mortality in diabetes-affected pregnancies. Despite major advances in diabetes management, the rate of birth defects remains unacceptably high and the knowledge of the biochemical and molecular basis for malformation remains unacceptably low. The understanding of the pathogenic mechanisms and the eventual resolution of this clinical dilemma will depend upon knowledge gained from experimental and clinical models of diabetic embryopathy (malformation). Human genetic studies are also being developed to further define the inherited vulnerability to diabetic embryopathy.

Evoking collaborative opportunities to work with Dr. Reece are responsible for the development of this important research area at the Arkansas Center for Birth Defects Research and Prevention.
Most people have 23 pairs of chromosomes, the structures in cells that contain an individual’s genetic information, but children born with Down syndrome possess an extra copy of chromosome 21 (trisomy 21). The presence of this extra chromosome is associated with several clinical problems, including mental retardation. Down syndrome also increases the risk for congenital defects of the heart and gastrointestinal system, and for childhood leukemia.

The prevalence of Down syndrome in Arkansas is about 11 per 10,000 live births, and trisomy 21 can be a cause of pregnancy loss, or miscarriage. The health consequences of having this extra chromosome are known, but researchers do not know what causes the extra chromosome to be present. Maternal age is a risk factor for Down syndrome, with mothers who are older than 35 years of age having a dramatically higher risk, but the reasons for this increased risk are not yet understood.

THE NATIONAL DOWN SYNDROME STUDY

The Arkansas Center for Birth Defects Research and Prevention is participating in the National Down Syndrome Project, which is being led by researchers at Emory University in Atlanta, Georgia, and is funded by the National Institute for Child Health and Human Development. This study involves recruiting families with children affected by Down syndrome to complete a telephone interview related to dietary, environmental, and other exposures to the parents that might have affected the outcome of the pregnancy. The families also provide DNA samples for genetic analyses that may offer clues as to what contributes to the risk of Down syndrome. Until we find out more about the causes of this syndrome, we do not yet know if dietary or other control measures taken by parents may be preventive.

BIological MECHANISMS AND RISK OF Down SYNDROME

Although the chromosomal basis of Down syndrome has been known for more than 30 years, little is known about the underlying factors that lead to Down syndrome. Led by Dr. Jill James, researchers affiliated with the Arkansas Center for Birth Defects Research and Prevention have examined the association between folic acid metabolism and the risk of trisomy 21. Using case-control and case-parental studies, these investigators found that women who had a pregnancy affected by trisomy 21 were more likely to possess certain variations in genes (polymorphisms) related to metabolism of folic acid. These common variants may demonstrate an inherited genetic interaction that affects genetic and metabolic components of a developing fetus. These early findings are leading researchers to gain a better understanding of the possible roles of maternal and fetal genetic make-up and maternal dietary status in the development of Down syndrome.

DNA BANK FOR CONGENITAL MALFORMATIONS

Repositories of biological specimens from which DNA can be extracted are quickly becoming a prominent feature in the development of “cutting-edge” research in human genomics. In 2002, the Center obtained intramural funding to establish such a DNA repository for birth defects research. This DNA “bank” comprises samples of umbilical cord and peripheral blood from all neonates with birth defects born at UAMS or treated at Arkansas Children’s Hospital, and their parents. A bank of DNA extracted from blood samples of infants with congenital malformations and their parents will support several local and national collaborative studies.

THE GENOMICS LABORATORY

The capacity to perform genetic studies at the Arkansas Center for Birth Defects Research and Prevention was greatly enhanced in 2002, with the support of the Arkansas Biosciences Institute (ABI). The ABI, funded through state appropriations from national tobacco settlement revenues, stimulates important research into areas of health that are affected by the use of tobacco products. Work being done at the Genomics Laboratory will strengthen the comprehensive understanding of risk factors for certain birth defects, including the role of genetic susceptibility to maternal smoking during pregnancy.

For example, maternal smoking has been reported to increase the risk of some congenital heart defects, the most common category of birth defects. A family history of birth defects may increase a fetus’ susceptibility to the effects of maternal smoking. Other hypothesized risk factors include maternal nutrient intake, environmental exposures, variation in the sequence of genes related to maternal nutrient metabolism, and variation in the sequence of genes that are involved in heart formation during early development.

Researchers at the Center seek a better understanding of the association between genetic sequence variations and other risk factors for congenital heart defects, in order to improve diagnosis, treatment, and prevention of these common defects. The Genomics Laboratory is located at the Arkansas Children’s Hospital Research Institute, and will play a key role in all of the major studies currently underway at the Arkansas Center for Birth Defects Research and Prevention. This state-of-the-art facility and its talent faculty and staff comprise an invaluable asset, reinforcing the competitive position of the Center for continued acquisition of long-term research funding.
Glossary of Terms

Anencephalus: a fatal defect involving absence of most of the brain and/or spinal cord

Aortic valve stenosis: narrowing of the valve between the left ventricle (lower chamber) of the heart and the major vessel carrying blood from the heart

Atrial septal defect: a hole in the wall of the heart between the right atrium and left atrium, the upper chambers of the heart

Bilary atresia: absence or closure of the bile ducts from the liver and gall bladder, blocking normal secretion of bile fluid

Choanal atresia: abnormal closure of the opening at the back of the nose, preventing or blocking breathing through the nose

Cleft lip with & without cleft palate: a split through the lip, sometimes extending into the roof of the mouth (hard and soft palate), caused by incomplete closure of these structures during development

Cleft palate without cleft lip: a split in part or the entire roof of the mouth (palate), occurring without a split in the lip

Coarctation of aorta: a constriction or narrowing of the aorta, the main blood vessel carrying blood from the heart to the rest of the body

Congenital cataract: a condition where the lens or capsule of the eye is obscured, causing impairment of vision or blindness in the newborn

Diaphragmatic hernia: the absence or a defect of the membrane between the chest cavity and the abdomen, allowing protrusion of organs such as the intestines into the chest

Down Syndrome: also called trisomy 21, this disorder is caused by the presence of an extra 21st chromosome, causing mild to moderate mental retardation, short stature, and a flattened face-shape; about 40 percent of babies with this condition also have congenital heart defects, and many have some visual and hearing impairment and/or various other health problems

Ebstein's anomaly: improper placement of the heart valve that normally keeps blood in the right ventricle from flowing backward into the right atrium; a portion of the right ventricle is located on the atrial side of the valve

Encephalocele: a gap or hole in the skull that usually results in a protrusion of brain tissue

Endocardial cushion defect: a defect or hole in the connecting tissue that divides the right and left chambers of the heart, between either the atria (upper chambers) or ventricles (lower chambers)

Esophageal atresia / tracheoesophageal fistula: these defects involve abnormal closure of, or abnormal holes within the esophagus, the tube between the mouth and the stomach, or within the trachea (windpipe)

Gastroscisis: a hole of the abdominal wall, causing protrusion of the digestive organs from the outside of the body

Hypoplastic left heart syndrome: incomplete development of the left chambers of the heart; one of the most life-threatening heart defects

Hypospadias & epispadias: abnormal development of the tube carrying urine from the bladder to the outside of the body (urethra), in which part of the urethra is open on the upper surface of the penis, or where the urethra opens into the vagina

Obstructive genitorinary defect: a malformation that blocks, by clumping or narrowing, the passageways of the genital or urinary tracts (such as the urethra)

Omphalocele: protrusion of abdominal organs through an enlarged opening at the base of the umbilical cord

Pulmonary valve atresia & stenosis: abnormal closure, absence, or narrowing of the duct that opens into the pulmonary artery, the vessel that carries blood to the lungs

Rectal & large intestinal atresia / stenosis: abnormal closure, absence, or narrowing of the duct or passageway of the digestive tract in the region of the rectum or large intestine

Reduction deformity, upper or lower limbs: deformity of the arms or legs, in which one or both arms or legs are shortened or missing

Renal agenesis / hypoplasia: a defect where the kidney never formed, or formed incompletely; this is a fatal defect if both kidneys are affected

Spina bifida: a defect in which the spinal column is imperfectly closed so that part of the spinal cord can protrude, often resulting in neurological disorders

Transposition of great arteries: a defect in which the aorta arises from the right ventricle and the pulmonary artery from the left ventricle, exactly opposite that of normal development

Trisomy 13 / Trisomy 18: the condition of having three copies of chromosome 13 or 18, conditions causing severe skull and facial deformation and mental retardation; most infants with either of these conditions do not survive past the first year of life

Truncus arteriosus: a complex congenital heart defect involving the heart valve that normally keeps blood in the right ventricle from flowing backward into the right atrium

Ventricular septal defect: a defect or hole in the septum (wall) between the right ventricle and the left atrium, the upper chambers of the heart, between either the atria (upper chambers) or ventricles (lower chambers)

Aortic valvular atresia / stenosis: absence or closure of the three-segmented valve of the heart that normally keeps blood flowing from the right ventricle into the right atrium

Bilateral cleft lip & palate: a split through the lip, sometimes extending into the roof of the mouth (hard and soft palate), caused by incomplete closure of these structures during development

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