



Review Article

BIRTH DEFECT: AN OVER VIEW

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Abstract

Birth defects are a leading cause of infant death, accounting for more than 1 of every 5 infant deaths. Every year more than 8.14 million children are born with a serious birth defect, due to genetic or environmental causes. In the low and middle income countries the burden of birth defects is much higher than in high-income countries. Birth defects may be due to chromosomal, single-gene or multifactorial causes. Environmental factors are responsible for 5–10% of total birth defects, and include nutritional deficiencies, infectious diseases, maternal medical conditions, teratogenic medications, alcohol, recreational drugs, and teratogenic pollutants. Birth defects can be diagnosed during pregnancy or after the baby is born, depending on the specific type of birth defect. Of course, many birth defects cannot be prevented; this is especially true of defects that have a genetic component. However, ultrasonography and maternal serum screening can be used to detect serious foetal anomalies, including neural tube defects and chromosomal disorders. Early detection and treatment of birth defects can help prevent stillbirth or physical and intellectual disabilities.

Key words: Birth defects, Congenital anomalies

Introduction

Birth defects are defined as abnormalities of structure, function, or body metabolism that are present at birth¹.

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Birth defects are a leading cause of infant death, accounting for more than 1 of every 5 infant deaths¹⁻². In addition, babies born with birth defects have a greater chance of illness and long term disability than babies without birth defects³. About 150,000 babies are born with birth defects each year in the United States⁴. The American College of Obstetricians and Gynecologists (ACOG) says that 3 out of every 100 babies born in the United States have some kind of birth defect.

Causes of birth defects

According to the March of Dimes, about 60% of birth defects have unknown causes. The rest are caused by environmental or genetic factors, or some combination of the two. Every year more than 8.14 million children are born with a serious birth defect, due to genetic or environmental causes⁴. Hundreds of thousands more are born with serious birth defects of post conception origin, including maternal exposure to environmental agents (teratogens) such as alcohol, rubella, syphilis and iodine deficiency that can harm a developing foetus. Serious birth defects can be lethal. For those who survive, these disorders can cause lifelong mental, physical, auditory or visual disability⁵⁻¹⁰.

Genetic causes

Chromosomes contain genes that determine a person's unique characteristics. Missing or faulty gene can cause a birth defect. An estimated 7.9 million children are born annually with a serious birth defect of genetic or partially genetic origin. More than 7,000 single gene defects have been described worldwide¹¹. In high-income countries, single gene defects affect approximately one percent of the

population. These countries have a cumulative birth prevalence of 3.6 per 1,000 live births and account for up to 7.5 percent of all birth defects in industrialized countries¹²⁻¹³.

Chromosomal defect

Alteration in the number or structure of chromosomes also can cause birth defects. Birth defects caused by chromosome problems include Down syndrome. The increasing risk of chromosomal abnormalities, particularly Down syndrome, with advancing maternal age is well recognized. Birth prevalence may be as high as 2-3 per 1,000 live births in middle- and low-income countries and as low as 1.2 per 1,000 live births in high-income countries. An estimated 217,300 infants with Down syndrome are born each year¹⁴⁻¹⁵.

Environmental causes

Environmental factors are responsible for 5–10% of total birth defects, and include nutritional deficiencies, infectious diseases, maternal medical conditions, teratogenic medications, alcohol, recreational drugs, and teratogenic pollutants¹⁶.

Multifactorial birth defects

This category is caused by a combination of genetic and environmental factors and accounts for an estimated 20-30 percent of all birth defects, a number

of which are lethal¹². Examples of multifactorial birth defects are numerous, are usually malformations of a single organ system or limb, and include congenital heart disease, neural tube defects, cleft lip and/ or cleft palate, clubfoot and developmental dysplasia of the hip.

Infections That Cause Birth Defects

Infections during pregnancy can cause a variety of birth defects. Examples include:

Congenital rubella

Rubella poses a serious threat to the foetus if the mother contracts it during the first 16 weeks of pregnancy. About 25 percent of babies whose mothers contract rubella during the first trimester of pregnancy are born with one or more birth defects, which, together, are referred to as congenital rubella syndrome (CRS). Congenital rubella syndrome is characterized by vision and/or hearing loss, heart defects, mental retardation, and cerebral palsy^{4,17}. After the fourth month, the mother's rubella infection is less likely to harm the developing baby. The number of babies born with congenital rubella has decreased dramatically since the introduction of the rubella vaccine¹⁸. Pregnant women who are not vaccinated for rubella and who have not had the disease in the past are at risk infecting themselves and their unborn baby.

Table-I
Causes, classification, and examples of selected birth defects

Cause	Classification	Birth defect examples
Genetic	Chromosomal	Down syndrome, Trisomy 18, Trisomy 13
	Single gene	thalassemia, sickle cell disorder, G6PD deficiency, albinism, cystic fibrosis, PKU, haemophilia A and B
Environmental (teratogenic)	Infectious Disease	Congenital rubella syndrome, congenital cytomegalovirus, toxoplasmosis
	Maternal nutritional deficiencies (folic acid, iodine)	NTDs, iodine deficiency disorder
	Other maternal illness	Insulin – dependent diabetes mellitus, PKU
	Medications: thalidomide, misoprostol, anticonvulsants, anticoagulants	Deformities of limbs
	Recreational drugs: alcohol	Several Neurological damage, foetal alcohol syndrome
	Pollutants: organic mercury	Neurological damage
Complex genetic and unknown	Congenital malformations involving single-organ systems	Congenital heart disease, NTDs, cleft lip and/ or palate, talipes (clubfoot), developmental dysplasia of the hip

Source: Modified from Bale, Stall and Lucas (2003)

Toxoplasmosis

Toxoplasmosis is a relatively widespread parasitic infection. A pregnant woman who contracts toxoplasmosis for the first time has about a 40 percent chance of passing the infection to her foetus. However, the risk and severity of the baby's infection depend on the time in the pregnancy when a mother's infection occurs. When mothers are infected in the first trimester, about 15 percent of fetuses become infected, compared to about 30 percent in the second trimester and about 60 percent in the third. However, the consequences of the foetal infection are more severe when the infection occurs earlier in pregnancy¹⁹. Toxoplasmosis infection of the mother can result in eye infections that threaten vision, hearing loss, learning disabilities, enlarged liver or spleen, mental retardation, and cerebral palsy in the infant^{4,20-21}.

Congenital varicella syndrome, which is caused by chickenpox, can lead to scars, defects of muscle and bone, malformed and paralyzed limbs, a smaller-than-normal head, blindness, seizures, and intellectual disability. This syndrome affects about 2 percent of babies whose mothers are infected with varicella during the first 20 weeks of pregnancy, but is rare if infection occurs after 20 weeks²².

Cytomegalovirus (CMV) is a virus that, if contracted by a woman during pregnancy, can lead to low birth weight, intellectual disability or learning disabilities, and hearing loss. Cytomegalovirus (CMV) infection is the most common congenital infection in high-income countries. About 10 percent of infected newborns have symptomatic CMV disease. Of these, most who survive suffer from progressive deafness and/or intellectual disability. An estimated four per 10,000 newborns are affected in middle- and low-income countries²³.

Congenital syphilis

Syphilis is a common sexually transmitted infection. Over 11 million new infections occur each year worldwide. In Haiti, 52 percent of infants with congenital syphilis die before their first birthday. Those who survive are at risk for brain damage, blindness, hearing loss, and bone and tooth problems if they are not treated with an antibiotic shortly after birth. Congenital syphilis is a major cause of neonatal mortality, particularly in many middle- and low-income countries²⁴⁻²⁶.

Common Birth Defects

Cleft lip and/or palate

This condition occurs when the tissues of the mouth or lip don't form properly during fetal development.

Clefts occur more frequently in children of Asian, Latino, or Native American descent. A number of potentially causative genes are under investigation though certain drugs and maternal smoking are considered to play a role²⁷⁻²⁸. Clefting is a birth defect that can be surgically repaired after birth.

Clubfoot

This is a relatively common birth defect, boys are affected almost twice compared to as girls. In most cases the cause is unknown, but some cases of clubfoot happen as a result of a genetic disorder, or problems inside a mother's uterus (oligohydramnios) that can affect or restrict the development of baby's foot²⁹.

Congenital hypothyroidism,

This condition occurs in about 1 in 3,000 to 4,000 births, results when the baby's thyroid gland is absent or underdeveloped at birth or if there is a metabolic defect blocking production of thyroid hormone. This causes the infant to be unable to produce adequate amounts of thyroid hormone, which is important for supporting normal growth and brain development. Developmental delay and permanent intellectual disability can result if the condition is not recognized and treated within the first few weeks of life. For this reason routinely screening of all newborns for the condition should be done shortly after birth³⁰⁻³¹.

Fetal alcohol syndrome

Fetal alcohol syndrome (FAS) is a condition that results from alcohol exposure during pregnancy. FAS include physical deformities, mental retardation, learning disorders, vision difficulties and behavioral problems. The problems caused by foetal alcohol syndrome vary from child to child, but defects are irreversible. There is no amount of alcohol that's known to be safe to consume during pregnancy. Every year between 2,000 and 12,000 babies in the United States are estimated to be born with defects caused by alcohol. FAS cannot be cured or treated, but can be prevented by avoiding alcohol intake during pregnancy³²⁻³³.

Neural tube defects (NTDs)

Spina bifida and anencephaly are the two most common forms of NTDs; an estimated 300,000 babies born with NTDs worldwide each year³⁴. Neural tube defects constitute one of the common forms of multifactorial congenital malformation, with recorded

birth prevalence as high as six per 1,000 live births in China, but varying widely depending on genetic and environmental conditions³⁵⁻³⁶. Studies have shown that the frequency of these defects may be substantially reduced when the mother gets enough folic acid before and during pregnancy, especially during the first trimester³⁷⁻⁴⁰.

Defects of the Heart

Congenital heart defects are the most common form of birth defect, occurring in 4-8 per 1,000 live births. The majority of congenital heart defects (about 90%) have a multifactorial cause. The remaining congenital heart defects are associated with chromosome abnormalities (5-8 percent), single gene defects (3-5 percent) and teratogens (2-3 percent). An estimated 1,040,800 infants are born each year with a multifactorial congenital heart defect⁴¹⁻⁴². Common heart defects include: atrial and ventricular septal defects, patent ductus arteriosus, aortic or pulmonary valve stenosis, coarctation of the aorta, transposition of the great arteries, hypoplastic left heart system, Tetralogy of Fallot etc.

Defects of the Gastrointestinal Tract

The frequencies of these disorders vary, ranging from 1 in 32,000 births to 1 in 10,000 births. Genetics play some role in all these defects, but it is unclear exactly what role or to what degree.⁴³⁻⁴⁴ Some of these defects are: esophageal atresia, diaphragmatic hernia, pyloric stenosis, Hirschsprung's disease, gastroschisis and omphalocele, anal atresia, biliary atresia

Diagnosis

Birth defects can be diagnosed during pregnancy or after the baby is born, depending on the specific type of birth defect.

Prenatal Testing

Screening Tests

During pregnancy, high risk pregnant women are usually offered these screening tests to check for birth defects or other problems for the woman or her baby.

First Trimester Screening

First trimester screening is a combination of tests completed between weeks 11 and 13 of pregnancy. It is used to look for certain birth defects related to the baby's heart or chromosomal disorders, such as Down

syndrome. This screen includes a maternal blood test and an ultrasound.

- **Maternal Blood Screen**
It measures the levels of two proteins, human chorionic gonadotropin (hCG) and pregnancy associated plasma protein A (PAPP-A). If the protein levels are abnormally high or low, there could be a chromosomal disorder in the baby.
- **Ultrasound**
The ultrasound for the first trimester screen looks for extra fluid behind the baby's neck. If there is increased fluid found on the ultrasound, there could be a chromosomal disorder or heart defect in the baby.

Second Trimester Screening

Second trimester screening tests are completed between weeks 15 and 20 of pregnancy. They are used to look for certain birth defects in the baby. Second trimester screening tests include a maternal serum screen and a comprehensive ultrasound evaluation of the baby looking for the presence of structural anomalies.

- **Maternal Serum Screen**
The maternal serum screen is a simple blood test used to identify if a woman is at increased risk for having a baby with certain birth defects, such as neural tube defects or chromosomal disorders such as Down syndrome. It is also known as a "triple screen" or "quad screen" depending on the number of proteins measured in the mother's blood. For example, a quad screen tests the levels of 4 proteins AFP (alpha-fetoprotein), hCG, estriol, and inhibin-A. Generally, the maternal serum screen is completed during the second trimester.
- **Anomaly Ultrasound**
This test is usually completed around 18–20 weeks of pregnancy. The ultrasound is used to look for birth defects or other problems with the baby.

Diagnostic Tests

If the result of a screening test is abnormal, diagnostic tests are done to determine if birth defects or other possible problems with the baby are present. These diagnostic tests are also offered to women with higher risk pregnancies, which may include women who are 35 years of age or older; women who have had a previous pregnancy affected by a birth defect.

High resolution Ultrasound

This ultrasound, also known as a level II ultrasound, is used to look in more detail for possible birth defects or other problems with the baby that were suggested in the previous screening tests. It is usually completed between weeks 18 and 22 of pregnancy.

Chorionic Villus Sampling (CVS)

CVS is a test where the doctor collects a tiny piece of the placenta, called chorionic villus, which is then tested to check for chromosomal or genetic disorders in the baby. Generally, a CVS test is offered to women who received an abnormal result on a first trimester screening test or to women who could be at higher risk. It is completed between 10 and 12 weeks of pregnancy, earlier than an amniocentesis.

Amniocentesis

An amniocentesis is test where a small amount of amniotic fluid is collected and tested to measure the baby's protein levels, which might indicate certain birth defects. Cells in the amniotic fluid can be tested for chromosomal disorders, such as Down syndrome, and genetic problems, such as cystic fibrosis or thalasaemia. Generally, an amniocentesis is offered to women who received an abnormal result on a screening test or to women who might be at higher risk. It is completed between 15 and 18 weeks of pregnancy. Below are some of the proteins for which an amniocentesis tests.

- **AFP**
AFP stands for alpha-fetoprotein, a protein the unborn baby produces. A high level of AFP in the amniotic fluid mean that the baby might has a neural tube defect (spina bifida), or a body wall defect.
- **AChE**
AChE stands for acetylcholinesterase, an enzyme that the unborn baby produces. This enzyme can pass from the unborn baby to the fluid surrounding the baby if there is an opening in the neural tube.

After the Baby is Born

Certain birth defects might not be diagnosed until after the baby is born. Sometimes, the birth defect is immediately seen at birth. For other birth defects including some heart defects, the condition might not be diagnosed until later in life. When there is a health problem with a child, the pediatric specialist might

look for birth defects by taking a medical and family history, doing a physical exam, and sometimes recommending further tests. If a diagnosis cannot be made after the exam, it may need to refer the child to a specialist in birth defects and genetics. Even if a child is evaluated by a specialist, sometime an exact diagnosis might not be reached.

Prevention of Birth Defects

Many birth defects can't be prevented; however some precautions can be taken before and during pregnancy:

Before pregnancy

Pre-conception counseling is a meeting with a health-care professional of a woman *before* attempting to become pregnant. It generally includes a pre-conception risk assessment for any potential complications of pregnancy as well as modifications of risk factors, such as increasing folic acid intake to reduce the risk of neural tube defects and counseling on smoking cessation, alcohol reduction, and medications that may compromise fetal development⁴⁵. Physicians recommend that a woman visit her physician as soon as the woman is contemplating having a child, and optimally around 3 to 6 months before actual attempts are made to conceive. If the women have any medical disorder and taking some drugs, consultation with her physician and changing to more safe drugs will help to prevent birth defect⁴. If the women have a history of any kind of birth defects in her family, if she has already had a child with a birth defect, or if she is part of a high-risk group (advance age, ethnic background, or medical history), consider consulting a genetic counselor before she get pregnant. Genetic testing and screening are becoming increasingly useful aspects of pre-pregnancy planning and pregnancy. A genetic counselor can give one advice about prenatal testing and help to deal with any concerns or fears one might have.

During pregnancy

The best thing that pregnant women can do to increase their likelihood of having a healthy baby is to make sure they take care of their bodies during pregnancy by:

Folic acid

Folic acid is a B vitamin, evidences shows that to take 0.4 mg of folic acid every day prevents NTD. If a woman has enough folic acid in her body at least 1

month *before* and *during* pregnancy, it can help prevent major birth defects of the baby's brain and spine (anencephaly and spina bifida). All women of child bearing age who are capable of being pregnant should consume 0.4 mg of folic acid daily. On the other hand woman with a previous pregnancy resulting in a foetus affected by NTD should consume 4mg folic acid daily to reduce the risk of recurrence of NTD by 72%³⁹⁻⁴⁰.

Not to drink alcohol any time during pregnancy

Alcohol in the woman's blood passes through the placenta to her baby through the umbilical cord. There is no known safe amount of alcohol to drink while pregnant. There also is no safe time during pregnancy to drink and no safe kind of alcohol. Drinking alcohol during pregnancy can cause a baby to be born with a fetal alcohol spectrum disorder (FASD)³²⁻³³.

Not to smoke during pregnancy

The dangers of smoking during pregnancy include premature birth, certain birth defects (cleft lip or cleft palate), and infant death. Even being around cigarette smoke puts a woman and her unborn baby at risk for problems. Quitting smoking before getting pregnant is best. But for a woman who is already pregnant, quitting as early as possible can still help protect against some health problems for the baby, such as low birth weight²⁷⁻²⁸.

Not to use "street" drugs

A woman who uses illegal—or "street"—drugs during pregnancy can have a baby who is born premature; is low birth weight; or has other health problems, such as birth defects. A woman who uses cocaine while pregnant is more likely to have a baby with birth defects of the arms, legs, urinary system, and heart³²⁻³³. If a woman use "street" drugs, consultation with doctor about quitting before she get pregnant is important.

To consult a health care provider about taking any medications

Taking certain medications during pregnancy can cause serious birth defects, but the safety of many medications taken by pregnant women has been difficult to determine. So before planning pregnancy consultation with physician is of utmost importance, who will help her by prescribing a safer drug during pregnancy period.

Prevention of infections

Some infections (TORCH) that a woman can get during pregnancy can be harmful to the unborn baby¹⁷⁻²⁰.

Vaccinations

Many vaccinations are safe and recommended during pregnancy, but some are not. Having the right vaccinations at the right time can help keep a woman and her baby healthy.

Control of diabetes before pregnancy

Poor control of diabetes during pregnancy increases the chances for birth defects and other problems for the baby. It can also cause serious complications for the woman. Proper control of diabetes mellitus before and during pregnancy can help prevent birth defects and other poor outcomes⁴⁶⁻⁴⁸.

To achieve and maintain a healthy weight

A woman who is obese (a BMI more than 30) before pregnancy is at a higher risk for complications during pregnancy. Obesity in the woman also increases the risk of several serious birth defects for the baby⁴⁹⁻⁵⁰.

If one is overweight or obese, consultation with doctor about ways to reach a healthy weight before getting pregnancy is vital.

Regular prenatal Care

A woman should be sure to consult her doctor when planning a pregnancy and start prenatal care as soon as she thinks that she is pregnant. It is important to consult the doctor regularly throughout pregnancy.

Detection and Early Treatment of Birth Defects

Of course, many birth defects cannot be prevented; this is especially true of defects that have a genetic component. However, ultrasonography and maternal serum screening can be used to detect serious fetal anomalies, including neural tube defects and chromosomal disorders. In addition, after birth, infants can be screened for a variety of genetic, hematological, metabolic, and hormonal disorders to provide early diagnoses.

Early detection and treatment of birth defects can help prevent stillbirth or physical and intellectual disabilities. Without early testing, a diagnosis of hearing loss might not occur until a child is two or three years old, resulting in delayed speech and language development

Surgery can also be used to treat many birth defects, including cleft lip and palate and spina bifida, sometimes even before a child is born. The idea behind prenatal surgery is to limit long-term damage through

early intervention. Prenatal heart and renal-tract defects are often treated surgically while the child is still in the womb, providing decompression and early correction for a better developmental prognosis. Finally, although gene therapy is also a possible option for treating certain genetic defects, it is not yet used on a wide scale.

Conclusion

Although many birth defects cannot be prevented, the probability of some such conditions can be reduced through awareness of the effects of various prenatal factors, including nutrients, teratogens, and mutagens. Furthermore, early detection and/or treatment of congenital defects can sometimes reduce the long-term impact of these conditions, perhaps even alleviating them completely.

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