Vivante
Midwifery & Women's Health

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Prenatal Testing and Genetic Counseling

Every parent hopes to have a healthy child. The good news is that most babies are born healthy. However, there are occasions where a genetic disease or birth defect may occur or the possibility of a birth defect might exist. In these cases, you may be given the choice of having one or several special tests done. This information will explain the most common types of birth defects, and some of the tests that would detect these conditions.

GENETIC COUNSELING

During a genetic counseling appointment, you will meet with an experienced professional genetic counselor and be asked questions about your family history, ethnicity, personal health and pregnancy history. The accuracy and appropriateness of prenatal diagnostic, genetic screening and other tests will vary depending on your individual health and family history. All of your specific questions about testing options will be reviewed. Depending on the number of questions or complexity of the family history, the counseling session may take 30 to 60 minutes. Your genetic counselor may provide you with the option of having testing performed, if appropriate, on the same day. However, you may need additional time to consider the information given to you or you may desire to speak with other family members or trusted advisors. In those cases, an appointment for testing will be made on a separate day. The goal of prenatal counseling is to give you the information you need to reach a decision. You will not be told what to do, but be helped in sorting through the complex information and choices that exist. Deciding to have a test done or deciding not to have a test done are both equally valid choices. The goal is to ensure that you and your family are comfortable with your decision and that you feel you made an informed choice.

You may desire prenatal genetic counseling for any of the following:

- you or your partner have a genetic disorder or birth defect
- you will be 35 years of age or more at the time of expected delivery
- you or your partner have a previous child with a birth defect or genetic condition
- you have experienced a stillbirth or multiple miscarriages with no known explanation
- you have a medical condition such as epilepsy or insulin-dependent diabetes that requires that you take medications
- you, your partner, or someone in your family have a child with mental retardation or developmental delay

- you want to know more about testing for recessive genetic diseases that are common for certain ethnic backgrounds (for example, sickle cell disease, Tay-Sachs disease, cystic fibrosis)
- you have a positive screening test result, such as the combined screen
- you have had an ultrasound examination that reveals a physical abnormality or variation in the fetus
- you have concerns about the chance of having a child with a birth defect or genetic disease and wish to learn more about available testing

COMMON BIRTH DEFECTS

There are three common causes of birth defects: **multifactorial, single gene disorders and chromosomal.**

Multifactorial*.* The most common birth defects are those that occur due to a combination of factors in the outside environment and some maternal or hereditary traits. These birth defects are usually called multifactorial, referring to the many different factors that come together to cause the problem. Two of the most common birth defects, congenital heart defects and cleft lip, are usually multifactorial conditions. Almost 1 child in 200 is born with a congenital heart defect and 1 in 500 with cleft lip. Another multifactorial condition is **spina bifida,** also known as an open neural tube defect. Spina bifida occurs in approximately 1 in 500 to 1 in 1000 births. Taking the vitamin folic acid may help reduce the chance of having a baby with spina bifida. You may wish to discuss this with your midwife.

An **ultrasound** examination of the fetus, performed between the 18th and 22nd weeks of pregnancy, may detect some of the more obvious multifactorial birth defects. Spina bifida, because it causes the spinal column to be open, may be detected by measuring a special protein in the mother's blood or the amniotic fluid. This protein is called **alpha-fetoprotein (AFP)** and is discussed in more detail under the prenatal screening section.

Single Gene Disorders*.* Normally, humans have 2 copies of each gene in our DNA. One copy is inherited from our mother and one from our father. Some birth defects are caused by changes directly in the genetic information. These changes are referred to as gene mutations. All of us carry some gene mutations. Most of these mutations do not affect our health, because the second copy of the gene functions well enough to compensate for the mutated gene. For certain genes, one of the genes having a mutation is enough to causes a disease to occur. We refer to these conditions as **dominant genetic diseases**. An example of a dominant genetic disease is Huntington disease. Unless a parent has a dominant genetic disease, the chance that a baby will have a dominant disease is very small, though not impossible. For some dominant genetic diseases, there may be specific DNA tests that could diagnose the disease. This is not true for all dominant genetic diseases, but it would be very important to discuss any concerns you may have about your family health history with your midwife or other health care provider.

Many genetic diseases only occur if both genes carry a mutation. These diseases are referred to as **recessive** genetic diseases. People who have only one copy of a recessive gene are healthy, but are referred to as a carrier of that disease. All of us are **carriers** of some recessive genetic disease. Most of these diseases are quite rare. It is not possible to anticipate if a rare recessive disease may occur, as there is almost never any family history suggestive of the condition and carrier screening is frequently not available. Fortunately, rare recessive diseases occur at a rate of 1 in

50,000 to 1 in 100,000 births, so the likelihood of any of these recessive conditions is quite low.

Condition	Carrier rate	High risk group
Cystic fibrosis	1 in 25	Caucasian
Sickle cell anemia	1 in 12	Black
Tay-Sachs disease	1 in 30	Ashkenazi Jewish
Beta-thalassemia	1 in 25	Greek/Italian
Alpha-thalassemia	1 in 22	Asian

Carrier tests do exist for most of these conditions. Please ask your health care provider for more information.

Chromosomal Disorders*.* The last major cause of birth defects are abnormalities involving the chromosomes. The chromosomes are the individual structures within which all of the genes are located. One way of understanding the difference between genes and chromosomes is to think of the chromosome as a book and the genes as the pages within the book. You cannot tell from looking at the outside of the book if all the pages are in the right order. In the same way, you cannot tell from looking at an intact chromosome if all of the genes are there and working. Tests that look at the genes do not tell you about the chromosomes and chromosome tests do not tell you about the genes.

A normal human cell should contain exactly 46 chromosomes. There are 23 pairs of the chromosomes. 22 of these pairs are numbered from the largest to the smallest, and are the same in men and women. The 23rd pair is referred to as the sex chromosome pair. Women normally have 2 of the same type, called an X chromosome, while men have 2 different chromosomes, one of which is an X and the other is called the Y. The shorthand way to refer to a normal set of chromosomes is 46, XX for women and 46, XY for men.

In order to analyze the chromosomes, a sample of blood or other tissue that contains cells is needed. Almost any type of cell could be used to look at the chromosomes. First the cells are allowed to divide, and then the cell is stopped at the best point to see the chromosomes. The cell is stained to make the chromosomes visible, the chromosomes are examined, and the numbers of chromosomes are counted. Photographs are taken of the cells. These pictures are then used to match the pairs of chromosomes together and the organized picture of the chromosomes is called a **karyotype**. An example of a normal karyotype is shown in Figure 1.

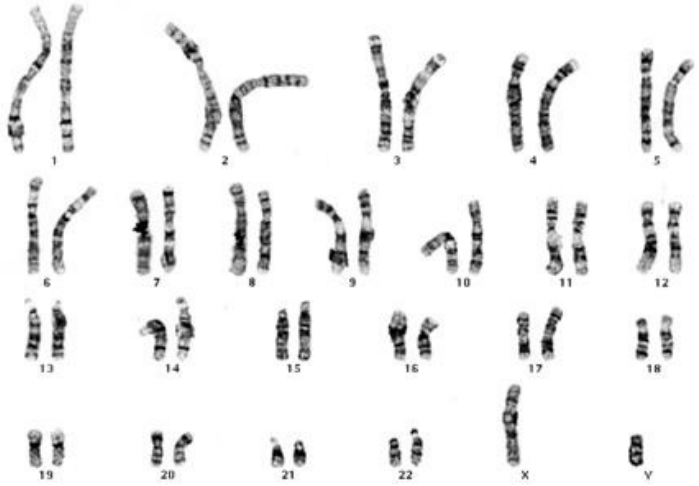

Figure 1

There are two major ways in which chromosomes may be abnormal. The first type of chromosome abnormality occurs when there are either too many or too few chromosomes. In a normal pregnancy, both the egg and the sperm should contribute exactly 23 chromosomes. When these 2 cells fuse, there are then exactly 23 pairs, or 46 individual chromosomes. Occasionally, a pregnancy may occur in which either the egg or the sperm has either 22 or 24 chromosomes. This would result in either 45 or 47 chromosomes in the fetus, not the normal 46. The most common example of this is **Down Syndrome**. In Down syndrome there is an extra copy of chromosome #21, creating a total of 47 chromosomes. For this reason, it is also known as **trisomy 21**. An example of a karyotype in Down syndrome is shown in figure 2.

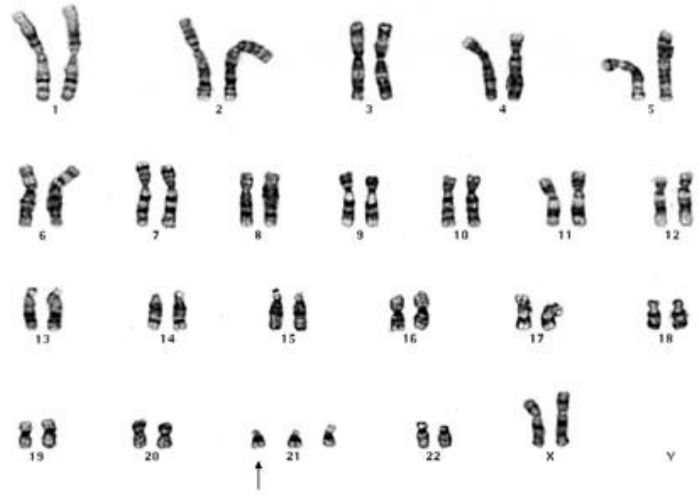

Figure 2

The most common type of Down syndrome is not inherited through the family. Even if there is no family history of Down syndrome, there are sporadic risks that increase with advancing maternal age. It is not known why an egg or a sperm may carry an extra copy of a chromosome. It is well known that as a woman gets older, the chance that she may have an abnormal pregnancy involving an extra or missing chromosome increases. Women's egg cells are in their bodies from the time they are born. If a woman is 20 years of age, her egg cells are also 20 years old. If a woman is 40, her egg cells are also 40. Sperm cells are newly made every day and have fewer aging issues. Down syndrome and other chromosome abnormalities may happen at any age, but increase each year along with a woman's age. A table showing how those risks change is listed below:

BIRTH RATES FOR CHILDREN WITH CHROMOSOMAL ABNORMALITIES (INCLUDING

DOWN SYNDROME) -- APPROXIMATE RISKS

Age 20 = 1 in 525
Age 25 = 1 in 475
Age 30 = 1 in 380
Age 35 = 1 in 180
Age 38 = 1 in 105
Age 40 = 1 in 65
Age 42 = 1 in 40
Age 45 = 1 in 20

A second type of chromosome problem is called a structural chromosome abnormality. Structural problems occur when a piece or portion of a chromosome is missing or extra or has attached to another chromosome. Common chromosome structural problems are **chromosome translocations**, where 2 chromosomes exchange pieces. Many times there may be a history of several miscarriages when a chromosome translocation is present. Structural chromosome rearrangements may be carried by the mother or the father in their cells – this is called a familial chromosome rearrangement. Other times, the structural problem may have occurred for the first time in the fetus, which causes concerns about possible birth defects. This is referred to as a *de novo* (first time) chromosome rearrangement. Tests that are used to look at the chromosomes are usually able to detect both abnormalities in the chromosome number and many structural chromosome abnormalities. There is no association of an increased risk for structural abnormalities with maternal age.

PRENATAL SCREENING AND DIAGNOSTIC TESTING

It is important to understand the differences between screening tests and diagnostic tests. A **screening test** does not give you a yes or no answer; it tells you if your risk is at an average level, above average or possibly below average chance of occurring. A **diagnostic test** gives you a more definite answer. If you have an abnormal result from a screening test, you most likely have a healthy pregnancy, but you may want to have a diagnostic test performed to get more detailed information. A normal result on a screening test does not mean you have a healthy pregnancy, but your chances of having a baby with certain problems are lower than most.

The most commonly used screening test for birth defects is called the **alpha fetoprotein (AFP)** test. This test is performed by analyzing a small amount of the blood from a pregnant woman, most commonly between 15th and 20th weeks in the pregnancy. AFP is a protein that is made only by the fetus while it is developing. AFP is present in a high concentration in the blood of the fetus and also in the spinal fluid. For this reason, a higher level than average of the AFP (elevated AFP) is used as a screening test for spina bifida and anencephaly, which together are known as open neural tube defects. These birth defects occur during the 3rd and 4th weeks of fetal development, and are caused by the failure of the neural tube (spinal column) to close completely. Open neural tube defects occur in approximately 1 to 2 per 1,000 births. Measuring the level of AFP in the mother's blood would detect about 85% of these open neural tube defects. Studies indicate that women who take folic acid on a regular basis before getting pregnant and in early pregnancy may reduce this risk by 50%. It is important to talk to your midwife or health care provider about this finding.

AFP is also affected by the presence of a fetus with Down syndrome. Two other hormones, called **hCG (human chorionic gonadotropin)** and estriol are also affected. A fetus with Down syndrome creates a pattern of lowered AFP, raised hCG and low-

ered estriol. Measuring all three of these substances together is called the **multiple marker screening**, or the **AFP triple marker screening**. This test will detect approximately 60-65% of pregnancies with Down syndrome. However, around 5% of normal pregnancies will have test results that are considered "abnormal", even when the fetus is actually healthy. ***These represent false-positive screening results. For all of these reasons, it is important not to make decisions about a pregnancy based only on the AFP blood test.*** A positive AFP screening result only indicates that the pregnancy is at higher risk than originally believed and that additional, more definitive fetal testing such as amniocentesis should be considered.

A newer screening test offered in the first trimester of pregnancy (between the 11th to 14th weeks) combines ultrasound screening with maternal blood testing. This is called the **integrated screen**. This screening begins with a maternal blood test and an ultrasound examination in the first trimester that takes a measurement of the fetal neck called a **nuchal translucency** measurement, followed by another maternal blood test in the second trimester. Elevated nuchal translucency measurements may indicate a chromosomal condition, a congenital heart defect or other birth defect, but may also be seen in normal fetuses. Maternal blood tests in the first and second trimesters measure certain pregnancy hormones, such as hCG, and pregnancy proteins and are combined with the ultrasound measurement for a more specific calculation of risk for Down syndrome. Results are not reported until after the second-trimester blood draw has been done. Data gathered to date suggests that the combination of ultrasound and first- and second-trimester blood screening has a greater detection rate for Down syndrome than the second-trimester blood screening tests alone. However, as with all screening tests, any abnormal finding is an indication that additional diagnostic testing should be considered.

Commonly available diagnostic tests are *amniocentesis*, *CVS* (chorionic villus sampling) and *high-resolution fetal ultrasonography***.** Prior to electing to have a CVS or amniocentesis, you will meet with a genetic counselor to discuss the test thoroughly. The following information may be of assistance by providing some background information prior to your appointment:

Amniocentesis**.** Amniocentesis involves removing a small amount (usually about a tablespoon) of the fluid that is surrounding the fetus. The amniotic fluid contains cells that have been shed by the fetus during normal development. These cells may then be used for either chromosome tests or genetic tests or both. The fluid itself may be tested for the level of AFP or for biochemical conditions. The amniocentesis procedure involves guiding a thin needle through the mother's abdomen and into the amniotic sac (see figure 3). Ultrasound is used to determine the location of the fetus and the best place to withdraw the fluid. Most women do not report the amniocentesis procedure to be painful. It usually takes a minute or less to perform, and is commonly described as feeling like "pressure" rather than pain. Most women experience mild cramping for up to a few hours afterwards, but generally describe the feeling as a mild menstrual type of cramping. Because the needle must pass through the amniotic sac, there is a chance of the fluid leaking or the sac rupturing. There is also a small chance that an infection may occur. Any of these complications may cause a miscarriage. The risk for miscarriage from an amniocentesis when performed by a highly experienced technician is approximately 1 in 400 (0.25%).

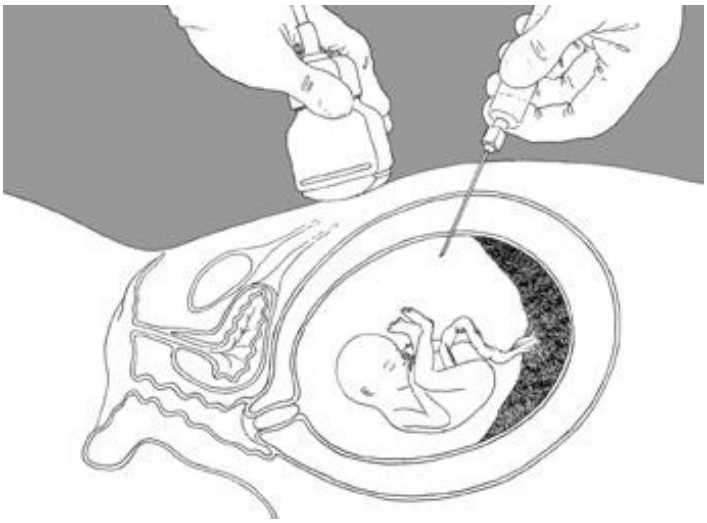

Figure 3

Amniocentesis is most commonly performed from the 15th to 20th weeks of pregnancy. The most common reasons why an amniocentesis may be recommended are:

- Maternal age of 35 years or more at expected time of delivery
- Prior birth of or family history of a child with chromosomal or genetic disorders
- Maternal and paternal carrier status for certain genetic conditions
- Abnormal AFP or triple marker result
- Ultrasound finding of a possible abnormality

***CVS (chorionic villus sampling*).** CVS is a specialized alternative test to amniocentesis. CVS is performed beginning at the 10th and up to the13th week of pregnancy, and involves removing a small amount of the tissue called the chorionic villi which is located on the outside of the fetal gestational sac. The chorion is a fetal tissue, and shares its genetic makeup with the fetus, not the mother. The chorion has many small, finger-like projections on its outer surface, and a few of these may easily be removed without disturbing the pregnancy. In later pregnancy, a portion of the chorion normally becomes very thin while a smaller portion thickens to form much of the placenta, which supplies oxygen and nutrition to the growing fetus. The chorionic villi cells may be used for chromosome analysis or other genetic testing. The chorionic villi cannot be used to test for open neural tube defects.

The CVS procedure usually takes a minute or two to perform, and most women do not consider it to be painful. The CVS may be done similar to an amniocentesis, in which a thin needle is guided into the chorionic villi and a small amount of this tissue is drawn out into a syringe attached to the needle. This is called transabdominal CVS. (See figure 4, A) Occasionally, particularly if the thickest location of the villi is in the lower portion of the uterus, the CVS is performed by using a thin flexible plastic catheter (hollow tube) which is guided through the cervical opening, somewhat like having a Pap smear done. This catheter is then used to remove a small amount of the villi. This is called a transcervical CVS (figure 4, B). Most women have noticeable but not painful cramping for a few hours. Some women experience light spotting or bleeding that usually goes away within a day or two.

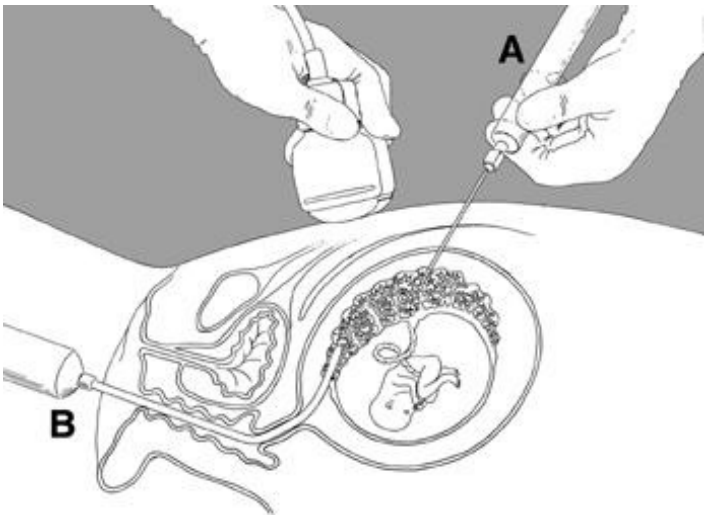

Figure 4

Women who have the CVS test done may experience a miscarriage. This risk is approximately 0.5% (1 in 200).

The most common reasons why a CVS may be recommended are:

- Maternal age of 35 years or more at expected time of delivery
- Prior birth of or family history of a child with certain chromosomal or genetic disorders
- Maternal or paternal carrier status for certain genetic conditions
- Ultrasound finding suggesting a higher risk for a chromosome abnormality
- A desire to obtain accurate test results as early as possible in pregnancy

High-resolution ultrasound. High-resolution fetal ultrasonography (also called Level 2 ultrasound) uses sound waves produced by an ultrasound machine to create an image of the fetus called a sonogram. The ability of the ultrasound to detect birth defects may be affected by gestational age, the position of the fetus or the ability to get clear images. Small physical abnormalities are not likely to be detected. It is also important that the high-resolution ultrasound be performed when the fetus is developed sufficiently for the anatomy to be seen. High-resolution ultrasound is best performed by a specialty radiology facility between the 18th and 22nd weeks of gestation. Sometimes this type of ultrasound may detect a physical variation that may or may not be serious. Additional ultrasound examinations or other testing may be recommended in order to monitor fetal growth and development.