Clinical Significance and Genetic Counseling for Common Ultrasound Findings

Patient Information Sheet
Ambiguous Genitalia

You have recently learned that your baby has ambiguous genitalia. We expect that you may have questions about what this could mean for your developing baby. Hopefully, this information will address some of your concerns; however, we encourage you to speak to your genetic counselor or healthcare provider for more information. It is important to remember that anyone can have a baby with a birth defect. Birth defects occur in 2-5% of all births and are rarely caused by something that the parents did or did not do before or during pregnancy. Currently, there are no tests available to detect all health problems.

What is ambiguous genitalia?

Ambiguous genitalia is a descriptive term used when the baby's external genitals (penis, clitoris, scrotum, labia, etc.) have not formed properly and do not appear to be clearly male or female. When ambiguous genitalia is seen on ultrasound it is a sign that the baby may have a condition that affects sex development, also called disorder of sex development (DSD). When we discuss sex development this will refer to aspects of sex that have to do with being male or female including physical parts of the body, such as the outer genitals, inner reproductive parts, such as the ovaries and testis (gonads), sex hormones, and genetic sex. It does not refer to sexual orientation. Some people may refer to individuals with DSD as "hermaphrodites" or "intersex". These terms are not used anymore, and the preferred term is DSD.

How many babies are found with ambiguous genitalia?

It is estimated that 1 out of 5,000 babies are born with ambiguous genitalia. Approximately 1 out of 1,000 babies are born with a DSD, not all of which have ambiguous external genitalia.

What causes ambiguous genitalia?

Ambiguous genitalia is caused when there is an interruption in the normal sex development when the baby is being formed. There are three steps involved in normal sex development:

1. First step that is determined when the baby is being formed is the "genetic sex", also referred to as "chromosomal sex". Chromosomes are packages of genetic information that carry the instructions (genes) necessary for our growth and development. Typically, there are 23 pairs of chromosomes in each cell of our bodies, for a total of 46 chromosomes. One copy of each pair is from our mother and one copy of each is from our father. The first 22 pairs of chromosomes are the same in males and females. The last pair is known as the sex chromosomes. Females typically have two X chromosomes (XX) and males usually have one X and one Y (XY).

2. Second step that is determined is the "gonadal sex". Ever baby starts off with two gonads, which can become either the testes or the ovaries. The Y chromosome carries a specific gene called the *SRY* gene. When the *SRY* gene is present it turns on many other genes with instruct the gonads to become testes. When the *SRY* gene is absent, gonads become ovaries.

3. Third step that is determined is the "anatomic sex" which includes inner and outer genitals. Ovaries and testes both make specific hormones that give instructions to the body and signals to the brain. Testes typically make "male sex hormones" such as androgen. Male sex hormones instruct the body to form the penis and the scrotum. When there are no male sex hormones made, the body will form the vagina, uterus, cervix, clitoris, and labia. Sex hormones will also signal for secondary sex characteristics that show up later in life such as body shape, body hair, pitch of the voice as well as production of sperm in men and ovulation and menstruation in women.

When any of these steps are interrupted it may lead to a DSD with or without ambiguous genitalia. This interruption may be because of an exposure (mother taking medications that have androgen) or by imbalances in genetic material (which may be inherited or happen by chance in the baby for the first time).

Imbalances in the genetic material may be caused by an extra or missing whole chromosome or sometimes only by extra or missing pieces of chromosomes. For example, some babies with a DSD will have a mix of sex chromosomes in their body (called mosaicism) where some cells in their body are missing an X chromosome and some cells have a normal XY. Other babies may have a small piece of chromosome that is missing, but that piece may have an important gene on it, such as the *SRY* gene, and may lead to a DSD.

Other genetic conditions are caused by changes in one or more genes in our genetic make-up that result in a particular set of characteristics or features (also called a syndrome). Examples of some DSD syndromes include Androgen Insensitivity syndrome (AIS) and congenital adrenal hyperplasia (CAH). Genetic testing, which can be performed either prior or after birth, can help identify what caused a DSD in a baby about 30% of the time. However, what is very important to know is that finding the exact genetic cause of a DSD is not always possible.

What problems could be associated with ambiguous genitalia for my baby and how are they treated?

Babies with ambiguous genitalia may have several health problems which may need to be closely followed in their lifetime. Some babies may get very sick right after delivery and it may be life-threatening, so it is important to plan to deliver the baby at a hospital that is familiar and comfortable taking care of babies with ambiguous genitalia. Some babies may have birth defects that will require special surgery or may have developmental delays or intellectual disability. Knowing what caused the ambiguous genitalia can sometimes help give more information about how your baby will develop and what type of testing and treatment is needed. However, because the cause of the DSD is not always found, your healthcare provider may not be able to know exactly what issues your baby will have.

All babies with ambiguous genitalia will be assigned a gender after birth (deciding if the baby will be raised as a boy or girl). However, the assignment may not be clear immediately after delivery which can be very difficult for parents. Before the gender can be assigned many different things have to be looked at including the genetic, gonadal, external, and hormonal sex of the baby. All babies born with ambiguous genitalia or a DSD should be evaluated by a team of specialists including: genetics, endocrinology, urology, gynecology, pediatric surgery, neonatology, psychology, social work, and ethics. Gender assignment should not be done without the specialist doctors looking at the baby and without openly taking about it with you. Some babies may also need to undergo surgery to reconstruct or reshape their inner or outer genitalia.

Having a DSD may lead to social and emotional problems; however, most people with DSDs are able to live productive and happy lives. Having a DSD does not affect sexual orientation. Some parents may choose to end a pregnancy that has been diagnosed with ambiguous genitalia or a DSD.

What further testing may be offered and what will it tell me?

Depending on how far along you are in pregnancy, a number of additional tests may be offered to you. If the ambiguous genitalia is found during a routine ultrasound, a more detailed ultrasound will usually be performed to look carefully at the baby's body and check for other birth defects. In some cases a fetal MRI and/or fetal echocardiogram (a specialized ultrasound looking at the baby's heart) may also be recommended. You may be referred to a high risk maternal-fetal-medicine (MFM) doctor or a fetal center, which is a high risk center where various specialists may gather to review the health problems identified in your baby, as well as the potential causes and prognosis.

You may also be offered several different genetic tests in your pregnancy. There are two types of prenatal tests, diagnostic and screening:

<u>Diagnostic Tests</u>

Depending on your gestational age, the first test you may be offered is to determine the "chromosome sex" of your baby and to make sure that the baby has the correct number of sex chromosomes. The most accurate way to do this is through a test called an amniocentesis. The amniocentesis is a diagnostic test in which a small sample of amniotic fluid is obtained to examine the baby's chromosomes. This fluid is obtained by inserting a thin needle through your belly and into the amniotic sac. Because the procedure is considered an invasive procedure, there is a risk, likely less than 1%, for complications that can lead to miscarriage.

If you choose to pursue an amniocentesis, you may be offered an additional test called a *SRY* FISH test which specifically looks to see if the SRY gene is present or missing in the baby. You may also be offered a test called a chromosome microarray (CMA) instead of the *SRY* FISH test. CMA is used to identify small missing or extra pieces of the baby's chromosomes that may be associated with genetic conditions. It can detect if the *SRY* is missing, but it can also give information about all of the other chromosomes that could cause a DSD. CMA cannot detect all genetic conditions and may detect variations in the chromosomes that have uncertain clinical significance. Parental blood samples may help to clarify the meaning of a variation, but effects of these changes may not be known until after the baby is born. CMA may also detect information such as non-paternity and close relationships between parents. Other testing would depend on if the baby is confirmed to have an XX chromosomes or XY chromosomes, if the baby has any other birth defects, or if there is any family history. You may be offered tests that read specific genes within the chromosomes or measure different enzymes in the fluid. Testing may also involve drawing blood form the mother and father to see if they may carry genetic changes in their genes which may be passed on to the baby.

Screening Tests

There are multiple screening tests to determine the chances for a baby to have a chromosome condition. These screening tests cannot diagnose or rule out the presence of a chromosome condition but may be used to help you decide whether or not you would like to pursue a diagnostic test.

Cell-free DNA (cfDNA), also referred to as Non-Invasive Prenatal Testing (NIPT) or Non-Invasive Prenatal Screening (NIPS), is a screening test for certain chromosome conditions. During pregnancy, some of your baby's placenta's chromosome material is in your blood, along with your own chromosome material. Cell-free DNA screen is a blood test that measures the amount of chromosome material in your blood to determine if your baby could have an extra chromosome. This test screens for Down syndrome, trisomy 18, trisomy 13 and may also screen for some less severe conditions that are caused by different numbers of the X or Y chromosome. Cell-free DNA screen may also screen for several conditions caused by small missing pieces of chromosomes. While cell-free DNA screen is a good screen it is not a diagnostic test, like the amniocentesis. The detection rate for these chromosome conditions is typically between 90-99%. Other screening blood tests (often called a triple, quad, penta, or first trimester screen) may also be offered.

The risks, benefits, and limitations of screening and diagnostic testing options should be discussed with you by your genetic counselor or other health care provider. Follow-up counseling and referrals for support can be made if a genetic diagnosis is made prenatally. As with all situations in which prenatal testing is discussed, it is your decision whether or not this test is done.

It is important to remember that prenatal screening and testing cannot detect or rule out all genetic conditions. After the baby is born an examination by a pediatric geneticist and endocrinologist will be recommended. The geneticist may recommend that a small amount of blood be taken from the baby to evaluate for a chromosome or genetic problem. This examination and possible additional tests are important, since an accurate diagnosis will provide you with the best information regarding the prognosis for your baby, the cause of the ambiguous genitalia, the risks to future children and that of other family members, as well as to determine appropriate tests to be offered to you in future pregnancies.

The decision to have one or more of the tests or to do no additional testing is a difficult and personal one. There is no one right decision. Some people will decide to have no further testing because they do not feel they need to know if their baby will have any of these chromosome or genetic conditions before delivery. Other people feel that they want more information as soon as possible. After gathering all of the information you need about ambiguous genitalia, you should make the decision that is right for you and your family.

What do I do now?

This information is only intended as an introduction to some of the terms and tests that you have already heard or will be hearing about from your genetic counselor and healthcare provider. We hope that this information sheet will be helpful as you begin to understand more about ambiguous genitalia. We understand that any time something of concern is found through prenatal screening and testing, parents are going to be worried. Please don't hesitate to contact your genetic counselor with any questions or concerns you have. We are here to help you and your baby.

You may find it useful to have a consultation with a medical geneticist and endocrinologist prior to delivery as well as a high risk maternal-fetal-medicine doctor to discuss the plan for your pregnancy and your baby after delivery. You may also find it useful to have a consultation and an evaluation performed at a fetal center experienced at taking care of babies with ambiguous genitalia. Your doctor may recommend delivery at a tertiary care center, a hospital equipped to take care of babies with ambiguous genitalia.

Support groups, either online or in person, can provide comfort for families facing this diagnosis. One-on-one therapy or family therapy may also be useful, both during and after the pregnancy. Some resources that parents may find helpful can be found at the following websites http://www.dsdguidelines.org/ and http://www.isna.org/.