Prenatal Diagnosis

The terms *prenatal screening* and *prenatal diagnosis* refer broadly to a number of different techniques and procedures that can be performed during a pregnancy to provide information about the health of a developing fetus. *Screening tests* indicate whether the fetus has an average, greater than average, or below average risk of being affected by a particular genetic condition or birth defect. When the result of a screening shows increased risk, the pregnant patient may be offered other diagnostic tests to confirm whether the fetus is, in fact, affected. Diagnostic tests may also be offered directly to women whose pregnancies are considered high risk because of age, family history, or other factors.

It is important to note that a normal result on either a diagnostic or screening test does not guarantee the birth of a normal baby. These tests are designed to look for specific conditions, but not all conditions can be detected and no test is 100 percent accurate.

Decisions About Prenatal Diagnosis

The decision to undergo a prenatal screening or diagnostic test should be carefully considered. Genetic counseling is often recommended prior to screening or to CVS or amniocentesis. After reviewing medical and family histories, a genetic counselor assesses the specific genetic risks to a pregnancy and helps the patient decide whether or not to undergo prenatal screening or testing based on the parent's own values and beliefs.

If an abnormality is detected, the options for the family will be specific to what is found and what treatment is available. The courses of action – including continuing or terminating the pregnancy – are determined solely by the parents-to-be in consultation with their primary care provider and other resources that they may choose to consult.

Prenatal Screening

Ultrasound is a noninvasive procedure that may be performed at any stage of a pregnancy. The procedure uses high frequency sound waves to produce an image of the fetus inside the uterus. When an abdominal ultrasound is performed, a gel that acts as a sound wave conductor is placed on the mother’s abdomen. The doctor or technician who is performing the ultrasound moves a small instrument, called a transducer, back and forth over the abdomen, directing sound waves into the uterus. The sound waves reflect off bones and tissue and are converted into black and white images to produce a picture of the fetus. Ultrasounds can also be done vaginally by introducing the transducer into the mother's vagina to allow a closer examination of the fetus.

Ultrasound is used to determine the age of a fetus based on fetal measurements, to monitor fetal growth, to determine why bleeding is occurring in a pregnancy, to check the baby's position in the uterus, to detect multiple births (e.g., twins), and to evaluate the general development of the fetus. Ultrasound may also provide the first indication of a problem with the fetus by revealing major fetal structural abnormalities or abnormalities of function in certain fetal organs. The procedure is also used as a guide to visualize the fetus when invasive prenatal diagnostic procedures, such as amniocentesis and chorionic villi sampling (CVS), are performed. Accurate ultrasound requires technically proficient physicians and technicians.

Nuchal fold translucency (NT) is an ultrasound performed by a specially trained ultrasonographer at approximately 11-13 weeks of pregnancy. The ultrasonographer measures the size of the fluid-filled sack at the back of the fetal neck, called the nuchal fold. An increase in the size of the nuchal fold may indicate the presence of a number of conditions, including a chromosome abnormality such as Down syndrome or other abnormalities such as a heart defect. An NT measurement is often done in conjunction with a first trimester maternal serum screen (see below).

Maternal serum marker screening is a blood test that is offered to pregnant women during the first (11-13 weeks) or second trimester (15-18 weeks of pregnancy) to screen for two chromosome disorders, Down syndrome and Trisomy 18, in the first trimester; and for Down syndrome, Trisomy 18, and neural tube defects in the second trimester.

Second trimester maternal serum marker screening measures the concentration of proteins (alpha-fetoprotein, unconjugated estriol, and human chorionic gonadotropin in the “triple screen,” and these three proteins plus inhibin A in the “quad screen”) that are made by the fetus during pregnancy, and that circulate in the blood of a pregnant woman. The normal levels of these proteins depend on a number of factors, including the gestational age of the fetus, the number of fetuses, maternal weight and race, and the presence of maternal diabetes.

To calculate risk for Down syndrome, the results of the maternal serum screen are used to adjust a woman’s age-related risk for Down syndrome up or down. If her adjusted risk equals that of a 35-year-old (who would generally be offered amniocentesis based on age alone), additional follow-up, possibly including diagnostic testing, is offered. A woman who is at risk because of age who would prefer not to go directly to an invasive procedure may use maternal serum screening to adjust her age-related risk. If her risk goes down based on the results of the serum screen, she may choose not to pursue additional diagnostic testing.

Maternal serum screening will not detect every baby with Down syndrome, Trisomy 18, or a neural tube defect. Seventy percent of pregnancies in which the baby has Down syndrome can be detected with the triple screen and 80 percent with the quad screen. The alpha-fetoprotein analysis detects about 90 percent of babies with open structural defects of the fetal abdominal wall or the neural tube (open spina bifida and anencephaly).

In addition, screening tests may yield what are called false positives. The false-positive rate is the chance that a test is abnormal, or "positive", even though the condition being tested for is not present. The goal of any screening program is to balance the possible benefits of detecting an abnormality with the risks of subjecting women to the anxieties of a positive result or the risks of invasive diagnostic testing.

First trimester maternal serum marker screening is becoming more available as an alternative or adjunct to second trimester screening. Two proteins are measured in the maternal serum, free beta human chorionic gonadotropin (free B-hCG) and pregnancy-associated plasma protein A (PAPP-A). The results of the blood test are often combined with the results of an NT measurement that is done at the same time to adjust the woman's age-related risk for Down syndrome up or down. When a first trimester serum screen is combined with an NT measurement, 80 to 85 percent of Down syndrome cases will be detected.

There are a number of ways that first trimester screening may be offered, either as a stand-alone test or in combination with a second trimester screen. When both first and second trimester screens are done, however, they should not be reported out independently as the false-positive rates (the chance that someone has a positive result, but the fetus is chromosomally normal) are additive, leading to more unnecessary invasive testing. Some of the approaches that physicians and patients may consider include:

Integrated screening – In integrated screening, first and second trimester screening is done but only one final result is reported after the second screen. This has the highest detection rate of all the approaches.

Stepwise sequential screening – In stepwise sequential screening, a woman has a first trimester serum screen, with or without a NT measurement. If she is found to have an increased risk, she is referred for follow-up counseling and possible diagnostic testing. If she is not at an increased risk based on the first screen, she is given the option of a second screen in the second trimester and given a final risk that incorporates the result of both tests.

Contingent sequential screening – In a variation on the above, a woman has a first trimester screen and if she is has an increased risk, she is referred for follow-up counseling and possible diagnostic testing just like in the stepwise sequential screen. However, if her risk is not significantly increased, what happens next depends on her result. If her risk is adjusted to a very low risk, no further screening is offered. If she has an intermediate risk, she is offered a second trimester screen to clarify that risk further.

Which approach is appropriate for any one woman or obstetrician's office will depend on many factors: a woman's gestational age at the time the pregnancy is diagnosed and her access to care in the first trimester, the availability of trained ultrasonographers to do NT measurement, the availability of first trimester diagnostic testing (CVS) if there is

a positive first trimester screen, the presence of multiple fetuses, and personal preference, among others.

Prenatal Diagnostic Tests

Amniocentesis is among the most commonly performed prenatal diagnostic procedures, and is used to detect chromosomal abnormalities as well as other specific genetic diseases. Amniocentesis is usually performed in the second trimester of pregnancy, at approximately 15-20 weeks from the first day of the last menstrual period. During the procedure a thin needle is inserted through the abdomen to allow for the withdrawal of a small quantity (usually one to two tablespoons) of amniotic fluid from the sac that holds the developing fetus. The fetal cells found in the amniotic fluid are grown in a cell culture and studied to detect chromosome abnormalities. Specific enzyme or DNA analyses, which may be indicated based on family or medical history, can also be performed on the fetal cells derived from amniotic fluid.

Amniocentesis is a relatively simple and safe procedure when performed by an experienced physician, but there is some risk for miscarriage. That risk has been quoted at being about 1 in 200. However, recent data suggests that in experienced hands, the risk may be much lower. Infection is another rare complication of amniocentesis. There is also a small increased risk of clubfoot when amniocentesis is performed before 13 weeks of pregnancy.

The results from amniocentesis are highly accurate. The complete chromosome analysis is usually completed one to two weeks after the procedure is performed. Additional testing such as biochemical (enzyme) analyses and DNA testing usually take an additional two to four weeks, while the amniotic fluid alpha-fetoprotein analysis takes only a few days.

Amniocentesis is commonly recommended for a variety of reasons:

1. Increased risk for fetal chromosome abnormalities

   a) Maternal age (35 or greater at delivery)
   b) Having a previous child with a chromosome problem, such as Down syndrome
   c) Increased risk of Down syndrome or Trisomy 18 based on maternal serum markers
   d) One of the parents has a balanced chromosome rearrangement

2. Increased risk for open neural tube defects or fetal abdominal wall defect

   a) One of the parents or a previous child has had a neural tube defect
   b) Elevated AFP (alpha-fetoprotein) concentration in the second trimester screening

3. Increased risk for a specific genetic condition

a) A previous child or relative has had birth defects or a metabolic or other known genetic condition
b) Both parents are known to carry genes for an inherited disorder, such as Tay-Sachs, sickle cell anemia, thalassemia or cystic fibrosis
c) The mother's male relatives (brothers, sons, uncles, fathers) have inherited conditions such as muscular dystrophy or hemophilia

If amniocentesis results indicate that the fetus is affected with a particular condition, further counseling is usually recommended.

Chorionic villi sampling (CVS) is a test performed to detect specific genetic abnormalities early in pregnancy. By performing a biopsy of the cells that will become the placenta (villi), fetal cells are obtained and genetic analyses can be performed. CVS is performed by inserting either a catheter through the vagina and cervix, or a needle through the abdomen, into the villi. CVS is generally done at 10-13 weeks from the first day of the pregnant woman's last menstrual period, significantly earlier than amniocentesis is usually performed. The greatest success exists when the physician performing the procedure is experienced at performing both the transcervical and transabdominal techniques because the location of the placenta and uterine anatomy will often dictate the best or easiest approach to obtaining villi.

Preliminary CVS results (which are not always accurate) can be available within two to four days after the procedure is performed; final results are available in about seven to ten days. Many biochemical and molecular (DNA) analyses can be accurately performed using chorionic villi.

CVS can be used to determine virtually all disorders that can be diagnosed by amniocentesis except the presence of neural tube defects (spina bifida).

CVS carries a slightly higher increased risk of miscarriage (still less than one percent) than amniocentesis. Other complications, such as vaginal bleeding (spotting) or cramping, and maternal infection, occur more frequently after CVS than after amniocentesis. There is concern about the risks of CVS performed before 10 weeks gestation because of reports of a higher risk of limb anomalies with this very early procedure.

Discovering a problem in the first trimester has several benefits. These include peace of mind for the family when no abnormality is detected, or earlier fetal treatment with surgery or medication if the condition detected is amenable to treatment. The option of a first trimester termination, which is safer and easier than a second trimester procedure, also makes CVS appealing to some individuals or couples whose pregnancy is at high risk.

Future Directions

New non-invasive techniques being developed focus on ensuring diagnostic accuracy while eliminating the risks associated with invasive procedures such as amniocentesis and CVS. Studies are underway to determine how to best obtain and concentrate fetal cells or fetal DNA that normally circulate in maternal blood during pregnancy so that chromosome, biochemical, and DNA analyses can be performed using those cells.

Ultrasound imaging techniques, such as three dimensional and color imaging, continue to improve to allow better visualization of fetal anomalies.

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