Prenatal Testing for Down Syndrome

July 21, 2011
By Len Leshin, MD [1]

Over the last 10 years, new technology has improved the methods of detection of fetal abnormalities, including Down syndrome.

Note: The subject of prenatal testing for Down syndrome is an emotionally charged one. I am presenting this essay as a guide to parents who are faced with the prenatal tests offered by their doctor. If your fetus has been diagnosed as having Down syndrome or is simply at high risk, please spend some time to learn more about the condition. An excellent website to start with is Down Syndrome: The WWW Page, especially its page on Welcoming New Babies. Also, check out the many home pages on my list of Down syndrome websites.

Introduction

Over the last 10 years, new technology has improved the methods of detection of fetal abnormalities, including Down syndrome. While there are ways to diagnose Down syndrome by obtaining fetal tissue samples by amniocentesis or chorionic villus sampling, it would not be appropriate to examine every pregnancy this way. Besides greatly increasing the cost of medical care, these methods do carry a slight amount of risk to the fetus. So screening tests have been developed to try to identify those pregnancies at "high risk." These pregnancies are then candidates for further diagnostic testing.

What is the difference between a screening test and a diagnostic test? In diagnostic tests, a positive result very likely means the patient has the disease or condition of concern. In screening tests, the goal is to estimate the risk of the patient having the disease or condition. Diagnostic tests tend to be more expensive and require an elaborate procedure; screening tests are quick and easy to do. However, screening tests have more chances of being wrong: there are "false-positives" (test states the patient has the condition when the patient really doesn't) and "false-negatives" (patient has the condition but the test states he/she doesn't).

Maternal Serum Screening

The mother's blood is checked for three items: alpha-fetoprotein (AFP), unconjugated estriol (uE3) and human chorionic gonadotropin (hCG). These three are independent measurements, and when taken along with the maternal age (discussed below), can calculate the risk of having a baby with Down syndrome.

- **Alpha-fetoprotein** is made in the part of the womb called the yolk sac and in the fetal liver, and some amount of AFP gets into the mother's blood. In neural tube defects, the skin of the fetus is not intact and so larger amounts of AFP is measured in the mother's blood. In Down syndrome, the AFP is decreased in the mother's blood, presumably because the yolk sac and fetus are smaller than usual.

- **Estriol** is a hormone produced by the placenta, using ingredients made by the fetal liver and adrenal gland. Estriol is decreased in the Down syndrome pregnancy. This test may not be included in all screens, depending on the laboratory.

- **Human chorionic gonadotropin** hormone is produced by the placenta, and is used to test for the presence of pregnancy. A specific smaller part of the hormone, called the beta subunit, is increased in Down syndrome pregnancies.
A very important consideration in the screening test is the **age of the fetus** (gestational age). The correct analysis of the different components depends on knowing the gestational age precisely. The best way to determine that is by ultrasound.

Once the blood test results are determined, a risk factor is calculated based on the "normal" blood tests for the testing laboratory. The average of normals is called the "population median." Test results are sometimes reported to doctors as "**Multiples of the Median (MoM).**" The "average" value is therefore called 1.0 MoM. Down syndrome pregnancies have lower levels of AFP and estriol, so their levels would be below the average, and therefore less than 1.0 MoM. Likewise, hCG in a Down syndrome pregnancy would be greater than 1.0 MoM. In the serum screening, the lab reports all results in either this way or as a total risk factor calculated by a software program.

### Effects of Maternal Age

Finally, the calculated risk is used to modify the risk already statistically calculated based on the mother's age. We already know that as the mother's age advances, the risk of having a baby with Down syndrome increases. [Click here](http://www.physicianspractice.com) to see a table of these risk values.)

The cut-off for high-risk versus low-risk has been set by the geneticists at 1 in 250; less then that is high-risk, and higher than that is low-risk. The reason for choosing 1 in 250 for the cut-off has to do with the risk of miscarriage from amniocentesis: if the risk is 1 in 250 or less, the risk of having a baby with Down syndrome is greater than the risk of having a miscarriage from the amniocentesis; and more than 1 in 250, the risk of having a miscarriage from amniocentesis is greater than the risk of having a baby with Down syndrome.

For example: Let's say the test results come back in the typical range for a pregnancy not associated with Down syndrome (that would be 1.0 MoM for all components). This result reduces the woman's risk of having a child with Down syndrome four-fold. ([Click here](http://www.physicianspractice.com) to see a table of these risk values.) If the woman is 25, this decreases her risk from 1 in 1100 to 1 in 275, which is still low-risk. If the woman is 35 years old, this decreases her risk from 1 in 250 to 1 in 62, which is still high-risk. The woman aged 45 goes from 1 in 20 to 1 in 5; and so stays high-risk also.

So, the age of the mother is the most important aspect when determining the blood screening test's result.

Also note that the way the tests are set up, the serum screening test has a 5 to 8% false-positive rate (see above for the discussion of what this means) and also has a false-negative rate of 35 to 40%, so we will only detect about 60 to 65% of all fetuses with Down syndrome.

At the present time, the screening is done at the beginning of the second trimester. However, research is ongoing to find some combination of serum markers (or even from maternal urine) that may help make screening possible in the first trimester. These new markers include serum pregnancy-associated plasma protein A (PAPP-A), serum inhibin A, and urinary metabolites of hCG.

However, first-trimester screening can't pick up neural tube defects, so if first trimester screening becomes routine for Down syndrome, pregnant women would then have to have two screening tests.

### Ultrasound Screening

The main usefulness of ultrasound (also called sonography) is to confirm the gestational age of the fetus (it's more accurate than dating from the mother's last menstrual cycle). Another benefit of the ultrasound can also pick up problems of a serious medical nature, such as blockage of the small intestine or heart defects. Knowing these defects exist as early as possible will benefit the treatment of the child after birth.
There are several items that can be found during an ultrasound exam that some researchers have felt may have a significant association with Down syndrome. These findings may be seen in normal fetuses, but some obstetricians believe that their presence increases the risk of the fetus having Down syndrome or other chromosomal abnormality. These "markers" include choroid plexus cyst, echogenic bowel, echogenic intracardiac focus, and dilation of the kidneys (pyelctasis). However, these markers as a sign of Down syndrome are still controversial, and parents-to-be should keep in mind that each marker can also be found in a small percentage of normal fetuses. These ultrasound markers are best used in women over 35 or those who have a positive blood screening test, to either downgrade the risk (in cases where no such findings are seen in the ultrasound exam) or confirm that the pregnancy is high-risk for Down syndrome. In women under 35 years of age with normal maternal serum screen test results, the identification of one of these findings on the ultrasound is not significant enough to make a pregnancy high-risk for Down syndrome. Many researchers have attempted to find if any combination of ultrasound findings and maternal blood or urine tests may be more likely to determine if a fetus has Down syndrome. The most common ultrasound marker used for identifying Down syndrome is the **nuchal translucency** marker. In a total of 22 studies involving pregnant women at high risk for having babies with chromosomal abnormalities, 30% of fetuses with increased nuchal translucency were found to have chromosomal abnormalities, and almost half of those abnormalities were Down syndrome. However, there are grave problems with the methodologies used and statistical analyses made in these studies. One recent review of the topic (Stewart & Malone, 1999) concluded:

"Results of nuchal translucency sonography are not yet sufficiently uniform to allow counseling of patients on the risk of aneuploidy [chromosomal abnormalities] based on a particular nuchal translucency thickness."

It is important to keep in mind that **even the best combination of ultrasound findings and other variables is only predictive and not diagnostic.** For true diagnosis, the chromosomes of the fetus must be examined.

**Amniocentesis**

This procedure is used to collect amniotic fluid, the liquid that is in the womb. It's performed in the doctor's office or in the hospital on an "out-patient" basis. A needle is inserted through the mother's abdominal wall into the uterus, using ultrasound to guide the needle. Approximately one ounce of fluid is taken for testing. This fluid contains fetal cells that can be examined for chromosome tests. It takes about 2 weeks to determine if the fetus has Down syndrome or not. Amniocentesis is usually carried out between the 14th and 18th week of pregnancy; some doctors may do them as early as the 13th week. Side effects to the mother include cramping, bleeding, infection and leaking of amniotic fluid afterwards. There is a slight increase in the risk of miscarriage: the normal rate of miscarriage at this time of pregnancy is 2 to 3%, and amniocentesis increases that risk by an additional 1/2 to 1%.

Which mothers should have an amniocentesis? The current recommendations by professional obstetric groups is that women with a risk of having a child with Down syndrome of 1 in 250 or greater should be offered amniocentesis. There is controversy over whether to use the risk at the time of screening or the predicted risk at the time of birth. (The risk at the time of screening is higher since many fetuses with Down syndrome abort spontaneously around the time of screening or afterwards. See the **risk table**.)

**Chorionic Villus Sampling (CVS)**

In this procedure, instead of amniotic fluid being taken, a small amount of tissue is taken from the young placenta (also called the chorionic layer). These cells contain the fetal chromosomes that can be tested for Down syndrome. The cells can be collected the same way as the amniocentesis, but another method is to insert a tube into the uterus through the vagina. The method depends on the mother's anatomy.

CVS is usually carried out between the 10th and 12th weeks of pregnancy. Side effects to the mother
are the same as with amniocentesis (above). The risk of miscarriage after CVS is slightly higher than with amniocentesis, increasing the normal risk of miscarriage to 3 to 5%. Studies have shown that the more experienced the doctor performing the CVS, the less the miscarriage rate. Early on in the use of CVS, a number of babies were identified with missing or shortened fingers or toes. However, that has been connected to the use of CVS before the 10th week of pregnancy.

Which mothers should have CVS? The same recommendations for amniocentesis apply to CVS. The decision as to use amniocentesis versus CVS is an individual one, and should be discussed thoroughly between the mother and her physician.

Disclosures:

Source URL: http://www.physicianspractice.com/articles/prenatal-testing-down-syndrome

Links: