Prenatal Screening for Down Syndrome

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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.

Introduction

Over the last 20 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" or "screen-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 a combination of different markers: alpha-fetoprotein (AFP), unconjugated estriol (uE3), and human chorionic gonadotropin (hCG) make up the standard tests, known together as the "triple test." Sometimes a marker called inhibin A is added, making the "quadruple screen." These tests are independent measurements, and when taken along with the maternal age (discussed below), can calculate the risk of having a baby with Down syndrome. Over the last fifteen years, these were done in the 15th to 18th week of pregnancy. Recently, another marker called PAPP-A was found to be of use even earlier.

- **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.

Inhibin A is a protein secreted by the ovary, and is designed to inhibit the production of the hormone FSH by the pituitary gland. The level of inhibin A is increased in the blood of mothers of fetuses with Down syndrome.

PAPP-A, which stands for pregnancy-associated plasma protein A, is produced by the covering of the newly fertilized egg. In the first trimester, low levels of this protein are seen 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.

Calculating the Risk

In the 1980s and 90s, the results of the prenatal tests were expressed to parents as "high risk" and "low risk," depending on whether the risk result was above or below an arbitrary cutoff point at 1 in 250. (I have seen the cutoff as low as 1 in 200 and as high as 1 in 270.) The reason for choosing that cutoff value was based on the risk of complications from an amniocentesis procedure. If the mother's risk was less than 1 in 250 of having a child with Down syndrome, then the risk of amniocentesis was greater and the mother was called "low risk." Likewise, if the mother's results showed a greater risk than 1 in 250, the pregnancy was called "high risk."

Recently, however, the American College of Obstetricians and Gynecologists ("ACOG") have advocated not using the terms "high risk" and "low risk," but instead presenting the parents with the actual numerical risk value.

Effects of Maternal Age

The final calculated risk from the lab results based on the fetal age 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 to see a table of these risk values.

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. (This four-fold number is based on clinical studies, and is standard.) If the woman is 25, this decreases her risk from 1 in 1100 to 1 in 4400. If the woman is 35 years old, this decreases her risk from 1 in 250 to 1 in 62. The woman aged 45, it decreases her risk from 1 in 20 to 1 in 5.

Now, let's take the example of the test results coming back with the levels normally associated with a pregnancy of a child with Down syndrome. This increases the risk by four-fold (again, this is a standard number). So the woman aged 25 has her screen go from 1 in 1100 to 1 in 275. The woman aged 36 goes from 1 in 250 to 1 in 62. The woman aged 45 goes from 1 in 20 to 1 in 5.

So, the age of the mother is still the most important aspect when determining the blood screening test's result.
Also note that the way the tests are set up, the serum quadruple screen 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%, and so will only detect about 80% of all fetuses with Down syndrome.

**Who and When?**

Because the risk of having a baby with Down syndrome rose above the 1 in 250 mark at the 35th birthday for women, it had become the standard of care to offer the screen for Down syndrome to all mothers 35 years and older. At the beginning of 2007, the American College of Obstetricians and Gynecologists stated that all women regardless of age should be offered the opportunity for screening.

Over the last two decades, the screening was done between the 15th and 20th week of gestation, but it was most accurate between the 16th week and the 18th week. However, research in the last 6 years has concentrated on finding a way to screen in the first trimester to enable parents to have time to make choices when given the results of a positive screen test. The first trimester screen now uses a combination of the maternal age, the serum quadruple screen, the serum marker PAPP-A, and an ultrasound measurement of the back of the neck of the fetus. When used correctly, this first trimester screen has a detection rate of approximately 95% of all cases of Down syndrome, with a false-positive rate of 5%.

**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.

Studies in the mid-1990s showed that there was a strong association between the size of a collection of fluid at the nack of the fetal neck, called nuchal transluceny, and the risk of Down syndrome. Early attempts to use a measurement of the nuchal area were limited by a wide variety in measurement techniques. Recently, standardized guidelines on measuring nuchal translucency along with specific training and certifications have been instituted, making this ultrasound measurement useful as part of the first trimester screen. There are now computer programs that can use this measurement to help calculate the risk of having a baby with Down syndrome. However, not every parent may have access to an ultrasound technician certified in measuring the nuchal translucency, so her risk factors will be calculated without this measurement.

There are several other items that can be found during an ultrasound exam that some researchers have felt that 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 echogenic bowel, echogenic intracardiac focus, and dilatation 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. In early 2001, a study (Smith-Bindman, 2001) was published that looked at all of the previous studies on this topic. The authors concluded that "[these markers] could not discriminate well between unaffected fetuses and those with Down syndrome." A more specific marker that is currently under investigation is the measurement of the fetal nose; fetuses with Down syndrome appear to have smaller noses on ultrasound than fetuses without chromosomal abnormalities. However, there is still no standardized technique to measuring the nasal bone and it is considered strictly investigational at this time.

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%. Amniocentesis is not recommended before the 14th week of pregnancy due to a higher risk of complications and loss of pregnancy.

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.

Want to know more about how Down syndrome occurs? Go to my article about trisomy 21.

References:


