



SCREENING FOR CHROMOSOMAL ABNORMALITIES IN THE FIRST TRIMESTER

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SYNOPSIS

Screening for chromosomal abnormalities during the first trimester has proven to be not only an effective screening tool, but also a way to reduce maternal anxiety and to minimize delay in learning about the risk of chromosomal abnormalities.

ABSTRACT

The last three decades have brought tremendous changes in screening practices for fetal aneuploidy (having less or more than the usual diploid number of chromosomes). Though serum screening tests performed during the second trimester were once the gold standard, they have limitations. Delaying screening until weeks 15 to 20 of pregnancy unnecessarily increases maternal anxiety, as well as the likelihood that bonding with the fetus has already occurred. The combination of serum screening tests with ultrasound in the first trimester increases the screening detection rate above that of screening tests in the second trimester, without increasing the rate of false-positives. First trimester screening tests not only allay parental anxiety by providing earlier results about chromosomal abnormalities, but also allow physicians to screen for some other forms of congenital anomalies. In the future, direct noninvasive maternal testing may eliminate serum screening tests altogether.

SCREENING OPTIONS

Prenatal screening for chromosomal abnormalities has dramatically changed during the last 30 years. At one time, amniocentesis and chorionic villus sampling were the only diagnostic tests available, but these are both invasive tests with a risk of inducing miscarriage. As a result, they were only offered to pregnant women 35 years or older or women who had a previous pregnancy with chromosomal abnormalities, particularly Down syndrome. Moreover, these methods only detected approximately 30 percent of babies with a chromosomal abnormality, and patients had to wait up to one month for results.

When maternal serum α -fetoprotein screening for neural tube defects became available in the mid-1980s,

the American College of Obstetrics and Gynecology (ACOG) encouraged physicians to offer it to all pregnant women. After this test became more common, physicians found a weak association between lower than normal α -fetoprotein values and Down syndrome, but although this association showed some initial promise as a screening test, it did not detect any more cases of Down syndrome than did amniocentesis alone.

Soon, measurements of two other biochemical markers were added to create multiple marker or triple serum screening, which detected α -fetoprotein, human chorionic gonadotropin (hCG), and unconjugated estriol during weeks 15 to 20 of pregnancy. This triple serum screening, with an estimated 65 percent screening detection rate, became the standard for screening for chromosomal abnormalities. Later, the addition of a fourth biochemical marker, inhibin-A, increased the detection rate for abnormalities to approximately 70 to 75 percent. Many hospitals have adopted the quadruple serum screening test, but in some states, such as California and New York, hospitals have continued to offer only the triple serum screening test.

The triple or quadruple serum screening test, although a substantial improvement over early screening efforts, has several disadvantages. First, the screening test can only be offered to women who are between week 15 and 20 of pregnancy. At this point in the pregnancy, the patient may have already perceived fetal movement and started the bonding process, making the decision to have invasive diagnostic testing complicated. If a patient is considering terminating the pregnancy, bonding with the fetus makes it very difficult to make an objective decision about terminating the pregnancy – a decision that is further complicated by the fact that many physicians do not perform second trimester abortions. In addition, by week 18 to 20, the patient's family and friends know she is pregnant, and their opinions play a role in her decision-making process.

These limitations of second trimester screening prompted researchers to pursue first trimester screening tests, but since the available serum tests – measurements of α -fetoprotein and estriol levels – could not detect chromosomal abnormalities, researchers had to find different biochemical markers. Sure enough, in the early 1990s, several studies reported that two biochemical markers, pregnancy-associated plasma protein A (PAPP-A) and free β -hCG, when measured between weeks nine and 13 of pregnancy, had a higher screening detection rate than second trimester serum screening tests. When PAPP-A levels are low and free β -hCG levels are high, the fetus has a greater risk of having Down syndrome.

Biochemical analysis of these markers alone yields screening detection rates of 53 to 58 percent. Further, first trimester serum screening cannot effectively screen for neural tube defects, nor for chromosomal abnormalities with multiple gestation pregnancies, because it requires accurate dating of the pregnancy, ideally based on ultrasound examination.

In the mid-1990s, Dr. Kypros Nicolaides and his research team at King’s College in London began screening for Down syndrome by using ultrasonography to measure the subcutaneous fluid-filled space between the back of the fetal neck and the skin (so-called “nuchal translucency” figure 1). Subsequently, researchers throughout the world examined the effectiveness of screening based on nuchal translucency alone, and reported wide variations in screening detection rates, from 29 to 100 percent. These studies had limitations because of the wide range in operator skill and success in obtaining measurements, among other factors. When researchers at different centers followed the protocol



Figure 1: Demonstration of a normal nuchal translucency measurement.

established by Nicolaides, however, they obtained similar screening efficiency results.

Nicolaides then reported that the combination of first trimester serum biochemical analyses with nuchal translucency measurements detected about 90 percent of fetuses with chromosomal abnormalities, with a false-positive rate of 5 percent.

Several major trials conducted in the United States, including the Biochemistry, Ultrasound, Nuchal Translucency (BUN) study, and the First and Second Trimester Evaluation of Risk for Fetal Aneuploidy (FASTER) trial, reported results that were similar to Nicolaides’ findings, with 85 and 87 percent screening detection rates, respectively. With these confirmatory clinical studies, the Society for Maternal Fetal Medicine and ACOG recognized the validity of first trimester screening.

DETECTION RATES FOR SCREENING TESTS

Screening Test	Screening Detection Rate	False Positive Rate
Tripe Serum Screen	60–65%	5%
Quadruple Serum Screen	67–81%	5%
Second Trimester Ultrasound	50–60%	12–13%
Nuchal Translucency Ultrasound (first trimester)	29–100%	6%
First Trimester Serum Screen	60%	5%
First Trimester Combined (serum and nuchal translucency)	85–90%	5%

Besides providing earlier screening results for pregnant women, first trimester screening has several distinct benefits over second trimester screening. A number of small analyses done recently have pointed out that first trimester screening is less expensive because it reduces the total number of amniocenteses offered to pregnant women. Also, because amniocentesis has a small but significant risk of miscarriage, reducing the number of amniocenteses will diminish the number of normal pregnancies that are lost as a result of the procedure.

First trimester screening provides a secondary benefit by allowing physicians to screen for and diagnose several anomalies early in the pregnancy, and to detect women at risk for pregnancy complications. Abnormal nuchal translucency in the first trimester correlates not only with a risk for Down syndrome, but also with a spectrum of heart, lung, and skeletal abnormalities. Early detection of a major congenital heart defect or diaphragmatic hernia, both major abnormalities that require delivery at a tertiary health center with the necessary technologies, allows physicians to prepare adequately well in advance of labor and delivery, and to tailor their management of pregnancies with these abnormalities. Also, first trimester ultrasonography enables early detection of some neural tube defects, primarily anencephaly, that substantially alter pregnancy care and choice of hospital for delivery.

In addition, physicians can identify all multiple pregnancies at an early stage and thus more efficiently determine whether the fetuses are mono or dizygotic, which affects pregnancy management. Further, performing an ultrasound during the first trimester also helps eliminate “post-dates” pregnancy, those going beyond 42 weeks’ gestation.

Because of the overwhelming evidence in favor of first trimester screening, the Maternal Fetal Medicine (MFM) Department at Lancaster General Women & Babies Hospital has offered that screening protocol since the practice was established in 2003. With accreditation from the Fetal Medicine Foundation in the United Kingdom and the Society of Maternal Fetal Medicine, the staff of MFM has a wealth of knowledge and experience in first trimester screening.

Despite all of the advantages of screening during the first trimester, why do a number of large medical centers continue to offer only second trimester serum screening?

A principal reason is that for any screening process to be effective, patients must be counseled in an efficient and understandable way on the meaning of the test results. Even second trimester screening, which has been available for more than a decade, still poses challenges in counseling patients effectively. ACOG recommends that perinatal networks should be available to perform invasive testing and to follow up results. In addition, ultrasound measurement for nuchal translucency is a time-intensive procedure that can be difficult to obtain accurately, depending on the skill of the ultrasound center.

Recently published research studies, such as the FASTER trial, have generated further confusion among obstetrical providers by investigating several methods of combining first and second trimester screening tests to enhance detection rates and decrease false-positive rates. One protocol uses an integrated screening approach in which the pregnant woman has serum screening and ultrasonography at 10-13 weeks gestation and a triple or serum screening test at 15-19 weeks gestation. The results of the studies are only given to the patient after both screening tests are performed. In an alternative stepwise sequential screening protocol, the woman has an ultrasound and serum analysis at 10-13 weeks gestation and the results are given immediately. Based on those results, the woman can decide to have an amniocentesis performed promptly, or to wait for the triple or quadruple serum screen during the second trimester.

Combining the first and second trimester serum screening tests causes several problems. A woman who has had the first trimester serum screening has her risk calculated in comparison with an unscreened population. A second screening test would skew the results because the woman has already been screened, and the likelihood of finding Down syndrome has already been reduced by 90 percent. Furthermore, triple serum screening increases the likelihood—as much as 12 to 13 percent—of a false-positive result. Thus, in some instances a woman may have had a first trimester screening test that determined she was at low risk for having a fetus with Down syndrome, but after a triple or quadruple screening test was performed, she was considered to be at high risk.

Which is the preferred screening protocol? Most academic centers that use the sequential screening protocol calculate the risk based on the first trimester screening

results and then use that result as the starting point for the triple or quad screening test. This process may be feasible at large academic centers, but it is impractical in a community setting because the laboratories analyzing the blood work may not have the proper algorithms to calculate risk based on both screening tests. Further, do the screening tests remain valid when hCG is measured in both free β and regular forms during both trimesters? Are these two forms of hCG really independent markers? Many more questions arise than are answered by combining the results of both screening tests.

At Lancaster General Women & Babies Hospital, first trimester screening is available to all interested patients between 11 and 13 weeks gestation. We provide two calculations of risk, one for Down syndrome, and one combined calculation for trisomy 13 and trisomy 18. Based on those results, patients then have the option of having invasive testing (i.e. amniocentesis) for abnormal results, or second trimester screening for neural tube defects in the form of either a maternal serum α -feto-protein screen or a level II ultrasound. Most patients choose to have the level II ultrasound performed, which is a superior evaluation test.

Screening practices continue to adapt to reduce false-positive rates. Two additional first trimester ultrasound findings—absence of the nasal bone (figure 2) and presence of tricuspid valve regurgitation (figure 3)—show promise in reducing false-positive rates, because they occur in approximately 70% of fetuses with Down syndrome.

The MFM specialists at Lancaster General Women & Babies Hospital are currently in training to receive accreditation through the Fetal Medicine Foundation to screen for these two ultrasound findings. Our experience with these ultrasound techniques indicates that the nuchal translucency and nasal bone measurements can be obtained in up to 98 percent of the women screened. In 90 percent of women, we are able to observe the tricuspid valve for regurgitation. To ensure the reproducibility of these detailed fetal findings, both a registered ultrasound technician and physician evaluate each patient.

Although other ultrasound findings, such as ductus venosus blood flow, have been studied for their potential to decrease the false-positive rate even further, they are difficult to obtain on ultrasound. Implementation of further screening markers must await confirmation from clinical trials.

Interestingly, all the excitement that has been generated over first trimester screening may be for naught. In the next five years, first trimester screening may be replaced by direct noninvasive fetal diagnosis that simply looks at the mother's blood for free fetal DNA or free fetal cells. In regard to the latter, the ratio of mother's blood cells to fetal cells is low (1 fetal cell to 1 million maternal blood cells), and the process for isolating these cells is difficult, so this method of direct testing is not likely to produce a clinical test. On the other hand, detecting the free fetal DNA in the mother's system could prove to be a practical direct test. According to one study, up to 3 percent of the free DNA available in the mother's serum



Figure 2: The arrow highlights the presence of a nasal bone.

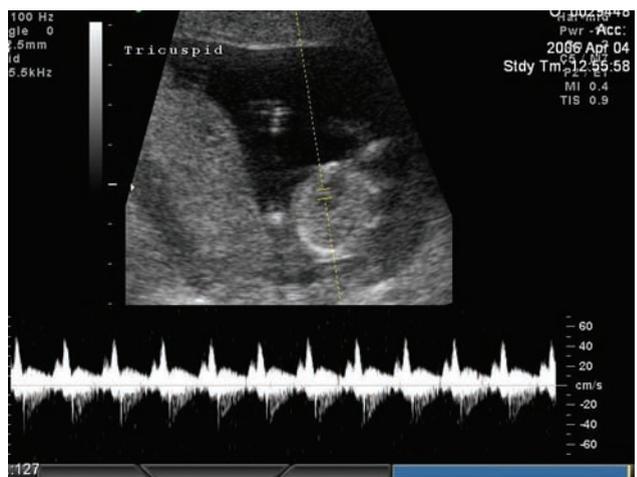


Figure 3: Doppler waveform of normal tricuspid valve flow.

is fetal DNA and could be used for testing, though this represents a very small amount of fetal DNA to process. Other studies have reported the ability to recover up to 20 to 50 percent or more of fetal DNA from a maternal blood sample, thus providing a much larger specimen size for chromosome testing. Similarly, researchers are investigating the acquisition of a sample of mothers' cervical mucus as a source for direct testing, since it contains cells from the placenta.

Currently, first trimester serum analysis is the best method for screening for chromosomal abnormalities during pregnancy. It has a higher detection rate and similar false-positive rate to second trimester screening, but provides the mother with earlier results. As screening practices continue to evolve, MFM physicians at Lancaster General Women & Babies Hospital will offer the newest advances and latest technologies in screening procedures.

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