Fetal Chromosomal Abnormalities: Antenatal Screening and Diagnosis

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Pregnant women of all ages should be offered screening and invasive diagnostic testing for chromosomal abnormalities before 20 weeks' gestation. New developments in screening methods have increased the number of options for patients. Diagnostic options include chorionic villus sampling in the first trimester and amniocentesis in the second trimester. Screening options in the first trimester include nuchal translucency testing in combination with measurement of pregnancy-associated plasma protein A and human chorionic gonadotropin. Nuchal translucency testing alone is not as effective. Screening options in the second trimester include serum screening using triple or quadruple screening, and ultrasonography. Patients may also choose a combination of first- and second-trimester screening in an integrated, stepwise sequential, or contingent sequential fashion. These options include an analysis of pregnancy-associated plasma protein A, with or without nuchal translucency testing, in combination with quadruple screening. An integrated test with nuchal translucency testing is the most effective method for women who present in the first trimester. If nuchal translucency testing is unavailable, the maternal serum-integrated test is safest and most effective. For women who do not present until the second trimester, the quadruple screen is recommended. Comprehensive counseling should be available to all pregnant women. Specific screening tests will depend on availability of the procedure and patient preference. (*Am Fam Physician*. 2009;79(2):117-123, 124.

▶ **Patient information:** A handout on genetic screening in pregnancy, written by the authors of this article, is provided on page 124.

Screening for fetal chromosomal abnormalities is an essential part of antenatal care. Historically, maternal age was the determinant of risk. Women older than 35 years at the time of delivery were offered genetic counseling and amniocentesis because of procedure-related loss rates. However, only 20 percent of infants with Down syndrome (trisomy 21) are born to women older than 35 years.[1] With the advent of maternal serum alpha-fetoprotein (AFP) testing in the mid-1980s, women younger than 35 years had an option for antenatal diagnosis.[2] In the past two decades, additional tests have been shown to increase the detection rate of chromosomal abnormalities while maintaining a low false-positive rate. This gives pregnant women of all ages the opportunity to undergo screening or invasive diagnostic testing before 20 weeks' gestation. *Table 1* provides a glossary of terms related to fetal screening.[3-6]

Invasive Diagnostic Testing

CHORIONIC VILLUS SAMPLING

Chorionic villus sampling (CVS) for genetic diagnosis is performed between 10 and 13 weeks' gestation. It allows for sampling of the placental tissue. There are two approaches to CVS: transabdominal and transcervical. Transcervical CVS has a higher incidence of spontaneous pregnancy loss, but it is the preferred method if the placenta is posterior or if the bowel inhibits a transabdominal approach. The main advantage of CVS is early and definitive chromosomal analysis.[3] However, it is an invasive test that carries a risk of pregnancy loss varying from 0.6 to 4.6 percent.[4]

CVS has an operator-dependent learning curve and may not be available in every community.[4] One study reported a 0.8 percent greater loss rate with CVS than with amniocentesis, and a cytogenetic diagnosis rate of 97.8 percent.[7] Although there have been concerns that CVS leads to limb

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendations	*Evidence rating*	*References*	*Comment*
Pregnant women should be offered screening and invasive diagnostic testing regardless of age.	B	5	Limited or inconsistent evidence
Combined testing is recommended for first-trimester screening.	A	45, 50, 51	Evidence-based practice guidelines
Quadruple screening is recommended for second-trimester screening.	A	5, 45, 50, 51	Evidence-based practice guidelines
Women with isolated nuchal thickening or isolated maternal serum AFP (with normal ultrasonography and normal karyotype) should be followed closely because they are at increased risk of poor pregnancy outcomes.	B	5	Limited or inconsistent evidence
Combined first- and second-trimester screening offers superior detection rates while maintaining low false-positive rates.	B	5, 45, 50, 51	Limited or inconsistent evidence
Genetics counseling and chorionic villus sampling or amniocentesis should be offered to all women with elevated risk, as determined by serum screening.	A	5, 45, 50, 51	Evidence-based practice guidelines
Women who pursue first-trimester screening alone should be offered maternal serum AFP testing in the second trimester to screen for neural tube defects.	A	5	Evidence-based practice guideline
Nuchal translucency testing and serum screening can be performed in multiple gestations, but they are less sensitive than first-trimester screening in singleton gestations.	B	5	Limited or inconsistent evidence

AFP = alpha-fetoprotein.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Table 1. Glossary of Terms

Term	*Definition*
Combined screening	Combination of nuchal translucency testing, serum measurement of PAPP-A and free or total hCG, and maternal age
Contingency screening	Nuchal translucency, PAPP-A, and hCG measurements are used to determine risk; no further testing is recommended in women at low risk of Down syndrome; maternal serum AFP should be performed in the second trimester to assess risk of neural tube defects
hCG	Hormone made from the fetal part of the placenta; elevated levels associated with increased risk of Down syndrome
Inhibin A	Hormone produced by the placenta; high levels associated with increased risk of Down syndrome
Integrated screening	Nuchal translucency testing and measurement of PAPP-A and hCG are integrated with the quadruple screen to produce a single risk result
Maternal serum AFP	Plasma protein found in mother's blood that is produced by the fetal liver; elevated levels associated with open neural tube defects, older than expected fetus (i.e., dating error), or multiple gestations; low levels associated with Down syndrome
Nuchal translucency	Thickness of the fluid under the skin of the fetal neck, measured by ultrasonography
PAPP-A	Zinc-binding protein that acts as an enzyme; low levels associated with increased risk of Down syndrome
Stepwise sequential screening	Nuchal translucency testing and measurement of PAPP-A and hCG are used to determine risk; if at increased risk, proceed directly to invasive testing; if not at increased risk, a second calculation with the addition of the quadruple screen produces another risk determination
Unconjugated estriol	Protein produced by the placenta and the fetal liver; low levels associated with Down syndrome

AFP = alpha-fetoprotein; hCG = human chorionic gonadotropin; PAPP-A = pregnancy-associated plasma protein A.

Information from references 3 through 6.

reduction defects, current data suggest that when performed between 10 and 13 weeks' gestation, there is no significant difference from the incidence in the general population (i.e., six in 10,000). CVS performed before 10 weeks' gestation increases the risk of limb reduction defects to 1 to 2 percent.[4]

AMNIOCENTESIS

Amniocentesis for genetic diagnosis is typically performed between 16 and 18 weeks' gestation, which is when the procedure is safest.[8] However, it can be performed from 14 to 20 weeks. During amniocentesis, a needle is inserted into the amniotic sac using ultrasound guidance, and amniotic fluid is aspirated.[3] The fetal loss rate associated with amniocentesis is often reported to be 1 percent,[9] although it has been reported to be as low as one in 370.[10] The cytogenetic diagnosis rate is reported to be 99.4 percent.[7] Complications are uncommon, but may include vaginal spotting, amniotic fluid leakage, chorioamnionitis, failure of fetal cells to grow in culture, fetal needle injury, and fetal loss.[3]

First-Trimester Screening

NUCHAL TRANSLUCENCY

Nuchal translucency refers to an ultrasonographic sonolucency in the posterior fetal neck.[11] The measurement is gestational-age dependent; on average, it increases 15 to 20 percent per week. Measuring nuchal translucency requires specialized training and certification to learn the standardized technique.[12] Having specific measurement guidelines helps maintain the detection rate of Down syndrome.[5] Using only nuchal translucency testing, there is a detection rate of approximately 70 to 71 percent for Down syndrome, with a 3.5 to 5 percent false-positive rate.[13,14] Increased nuchal translucency of greater than 3.5 mm is associated with major congenital heart defects, defects of the great vessels, fetal malformations, dysplasias, deformations, disruptions, and genetic syndromes.[15-17] Abnormal nuchal translucency may lead to an earlier diagnosis of congenital heart defects.[18] However, if aneuploidy is excluded and targeted ultrasonography at 20 to 22 weeks' gestation is normal, there is no significantly increased risk of adverse outcome.[17]

COMBINED SCREENING

Nuchal translucency testing should be combined with serum measurements of pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (hCG) during the first trimester to improve the detection rate of Down syndrome to 78.7 to 89 percent, with a false-positive rate of 5 percent.[19-22] Low levels of both markers are associated with adverse pregnancy outcomes, such as spontaneous loss before fetal viability, gestational hypertension, preeclampsia, preterm premature rupture of membranes, placental abruption, preterm birth, low birth weight, and stillbirth.[23,24]

In women younger than 35 years, combined screening is equivalent to quadruple screening for the detection of Down syndrome. In women older than 35 years, combined screening detects approximately 90 percent of Down syndrome, but the false-positive rate increases to 16 to 22 percent. For all women, the detection rate of combined screening for trisomy 18 is 90 percent, with a false-positive rate of 2 percent.[5] First-trimester screening affords the advantage of early diagnosis so that confirmatory testing can be undertaken. If desired, termination can be performed at an early gestational age, allowing greater privacy and less risk. The American College of Obstetrics and Gynecology (ACOG) recommends that first-trimester screening should be offered to patients only if appropriate sonographic training, ongoing quality assurance, sufficient comprehensive counseling, and diagnostic testing are available.[25] Most laboratories that offer serum analysis require certification and ongoing quality assurance by the ultrasonographer.[5]

Second-Trimester Screening

SERUM SCREENING

Second-trimester maternal serum testing includes the triple and quadruple screens. After the introduction of maternal serum AFP testing in the mid-1980s, hCG and unconjugated estriol testing were added, resulting in the triple screen.[26] The addition of inhibin A testing to the triple screen yielded the quadruple screen.[27,28] Serum screening is calculated using an algorithm based on the age, race, weight, and diabetic status of a patient. As early as 1996, the Agency for Healthcare Research and Quality recommended that all pregnant women be offered maternal serum screening for Down syndrome and neural tube defects if adequate counseling and follow-up are available.[29,30] Current data suggest that with a fixed screen-positive rate of 5 percent, the detection rate for Down syndrome is 69 percent for the triple screen and 81 percent for the quadruple screen.[5] Women with isolated elevated maternal serum AFP should be followed closely because they are at increased risk of poor pregnancy outcomes.[5]

The cytogenetic diagnosis rate of amniocentesis is more than 99 percent.

ULTRASONOGRAPHY

Ultrasonography may also be used for screening in the second trimester, either alone or as an adjunct to maternal serum testing. Targeted imaging for fetal anomalies can help determine whether invasive testing should be persued.[11,31] Various markers of fetal chromosomal abnormalities may be detected by ultrasonography (e.g., facial cleft, micrognathia, atrioventricular septal defects, echogenic bowel).[32-34] There have been attempts to identify patterns of sonographic findings and their associations.[35,36] A 2005 study reported that in the absence of any marker for Down syndrome, the risk of having an affected fetus is reduced 60 to 80 percent, because 75 percent of fetuses with Down syndrome can be detected using ultrasonography.[37]

Another study found a similar sensitivity rate of 79.9 percent, with a false-positive rate of 6.7 percent, when measuring nuchal fold thickness and proximal long bone length.[38] Nuchal fold thickening does not connote the risk level of Down syndrome found with nuchal translucency. However, women with isolated nuchal fold thickening with normal ultrasonography and normal karyotype should be followed closely because they are at increased risk of poor pregnancy outcomes.[5] When performed in combination with the quadruple screen, ultrasound sensitivity approaches 90 percent, with a 3.1 percent false-positive rate.[38] Other studies have placed the detection rate of ultrasonography at a more modest rate of 35 to 47 percent.[39,40]

In 1996, the U.S. Preventive Services Task Force found insufficient evidence to recommend for or against routine second-trimester ultrasonography in low-risk pregnancies.[41] It noted that ultrasonography in pregnancy has become common, and that updating the recommendation would have limited potential impact on clinical practice. A meta-analysis of 56 studies analyzing 1,930 fetuses with Down syndrome and 130,365 unaffected fetuses found that using ultrasonographic markers alone as a basis to offer amniocentesis would result in a decrease in perinatal detection of Down syndrome.[42]

Combined First- and Second-Trimester Screening

Further efforts to improve detection rates of aneuploidy with antenatal screening led to the combining of existing first- and second-trimester screening. With combined testing, detection rates are improved to 92 to 96 percent, with false-positive rates of 5 percent.[43,44]

INTEGRATED SCREENING

Integrated screening involves PAPP-A and nuchal translucency testing in the first trimester and the quadruple screen in the second trimester. After the first trimester tests are completed, the results are held until the quadruple screen is performed. A single risk determination is made using all available data and the patient's age-associated risk. Integrated serum screening uses PAPP-A and quadruple screening without nuchal translucency, if it is unavailable.

STEPWISE SEQUENTIAL SCREENING

Stepwise sequential screening combines PAPP-A and nuchal translucency testing with an age-associated risk to provide a risk determination in the first trimester. If the patient is at increased risk based on results of the first trimester PAPP-A and nuchal translucency testing, she may undergo invasive diagnostic testing or await the triple or quadruple screen in the second trimester for revised risk determination. If the patient chooses to undergo second-trimester serum testing, a second risk determination is made with all available data.

CONTINGENCY SCREENING

Contingency screening also involves PAPP-A and nuchal translucency testing with an age-associated risk to provide a risk determination in the first trimester. However, with contingency testing, the risk determination is stratified. If the risk is above a certain cut-off, invasive diagnostic testing is offered. If the risk is below a second cut-off, the patient is told that no further testing is required. If the patient's risk determination falls between these two cut-offs, then second-trimester maternal serum screening is advised.[24,44,45]

Recommendations

New guidelines have been released in response to the availability of these testing strategies. *Table 2* summarizes available testing options.[5,7-9,13,14,20,23,37,39,40,43,46-49] The British Medical Association recommends the integrated test or the serum-integrated test if nuchal translucency testing is not available.[50,51] For women presenting in the second trimester, the quadruple screen is recommended. For first-trimester screening, the combined test is recommended. The triple screen or nuchal translucency testing alone are not recommended. The National Collaborating Centre for Women's and Children's Health makes similar recommendations.[52] It acknowledges that the integrated test is cost-effective and results in the fewest losses of normal fetuses. However, because of concerns about the practicality of the integrated test and because most women prefer a one-stage test, it recommends combined testing in the first trimester and the quadruple or triple screen in the second trimester.[52]

ACOG released its most recent recommendations in January 2007, stating that the combined test is comparable to the quadruple test for screening.[5] The recommendations also state that nuchal translucency testing is less effective than the combined test, and it requires training, standardization, and ongoing quality assessment. Women who are identified as high risk with first-trimester screening should be offered invasive diagnostic testing and genetics counseling. Women who elect to undergo the combined test alone still need maternal serum AFP testing for neural tube defects in the second trimester. Additional recommendations include offering all women screening and invasive diagnostic testing before 20 weeks' gestation.

Advantages of antenatal screening include increasing the odds of identifying an abnormal fetus and reducing the number of invasive diagnostic tests and procedure-related losses of normal fetuses. The disadvantage of screening is that not all aneuploid fetuses are identified with screening. Because of this, all patients have the option of proceeding directly with invasive testing. ACOG notes that integrated testing is better than first-trimester screening alone, and that if nuchal translucency testing is unavailable, serum-integrated testing is a useful option.[5] Abnormal second-trimester ultrasonography warrants counseling and offering a diagnostic procedure. If the nuchal translucency is greater than or equal to 3.5 mm, invasive diagnostic testing should be offered, and if it is normal, targeted ultrasonography, fetal echocardiography, or both should be offered.

First- or second-trimester testing can be performed on multiple gestations, but it is less sensitive because the maternal serum value may represent an average of normal and abnormal fetuses, thus masking the abnormal result. Nuchal translucency testing for multiple gestations is feasible, with invasive diagnostic testing to follow if indicated and desired by the patient. First- and second-trimester screening for Down syndrome is not indicated unless it is offered as part of integrated, stepwise, or contingent testing.[5]

Based on these recommendations, all pregnant women should be offered screening for aneuploidy. It is important

Table 2. Available Options for Antenatal Testing

Test	*Timing (weeks)*	*Detection rate of Down syndrome (%)*	*False-positive rate (%)*
First trimester			
Chorionic villus sampling	10 to 13	97.8	1 to 2
Nuchal translucency	10-4/7 to 13-6/7	70 to 71	3.5 to 5
hCG and PAPP-A	10 to 12	53 to 58	5
hCG, PAPP-A, and nuchal translucency	11 to 14	78.7 to 89	Less than 3 to 5
Second trimester			
Amniocentesis	16 to 18	99.4	0.1 to 0.6
Triple screen (hCG, maternal serum AFP, unconjugated estriol)	15 to 20	60 to 69	5
Quadruple screen (hCG, inhibin A, maternal serum AFP, unconjugated estriol)	15 to 20	67 to 81 (up to 90 with ultrasonography)	Less than 3 to 5
Ultrasonography	18 to 22	35 to 79	6.7
First and second trimester			
Integrated serum screening (PAPP-A with nuchal translucency)	11 to 14 and 15 to 20	94 to 96	Less than 3 to 5
Integrated serum screening (PAPP-A without nuchal translucency)	11 to 14 and 15 to 20	85 to 88	Less than 3 to 5
Stepwise sequential screening (PAPP-A with nuchal translucency)	11 to 14 and 15 to 20	95	5
Contingency screening (PAPP-A with nuchal translucency)	11 to 14 and 15 to 20	92	5

AFP = alpha-fetoprotein; hCG = human chorionic gonadotropin; PAPP-A = pregnancy-associated plasma protein A.

Information from references 5, 7 through 9, 13, 14, 20, 23, 37, 39, 40, 43, and 46 through 49.

to review which tests are locally available.[5] Patients may benefit from the expertise of a genetics counselor because comprehensive counseling can be difficult during a short office visit. Understanding patients' worldviews is essential, as is discussing early diagnosis and options for termination, and recognizing that not all patients will desire screening. Minimizing the risk of the screening and maximizing safety is also crucial.[1,44,46] With the advent of first-trimester options, patients will need to choose early and be comfortable with their choice.

Pregnant women have the option of undergoing invasive testing without previous screening tests, because screening does not always identify aneuploidy.

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