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Practice Guidelines

ACOG Releases Guidelines on Screening for Fetal Chromosomal Abnormalities

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Various Down syndrome screening and diagnostic tests have been developed over the past 10 years, and the use of combined ultrasonography and serum markers has been assessed. Some physicians offer these tests only to women of a certain age, a practice that is controversial. The American College of Obstetricians and Gynecologists (ACOG) has developed guidelines that evaluate the use of ultrasonography and serum markers for selected aneuploidy screening in pregnant women, and that provide recommendations for the use of Down syndrome screening.

Women 35 years and older are typically considered to be at highest risk of having a child with Down syndrome. Screening methods for these women include chorionic villus sampling (CVS) or genetic counseling and amniocentesis. Women younger than 35 can be screened using human chorionic gonadotropin (hCG) and unconjugated estriol combined with maternal serum alpha-fetoprotein levels. When all three of these markers are used (i.e., the triple screen), the detection rate for Down syndrome is about 70 percent, with about 5 percent of all pregnancies having a positive screening result. Adding inhibin A to the triple screen (i.e., quadruple screen) can improve the detection rate for Down syndrome to about 80 percent. Screening with biochemical markers, ultrasonography, or both is increasingly being offered to provide a more accurate risk assessment. These screening tests also have higher sensitivities and lower false-positive rates.

Studies have found that, in the first trimester, there is an association between the size of fluid collection at the back of the fetal neck (i.e., nuchal translucency) and trisomy 21 risk. Large studies have shown that nuchal translucency can be combined with free beta-hCG and

pregnancy-associated plasma protein A (PAPP-A) to screen for Down syndrome. PAPP-A and hCG measurements are effective for screening only in the first trimester, and alpha-fetoprotein, unconjugated estriol, and inhibin are useful only in the second trimester (Table 1).

Table 1
Down Syndrome Screening Tests and Detection Rates

Screening test	**Detection rate (%)**
First trimester	
NT measurement	64 to 70
NT measurement, PAPP-A, free or total beta-hCG	82 to 87
Second trimester	
Triple screen (maternal serum alpha-fetoprotein, hCG, unconjugated estriol)	69
Quadruple screen (maternal serum alpha-fetoprotein, hCG, unconjugated estriol, inhibin A)	81
First and second trimesters	
Integrated (NT, PAPP-A, quadruple screen)	94 to 96
Serum integrated (PAPP-A, quadruple screen)	85 to 88
Stepwise sequential	95
First-trimester test result:	
Positive: diagnostic test offered	
Negative: second-trimester test offered	
Final: risk assessment incorporates first- and second-trimester results	
Contingent sequential	88 to 94
First-trimester test result:	
Positive: diagnostic test offered	
Negative: no further testing	
Intermediate: second-trimester test offered	
Final: risk assessment incorporates first- and second-trimester results	

NT = nuchal translucency; PAPP-A = pregnancy-associated plasma protein A; hCG = human chorionic gonadotropin.

note:Detection rates are based on a 5 percent positive screen rate.

Adapted with permission from ACOG Committee on Practice Bulletins. Screening for fetal chromosomal abnormalities. Obstet Gynecol 2007;109:218.

Recommendations and Supporting Evidence

ANEUPLOIDY SCREENING

All women, regardless of age, should be offered aneuploidy screening before 20 weeks' gestation. Before determining which screening tests to offer, physicians should evaluate the

evidence behind recommendations for testing and test availability, and they should assess which test best meets the needs of the patient. Women seen during the second trimester are limited to ultrasonography or quadruple screening. Those seen in the first trimester can be offered both first- and second-trimester screening tests.

When discussing options with patients, physicians should provide information on detection and false-positive rates, advantages and disadvantages, limitations, and the risks and benefits of each screening test and diagnostic procedure so that the patient can make an informed decision. Choosing a screening test can depend on many factors, such as gestational age, number of fetuses, obstetric history, family history, test availability, test sensitivity and limitations, risk of invasive diagnostic procedures, desire for early test results, and options for early termination. Some patients may benefit from meeting with a genetics or maternal-fetal medicine specialist.

Screening typically provides information about the patient's age-related risk; serum analyte levels; and, if available, nuchal translucency measurements. A numeric risk assessment allows the patient to determine the risk and consequences of giving birth versus proceeding with diagnostic testing. If useful, the patient can compare her personal age-related risk with that of the general population.

ANEUPLOIDY SCREENING VS. DIAGNOSTIC TESTING

Aneuploidy screening can identify fetuses that are at an increased risk of Down syndrome and trisomy 13 or 18. If the screening test is positive and the patient chooses to proceed with a diagnostic procedure (e.g., CVS, amniocentesis), there is a higher chance of discovering an aneuploid fetus than if the woman had not undergone screening. If screening is done, fewer invasive diagnostic procedures would be needed to find a fetus with aneuploidy, and performing fewer diagnostic tests would reduce the number of procedure-related losses of normal fetuses. However, screening will not identify all affected fetuses. Diagnostic testing has the ability to detect all autosomal trisomies and reliably detect sex chromosome aneuploidies, large deletions and duplications of chromosomes, and mosaicism.

NUCHAL TRANSLUCENCY MEASUREMENTS

The best time to perform nuchal translucency measurements is at 12 to 13 weeks' gestation. Although nuchal translucency measurement alone is a good detector of Down syndrome, trials have shown even higher detection rates and lower false-positive rates when it is combined with biochemical markers. Nuchal translucency measurements also may be useful for assessing multiple pregnancies in which serum screening is not as accurate or is unavailable.

FIRST-TRIMESTER SCREENING

Combined screening (nuchal translucency measurements, serum markers [PAPP-A and beta-hCG], and maternal age) is effective for testing for Down syndrome. For women younger than 35, combined screening in the first trimester has a detection rate similar to that of quadruple screening in the second trimester. For women 35 years and older, combined screening has a detection rate of 90 percent, but it has a higher screen-positive rate (16 to 22 percent).

One advantage of first-trimester screening is the earlier availability of information. Also, if the woman is at increased risk of fetal aneuploidy, genetic counseling and CVS, as well as second-trimester amniocentesis, can be offered.

EVALUATION AFTER FIRST-TRIMESTER SCREENING

Genetic counseling and CVS or second-trimester amniocentesis should be offered to women who are found to have an increased risk of aneuploidy during first-trimester screening. Those who have chosen to have only one screening in the first trimester or who have had normal results from CVS should be offered neural tube defect screening (e.g., ultrasonography, serum alpha-fetoprotein levels) in the second trimester. Women should be offered targeted ultrasonography, fetal echocardiography, or both if they have a fetal nuchal translucency measurement of at least 3.5 mm despite other factors (e.g., negative result on aneuploidy screen, normal fetal chromosomes) because these fetuses are at a significant risk of congenital heart defects, abdominal wall defects, diaphragmatic hernias, and genetic syndromes.

It is unknown if ultrasonography in the second trimester is helpful if the first-trimester screenings are negative. Down syndrome has been associated with a variety of ultrasound markers. Major findings (e.g., cardiac defect) may require further assessment, whereas lesser findings or "soft markers" (e.g., pyelectasis, shortened femur) are not significantly associated with Down syndrome. However, even the lesser findings should be evaluated in the context of all other screening results, as well as patient age and medical history.

INTEGRATED SCREENING

Integrated screening is when first- and second-trimester markers are used to adjust the patient's age-related risk and are reported after both first- and second-trimester tests are done. Integrated screening can be performed using serum markers from the first and second trimesters. One trial found that integrated screening using only serum had a detection rate of 85 to 88 percent; another trial found that, in a population of patients with limited access to CVS, serum-only screening was acceptable to most patients.

Integrated screening has the highest detection rate and lowest false-positive rate. However, there is a longer wait time (three to four weeks) between initiation and completion of screening, which may cause increased anxiety for some patients. The patient also loses the ability to consider CVS if the first-trimester screening detects a high risk of fetal aneuploidy. Additionally, patients who choose not to continue with screening in the second trimester would be left with no screening results.

SEQUENTIAL SCREENING

There are two types of sequential screening: stepwise and contingent. With stepwise screening, high-risk patients can opt out of continued screening and instead receive genetic counseling and diagnostic testing, and low-risk patients can continue with second-trimester screening. With contingent screening, pregnancy is classified as low, intermediate, or high risk based on first-trimester screening results. Women at high risk are offered CVS, women at intermediate risk are

offered continued screening in the second trimester, and women at low risk have no further testing. In theory, contingent-type sequential testing would maintain a higher detection rate while reducing the number of second-trimester screening tests being performed. However, results of large studies of contingent sequential screening have yet to be published.

ULTRASOUND MARKERS

First Trimester

Potential markers for Down syndrome include nonvisualized nasal bone, tricuspid regurgitation, crown-rump length, femur and humeral length, head and trunk volume, and umbilical cord diameter. Although studies of high-risk fetuses have shown an association between nonvisualization of the nasal bone and Down syndrome, nasal bone assessment in the general population is controversial. Nasal bone assessment could be a more useful tool if testing was standardized, if there were more intense training methods for physicians, and if quality-control programs were initiated.

Second Trimester

Second-trimester ultrasound markers have low sensitivity and specificity for detecting Down syndrome, especially in a low-risk population. The highest detection rate is acquired with ultrasound markers combined with gross anomalies. Although the detection rate with this combination of markers is high in a high-risk population (50 to 75 percent), false-positive rates are also high (22 percent for a 100 percent Down syndrome detection rate). Relying only on ultrasonography to identify Down syndrome is not recommended; one study found that major fetal anomalies are often missed. Use of second-trimester ultrasound markers is also limited by a lack of standardized measurements and definitions, which contributes to inconsistency in diagnosing. Therefore, risk adjustment based on these markers should be limited to experts and clinical research centers, so that they help standardize their use.

SCREENING IN MULTIPLE PREGNANCIES

Data on multiple pregnancies with one aneuploid fetus are limited; therefore, when performing screening tests, analyte levels must be estimated. Additionally, analytes from all the fetuses will enter the mother's serum and will be averaged, which could hide the abnormal levels of the aneuploid fetus. Therefore, serum screening is not as sensitive in multiple pregnancies as it is in single pregnancies. Counseling also could prove more difficult because women who are pregnant with one or more normal fetuses and one aneuploid fetus have different screening and diagnostic options. Until further evaluation is performed, assessing risk in multiple pregnancies should be done cautiously.

Conclusion

Maternal age of 35 years should not be used as a cutoff for offering diagnostic testing. The decision to offer screening or invasive testing should not be based on age alone but should take into account patient preferences. The goal is to offer screening tests with high detection rates and

low false-positive rates that also provide patients with the diagnostic options they might want to consider, with women being offered integrated or sequential screening earlier in their pregnancies. Other screening options will depend on CVS availability and physician expertise with nuchal translucency measurement.