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Screening for Fetal Chromosomal Abnormalities

In the past decade, numerous markers and strategies for Down syndrome screening have been developed. Algorithms that combine ultrasound and serum markers in the first and second trimesters have been evaluated. Furthermore, the practice of using age cutoffs to determine whether women should be offered screening or invasive diagnostic testing has been challenged. The purpose of this document is to 1) present and evaluate the best available evidence for the use of ultrasonographic and serum markers for selected aneuploidy screening in pregnancy and 2) offer practical recommendations for implementing Down syndrome screening in practice.

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Obstetrics, the ACOG Committee on Genetics, and the Society for Maternal–Fetal Medicine Publications Committee with the assistance of Ray Bahado-Singh, MD, and Deborah Driscoll, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

The Society for Maternal-Fetal Medicine

Background

Historically, maternal age 35 years or older at the time of delivery has been used to identify women at highest risk of having a child with Down syndrome, and these women have been offered genetic counseling and amniocentesis or chorionic villus sampling (CVS). Biochemical serum screening for Down syndrome in women younger than 35 years was introduced in 1984, when an association between low maternal serum alpha-fetoprotein (AFP) levels and Down syndrome was reported (1). In the 1990s, human chorionic gonadotropin (hCG) and unconjugated estriol were used in combination with maternal serum AFP to improve the detection rates for Down syndrome and trisomy 18. The average maternal serum AFP level in Down syndrome pregnancies is reduced to 0.74 multiples of the median (MoM) observed in euploid pregnancies (2). Intact hCG is increased in affected pregnancies, with an average level of 2.06 MoM, whereas unconjugated estriol is reduced to an average level of 0.75 MoM (2). When the levels of all three markers (triple test) are used to modify the mater-

nal age-related Down syndrome risk, the detection rate for Down syndrome is approximately 70%; approximately 5% of all pregnancies will have a positive screen result. Typically, the levels of all three markers are reduced when the fetus has trisomy 18. Adding inhibin A to the triple test (quadruple screen) improves the detection rate for Down syndrome to approximately 80%. The median value of the maternal inhibin A level is increased at 1.77 MoM in Down syndrome pregnancies (3), but inhibin A is not used in the calculation of risk for trisomy 18. Screening with biochemical markers, ultrasonography, or both is being offered increasingly to the entire pregnant population to provide a more accurate estimate of individual Down syndrome risk. Higher sensitivity or detection rates (defined as the percentage of Down syndrome pregnancies identified with a positive test result) at low false-positive rates have led to increased use of screening and a decline in the number of amniocenteses performed.

Studies done in the early and mid-1990s revealed a strong association between the size of a fluid collection at the back of the fetal neck in the first trimester, referred to as "nuchal translucency," and the risk of trisomy 21 (4). An increase in nuchal translucency is now widely recognized to be an early presenting feature of a broad range of fetal chromosomal, genetic, and structural abnormalities. However, considerable variability in the detection rates for Down syndrome among the early studies of nuchal translucency measurement limited the practical utility of the test (5). Now guidelines for the systematic measurement of nuchal translucency have been standardized (6). Specific training for a standardized method of measurement and ongoing audits of examination quality are recommended for screening programs that include nuchal translucency measurement (7). Other first-trimester ultrasonographic markers such as nonvisualization of the nasal bone and tricuspid regurgitation are being evaluated for their potential as screening tests for Down syndrome, but their clinical usefulness remains uncertain.

A significant breakthrough in first-trimester screening for Down syndrome was achieved when large studies in the United States and the United Kingdom demonstrated that, when expressing the nuchal translucency measurement as an MoM, it could be combined with two first-trimester serum analytes, free β-hCG and pregnancy-associated plasma protein A (PAPP-A). The average level of free β-hCG in first-trimester Down syndrome pregnancies is elevated to 1.98 MoM (8), and the average level of PAPP-A, a glycoprotein that, like hCG, is produced by the trophoblast, is reduced to approximately 0.43 MoM (9). Maternal serum analytes, PAPP-A, and hCG or free β-hCG are effective for screening in the first trimester, whereas AFP, unconjugated estriol, and inhibin A are useful only in the second trimester.

Several approaches to Down syndrome screening in the first and second trimesters have been evaluated and are described in this document (Table 1). Not all strategies include nuchal translucency measurement because this screening approach is not available in all regions due to the need for specialized training to obtain it, and this measurement might not be obtained successfully in an individual patient.

Table 1. Down Syndrome Screening Tests and Detection Rates (5% Positive Screen Rate)

Screening Test	Detection Rate (%)
First Trimester	
NT measurement	64–70*
NT measurement, PAPP-A, free or total β-hCG†	82–87*
Second trimester	
Triple screen (MSAFP, hCG, unconjugated estriol)	69*
Quadruple screen (MSAFP, hCG, unconjugated estriol, inhibin A)	81*
First Plus Second Trimester	
Integrated (NT, PAPP-A, quad screen)	94–96*
Serum integrated (PAPP-A, quad screen)	85–88*
Stepwise sequential	95*
First-trimester test result:	
Positive: diagnostic test offered	
Negative: second-trimester test offered	
Final: risk assessment incorporates first and second results	
Contingent sequential	88–94%‡
First-trimester test result:	
Positive: diagnostic test offered	
Negative: no further testing	
Intermediate: second-trimester test offered	
Final: risk assessment incorporates first and second results	

Abbreviations: hCG, human chorionic gonadotropin; MSAFP, maternal serum alpha-fetoprotein; NT, nuchal translucency; PAPP-A, pregnancy-associated plasma protein A; quad, quadruple.

*From the FASTER trial (Malone F, Canick JA, Ball RH, Nyberg DA, Comstock CH, Buckowski R, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. First- and Second-Trimester Evaluation of Risk (FASTER) Research Consortium. N Engl J Med 2005;353:2001–11.)

†Also referred to as combined first-trimester screen

‡Modeled predicted detection rates (Cuckle H, Benn P, Wright D. Down syndrome screening in the first and/or second trimester: model predicted performance using meta-analysis parameters. Semin Perinatol 2005;29:252–7.)

Clinical Considerations and Recommendations

▶ *Should all patients be counseled about screening for aneuploidy?*

Ideally, all women should be offered aneuploidy screening before 20 weeks of gestation, regardless of maternal age. It is not practical to have patients choose from among the large array of screening strategies that might be used. Before deciding which strategy or strategies to offer patients, review the evidence presented in this document, identify which tests are available in your area, and determine which strategy or strategies will best meet the needs of your patients. The options for women who are first seen during the second trimester are limited to quadruple (or "quad") screening and ultrasound examination. A strategy that incorporates both first- and second-trimester screening should be offered to women who seek prenatal care in the first trimester.

Regardless of which screening tests you decide to offer your patients, information about the detection and false-positive rates, advantages, disadvantages, and limitations, as well as the risks and benefits of diagnostic procedures, should be available to patients so that they can make informed decisions. Patients may decline Down syndrome screening because they would not use the information in deciding whether to have a diagnostic test or because they wish to avoid the chance of a false-positive screening test result. The choice of screening test depends on many factors, including gestational age at first prenatal visit, number of fetuses, previous obstetric history, family history, availability of nuchal translucency measurement, test sensitivity and limitations, risk of invasive diagnostic procedures, desire for early test results, and options for earlier termination. Some patients may benefit from a more extensive discussion with a genetics professional or a maternal–fetal medicine specialist, especially if there is a family history of a chromosome abnormality, genetic disorder, or congenital malformation.

▶ *What are the advantages and disadvantages of screening for aneuploidy compared with diagnostic testing?*

Screening for aneuploidy identifies a population of women whose fetuses are at increased risk for Down syndrome, trisomy 18, or trisomy 13. If women who have had a positive screening test result choose to undergo a diagnostic procedure, such as CVS or amniocentesis, there is a higher chance of identifying an affected fetus than there would be if the diagnostic test was performed in an unscreened population. Fewer invasive procedures will be required to identify an aneuploid fetus in patients who have screening, thus resulting in a decreased number of procedure-related losses of normal fetuses.

The main disadvantage of screening approaches for the detection of aneuploidies is that not all affected fetuses will be detected. Although the currently available approaches have relatively high detection rates (sensitivity) at low screen positive rates, women should understand that screening provides an individual risk assessment but is not diagnostic and thus will not detect all chromosomal abnormalities. Counseling should be provided regarding the specific detection rates and false-positive rates of the screening strategy or strategies they are considering.

In comparison with the sensitivity of screening, the main advantage of invasive diagnostic testing is that all autosomal trisomies will be detected. Diagnostic testing also will reliably detect sex chromosome aneuploidies, large deletions or duplications of chromosomes, and chromosomal mosaicism. However, in an unscreened population, more invasive procedures will be performed for each affected fetus identified, resulting in a greater loss of normal fetuses when compared with a screened population. Patients informed of the risks, particularly those at increased risk of having an aneuploid fetus, may opt to have diagnostic testing without first having screening.

▶ *How are aneuploidy screening test results interpreted?*

Laboratories that report screening test results generally provide the clinician with numerical information regarding the patient's age-related risk and a revised risk assessment based on age, the serum analyte levels, and nuchal translucency measurement if available. Communicating a numerical risk assessment after screening enables women and their partners to balance the risk and the consequences of having a child with the particular problem against the risk and consequences of an invasive diagnostic test. Because this decision involves personal values, it is preferable to provide patients with their numerical risk determined by the screening test, rather than a positive versus negative screening result using an arbitrary cutoff. It is often useful to contrast this risk with the general population risk and their age-related risk before screening.

Screening test results may be reported as screen positive or screen negative based on fixed cutoff values. The use of fixed cutoffs in clinical studies is of value because they provide a basis for comparison of sensitivity (detection rates), false-positive rates, and acceptability to patients within various study groups or between different studies. Often these fixed cutoffs have been

arbitrarily selected at levels that are comparable with the risk for women at certain ages and seem to provide an appropriate balance against the risk of pregnancy loss as the result of an invasive diagnostic test. Fixed screening cutoffs also are useful in public policy considerations when the benefits, risks, and costs in a population are being considered.

▶ *Is nuchal translucency measurement alone a sensitive screening test for aneuploidy in the first trimester?*

Despite the relatively high detection rate using nuchal translucency measurement alone, recent trials in the United States and the United Kingdom demonstrate improved detection of Down syndrome at lower false-positive rates when nuchal translucency measurement is combined with biochemical markers. Nuchal translucency measurements may be useful in the evaluation of multifetal gestations, for which serum screening is not as accurate (twins) or is unavailable (triplets or higher), compared with a singleton gestation.

Use of standardized techniques for measuring nuchal translucency has resulted in higher detection rates for Down syndrome, trisomy 18, trisomy 13, and Turner's syndrome. The optimal time to schedule nuchal translucency measurement appears to be 12–13 weeks of gestation, although the measurement is valid from 10⅐ to 13⅐ weeks. Training is required to learn standardized techniques for measuring nuchal translucency, and specific guidelines for measuring it must be adhered to in order to maintain the detection rate. This has resulted in Down syndrome detection rates of 72% at a screen-positive rate of 5% in an unselected population (10). In addition, 74.8% of trisomy 18 cases, 72% of trisomy 13 cases, 87% of Turner's syndrome cases, 59% of triploidy cases, and 55% of other significant chromosomal defects were detected. A recent review of prospective first-trimester screening studies performed in the past 10 years, which included 871 Down syndrome cases, reported a Down syndrome detection rate with nuchal translucency measurement alone of 76.8%, with a screen- positive rate of 4.2% (11). Among first-trimester fetuses with increased nuchal translucency measurement, approximately one third will have chromosome defects. Down syndrome accounts for approximately 50% of these chromosomal disorders (10).

▶ *What is the sensitivity of first-trimester screening?*

Several large, multicenter trials have shown that, in the first trimester, a combination of nuchal translucency measurement, serum markers (PAPP-A and free or total β-hCG), and maternal age is a very effective screening test for Down syndrome (Table 2). This approach has been called combined screening. The detection rates for first-trimester Down syndrome screening are comparable to the second-trimester quadruple screen for women younger than 35 years at the time of delivery. For older women (35 years or older), the detection rate is approxi-

Table 2. Combined First-Trimester Screening Prospective Study Outcomes*

Study	Patients	Down Syndrome Cases	Detection Rate† (%)
BUN‡	8,216	61	79
FASTER§	33,557	84	83
SURUSS¶	47,053	101	83
OSCAR#	15,030	82	90
Total	103,856	328	84

*First-trimester detection rate (DR) at 5% of false-positive rate (FPR)

†95% CI: 79.7–87.0%

‡Wapner RJ, Thom EA, Simpson JL, Pergament E, Silver R, Filkins K, et al. First-trimester screening for trisomies 21 and 18. First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening (BUN) Study Group. N Engl J Med 2003;349:1405–13.

§Malone FD, Wald NJ, Canick JA, Ball RH, Nyberg DA, Comstock CH, et al. First- and second-trimester evaluation of risk (FASTER) trial: principal results of the NICHD multicenter Down syndrome screening study [abstract]. Am J Obstet Gynecol 2003;189:(suppl 1):s56.

¶Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS) [published erratum appears in J Med Screen 2006;13:51–2]. J Med Screen 2003;10:56–104.

#Spencer K, Spencer CE, Power M, Dawson C, Nicolaides KH. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years prospective experience. BJOG 2003;110:281–6.

Reprinted from: Wapner RJ. First trimester screening: the BUN study. Semin Perinatol 2005;29:236–9. With permission from Elsevier.

mately 90%, but at a higher screen-positive rate (approximately 16–22%) (12, 13). For women of all ages, 90% of trisomy 18 cases are detected at a 2% screen-positive rate (13).

▶ *What is the advantage of first-trimester screening?*

The advantage of first-trimester screening is that women who present for prenatal care before 14 weeks of gestation can have information sooner. If the woman is found to be at an increased risk of fetal aneuploidy, she can be offered genetic counseling and CVS, if the procedure is available. Alternatively, she may choose to have a second-trimester amniocentesis.

▶ *Should first- and second-trimester screening tests be performed independently?*

When first-trimester and second-trimester screening tests are performed during the pregnancy and interpreted independently, there is a high Down syndrome detection rate (94–98%); however, the false-positive rates are additive, leading to many more unnecessary invasive procedures (11–17%) (12, 14). For this reason, women who have had first-trimester screening for aneuploidy should not undergo independent second-trimester serum screening in the same pregnancy. Instead, women who want a higher detection rate can have an integrated or a sequential screening test, which combines both first- and second-trimester screening results.

▶ *What is integrated screening?*

The "integrated" approach to screening uses both the first-trimester and second-trimester markers to adjust a woman's age-related risk of having a child with Down syndrome (15). The results are reported only after both first- and second-trimester screening tests are completed. In the FASTER (First- and Second-Trimester Evaluation of Risk) trial, the detection rate was 94–96% at a 5% screen-positive rate (12). Similar results were achieved in the SURUSS (Serum, Urine, and Ultrasound Screening Study) trial (16). Further refinements in interpretation may result in additional sensitivity and reduction of screen-positive rates.

Integrated screening also can be performed using only first- and second-trimester serum markers, without incorporating a nuchal translucency measurement. In the FASTER trial, the serum integrated screen resulted in an 85–88% detection rate (12). This approach is ideal for patients without access to nuchal translucency measurement or for whom reliable measurement cannot be obtained. A recent prospective trial of serum-only integrated screening in a population with limited access to CVS reported acceptance of this screening algorithm by most patients surveyed (17).

▶ *What are the advantages and disadvantages of having an integrated first- and second-trimester Down syndrome screening test (first- and second-trimester markers analyzed together [integrated], with only one result given in the second trimester)?*

Integrated screening best meets the goal of screening by providing the highest sensitivity with the lowest false-positive rate. The lower false-positive rate results in fewer invasive tests and thus fewer procedure-related losses of normal pregnancies (12, 18). Although some patients value early screening, others are willing to wait several weeks if doing so results in an improved detection rate and less chance that they will need an invasive diagnostic test (19). Concerns about integrated screening include possible patient anxiety generated by having to wait 3–4 weeks between initiation and completion of the screening and the loss of the opportunity to consider CVS if the first-trimester screening indicates a high risk of aneuploidy (20). The possibility that patients might fail to complete the second-trimester portion of the screening test after performing the first-trimester component is another potential disadvantage because the patient would be left with no screening results.

▶ *Is there an advantage to using a sequential screening test for Down syndrome?*

Sequential screening approaches that obviate some of the disadvantages of integrated screening have been developed. With this strategy, the patient is informed of the first-trimester screening result. Those at highest risk might opt for an early diagnostic procedure and those at lower risk can still take advantage of the higher detection rate achieved with additional second-trimester screening.

Two strategies have been proposed: "stepwise sequential screening" and "contingent sequential screening." In the stepwise model, women determined to be at high risk (Down syndrome risk above a predetermined cutoff) after the first-trimester screen are offered genetic counseling and the option of invasive diagnostic testing, and women below the cutoff are offered second-trimester screening. Contingent sequential screening has been proposed as a model, but large clinical trials using this approach have not yet been published. The contingent model classifies pregnancy risk as high, intermediate, or low on the basis of the first-trimester screen results; women at high risk would be offered CVS, and those at low risk would have no further screening or testing. Only women at intermediate risk

would be offered second-trimester screening. Hence, fewer women would go on to second-trimester screening. In both the stepwise and contingent models, the patients at highest risk identified by first-trimester screening are offered an early diagnostic procedure. Both first- and second-trimester results are used to calculate a final risk for aneuploidy in patients at lower risk. The sequential approach takes advantage of the higher detection rate achieved by incorporating the first- and second-trimester results with only a marginal increase in the false-positive rate. Theoretically, the contingent approach should maintain high detection rates with low false-positive rates while reducing the number of second-trimester tests performed.

▶ *What subsequent evaluation should be offered after first-trimester screening?*

Women found to have an increased risk of aneuploidy with first-trimester screening should be offered genetic counseling and diagnostic testing by CVS or a second-trimester genetic amniocentesis. Neural tube defect screening should be offered in the second trimester to patients who elected to have only first-trimester screening for aneuploidy or who have had a normal result from CVS. Neural tube defect screening may include second-trimester serum AFP screening or ultrasonography. Patients who have a fetal nuchal translucency measurement of 3.5 mm or greater in the first trimester, despite a negative result on an aneuploidy screen, normal fetal chromosomes, or both, should be offered a targeted ultrasound examination, fetal echocardiogram, or both, because such fetuses are at a significant risk for nonchromosomal anomalies, including congenital heart defects, abdominal wall defects, diaphragmatic hernias, and genetic syndromes (21–25).

Patients with abnormal first-trimester serum markers or an increased nuchal translucency measurement also may be at increased risk for an adverse pregnancy outcome such as spontaneous fetal loss before 24 weeks of gestation, fetal demise, low birth weight, or preterm birth (26, 27). At the present time, there are no data indicating whether or not fetal surveillance in the third trimester will be helpful in the care of these patients.

The significance of ultrasonographic markers identified by a second-trimester ultrasound examination in a patient who has had a negative first-trimester screening test result is unknown. A variety of ultrasound findings have been associated with Down syndrome. A major anomaly, such as a cardiac defect, deserves further evaluation. More subtle findings ("soft markers"), such as pyelectasis, shortened femur or humerus, or echogenic bowel individually, do not significantly increase the risk of Down syndrome. However, these findings should be considered in the context of the screening results, patient's age, and history.

▶ *Are there other first-trimester ultrasonographic markers that are useful for Down syndrome screening?*

Several other first-trimester ultrasonographic markers, including nonvisualized nasal bone, tricuspid regurgitation, crown–rump length, femur and humeral length, head and trunk volumes, and umbilical cord diameters, have been evaluated as potential markers for aneuploidy in the first trimester. Studies in high-risk first-trimester populations indicate a high rate of nonvisualization of the nasal bone in fetuses with Down syndrome. Three European studies reported a 66.7–80% Down syndrome detection rate at a 0.2–1.4% false-positive rate (28–30). The value of nasal bone assessment as a Down syndrome screening test in the general population is controversial. A first-trimester study performed in the United States did not find the test to be useful (12). In addition, there are considerable ethnic differences in the prevalence of absent nasal bone; absence of the nasal bone in a euploid fetus is found in only 2.8% of Caucasians, compared with 6.8% of Asians and 10.4% of Afro-Caribbeans (31). It has been suggested that standardization of nasal bone assessment (32), along with extensive teaching and quality control programs, should be developed before this technique is used in the general population (33). Strategies restricting assessment of nasal bone to a subset of pregnant women at the highest risk after first-trimester combined screening, rather than the entire population, appear to be more practical and are being investigated.

▶ *What are the benefits and limitations of second-trimester ultrasound examination as a screening test for Down syndrome?*

Individual second-trimester ultrasonographic markers, such as echogenic bowel, intracardiac echogenic focus, and dilated renal pelvis, have a low sensitivity and specificity for Down syndrome particularly when used to screen a low-risk population (34). Studies indicate that the highest detection rate is achieved with systematic combination of ultrasonographic markers and gross anomalies, such as thick nuchal fold or cardiac defects (35, 36). Studies done in high-risk populations have reported detection rates of approximately 50–75% in the second trimester. However, the false-positive rates are high (eg, a 21.9% false-positive rate for a 100% Down syndrome detection rate) (37). One group has reported that if no abnormal ultrasonographic markers are identified after a carefully performed scan at a specialized center with skilled ultrasonographers, the *a priori* risk of Down syndrome in a high-risk patient (advanced mater-

nal age, abnormal serum screen) may be reduced by 82–88% (38). Because the RADIUS (Routine Antenatal Diagnostic Imaging With Ultrasound) trial (39) and others showed that even major fetal anomalies are frequently missed by ultrasound examination, the disadvantages of relying solely on ultrasonography for Down syndrome screening should be considered carefully. Combining second-trimester ultrasonographic and biochemical markers is a relatively new development that has been shown to be a feasible method to improve Down syndrome screening performance over either ultrasonography or second-trimester serum markers by themselves (40), provided that the ultrasound examination is performed as part of a specific screening protocol (37).

A major limitation of the use of second-trimester ultrasonographic markers has been the lack of standardization in measurements and definitions of what constitutes abnormal findings. This has contributed to variability in the diagnostic performance reported by different groups. Recent prospective studies that used specific criteria to define abnormal markers in large groups of unselected patients in the United States confirm a statistically significant increase in the frequency of individual ultrasonographic markers in Down syndrome compared with normal second-trimester cases (41, 42). At this time, risk adjustment based on second-trimester ultrasonographic markers should be limited to centers with ultrasonographic expertise and centers engaged in clinical research to develop a standardized approach to evaluating these markers. However, an abnormal second-trimester ultrasound finding identifying a major congenital anomaly significantly increases the risk of aneuploidy and warrants further counseling and the offer of a diagnostic procedure.

▶ *How does screening for aneuploidy differ in multifetal gestations?*

Serum screening tests are not as sensitive in twin or triplet gestations, in part because data from multiple gestations that include an aneuploid fetus is so scarce that expected analyte levels must be estimated by mathematical modeling. In addition, analytes from both the normal and the affected fetuses enter the maternal serum and are in effect averaged together, thus masking the abnormal levels of the affected fetus. In monochorionic twin pregnancies, the median nuchal translucency values are larger in 38% of twin pairs destined to develop severe twin–twin transfusion syndrome (43). Furthermore, counseling is more complex because women must consider a different set of options in the event that only one of the fetuses is affected. Nuchal translucency screening in the first trimester with the option of a CVS and earlier selective reduction may be desirable for some women. Experience is limited with triplet gestations, but studies suggest that nuchal translucency measurement is feasible. Until further studies are done, however, risk assessment in multiple gestations should be performed judiciously, and patients who are at increased risk of aneuploidy should be counseled regarding diagnostic testing.

▶ *Should invasive diagnostic testing for aneuploidy be available to all women?*

All women, regardless of age, should have the option of invasive testing. A woman's decision to have an amniocentesis or CVS is based on many factors, including the risk that the fetus will have a chromosomal abnormality, the risk of pregnancy loss from an invasive procedure, and the consequences of having an affected child if diagnostic testing is not done. Studies that have evaluated women's preferences have shown that women weigh these potential outcomes differently. The decision to offer invasive testing should take into account these preferences and should not be solely age based. The differences between screening and diagnostic testing should be discussed with all women. Thus, maternal age of 35 years alone should no longer be used as a cutoff to determine who is offered screening versus who is offered invasive testing.

▶ *With so many Down syndrome screening tests available, how do I decide which tests to offer?*

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. Ideally, patients seen early in pregnancy should be offered aneuploidy screening that combines first- and second-trimester testing (integrated or sequential). The screening strategy chosen will depend on availability of CVS and of personnel trained in nuchal translucency measurement in the area. When CVS is not available, it makes sense to offer integrated screening to patients who present in the first trimester in order to take advantage of the improved detection rate and low false-positive rate and to offer second-trimester screening to patients who present after 13⅐ weeks. If nuchal translucency measurement is not available or cannot be obtained in an individual patient, a reasonable approach is to offer serum integrated screening to patients who present early and second-trimester screening to those who present later. In areas where every screening strategy is possible, it is reasonable to choose two screening strategies for the practice, such as sequential screening for patients who present for prenatal care before 14 weeks of gestation (because it provides them with a first-trimester risk

assessment and the option of waiting until the second trimester for an adjusted risk assessment that includes their second-trimester serum results), and second-trimester serum screening for patients who present after 13⅐ weeks of gestation. In some instances, patients who would consider first-trimester termination of pregnancy but not second-trimester termination of pregnancy may want only first-trimester screening.

Summary of Recommendations and Conclusions

The following recommendations are based on good and consistent scientific evidence (Level A):

- First-trimester screening using both nuchal translucency measurement and biochemical markers is an effective screening test for Down syndrome in the general population. At the same false-positive rates, this screening strategy results in a higher Down syndrome detection rate than does the second-trimester maternal serum triple screen and is comparable to the quadruple screen.
- Measurement of nuchal translucency alone is less effective for first-trimester screening than is the combined test (nuchal translucency measurement and biochemical markers).
- Women found to have increased risk of aneuploidy with first-trimester screening should be offered genetic counseling and the option of CVS or second-trimester amniocentesis.
- Specific training, standardization, use of appropriate ultrasound equipment, and ongoing quality assessment are important to achieve optimal nuchal translucency measurement for Down syndrome risk assessment, and this procedure should be limited to centers and individuals meeting these criteria.
- Neural tube defect screening should be offered in the second trimester to women who elect only first-trimester screening for aneuploidy.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Screening and invasive diagnostic testing for aneuploidy should be available to all women who present for prenatal care before 20 weeks of gestation regardless of maternal age. Women should be counseled regarding the differences between screening and invasive diagnostic testing.
- Integrated first- and second-trimester screening is more sensitive with lower false-positive rates than first-trimester screening alone.
- Serum integrated screening is a useful option in pregnancies where nuchal translucency measurement is not available or cannot be obtained.
- An abnormal finding on second-trimester ultrasound examination identifying a major congenital anomaly significantly increases the risk of aneuploidy and warrants further counseling and the offer of a diagnostic procedure.
- Patients who have a fetal nuchal translucency measurement of 3.5 mm or higher in the first trimester, despite a negative aneuploidy screen, or normal fetal chromosomes, should be offered a targeted ultrasound examination, fetal echocardiogram, or both.
- Down syndrome risk assessment in multiple gestation using first- or second-trimester serum analytes is less accurate than in singleton pregnancies.
- First-trimester nuchal translucency screening for Down syndrome is feasible in twin or triplet gestation but has lower sensitivity than first-trimester screening in singleton pregnancies.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- After first-trimester screening, subsequent second-trimester Down syndrome screening is not indicated unless it is being performed as a component of the integrated test, stepwise sequential, or contingent sequential test.
- Subtle second-trimester ultrasonographic markers should be interpreted in the context of a patient's age, history, and serum screening results.

Proposed Performance Measure

Percentage of patients with documentation of discussion regarding Down syndrome screening

Glossary

Aneuploidy: In this condition there is an extra or missing chromosome.

Screen-positive rate: percentage of the population with a positive screening test result. This includes true positives and false positives.

Nuchal translucency measurement: Accumulated fluid behind the fetal neck is measured in a standardized way.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and September 2006. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and ACOG were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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