41. Screening for Down Syndrome

RECOMMENDATION

The offering of amniocentesis or chorionic villus sampling (CVS) for chromosome studies is recommended for pregnant women at high risk for Down syndrome. The offering of screening for Down syndrome by serum multiple-marker testing is recommended for all low-risk pregnant women, and as an alternative to amniocentesis and CVS for high-risk women (see ***Clinical Intervention***). This testing should be offered only to women who are seen for prenatal care in locations that have adequate counseling and follow-up services. There is currently insufficient evidence to recommend for or against screening for Down syndrome by individual serum marker testing or ultrasound examination, but recommendations against such screening may be made on other grounds (see ***Clinical Intervention***).

Burden of Suffering

Down syndrome, a congenital syndrome caused by trisomy of all or part of chromosome 21, is the most common chromosome abnormality.[1] Population-based surveillance programs have reported a Down syndrome birth prevalence of 0.9/1,000 live births.[2] The incidence of Down syndrome is higher than the birth prevalence, however, since many fetuses are spontaneously aborted, some are recognized in utero and electively aborted, and some cases are not recognized at birth. Affected children are characterized by physical abnormalities that include congenital heart defects and other dysmorphisms, and varying degrees of mental and growth retardation. Although there are therapies for some of the specific malformations associated with Down syndrome, there are no proven therapies available for the cognitive deficits. Life expectancy for infants born with Down syndrome is substantially lower than that of the general population.[3] Based on 1988 cross-sectional data, the lifetime economic costs of Down syndrome have been estimated to be $410,000 per case.[4]

The risk for Down syndrome and certain other chromosome anomalies increases substantially with advancing maternal age.[1,5–10] Parents carrying chromosome-21 rearrangements are also at an increased risk of Down syn-

drome pregnancies,[11–13] with the risk being much higher if the mother carries the rearrangement than if the father does. Also at higher risk are those who have previously had an affected pregnancy, independent of advancing maternal age and chromosome rearrangements.[14,15]

Accuracy of Screening Tests

Down syndrome is diagnosed prenatally by determining karyotype in fetal cell samples obtained by amniocentesis or chorionic villus sampling (CVS). Because of their invasiveness, risks, and cost, these procedures are generally reserved for women identified as high-risk either by history (i.e., advanced maternal age, prior affected pregnancy, known chromosome rearrangement) or by screening maneuvers (e.g., serum markers, ultrasound). Chromosome analysis of fetal cells obtained by second-trimester amniocentesis has been demonstrated to be accurate and reliable for prenatal diagnosis of Down syndrome in a randomized controlled trial and several cohort studies.[16–19] CVS, a technique for obtaining trophoblastic tissue, is an alternative to amniocentesis for detecting chromosome anomalies. The advantages of this procedure include the ability to perform karyotyping as early as 10–12 weeks and more rapid cytogenetic analysis. Potential disadvantages of CVS include apparent discrepancies between the karyotype of villi and the fetus due to maternal cell contamination or placental mosaicism, and failure to obtain an adequate specimen, resulting in a repeat procedure (usually amniocentesis) in up to 5% of tested women.[20–22] In randomized controlled trials[20–22] and cohort studies[23–29] comparing CVS to amniocentesis, accurate prenatal diagnosis has been obtained in over 99% of high-risk women when CVS is accompanied by both direct and culture methods of cytogenetic examination and when amniocentesis is provided to clarify CVS diagnoses of mosaicism or unusual aneuploidy. Transabdominal CVS has been reported to have comparable accuracy to transcervical CVS in randomized controlled trials.[20,30,31] First-trimester amniocentesis (at 10–13 weeks) has been compared to CVS in one randomized controlled trial.[32] Success rates were the same for the two procedures (97.5%); early amniocentesis failures were primarily due to failed culture. First- and second-trimester amniocentesis have not been directly compared in controlled trials.

For low-risk women, the risks associated with prenatal diagnostic testing (see *Adverse Effects of Screening and Early Detection*, below) are generally considered to outweigh the potential benefits because of the low likelihood of diagnosing a Down syndrome gestation. If screening tests, such as measurement of maternal serum markers or ultrasound imaging, can identify women who are at high risk for carrying a Down syndrome fetus, the relative benefit of prenatal diagnostic testing increases, potentially justifying the more invasive diagnostic procedures. Reduced levels of maternal

serum α-fetoprotein (MSAFP) and unconjugated estriol, and elevated levels of human chorionic gonadotropin (hCG), have each been associated with Down syndrome gestations. Intervention studies of screening have not been carried out with unconjugated estriol alone, while cohort intervention studies evaluating MSAFP and hCG have found them to have relatively poor discriminatory power as individual tests.[33–36] Multiple-marker screening uses results from two or three individual maternal serum marker tests, combined with maternal age, to calculate the risk of Down syndrome in the current gestation.[37,38] Amniocentesis and diagnostic chromosome studies are then offered to women whose screening test results suggest a high risk of Down syndrome, with high risk often defined as having the same or greater risk of an affected pregnancy that a 35-year-old woman has (i.e., 1 in 270).

Six interventional cohort studies that analyzed low-risk women younger than 35 years,[39–41] 36 years,[42] 37 years,[43] or 38 years,[44] and six that included women of any age desiring screening (90–95% ≤35 years),[45–50] have evaluated the proportion of Down syndrome pregnancies identified through double-marker (hCG and either MSAFP or estriol) or triple-marker screening in the midtrimester compared to the total number of such pregnancies identified. Interpretation of sensitivity is affected by incomplete ascertainment of karyotype and incomplete diagnosis at birth in these studies, although most had active surveillance systems for Down syndrome cases born to screened women. The reported sensitivity of multiple-marker screening for Down syndrome ranged from 48 to 91% (median 64.5%) and the false-positive rate (after revision of dates by ultrasound) ranged from 3% to 10%. The likelihood of Down syndrome given a positive screening test result was 1.2–3.8%, depending on the threshold for high risk used to define a positive test result. In these studies, the threshold chosen ranged from a 1 in 125 to a 1 in 380 chance of having an affected pregnancy given a positive test result. A young woman with a prescreen risk of about 1 in 1,000 who tested positive would have a post-screen risk similar to the risk in women of advanced age who are currently offered prenatal diagnosis.

Multiple-marker screening has also been evaluated in women 35 years of age or older, for whom prenatal diagnosis using amniocentesis or CVS is routinely recommended because of their increased risk of Down syndrome. Studies suggest that multiple-marker screening in these women might reduce the need for more invasive diagnostic tests. In a cohort study of 5,385 women ≥35 years of age with no other risk factors, all of whom were undergoing routine amniocentesis and chromosome studies (thus allowing complete ascertainment of chromosome abnormalities), estimates of the individual risk of Down syndrome were calculated based on maternal age in combination with the results of multiple-marker screening using

MSAFP, hCG, and unconjugated estriol.[51] If amniocentesis were performed only on older women with at least a 1 in 200 risk of carrying a fetus with Down syndrome based on triple-marker screening, 89% of affected fetuses would have been detected, 25% of women with unaffected fetuses would have been identified by screening as needing amniocentesis. A threshold of 1 in 300 (similar to risk based on age ≥35 years alone) did not add sensitivity but did increase the screen-positive rate to 34%. Thus, triple-marker screening could have avoided 75% of amniocenteses in older women, with their attendant risk of fetal loss, at a cost of missing 11% of cases of Down syndrome. In this study, performing amniocenteses only on women with postscreen risks of at least 1 in 200 for Down syndrome would also have detected 47% of fetuses with other autosomal trisomies, 44% of fetuses with sex aneuploidy, and 11% with miscellaneous chromosome abnormalities. In previously cited interventional cohort studies of double- or triple-marker screening that reported separate results for older women, the Down syndrome detection rate was reported as 80–100% for women ≥35 years[43,46,47,50] and 100% for women ≥36 years,[42,45] with false-positive screening results of 19–27%. Incomplete case ascertainment was possible, however, since screen-negative women rarely had diagnostic chromosome studies.

Although no controlled trials have directly compared double-marker to triple-marker screening, several cohort studies of triple-marker screening have reported the detection rates for double-marker screening with hCG and MSAFP only. Three markers appear to be somewhat more sensitive than two for detection of Down syndrome; the net difference in sensitivity ranged from –2 to +18% in these studies, depending on the false-positive rate and risk cut-off used.[43,48,50,51]

Ultrasonography is another potential screening test for Down syndrome. Abnormalities associated with Down syndrome (including intrauterine growth retardation, cardiac anomalies, hydrops, duodenal and esophageal atresia) and differences in long-bone length and nuchal fold thickness between Down syndrome and normal pregnancies observable on midtrimester ultrasound have been reviewed.[52] In prospective cohort studies of midtrimester ultrasound screening in high-risk women who were undergoing amniocenteses for chromosome studies, nuchal fold thickening identified 75% of Down syndrome fetuses; shortened humerus or femur length detected 31%; and an index based on thickened nuchal fold, major structural defect, and certain other abnormalities identified 69%.[53–55] The likelihood of Down syndrome given a positive result was 7–25% in these high-risk samples, but would be substantially lower in low-risk women. No published cohort studies have evaluated the accuracy of ultrasound screening for detection of chromosome abnormalities in low-risk women, nor have interventional cohort studies evaluated its efficacy as a screening tool in high-risk women. The

use of ultrasound as a screening test for Down syndrome is limited by the technical difficulty of producing a reliable sonographic image of critical fetal structures.[56,57] Incorrect positioning of the transducer, for example, can produce artifactual images resembling a thickened nuchal skin fold in a normal fetus.[58] Sonographic indices are therefore subject to considerable variation. Imaging techniques require further standardization before routine screening by ultrasound for Down syndrome can be considered for the general population.[56,59,60] In addition, results obtained by well-trained and well-equipped operators in a research context may not generalize to widespread use. In a multicenter cohort study in high-risk women that involved a large number of ultrasonographers of varying ability, the sensitivity of nuchal fold thickening for Down syndrome was only 38%.[59] The false-positive rate in this study was 8.5%, many times higher than that reported in studies involving expert ultrasonographers.[55,61]

Effectiveness of Early Detection

The detection of Down syndrome and other chromosome anomalies in utero provides as its principal benefit the opportunity to inform prospective parents of the likelihood of giving birth to an affected child. Parents may be counseled about the consequences of the abnormality and can make more informed decisions about optimal care for their newborn or about elective abortion. No controlled trials have been performed to assess clinical outcomes for those using screening or prenatal diagnosis for Down syndrome compared to those who do not. Therefore, the usefulness of this information depends to a large extent on the personal preferences and abilities of the parents.[62] Whether or not parents choose to use prenatal screening or diagnosis is related both to their views on the acceptability of induced abortion and their perceived risk of the fetus being abnormal.[63] The perception of the harm or nature of the disability may play a greater role in the decision than the actual probability of its occurrence.[64–67]

Induced abortion is currently sought by the majority of women whose prenatal diagnostic studies (i.e., karyotyping) reveal fetuses with Down syndrome.[33–35,39,40,45,48,68] Estimates of the reduction in birth prevalence of Down syndrome associated with offering prenatal diagnosis to women 35 years and older range from 7.3% to 29% in the U.S. and other developed countries.[2,69–73] The effect of this approach on the total number of Down syndrome births is limited because older women have low birth rates and therefore account for a relatively small proportion of affected pregnancies despite their exponentially increased risk for having an affected pregnancy.[74] Limited data are available to estimate the impact of serum-marker screening in younger women on Down syndrome birth prevalence. In England and Wales, the proportion of all cytogenetically diagnosed Down syndrome cases detected prenatally (thus potentially preventable) increased

from 31% to 46% after the introduction of screening by maternal serum analysis and ultrasound for low-risk women.[68] In cohort studies evaluating double- or triple-marker screening, when the proportions of screen-positive women who decided not to undergo amniocentesis or induced abortion were taken into account, the proportion of Down syndrome births to screened women that were actually prevented ranged from 36% to 62%.[39,40,45,48] Up to 25% of screen-positive women declined prenatal diagnosis by amniocentesis in these studies. The effectiveness of screening in preventing Down syndrome births may be further reduced by incomplete uptake of screening. In antenatal screening programs in which double- or triple-marker screening was offered to all women and amniocentesis or CVS was offered to women over 35 years of age, nearly 60% of all Down syndrome births were potentially preventable, the remainder either being missed by screening (14–23%) or occurring in women who were not screened (17–27%).[47,49] Neither study evaluated acceptance of induced abortion, however. In another population, offering double-marker screening to all women prevented 59% of all Down syndrome births.[45] This population had high rates of screening (89%), largely due to the fact that pregnant women had to specifically ask to be excluded. There was also high acceptance of amniocentesis in screen-positive women (89%), and of induced abortion of cytogenetically confirmed cases (91%). The birth prevalence of Down syndrome decreased from approximately 1.1/1,000 to 0.4/1,000 after initiation of prenatal screening in this population.

Other potential effects of prenatal detection of Down syndrome have not been adequately explored. In families at high risk of Down syndrome births, such as those with advanced maternal age, a previous affected pregnancy, or known carriage of translocations, the availability of prenatal diagnosis may reduce the induced abortion rate by identifying normal pregnancies that might otherwise be electively aborted. This benefit has been reported with screening for cystic fibrosis,[75] but it has not been evaluated for Down syndrome. The diagnosis of a chromosome abnormality may spare unsuspecting parents some of the trauma associated with delivering an abnormal infant, and may help parents to prepare emotionally. Studies evaluating these potential psychological benefits have not been reported, however. Prenatal diagnosis may also enable clinicians to better prepare for the delivery and care of the baby. Studies are lacking regarding the impact of these measures on neonatal morbidity and mortality.

An indirect benefit of testing to detect Down syndrome is the discovery during testing of abnormalities other than the target condition. Chromosome studies on specimens obtained by amniocentesis or CVS will detect other abnormalities besides Down syndrome. Autosomal trisomies other than Down syndrome are usually spontaneously aborted, so the principal benefit of screening may be avoidance of late fetal death.[76] The health

consequences of sex aneuploidy are less significant than trisomies, but about half such pregnancies are nevertheless electively aborted when discovered prenatally.[77,78] Serum marker screening for Down syndrome will also identify some patients carrying fetuses with other chromosome abnormalities (e.g., Turner syndrome, trisomy-13 or -18); sensitivity is low,[51] however, because some of these abnormalities have different effects on serum markers than does Down syndrome, and require different risk thresholds.[50,79] Ultrasound screening for Down syndrome leads to a more accurate assessment of gestational age in women with uncertain dates, and some studies suggest that acting on this information may reduce the likelihood of induced labor for erroneously diagnosed postterm pregnancy (see Chapter 36). Multiple gestations and major congenital anomalies, such as diaphragmatic hernia, gastroschisis, nonimmune fetal hydrops, and obstructive uropathy, may also be detected by ultrasound. These discoveries permit antenatal treatment as well as delivery and neonatal care planning. Controlled trials proving that early detection by ultrasound of multiple gestations or congenital anomalies improves outcome have not been published, however (see Chapter 36).

Adverse Effects of Screening and Early Detection. The most important risks of early detection of Down syndrome include those to the fetus from amniocentesis and CVS performed as a primary or follow-up diagnostic test, the psychological effects of a positive test on the parents, and the complications resulting from induced abortion. The risks of amniocentesis include rare puncture of the fetus, bleeding, infection, and possibly isosensitization.[80,81] The procedure-related rate of fetal loss with current technique appears to be about 0.5–0.8%.[16,17,29] The best evidence on amniocentesis risks comes from a randomized controlled trial of screening,[16] which reported a procedure-related risk of fetal loss of 0.8% of pregnancies. This may nevertheless overestimate current rates of loss as techniques have improved. In a more recent series of patients undergoing amniocentesis as part of a clinical trial, the risk of fetal loss was 0.04%.[22] In a randomized controlled trial, neonatal respiratory distress syndrome and neonatal pneumonia were more frequent after amniocentesis, independent of birth weight and gestational age; the additional risk was about 1%.[16] A similar trend was seen in the Medical Research Council study,[18] but has not been confirmed in other studies. Infection has not been identified as a significant problem in any large studies. No clinically important effects on development, behavior, or physical status were identified in 4-year-old children whose mothers had undergone midtrimester amniocentesis.[83] Case series of women undergoing first-trimester amniocentesis suggest a procedure-related fetal loss rate of 3–7%.[84–87] In a randomized controlled

trial, the total fetal loss rate with early amniocentesis was significantly higher than with CVS (5.9 vs. 1.2%).[32]

Several randomized controlled trials comparing amniocentesis and CVS have reported significantly higher fetal loss rates with CVS (1.0–1.5%) when compared with second-trimester amniocentesis.[20–22] Inexperience and the use of transcervical CVS appear related to a greater risk of fetal loss, although at least one trial found no significant difference in fetal loss rates between transcervical and transabdominal CVS (2.5% vs. 2.3%).[31] An increased risk of transverse limb reduction anomalies in infants born after CVS has been reported in case-control and case-series studies.[88–93b] Conflicting evidence from cohort studies may relate to varying methods of case ascertainment or classification.[94–99a] Decreasing risk and a trend from proximal to distal limb damage with increasing gestational age at CVS provide biologic plausibility for a true association with limb reduction defects.[93,99b] Current estimates for the overall risk of transverse limb deficiency from CVS range from 0.03% to 0.10% of procedures.[99a] Severe maternal complications from CVS are rarely reported, but the Canadian Collaborative Study suggested a higher risk of bleeding requiring intervention for women undergoing CVS compared to amniocentesis.[22] None of the CVS trials has reported increased risks of birth defects or major infant health problems, but sample size is inadequate in these trials to rule out rare adverse effects.

A positive screening test result can produce a harmful psychological effect on parents. This is especially important because the large majority of positive screening tests occur in normal pregnancies. Adverse psychological effects of screening tests include the fear of discovering an abnormal pregnancy as well as anxiety over possible complications from diagnostic and therapeutic procedures. Women who have been identified as being at high risk because of a positive serum-marker screening test may have greater distress than women who are identified as high risk because of advanced age.[100,101] Distress is reduced following a diagnostic procedure confirming a normal pregnancy, but some anxiety related to the false-positive screening test may persist.[102,103] Most women screened will have normal results, however, and this may have psychological benefits for the reassured parents.

The potential complications of induced abortion must also be considered, since this is the outcome of the majority of positive diagnostic test results. Morbidity from first-trimester induced abortion, including infection, hemorrhage, and injury, occurs in 2–3% of procedures, but serious complications are rare; in one series of 170,000 cases, 0.07% required hospitalization and none resulted in death.[104–107] Complication rates, including maternal case-fatality rates, are higher with second-trimester abortions, but remain uncommon.[108–110] The case-fatality rate from legally induced abor-

tion, 0.4/100,000 procedures, is substantially lower than the risk of pregnancy-related death, which is 8–9/100,000 live births.[108,109,111,112] The most serious consequence of false-positive test results, the induced abortion of a normal pregnancy, was not reported in any of the trials, and appears to be rare with current techniques. The likelihood of diagnostic error is slightly higher with CVS than with amniocentesis, but the risk of induced abortion as a consequence has not been fully evaluated.

Recommendations of Other Groups

Most organizations recommend offering amniocentesis or CVS for prenatal diagnosis to all pregnant women who are aged 35 years and older or otherwise at high risk for chromosome abnormalities.[113–115] The Canadian Task Force on the Periodic Health Examination concluded that there is fair evidence to offer second-trimester triple-marker screening to all pregnant women less than 35 years of age, and as an alternative to prenatal diagnosis by karyotyping in women 35 years and older; such offering should be accompanied by education on its limited efficacy, as well as on the risks of second-trimester diagnosis and abortion, and on the psychological implications of screening and of a Down syndrome birth.[114] Offering multiple-marker screening between 15 and 18 weeks of gestation to low-risk women under 35 years of age to assess Down syndrome risk is also recommended by the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG); neither group recommends a specific multiple-marker protocol.[115,116] Neither ACOG nor ACMG recommends prenatal cytogenic screening by multiple-marker testing in women 35 years and older; ACOG recommends that multiple-marker testing may be offered as an option for those women who do not accept the risk of amniocentesis or who wish to have this additional information prior to making a decision. No organizations currently recommend routine screening for Down syndrome by ultrasound. ACOG[117] and a National Institutes of Health consensus development conference[118] have recommended that ultrasound imaging be performed during pregnancy only in response to a specific medical indication.

Discussion

Prenatal diagnostic testing is accurate and reliable for detecting Down syndrome, but it is associated with a procedure-related fetal loss risk of about 0.5% for second-trimester amniocentesis and 1–1.5% for CVS, and a measurable risk of transverse fetal limb deficiency after CVS. The currently accepted medical practice of routinely offering amniocentesis or CVS for prenatal diagnosis to pregnant women aged 35 years and older or otherwise at high risk is based on the mother's increased risk of having a fetus with a chromosome abnormality balanced against the risk of fetal loss as-

sociated with these procedures, and therefore includes an element of judgment. It can be predicted from available data (odds of Down syndrome during the second trimester) that a program offering amniocentesis to all pregnant women at age 35 has the potential of exposing 200–300 normal fetuses to this procedure for every case detected.[10] With an estimated procedure-related fetal loss rate of 0.5%, one normal fetus would be lost by amniocentesis for every one to two chromosome anomalies detected in such women. For CVS, the number of normal fetuses lost per case detected would be higher, and for first-trimester amniocentesis, it may be higher still. The older the maternal age, the more favorable the ratio of affected fetuses to fetal loss. Most women who request such testing and receive a diagnosis of a Down syndrome pregnancy choose to abort the pregnancy, resulting in a measurable reduction in Down syndrome births. There is little good evidence of the effect on personal and family outcomes, however, or on the balance of risks and benefits for the group as a whole. Nevertheless, those women at high risk who desire prenatal diagnosis of Down syndrome may benefit substantially from it. Thus, there is fair evidence to support offering prenatal diagnosis to high-risk pregnant women who are identified by age, history, or screening tests when a comprehensive prenatal diagnosis program that includes education, interpretation, and follow-up is available.

In low-risk pregnant women, maternal serum multiple-marker screening in the second trimester can detect nearly two thirds of Down syndrome fetuses, but it will result in a large number of young women being offered amniocentesis who would not otherwise be subjected to its risks. The ratio of affected fetuses detected to procedure-related fetal loss in women with positive multiple-marker screening would be similar to or more favorable than that of women 35 years and older. The risk of fetal loss may be acceptable to parents with strong fears of having an affected child.[64,119–121] There is also evidence that multiple-marker screening in women 35 years and older can detect 80% or more of Down syndrome pregnancies while allowing the majority of such women to avoid the risks associated with invasive diagnostic testing. Multiple-marker screening is not supported by the same strength of evidence as is amniocentesis or CVS, however. Potential problems include the reduced sensitivity for Down syndrome and other chromosome abnormalities, the large proportion of false-positive tests, and the substantial number of women who refuse or do not receive follow-up amniocentesis and chromosome studies. This is of particular concern if such screening is offered to women 35 years and older who might otherwise receive amniocentesis or CVS. Nevertheless, in some older women, particularly those who may have had difficulty conceiving or carrying a pregnancy, the reduced likelihood of amniocentesis or CVS and consequent risk of fetal loss or injury may outweigh the reduced sensitivity

of multiple-marker screening. There is therefore fair evidence to support offering multiple-marker screening to pregnant women of all ages when a comprehensive prenatal diagnosis program is available that includes education, interpretation, and follow-up.

There is a lack of sound evidence to support the use of individual maternal serum markers to screen for Down syndrome, and currently available evidence suggests that sensitivity is substantially lower than with multiple-marker screening. Similarly, ultrasonography has not been adequately evaluated as a routine screening test for Down syndrome, and there are important concerns about the measurement reliability and generalizability of this technology to widespread use. Since there is evidence supporting the effectiveness of other screening and diagnostic methods, neither individual serum markers nor ultrasonography can be recommended as screening tests for Down syndrome outside clinical trials.

Identification and selective abortion of Down syndrome pregnancies raises important ethical concerns, a full discussion of which is beyond the scope of this chapter. These concerns include the implicit message that Down syndrome is an undesirable state, the interpretation of induced abortion in eugenic terms by some persons, and societal and economic pressures that may stigmatize families with a Down syndrome member. Attitudes held by both physicians and by society toward individuals with Down syndrome have changed over time, and various Down syndrome associations now offer support for families and individuals with Down syndrome, promote their participation in society, and seek respect for them.[122,123] These issues highlight the importance of offering screening and prenatal diagnosis of Down syndrome in a value-sensitive fashion with emphasis on reliable information about Down syndrome itself as well as about the potential risks and benefits of screening procedures.

In these recommendations, primary consideration has been given to the prenatal detection of Down syndrome. Other chromosome anomalies (e.g., Turner syndrome, trisomy-18) are often detected during prenatal screening and diagnosis and many may consider their detection important. There are few studies directly addressing screening for these conditions, however, and screening protocols have not been sufficiently evaluated to warrant review at this point.

CLINICAL INTERVENTION

The offering of amniocentesis or CVS for chromosome studies to pregnant women aged 35 years and older and to those at high risk of Down syndrome for other reasons (e.g., previous affected pregnancy, known carriage of a chromosome rearrangement associated with Down syndrome) is recommended (“B” recommendation). In some circumstances,

depending on resources, preferences, and other factors, the selection of a different age threshold for offering prenatal diagnosis may be considered. Counseling before the procedure should include a comparison of the risks to the fetus from the procedure and the probability of a chromosome defect given the patient's age or other risk factors, as well as a full discussion of the potential outcomes associated with delivering a child with Down syndrome and of aborting a Down syndrome fetus.

The offering of screening for Down syndrome by maternal serum multiple-marker testing at 15–18 weeks of gestation is recommended for all pregnant women who have access to counseling and follow-up services, skilled high-resolution ultrasound and amniocentesis capabilities, and reliable, standardized laboratories ("B" recommendation). There is currently insufficient evidence to recommend a specific multiple-marker screening protocol. Counseling regarding screening should include information on the procedure itself, the likelihood of follow-up testing with amniocentesis and its associated risks, as well as a full discussion of the potential outcomes associated with delivering a child with Down syndrome and of aborting a Down syndrome fetus. Women with a positive screen should receive detailed information comparing the increased risk of trisomy and the risks of fetal loss from amniocentesis. For women aged 35 years and older, the choice of serum multiple-marker screening versus amniocentesis or CVS for chromosome studies depends on patient preferences and therefore requires a detailed discussion of the potential risks and benefits of each procedure. In particular, the patient should understand the reduced sensitivity of multiple-marker screening for Down syndrome and for other chromosome abnormalities compared to prenatal diagnosis by chromosome studies, and the increased risk of fetal loss or injury with amniocentesis and CVS.

There is currently insufficient evidence to recommend for or against routine ultrasound examination or the use of individual maternal serum markers in pregnant women as screening tests for Down syndrome ("C" recommendation). Recommendations against these tests may be made on other grounds, however, including the availability of other screening tests of proven effectiveness.

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by Carolyn DiGuiseppi, MD, MPH, based in part on material prepared for the Canadian Task Force on the Periodic Health Examination by Paul Dick, MDCM, FRCPC.

REFERENCES

1. National Center for Health Statistics Advance report of maternal and infant health data from the birth certificate, 1991. Monthly vital statistics report; vol 42, no 11 (suppl). Hyattsville, MD: Public Health Service, 1994.
2. Centers for Disease Control and Prevention. Down syndrome prevalence at birth—United States, 1983–1990. MMWR 1994;43:617–622.

3. Baird PA, Sadovnick AD. Life tables for Down syndrome. Hum Genet 1989;82:291–292.
4. Waitzman NJ, Romano PS, Scheffler RM. Estimates of the economic costs of birth defects. Inquiry 1994;31:188–205.
5. Hansen JP. Older maternal age and pregnancy outcome: a review of the literature. Obstet Gynecol 1986;41:726–742.
6. Ferguson-Smith M, Yates JRW. Maternal age specific rates for chromosome aberrations and factors influencing them: report of a collaborative European study on 52965 amniocenteses. Prenatal Diag 1984;4:5–44.
7. Hook EB. Rates of chromosome abnormalities at different maternal ages. Obstet Gynecol 1981;58: 282–285.
8. Hook E, Topol BB, Cross PK. The natural history of cytogenetically abnormal fetuses detected at midtrimester amniocentesis: new data and estimates of the excess and relative risk of late fetal death associated with 47,+21 and some other abnormal karyotypes. Am J Hum Genetics 1989;45:855–861.
9. Cuckle HS, Wald NJ, Thompson SG. Estimating a woman's risk of having a pregnancy with Down's syndrome using her age and serum alpha-fetoprotein level. Br J Obstet Gynaecol 1987;94:387–402.
10. Palomaki GE, Haddow JE. Maternal serum alpha-fetoprotein, age, and Down syndrome risk. Am J Obstet Gynecol 1987;156:460–463.
11. Boue A, Gallano P. A collaborative study of the segregation of inherited chromosome structural rearrangements in 1356 prenatal diagnoses. Prenat Diagn 1984;4:45–67.
12. Stene J. Statistical inference on segregation ratios for D/G translocations, when the families are ascertained in different ways. Ann Hum Genet 1970;34:93–115.
13. Stene J. A statistical segregation analysis of (21q22q)- translocations. Hum Hered 1970;20:465–472.
14. Carter C, Evans KA. Risk of parents who have had one child with Down's syndrome (mongolism) having another child similarly affected. Lancet 1961;ii:785–788.
15. Stene J. Detection of higher recurrence risk for age dependent chromosome abnormalities with application to G1 (Down syndrome). Hum Hered 1970;20:112–122.
16. Tabor A, Madsen M, Obel EB, et al. Randomized controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet 1986;i:1287–1292.
17. The NICHD National Registry for Amniocentesis Study Group. Midtrimester amniocentesis for prenatal diagnosis: safety and accuracy. JAMA 1976;236:1471–1476.
18. Medical Research Council Working Party on Amniocentesis. An assessment of the hazard of amniocentesis. Br J Obstet Gynaecol 1978;85(Suppl 2):1–41.
19. Simpson N, Dallaire L, Miller JR, et al. Prenatal diagnosis of genetic disease in Canada: report of a collaborative study. Can Med Assoc J 1976;115:739–748.
20. Smidt-Jensen S, Permin M, Philip J, et al. Randomized comparison of amniocentesis and transabdominal and trans-cervical chorionic villus sampling. Lancet 1992;340:1237–1244.
21. Medical Research Council Working Party on the Evaluation of Chorion Villus Sampling. Medical Research Council European trial of chorion villus sampling. Lancet 1991;337:1491–1499.
22. Lippman A, Tomkins DJ, Shime J, et al. Canadian multicentre randomized clinical trial of chorion villus sampling and amniocentesis. Final report. Prenat Diagn 1992;12:385–476.
23. Hogge WA, Schonberg SA, Golbus MS. Chorionic villus sampling: experience of the first 1000 cases. Am J Obstet Gynecol 1986;154:1249–1252.
24. Brambati B, Oldrini A, Ferrazzi E, et al. Chorionic villus sampling: an analysis of the obstetric experience of 1000 cases. Prenat Diag 1987;7:157–169.
25. Jahoda M, Piijpers L, Reuss A, et al. Evaluation of transcervical chorionic villus sampling with a completed follow-up of 1550 consecutive pregnancies. Prenat Diagn 1989;9:621–628.
26. Leschot N, Wolf H, Van Prooijen-Knegt AC, et al. Cytogenetic findings in 1250 chorionic villus samples obtained in the first trimester with clinical follow-up of the first 1000 pregnancies. Clin Genet 1989;96:663–670.
27. Simoni G, Gimelli G, Cuoco C, et al. First trimester fetal karyotyping: one thousand diagnoses. Hum Genet 1986;72:203–209.
28. Green J, Dorfmann A, Jones SL, et al. Chorionic villus sampling: experience with an initial 940 cases. Obstet Gynecol 1988;71:208–212.
29. Rhoads GG, Jackson LG, Schlesselman SE, et al. The safety and efficacy of chorionic villus sampling for early prenatal diagnosis of cytogenetic abnormalities. N Engl J Med 1989;320:609–617.
30. Brambati B, Terzian E, Tognoni G. Randomized clinical trial of transabdominal versus transcervical chorionic villus sampling methods. Prenat Diagn 1991;11:285–293.

31. Jackson L, Zachary JM. A randomized comparison of transcervical and transabdominal chorionic villus sampling. N Engl J Med 1992;327:594–598.
32. Nicolaides K, Brizot MD, Patel F, et al. Comparison of chorionic villus sampling and amniocentesis for fetal karyotyping at 10–13 weeks' gestation. Lancet 1994;344:435–439.
33. DiMaio MS, Baumgarten A, Greenstein RM, et al. Screening for fetal Down's syndrome in pregnancy by measuring maternal serum alpha-fetoprotein levels. N Engl J Med 1987;317:342–346.
34. New England Regional Genetics Group. Combining maternal serum alpha fetoprotein measurements and age to screen for Down syndrome in pregnant women under age 35. Am J Obstet Gynecol 1989; 160:575–581.
35. Lustig L, Clarke S, Cunningham G, et al. California's experience with low MS-AFP results. Am J Med Genet 1988;31:211–222.
36. Muller F, Boue A. A single chorionic gonadotropin assay for maternal serum screening for Down's syndrome. Prenat Diagn 1990;10:389–398.
37. Wald NJ, Cuckle HS, Densem JW, et al. Maternal serum screening for Down's syndrome in early pregnancy [published erratum appears in BMJ 1988;297:1029]. BMJ 1988;297:883–887.
38. Reynolds TM. Software for screening to assess risk of Down's syndrome [letter]. BMJ 1991;302:6782.
39. Wald NJ, Kennard A, Densem JW, et al. Antenatal maternal serum screening for Down's syndrome: results of a demonstration project. BMJ 1992;305:391–394.
40. Phillips OP, Elias S, Shulman LP, et al. Maternal serum screening for fetal Down syndrome in women less than 35 years of age using alpha-fetoprotein, hCG, and unconjugated estriol: a prospective 2-year study. Obstet Gynecol 1992;80:353–358.
41. Macri JN, Spencer K, Garver K, et al. Maternal serum free beta hCG screening: results of studies including 480 cases of Down syndrome. Prenat Diagn 1994;14:97–103.
42. Mancini G, Perona M, Dall'Amico D, et al. Maternal serum markers. Estimation of the risk of Down's syndrome: a prospective study. Int J Clin Lab Res 1994;24:49–53.
43. Cheng EY, Luthy DA, Zebelman AM, et al. A prospective evaluation of a second-trimester screening test for fetal Down syndrome using maternal serum alpha-fetoprotein, hCG, and unconjugated estriol. Obstet Gynecol 1993;81:72–77.
44. Herrou M, Leporrier N, Leymarie P. Screening for fetal Down syndrome with maternal serum hCG and oestriol: a prospective study. Prenat Diagn 1992;12:887–892.
45. Spencer K, Carpenter P. Prospective study of prenatal screening for Down's syndrome with free β human chorionic gonadotrophin. BMJ 1993;307:764–769.
46. Mooney RA, Peterson CJ, French CA, et al. Effectiveness of combining maternal serum alpha-fetoprotein and hCG in a second-trimester screening program for Down syndrome. Obstet Gynecol 1994;84: 298–303.
47. Crossley JA, Aitken DA, Berry E, et al. Impact of a regional screening programme using maternal serum α fetoprotein (AFP) and human chorionic gonadotrophin (hCG) on the birth incidence of Down's syndrome in the west of Scotland. J Med Screening 1994;1:180–183.
48. Haddow JE, Palomaki GE, Knight GJ, et al. Prenatal screening for Down's syndrome with use of maternal serum markers [see comments]. N Engl J Med 1992;327:588–593.
49. Piggott M, Wilkinson, J Bennett, et al. Implementation of an antenatal serum screening programme for Down's syndrome in two districts (Brighton and Eastbourne). J Med Screening 1994;1:45–49.
50. Burton BK, Prins GS, Verp MS. A prospective trial of prenatal screening for Down syndrome by means of maternal serum α-fetoprotein, human chorionic gonadotropin, and unconjugated estriol. Am J Obstet Gynecol 1993;169 :526–530.
51. Haddow JE, Palomaki GE, Knight GJ, et al. Reducing the need for amniocentesis in women 35 years of age or older with serum markers for screening. N Engl J Med 1994;330:1114–1118.
52. Lockwood JC, Lynch L, Berkowitz RL. Ultrasonographic screening for Down syndrome fetus. Am J Obstet Gynecol 1991;165:349–352.
53. Benacerraf BR, Nadel A, Bromley B. Identification of second-trimester fetuses with autosomal trisomy by use of a sonographic scoring index. Radiology 1994;193:135–140.
54. Nyberg DA, Resta RG, Luthy DA, et al. Humerus and femur length shortening in the detection of Down's syndrome. Am J Obstet Gynecol 1993;168:534-538.
55. Crane JP, Gray DL. Sonographically measured nuchal skinfold thickness as a screening tool for Down syndrome: results of a prospective clinical trial. Obstet Gynecol 1991;77:533–536.
56. Lockwood C, Benacerraf B, Krinsky A, et al. A sonographic screening method for Down syndrome. Am J Obstet Gynecol 1987;157:803–808.

57. Benacerraf BR, Gelman R, Frigoletto FD. Sonographic identification of second-trimester fetuses with Down's syndrome. N Engl J Med 1987;317:1371–1376.
58. Toi A, Simpson GF, Filly RA. Ultrasonically evident fetal nuchal skin thickening: is it specific for Down syndrome? Am J Obstet Gynecol 1987;156:150–153.
59. Grandjean H, Sarramon M-F, and the AFDPHE Study Group. Sonographic measurement of nuchal skinfold thickness for detection of Down syndrome in the second-trimester fetus: a multicenter prospective study. Obstet Gynecol 1995;85:103–106.
60. Elias S, Annas GJ. Routine prenatal genetic screening. N Engl J Med 1987;317:1407–1409.
61. Benacerraf BR, Barss VA, Laboda LA. A sonographic sign for the detection in the second trimester of the fetus with Down syndrome. Am J Obstet Gynecol 1985;151:1078–1079.
62. Reed BD, Ratcliffe S, Sayres W. Maternal serum alpha-fetoprotein screening. J Fam Pract 1988;27:20–23.
63. Marteau T, Kidd J, Cook R, et al. Perceived risk not actual risk predicts uptake of amniocentesis. Br J Obstet Gynaecol 1991;98:282–286.
64. Thornton J, Lilford RJ, Howell D. Safety of amniocentesis [letter]. Lancet 1986;ii:225–226.
65. Evans M, Bottoms SF, Critchfield GC, et al. Parental perceptions of genetic risk: correlation with choice of prenatal diagnostic procedures. Int J Gynaecol Obstet 1990;31:25–28.
66. Ekwo E, Kim J, Gosselink CA. Parental perceptions of the burden of genetic disease. Am J Med Genet 1987;28: 955–963.
67. Drugan A, Greb A, Johnson P, et al. Determinants of parental decisions to abort for chromosomal abnormalities. Prenat Diagn 1990;10:483–490.
68. Morris JK, Mutton DE, Ide R, et al. Monitoring trends in prenatal diagnosis of Down's syndrome in England and Wales, 1989–92. J Med Screening 1994;1:233–237.
69. Bell J, Hilden J, Bowling F, et al. The impact of prenatal diagnosis on the occurrence of chromosome abnormalities. Prenat Diagn 1986;6:1–11.
70. Cuckle H, Nanchahal K, Wald N. Birth prevalence of Down's syndrome in England and Wales. Prenat Diagn 1991;11:29–34.
71. Walker S, Howard PJ. Cytogenetic prenatal diagnosis and its relative effectiveness in the Mersey Region and North Wales. Prenat Diagn 1986;6:13–23.
72. Wilson N, Bickley D, McDermott A. The prevention of Down's syndrome in the southwestern region of England 1975–1985. West Engl Med J 1990;105:15–17.
73. Youings S, Gregson N, Jacobs P. The efficacy of maternal age screening for Down's syndrome in Wessex. Prenat Diagn 1991;11:419–425.
74. Ventura SJ, Martin JA, Taffel SM, et al. Advance report of final natality statistics, 1992. Monthly vital statistics report; vol 43 no 5 (suppl). Hyattsville, MD: National Center for Health Statistics, 1994.
75. Borgo G, Fabiano T, Perobelli S, et al. Effect of introducing prenatal diagnosis on the reproductive behavior of families at risk for cystic fibrosis: a cohort study. Prenat Diagn 1992;12:820–830.
76. Hook EB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. JAMA 1983;249:2034–2038.
77. Robinson A, Bender BG, Linden MG. Decisions following the intrauterine diagnosis of sex chromosome aneuploidy. Am J Med Genet 1989;34:552–554.
78. Holmes-Siedle M, Ryynanen M, Lindenbaum RH. Parental decisions regarding termination of pregnancy following prenatal detection of sex chromosome abnormality. Prenat Diagn 1987;7:239–244.
79. Barkai G, Goldman B, Ries L, et al. Expanding multiple marker screening for Down's syndrome to include Edward's syndrome. Prenat Diagn 1993;13:843–850.
80. Campbell TL. Maternal serum alpha-fetoprotein screening: benefits, risks, and costs. J Fam Pract 1987;25:461–467.
81. Cuckle HS, Wald NJ, Lindenbaum RH. Maternal serum alpha-fetoprotein measurement: a screening test for Down syndrome. Lancet 1984;1:926–929.
82. *Deleted in proof.*
83. Finegan J, Quarrington BJ, Hughes HE, et al. Child outcome following mid-trimester amniocentesis: development, behavior, and physical status at age 4 years. Br J Obstet Gynaecol 1990;97:32–40.
84. Nevin J, Nevin NC, Dornan JC, et al. Early amniocentesis: experience of 222 consecutive patients, 1987–1988. Prenat Diagn 1990;10:79–83.
85. Stripparo L, Buscaglia M, Longatti L, et al. Genetic amniocentesis: 505 cases performed before the sixteenth week of gestation. Prenat Diagn 1990;10:359–364.

86. Penso CA, Sandstrom MM, Garber MF, et al. Early amniocentesis: report of 407 cases with neonatal follow-up. Obstet Gynecol 1990;76:1032–1036.
87. Hanson FW, Tennant F, Hune S, et al. Early amniocentesis: outcome, risks, and technical problems at ≤12.8 weeks. Am J Obstet Gynecol 1992;166:1707–1711.
88. Firth H, Boyd PA, Chamberlain P, et al. Severe limb abnormalities after chorion villus sampling at 56–66 days' gestation. Lancet 1991;337:762–763.
89. Mastroiacovo P, Botto LD, Cavalcanti DP, et al. Limb anomalies following chorionic villus sampling: a registry based case-control study. Am J Med Genet 1992;44:856–864.
90. Burton BK, Schulz CJ, Burd LI. Limb anomalies associated with chorionic villus sampling. Obstet Gynecol 1992;79: 726–730.
91. Brambati B, Simoni G, Travi M, et al. Genetic diagnosis by chorionic villus sampling before 8 gestational weeks: efficiency, reliability, and risks on 317 completed pregnancies. Prenat Diagn 1992;12: 789–799.
92. Hsieh FJ, Shyu MK, Sheu BC, et al. Limb defects after chorionic villus sampling. Obstet Gynecol 1995; 85:84–88.
93. Firth HV, Boyd PA, Chamberlain PF, et al. Analysis of limb reduction defects in babies exposed to chorionic villus sampling. Lancet 1994;343:1069–1071.
93a. Olney RS, Khoury MJ, Alo CJ, et al. Increased risk for transverse digital deficiency after chorionic villus sampling: results of the United States Multistate Case-Control Study, 1988–1992. Teratology 1995; 51:20–29.
93b. Dolk H, Bertrand F, Lechat MJ, for the EUROCAT Working Group. Chorionic villus sampling and limb abnormalities [letter]. Lancet 1992;339:876–877.
94. Mahoney JM. Limb abnormalities and chorionic villus sampling [letter]. Lancet 1991;337:1422–1423.
95. Jackson LG, Wapner RJ, Brambati B. Limb abnormalities and chorionic villus sampling [letter]. Lancet 1991; 337:1423.
96. Monni G, Ibba RM, Lai R, et al. Limb-reduction defects and chorion villus sampling [letter]. Lancet 1991; 337:1091.
97. Froster-Iskenius UG, Baird PA. Limb-reduction defects in over one million consecutive livebirths. Teratology 1989;39:127–135.
98. Froster UG, Baird PA. Limb-reduction defects and chorionic villus sampling [letter]. Lancet 1992;339:66.
99. Blakemore K, Filkins K, Luthy DA, et al. Cook obstetrics and gynecology catheter multicenter chorionic villus sampling trial: comparison of birth defects with expected rates. Am J Obstet Gynecol 1993; 169:1022–1026.
99a. Centers for Disease Control and Prevention. Chorionic villus sampling and amniocentesis: recommendations for prenatal counseling. MMWR 1995;44(RR-9):1–12.
99b. Olney RS, Khoury MJ, Botto LD, et al. Limb defects and gestational age at chorionic villus sampling [letter]. Lancet 1994;344:476.
100. Tunis S, Golbus MS, Copeland KL, et al. Patterns of mood states in pregnant women undergoing chorionic villus sampling or amniocentesis. Am J Med Genet 1990;37:191–199.
101. Abuelo D, Hopmann MR, Barsel-Bowers G, et al. Anxiety in women with low maternal serum alpha-fetoprotein screening results. Prenat Diagn 1991;11:381–385.
102. Burton B, Dillard RG, Clark EN. The psychological impact of false positive elevations of maternal serum alpha fetoprotein. Am J Obstet Gynecol 1985;151:77–82.
103. Robinson JO, Hibbard BM, Laurence KM. Anxiety during a crisis: emotional effects of screening for neural tube defects. J Psychosom Res 1984;28:163–169.
104. Hakim-Elahi E, Tovell HMM, Burnhill MS. Complications of first-trimester abortion: a report of 170,000 cases. Obstet Gynecol 1990;76:129–135.
105. Lawson H, Atrash HK, Franks AL. Fatal pulmonary embolism during legal induced abortion in the United States from 1972 to 1985. Am J Obstet Gynecol 1990;162:986–990.
106. Osborn JF, Arisi E, Spinelli A, et al. General anaesthesia, a risk factor for complication following induced abortion? Eur J Epidemiol 1990;6:416–422.
107. Stray-Pedersen B, Biornstad J, Dahl M, et al. Induced abortion: microbiological screening and medical complications. Infection 1991;19:305–308.
108. Lawson HW, Frye A, Atrash HK, et al. Abortion mortality, United States, 1972 through 1987. Am J Obstet Gynecol 1994;171:1365–1372.
109. Council on Scientific Affairs, American Medical Association. Induced termination of pregnancy before and after Roe v Wade. Trends in the mortality and morbidity of women. JAMA 1992;268: 3231–3239.

110. Mishell DR Jr. Contraception, sterilization, and pregnancy termination. In: Herbst AL, Mishell DR Jr, Stenchezer MA, Droegemueller W, eds. Comprehensive gynecology. 2nd ed. St. Louis, MO: Mosby-Year Book, 1992:295–361.
111. Kochanek KD, Hudson BL. Advance report of final mortality statistics, 1992. Monthly vital statistics report; vol 43, no 6 (suppl). Hyattsville, MD: National Center for Health Statistics, 1995.
112. Centers for Disease Control and Prevention. Differences in maternal mortality among black and white women—United States, 1990. MMWR 1995;44:6–7,13–14.
113. American Academy of Pediatrics and American College of Obstetricians and Gynecologists. Guidelines for perinatal care. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics, 1992.
114. Canadian Task Force on the Periodic Health Examination. Canadian guide to clinical preventive health care. Ottawa: Canada Communication Group, 1994:84–98.
115. American College of Medical Genetics Clinical Practice Committee. ACMG position statement on multiple marker screening in women 35 and older. American College of Medical Genetics Newsletter, Jan 1994, vol. 2.
116. American College of Obstetricians and Gynecologists. Down syndrome screening. Committee Opinion no. 141. Washington, DC: American College of Obstetricians and Gynecologists, 1994.
117. American College of Obstetricians and Gynecologists. Ultrasonography in pregnancy. Technical Bulletin no. 187. Washington, DC: American College of Obstetricians and Gynecologists, 1993.
118. National Institutes of Health Consensus Development Conference. The use of diagnostic ultrasound imaging during pregnancy. JAMA 1984;252:669–672.
119. Thornton JG, Lilford RJ. Prenatal diagnosis of Down's syndrome: a method for measuring the consistency of women's decisions. Med Decis Making 1990;10:288–293.
120. Brock DJH. Screening for Down syndrome [letter]. Lancet 1987;2:1083–1084.
121. Hershey DW. Screening for Down's syndrome. N Engl J Med 1988;318:927–928.
122. Haslam R, Milner R. The physician and Down syndrome: are attitudes changing? J Child Neurol 1992; 7:304–310.
123. Inglese C. Is the cultural approach towards Down's syndrome people changing? Am J Med Genet 1990;7:322–323.