

## 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.<sup>1</sup> Population-based surveillance programs have reported a Down syndrome birth prevalence of 0.9 per 1,000 live births.<sup>2</sup> 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.<sup>3</sup> Based on 1988 cross-sectional data, the lifetime economic costs of Down syndrome have been estimated to be \$410,000 per case.<sup>4</sup>

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

drome pregnancies,<sup>11–13</sup> 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.<sup>14,15</sup>

#### 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.<sup>16–19</sup> 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.<sup>20–22</sup> In randomized controlled trials<sup>20–22</sup> and cohort studies<sup>23–29</sup> 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.<sup>20,30,31</sup> First-trimester amniocentesis (at 10–13 weeks) has been compared to CVS in one randomized controlled trial.<sup>32</sup> 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  $\alpha$ -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.<sup>33-36</sup> 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.<sup>37,38</sup> 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,<sup>39-41</sup> 36 years,<sup>42</sup> 37 years,<sup>43</sup> or 38 years,<sup>44</sup> and six that included women of any age desiring screening (90-95%  $\geq$  35 years),<sup>45-50</sup> 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  $\geq$  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

conjugated estriol.<sup>51</sup> If amniocentesis were performed on women with at least a 1 in 200 risk of carrying a fetus based on triple-marker screening, 89% of affected fetuses would be detected, 25% of women with unaffected fetuses would be identified by screening as needing amniocentesis. A similar 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  $\geq 35$  years<sup>43,46,47,50</sup> and 100% for women  $\geq 36$  years,<sup>42,45</sup> with false-positive screening results of 4–27%. 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.<sup>43,48,50,51</sup>

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.<sup>52</sup> 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%.<sup>53–55</sup> 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.<sup>56,57</sup> Incorrect positioning of the transducer, for example, can produce artifactual images resembling a thickened nuchal skin fold in a normal fetus.<sup>58</sup> 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.<sup>56,59,60</sup> 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%.<sup>59</sup> The false-positive rate in this study was 8.5%, many times higher than that reported in studies involving expert ultrasonographers.<sup>55,61</sup>

#### 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.<sup>62</sup> 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.<sup>63</sup> 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.<sup>64-67</sup>

Induced abortion is currently sought by the majority of women whose prenatal diagnostic studies (i.e., karyotyping) reveal fetuses with Down syndrome.<sup>33-35,39,40,45,48,68</sup> 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.<sup>2,69-73</sup> 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.<sup>74</sup> 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.<sup>68</sup> 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%.<sup>39,40,45,48</sup> 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%).<sup>47,49</sup> 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.<sup>45</sup> 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,<sup>75</sup> 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.<sup>76</sup> The health

consequences of sex aneuploidy are less significant than trisomies, but about half such pregnancies are nevertheless electively aborted when discovered prenatally.<sup>77,78</sup> 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,<sup>51</sup> however, because some of these abnormalities have different effects on serum markers than does Down syndrome, and require different risk thresholds.<sup>50,79</sup> 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.<sup>80,81</sup> The procedure-related rate of fetal loss with current technique appears to be about 0.5–0.8%.<sup>16,17,29</sup> The best evidence on amniocentesis risks comes from a randomized controlled trial of screening,<sup>16</sup> 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%.<sup>22</sup> 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%.<sup>16</sup> A similar trend was seen in the Medical Research Council study,<sup>18</sup> 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.<sup>83</sup> Case series of women undergoing first-trimester amniocentesis suggest a procedure-related fetal loss rate of 3–7%.<sup>84–87</sup> In a randomized controlled

trial, the total fetal loss rate with early amniocentesis was significantly higher than with CVS (5.9 vs. 1.2%).<sup>32</sup>

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.<sup>20–22</sup> 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%).<sup>31</sup> An increased risk of transverse limb reduction anomalies in infants born after CVS has been reported in case-control and case-series studies.<sup>88–93b</sup> Conflicting evidence from cohort studies may relate to varying methods of case ascertainment or classification.<sup>94–99a</sup> 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.<sup>93,99b</sup> Current estimates for the overall risk of transverse limb deficiency from CVS range from 0.03% to 0.16% of procedures.<sup>99a</sup> 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.<sup>22</sup> 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.<sup>100,101</sup> Distress is reduced following a diagnostic procedure confirming a normal pregnancy, but some anxiety related to the false-positive screening test may persist.<sup>102,103</sup> 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.<sup>104–107</sup> Complication rates, including maternal case-fatality rates, are higher with second-trimester abortions, but remain uncommon.<sup>108–110</sup> The case-fatality rate from legally induced abor-

tion, 0.4/100,00 procedures, is substantially lower than the risk of pregnancy-related death, which is 8–9/100,000 live births.<sup>108,109,111,112</sup> 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.<sup>113–115</sup> 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.<sup>114</sup> 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.<sup>115,116</sup> Neither ACOG nor ACMG recommends prenatal cytogenetic 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<sup>117</sup> and a National Institutes of Health consensus development conference<sup>118</sup> 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.<sup>10</sup> 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.<sup>64,119–121</sup> 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.<sup>122,123</sup> 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 DiGuseppi, MD, MPH, based in part on material prepared for the Canadian Task Force on the Periodic Health Examination by Paul Dick, MDCM, FRCPC.

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