PERIODIC HEALTH EXAMINATION, 1996 UPDATE: 1. PRENATAL SCREENING FOR AND DIAGNOSIS OF DOWN SYNDROME

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Abstract • Résumé

Objective: To make recommendations to physicians providing prenatal care on (1) whether prenatal screening for and diagnosis of Down syndrome (DS) is advisable and (2) alternative screening and diagnosis manoeuvres.

Options: "Triple-marker" screening of maternal serum levels of α-fetoprotein, human chorionic gonadotropin and unconjugated estriol; fetal ultrasonographic examination; amniocentesis; and chorionic villus sampling (CVS).

Outcomes: Accuracy of detection of DS in fetuses; and risks to the mother, including psychologic distress, and to the fetus from the screening and diagnostic interventions.

Evidence: A MEDLINE search for relevant articles published from Jan. 1, 1966, to Mar. 31, 1994, with the use of MeSH terms "Down syndrome," "prenatal diagnosis," "screening," "prevention," "amniocentesis," "chorionic villus sampling," "ultrasonography," "anxiety," "depression" and "psychological stress" and a manual search of bibliographies, recent issues of key journals and *Current Contents*.

Values: The evidence-based methods and values of the Canadian Task Force on the Periodic Health Examination were used. A high value was placed on providing pregnant women with the opportunity to determine whether they are carrying a fetus with DS and to make choices concerning the termination of the pregnancy. The economic issues involved are complex and were not considered.

Benefits, harms and costs: Triple-marker screening identifies an estimated 58% of fetuses with DS, but it has an estimated rate of true-positive results of 0.1% and of false-positive results of 3.7% (given a risk cut-off of one chance in 190 of DS). These rates vary with maternal age and the risk cut-off chosen. Women with a known risk of having a fetus with DS (e.g., those who have had a previous child with DS) may benefit from a reduction in anxiety after confirmation that their fetus does not have DS. Screening allows women at low risk of having a child with DS to detect fetuses with the syndrome, but may cause psychologic distress if there is a false-positive screening test result. Up to 20% of women with positive results of screening tests may decline to undergo a subsequent amniocentesis. Amniocentesis and CVS are very accurate in diagnosing DS in fetuses and have a very low rate of serious complications for the mother. Amniocentesis is associated with a 1.7% rate of fetal loss when it is performed after 16 weeks' gestation, whereas the rate among controls is 0.7% (for a difference of 1%, 95% confidence interval 0.3% to 1.5%). CVS entails a greater risk of fetal loss than amniocentesis (odds ratio 1.32, 95% confidence interval 1.11 to 1.57). There is little evidence from controlled trials of significant

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associations between amniocentesis or CVS and neonatal morbidity or malformations; however, samples have been too small to show differences in rare outcomes. Results from some case–control studies suggest that CVS increases the risk of transverse limb deficiency. Costs were not considered because they are beyond the scope of this review.

Recommendations: There is fair evidence to offer triple-marker screening through a comprehensive program to pregnant women under 35 years of age (grade B recommendation). Women given detailed information about serum-marker screening show more satisfaction with the screening than those not given this information. There is fair evidence to offer amniocentesis or CVS to pregnant women 35 years of age and older and to women with a history of a fetus with DS or of a chromosome 21 anomaly (grade B recommendation). Information on the limitations and advantages of each procedure should be offered. Triple-marker screening may be offered as an alternative to CVS or amniocentesis to pregnant women over 35.

Validation: Recommendations concerning prenatal diagnosis are similar to those of the US Preventive Services Task Force, the Society of Obstetricians and Gynaecologists of Canada, the Canadian College of Medical Geneticists and the Cochrane Pregnancy and Childbirth Group. No previous specific recommendations concerning triple-marker screening exist.

Sponsor: These guidelines were developed and endorsed by the Canadian Task Force on the Periodic Health Examination, which is funded by Health Canada and the National Health Research and Development Program.

Objectif : Formuler des recommandations aux médecins qui fournissent des soins prénataux pour (1) savoir si le dépistage et le diagnostic prénataux du syndrome de Down (SD) sont souhaitables et (2) proposer des moyens de dépistage et de diagnostic.

Options : Dépistage «à triple marqueur», chez la mère, des taux sériques d'α-foetoprotéine, de gonadotrophine chorionique humaine et d'oestriol non conjugué; ultrasonographie du foetus; amniocentèse et biopsie de villosités choriales (BVC).

Résultats : Précision du dépistage des foetus atteints du syndrôme de Down; et risques pour la mère, y compris détresse psychologique, et pour le foetus causés par les interventions de dépistage et de diagnostic.

Preuve : Recherche dans MEDLINE d'articles pertinents, publiés entre le 1er janv. 1966 et 31 mars 1994, à l'aide des termes MeSH «Down syndrome», «prenatal diagnosis», «screening», «prevention», «amniocentesis», «chorionic villus sampling», «ultrasonography», «anxiety», «depression» et «psychological stress» et recherche manuelle dans des bibliographies et des numéros récents de journaux clés et dans *Current Contents*.

Valeurs : On a utilisé les méthodes et les valeurs fondées sur des données probantes du Groupe d'étude canadien sur l'examen médical périodique. On a accordé une grande valeur à la possibilité d'offrir aux femmes enceintes la chance de déterminer si elles portent un foetus atteint du syndrome de Down et de faire des choix au sujet de l'interruption de la grossesse. Les questions économiques en cause sont complexes et il n'en a pas été tenu compte.

Avantages, préjudices et coûts : On estime que le dépistage à triple marqueur permet de repérer 58 % des foetus atteints du syndrome de Down, mais qu'il présente un taux estimatif de résultats vraiment positifs de 0,1 % et de résultats faussement positifs de 3,7 % (compte tenu d'une limite de risque d'une chance de syndrome de Down sur 190). Ces taux varient selon l'âge de la mère et la limite de risque choisi. Les femmes dont le risque de porter un foetus atteint du syndrome de Down (p. ex., celles qui ont déjà eu un enfant atteint du syndrome de Down) est connu peuvent bénéficier d'une réduction de l'anxiété après avoir obtenu la confirmation que leur foetus n'est pas atteint du syndrome de Down. Le dépistage permet de détecter les foetus atteints du syndrome de Down chez les femmes à faible risque d'avoir un enfant atteint du syndrome, mais il peut être une cause de détresse psychologique si le résultat du dépistage est faussement positif. Jusqu'à 20 % des femmes chez lesquelles les tests de dépistage donnent des résultats positifs peuvent refuser de subir une amniocentèse par la suite. L'amniocentèse et la BVC permettent de diagnostiquer avec beaucoup de précision la présence du syndrome de Down dans les foetus et ont un taux très faible de complications graves pour la mère. L'amniocentèse est liée à un taux de 1,7 % de perte du foetus lorsqu'elle est effectuée après 16 semaines de gestation, tandis que le taux chez les sujets témoins est de 0,7 % (pour une différence de 1 %, intervalle de confiance à 95 % de 0,3 % à 1,5 %). La BVC présente un plus grand risque de perte du foetus que l'amniocentèse (ratio des probabilités de 1,32, intervalle de confiance à 95 % de 1,11 à 1,57). Des essais contrôlés ont donné peu de preuves de liens importants entre l'amniocentèse ou la BVC et la morbidité néonatale ou les malformations. Toutefois, les tailles des échantillons sont trop petites pour révéler des différences au niveau des résultats rares. Les résultats de certaines études de cas–témoin indiquent que la BVC accroît le risque de déficience transverse des membres. Il n'a pas été tenu compte des coûts parce qu'ils échappent à la portée de cette étude.

Recommandations : Il y a assez de données probantes pour offrir aux femmes enceintes de moins de 35 ans un dépistage à triple marqueur dans le cadre d'un programme complet (recommandation de catégorie B). Les femmes qui ont reçu des renseignements détaillés sur le dépistage à l'aide de marqueurs sériques se disent plus satisfaites du dépistage que celles qui n'en ont pas reçu. Il y a assez de données probantes pour offrir l'amniocentèse ou la BVC aux femmes enceintes de 35 ans et plus et aux femmes qui ont déjà porté un foetus atteint du syndrome de Down ou d'une anomalie du chromosome 21 (recommandation de catégorie B). Il faudrait fournir des renseignements sur les limites et les avantages de chaque intervention. Le dépistage à triple marqueur peut être offert aux femmes enceintes de plus de 35 ans comme solution de rechange à la BVC ou à l'amniocentèse.

Validation : Les recommandations relatives au diagnostic prénatal sont semblables à celles du US Preventive Services Task Force, de la Société des obstétriciens et gynécologues du Canada, du Collège canadien de généticiens médicaux et du Cochrane Pregnancy and Childbirth Group. Il n'existe pas de recommandations précises antérieures sur le dépistage à triple marqueur.

Commanditaire : Ces lignes directrices ont été mises au point et appuyées par le Groupe d'étude canadien sur l'examen médical périodique, qui est financé par Santé Canada et par le Programme national de recherche et développement en matière de santé.

In 1979 the Canadian Task Force on the Periodic Health Examination made a grade B recommendation that amniocentesis be offered to pregnant women at a high risk of having a child with Down syndrome (DS) because the parents have a translocation of chromosome 21, there is a family history of DS or the mother's age is 35 years or older (fair evidence for inclusion in the periodic health examination).[1] Evidence concerning multiple maternal serum markers, prenatal ultrasonographic examination and chorionic villus sampling (CVS) for the diagnosis of DS in fetuses has subsequently emerged. The purpose of this article is to evaluate the evidence and develop recommendations for physicians who provide prenatal care on whether prenatal screening for and diagnosis of DS is advisable and on alternative manoeuvres for screening and diagnosis.

The task force assigned a high value to providing pregnant women with reproductive choice, in accordance with current societal values. Elective abortion, although still a divisive issue, is regarded by many as a matter of reproductive choice.[2] The Ethics and Public Policy Committee of the Canadian College of Medical Geneticists[3] and participants at a recent workshop on genetic testing held by the US National Institutes of Health[4] concur that prenatal diagnosis should involve allowing all women to make informed choices.

Selective abortion has been criticized for compromising the ideals of medicine by rejecting the weak and the sick,[5] and for focusing on "problematic genes" rather than on society's response to people with disabilities.[6] Society may interpret the availability of diagnosis of fetal DS, and subsequent termination, as an implicit message that having DS is undesirable. Many people are unwilling to care for children with DS. Growing societal pressure to avoid having a child with DS may create a stigma for families that include a person with DS.[7] Preventive services must therefore be carefully designed to increase patients' control; the use of these services must be voluntary, not routine or expected.

Some parents may wish to detect a fetus with DS through screening and diagnosis in order to prepare psychologically for the birth of the child rather than to decide to terminate the pregnancy. Evaluating the benefits and harms (e.g., fetal loss due to prenatal diagnosis) of diagnosis for this purpose is beyond the scope of this article. Furthermore, although cost–benefit or cost-effectiveness analysis of prenatal screening and diagnostic services may be considered relevant in designing prenatal-services programs, such analysis is complex and value laden. Cost is not currently an issue affecting physicians' provision of prenatal care or advice to women about their options. Therefore, it was not considered in this review.

The clinical options considered were "triple-marker" screening of maternal serum levels of α-fetoprotein (AFP), human chorionic gonadotropin (hCG) and unconjugated estriol (uE3), screening with the use of fetal ultrasonographic examination and prenatal diagnosis with amniocentesis or CVS. The health outcomes considered included maternal psychologic distress and physical risks to the mother and fetus from the diagnostic interventions.

These recommendations are concerned solely with the prenatal diagnosis of DS. Other chromosome anomalies (Turner's syndrome, trisomy 13 syndrome and others) are sometimes detected during prenatal diagnosis; these anomalies have not been considered independently because the diagnostic issues are similar to those involved in DS and because there are too few studies of other anomalies.

MEDLINE was searched for relevant articles published between Jan. 1, 1966, and Mar. 31, 1994, with the use of MeSH terms "Down syndrome," "prenatal diagnosis," "screening," "prevention," "amniocentesis," "chorionic villus sampling," "ultrasonography," "anxiety," "depression" and "psychological stress," in conjunction with a manual search of bibliographies, recent articles in key journals and *Current Contents*. Studies were evaluated using

the task force's grades of evidence.[8] Graded recommendations are made on the basis of the evidence on the burden of illness, the efficacy of detection, adverse effects and overall effectiveness of the manoeuvres.

The principal author conducted the literature review and provided a written and oral report to the task force members. This report was then critically reviewed by the task force and by independent reviewers.

Prevalence

DS is a congenital syndrome associated with chromosomal aneuploidy of all or part of chromosome 21. It is the most common pattern of malformation in humans.[9] The median incidence rate is approximately 1 per 1000 births (estimates range from 0.85 to 1.43 children with DS per 1000 births) in several countries.[10] More than 90% of DS cases are due to nondisjunction, and the rest are due to translocation and mosaicism.[11–13]

Burden of suffering

Clinically important problems caused by DS include hypotonia, mental retardation and growth retardation. Approximately 40% of children with DS have a congenital heart defect.[9] Between 10% and 25% of infants with DS die during the first year of life.[14–16] Those who survive have a shortened life expectancy.[15–18]

Literature on people with DS and their families has focused on dysfunctional outcomes.[19] Up to 10% of families with a child with DS appear unable or unprepared to cope with such a child.[20] Maternal depression and difficulty in marital and sibling relationships are often noted in these families, although other factors may play a role in these problems.[19,20] No study has shown adequately the financial burden caused by a child with DS, or the effect of having a child with DS on the careers of the parents.[21] Despite the special challenges involved with DS, many families with children with DS are intact and functional.[19–21]

Some of the manifestations of DS, such as congenital heart disease, may be amenable to specific therapies. However, there are no proven medical therapies for the cognitive deficits caused by DS.[22–25] Studies of early developmental intervention suggest that children's fine motor skills and social repertoire benefit from such intervention, but controlled trials of intervention are lacking and the evidence of long-term amelioration of developmental difficulties is poor.[26,27]

Manoeuvres

There are currently two approaches to prenatal diagnosis of DS. In the first, all pregnant women are screened during the second trimester by testing of three maternal serum markers or by fetal ultrasonographic examination. Amniocentesis is then offered to women with a positive result of the screening manoeuvre. In the second, pregnant women are identified as having a high risk of bearing a child with DS because they have had a previous child with DS, they are 35 years of age or older or they have a family history of chromosome rearrangement. These women are offered prenatal diagnosis with the use of amniocentesis, during the second trimester, or CVS, late in the first trimester.

Screening for DS

Maternal serum-marker screening

The maternal serum level of AFP was the first widely used serum marker for DS. However, the sensitivity of this test is relatively poor; fewer than one third of fetuses with DS are detected through regular testing of AFP levels.[28–30] Tests for other maternal serum markers (levels of hCG and uE3) were also examined[31–36] but do not appear to be adequately sensitive when used individually.

However, the simultaneous measurement of the three maternal serum markers (levels of AFP, hCG and uE3) during the second trimester has gained attention recently. In "triple-marker" screening, the probabilities of a fetus with DS derived from the individual tests of the three markers are combined with the maternal age-specific risk to produce a summary probability that the fetus has DS.[37–39] Women with a calculated probability exceeding a predetermined cut-off (e.g., a 1-in-250 risk of DS in the fetus) undergo a fetal ultrasonographic examination to verify the estimated dating of the pregnancy. If, on the basis of the accurate dating, the risk still exceeds the cut-off, the woman is offered amniocentesis. Many experts advocate routine ultrasonographic examination to establish accurate dating before screening. However, the value of this manoeuvre is contested.[40–42]

Four cohort studies (Table 1) have compared the number of fetuses with DS identified through triple-marker screening with the total number of fetuses with DS and infants born with DS detected through follow-up by the regional cytogenetics laboratory[44–46] or with the total number of infants expected to be born with DS on the basis of age-specific rates (in agreement with the actual number of infants born with DS, as detected through follow-up).[43] With the exception of one,[43] these studies involved low-risk pregnancies (mainly among women less than 35 or 37 years of age, depending on the study).

The rate of detection of DS through triple-marker screening ranged from 48% to 91%, with a median rate of 58% (95% confidence interval [CI] 44% to 72%). In

one of the studies, of the women screened, 3.8% were offered amniocentesis.[43] In this study, the risk cut-off at which women were offered amniocentesis was 1 in 190. The positive predictive value (PPV) achieved among women at a low risk of having a fetus with DS (1.5% when the age-related risk is 1 in 1000) is well within the range of risk at which prenatal diagnosis is now offered on the basis of maternal age or a previous child with DS. A recent report[47] on implementation of a triple-marker screening program shows results consistent with those of this study.

Two studies reported that the sensitivity of the test was lower among younger women than among older women (39% among women younger than 37 years v. 71% among those 37 and older,[45] and 67% among women younger than 30 years v. 100% among those 30 to 39[46]). In addition, the studies showed, without an explanation, that a significant proportion of women (21% to 31%) with a positive result of the screening tests did not undergo prenatal diagnosis (Table 1). The reason for this is not made apparent. The more limited sensitivity and the lack of diagnostic follow-up of positive results reduce the manoeuvre's effectiveness in preventing the birth of children with DS in young women with a low prior risk.

Ultrasonographic screening

Abnormalities associated with DS (intrauterine growth retardation, hydrops and some cardiac anomalies) can be observed in an ultrasonographic examination of a fetus during the second trimester.[48,49] Attention has focused on differences in long-bone length and nuchal skinfold thickness between fetuses with and without DS. One prospective clinical trial of ultrasonographic screening for DS has been reported. In a sample of 3338 pregnancies, 47 fetuses (1.4%) had nuchal skinfold measurements of 6 mm or more, found by ultrasonographic examination.[50] The sensitivity of this manoeuvre was 75% and the PPV was 25%; 12 of the 16 fetuses with DS were detected by ultrasonography. This sample consisted mainly of pregnant women at a high risk of having a fetus with DS because of their age or other factors. Hence, although the results seem promising, the PPV of ultrasonographic screening is expected to be significantly lower among pregnant women at a low risk of having a fetus with DS.

Interobserver and intraobserver reliability in ultrasonographic screening have not been adequately addressed. Differences in technique among those performing ultrasonography may have a substantial effect on screening performance, and the results obtained from a select group of ultrasonographers are not necessarily generalizable. This may explain some of the variation in the reported results and indicate a need for evaluation of the manoeuvre in large, community-based trials.[51–53]

Risk factors for having a fetus with DS

Several epidemiologic studies based on data from cytogenetics registries, birth certificates and examinations of newborns have shown that the risk of having a fetus with DS increases with increasing maternal age.[13,54–65] Risk estimates at various ages are given in Table 2. A link between the incidence of DS and paternal age has been suggested[66–69] but not routinely shown.[13,54,70–73]

Birth of a previous child with nondisjunction trisomy 21, one form of DS, is a risk factor for subsequent births of children with DS.[74,75] The observed recurrence rate of pregnancy involving a fetus with DS is approximately 0.5%, and this rate is apparently independent of age among women younger than 35 years of age.[76]

Parents who have previous children with DS caused

Table 1: Summary of studies of triple-marker screening with follow-up amniocentesis for prenatal diagnosis of Down syndrome (DS)

Study	Level of evidence*	Study sample	Age of pregnant women in sample, yr	Cut-off risk for offering amniocentesis†	Detection rate for DS, %†	No. (and %) of women offered amniocentesis	Amniocentesis uptake rate, %‡
Haddow et al, 1992[43]	Cohort study (II-2)	25 207	16–41	1 in 190	58 (21/36)	962 (3.8)	79 (760/962)
Phillips et al, 1992[44]	Cohort study (II-2)	9 530	< 35	1 in 274	57 (4/7)	307 (3.2)	70 (214/307)
Wald et al, 1992[45]	Cohort study (II-2)	12 603	< 37§	1 in 250	48 (12/25)	514 (4.1)	77 (397/514)
Cheung et al, 1993[46]	Cohort study (II-2)	7 718	< 35‖	1 in 195	91 (20/22)	461 (6.0)	69 (319/461)

*For descriptions of the levels of evidence, see Appendix 1 in part 1 of the 1992 update (*Can Med Assoc J* 1992; 147: 443).
†For an explanation, see the text.
‡The amniocentesis uptake rate is the number of women with a positive result of a screening test who subsequently undergo amniocentesis divided by the total number of women with a positive result.
§95% of the sample was in this age group.
‖90% of the sample was in this age group.

by chromosome rearrangements, and who are carriers of certain chromosome rearrangements, have an increased risk of having subsequent fetuses with DS. The estimated risk of having a fetus with DS caused by chromosome rearrangements involving chromosome 21 is specific to the type of rearrangement; the risk ranges up to 15%.[77–79]

Prenatal diagnosis of DS

Screening versus diagnosis

Women who are at high risk of having a fetus with DS are usually offered prenatal diagnosis through amniocentesis or CVS. The usual age threshold at which amniocentesis or CVS is offered is 35 years, if there are no other risk factors.[80] Triple-marker screening may lead to more efficient use of amniocentesis among women of advanced age, with little loss of detection ability.[43,80] Among 5385 women 35 years of age and older who underwent amniocentesis, 89% of the fetuses with DS were borne by the 25% of women who had had a positive result of a triple-marker screening test.[80] In a study of the implementation of antenatal screening, 64% of women 36 years of age and older participating chose serum-marker screening over amniocentesis.[47] It is unclear whether this choice would be significantly influenced by the availability of CVS, which may be used to diagnose DS earlier in the pregnancy.

Amniocentesis

In one randomized controlled trial of amniocentesis, DS was detected in 0.17% of pregnancies among 2239 women at low risk of having a fetus with DS.[81] No fetus with DS was missed, nor were any fetuses without DS misdiagnosed as a result of amniocentesis. Among 2268 controls, 0.13% delivered an infant with DS.[81] Apart from some increase in reports of abdominal pain and amniotic-fluid leakage, the rate of pregnancy complications in the group receiving amniocentesis was no higher than in the control group. Other studies that are not randomized controlled trials have shown a similar accuracy rate for amniocentesis.[82–84]

In a randomized controlled trial by Tabor and associates[81] involving women 25 to 34 years of age, there was a statistically significant higher rate of fetal loss after 16 weeks' gestation in the group receiving amniocentesis (1.7%) than in the control group (0.7%), for a difference of 1.0% (95% confidence interval [CI] 0.3% to 1.5%). The difference between groups in the rate of fetal loss during the entire pregnancy was 0.8%. Neonatal respiratory distress syndrome and neonatal pneumonia were more frequent among the infants of mothers who had undergone amniocentesis than among infants in the control group, regardless of the infants' birth weight and gestational age (1.8% v. 0.8%, $p < 0.05$).[81]

The increased neonatal morbidity and fetal loss observed in Tabor and associates' study has been attributed to their reported use of 18-gauge needles to perform amniocentesis.[84–87] Others have given lower estimates of fetal loss (approximately 0.5%) with the use of smaller-bore needles.[88] Tabor and associates subsequently published a correction in which they stated that, among most of the women who participated in their trial, amniocentesis was performed with a 20-gauge needle, and that the rate of fetal loss was not increased in the small group among whom amniocentesis was performed with an 18-gauge needle.[89]

In a trial of amniocentesis conducted by the Medical Research Council in Britain, the investigators noted increased rates of fetal loss, neonatal morbidity and orthopedic anomalies among the infants of the mothers who had undergone amniocentesis.[83] However, this study had a cohort design with inadequately matched controls; therefore, the strength of this evidence is poor. Other studies have shown that the risk of spontaneous abortion appears to be increased if there is a bloody tap or placental perforation.[81,82,90] Among children followed up for 4 years after amniocentesis, no clinically significant effects on development or physical status were evident.[91]

Table 2: Maternal-age-specific risk estimates of having a child with DS (based on a singleton gestation)*

Maternal age, yr	Risk of DS in infant
20	1 in 1500
25	1 in 1350
30	1 in 900
35	1 in 380
40	1 in 110
45	1 in 30

*Adapted from Cuckle, Wald and Thompson, 1987.[63]

CVS

CVS is an alternative to amniocentesis for obtaining tissue for karyotype analysis and, hence, diagnosis of DS in a fetus. CVS has the advantage of being performed late in the first trimester, several weeks before amniocentesis or triple-marker screening can be undertaken. Like amniocentesis, it may be offered to women who are at a high risk of having a fetus with DS (as a result of advanced age or of having had a previous infant with DS). Six uncontrolled studies have shown that transcervical CVS provides accurate prenatal diagnosis in more than

99% of women at a high risk of having a fetus with DS.[92–97] Subsequent amniocentesis was necessary among up to 5% of women, to clarify the diagnosis or to obtain a karyotype, because CVS failed to provide a definitive diagnosis.

The rates of fetal loss following CVS (2.4% to 6.2%) were similar to rates after a routine first-trimester ultrasonographic examination[98–101] (except in one centre[95]), but this evidence is of poor quality. Better estimates of risk were obtained from comparative studies of amniocentesis and CVS (see the next section). No increases or unusual patterns in neonatal morbidity or congenital anomalies as a result of CVS were noted in these uncontrolled trials.

Three large registry-based case–control studies have evaluated a possible link between CVS and fetal limb defects.[102–104] Results from one of these supports an association between CVS and increased risk of transverse limb deficiency,[102] and another supports an association with transverse digital deficiency.[103] The estimated absolute risk of such a deficiency is 0.03%,[103] lower than the risk of DS or of fetal loss among women undergoing CVS. The risk may be limited by performing CVS after 70 days' gestation, since the strength of the association and the severity of the deficiency appear to decrease as the gestational age of the fetus increases.[102,103]

Transabdominal CVS is a new alternative to transcervical CVS with comparable accuracy.[105–107] Transabdominal CVS appears to be associated with a lower risk of fetal loss. The ease with which the sample is obtained, and the choice of sampling technique, may depend on uterine and placental position.

CVS versus amniocentesis

Three randomized controlled trials have compared CVS with amniocentesis.[61,105,108] Interpretation of karyotypes was more difficult in samples obtained through CVS than in those obtained through amniocentesis because contamination of the sample with maternal cells is more common in CVS and because karyotypic abnormalities confined to the placenta are sampled by CVS but not by amniocentesis. Although accurate diagnosis was ultimately obtained in more than 99% of the pregnancies in the group undergoing CVS, the rate of repeat procedures was up to 4.7%, whereas it was 1.0% in the group undergoing amniocentesis. The Association of Cytogenetic Technologists has published guidelines for the use of direct and culture methods to aid in the interpretation of maternal cell contamination and placental mosaicism.[109]

These studies have shown that CVS results in higher rates of all fetal loss (including pregnancy termination and perinatal death),[105,108] and of fetal loss before 28 weeks' gestation (excluding terminations)[108] compared with amniocentesis (these results are statistically significant). More bleeding and spotting[61,105,108] and a greater trend toward maternal complications requiring inpatient treatment (e.g., sepsis or bleeding necessitating a transfusion)[61] have been observed after CVS than after amniocentesis. However, in the study of these complications, the rate in both groups was low (less than 1%).[61]

Another study showed that, among women 38 years of age, on average, CVS appears to entail a greater risk of fetal loss than amniocentesis.[110] The best estimates of risk come from two recent Canadian and European trials of CVS and amniocentesis.[61,108] Both studies involved pregnant women with an increased risk of having a fetus with DS as a result of age (mean 38 years), previous birth of an infant with DS or chromosomal-abnormality carrier status. The European trial reported a rate of spontaneous fetal loss before 28 weeks' gestation of 9% in the CVS group and of 6% in the amniocentesis group (statistically significant difference of 2.9%, 95% CI 0.6 to 5.3).[108] The Canadian trial reported a rate of total fetal loss (including induced abortions) of 16.9% in the CVS group and of 15.2% in the amniocentesis group (difference of 1.7%, 95% CI −1.4 to 4.4).[61] For these two trials, the combined odds ratio for fetal loss before 28 weeks' gestation after CVS, compared with amniocentesis, is 1.32 (95% CI 1.11 to 1.57).[110]

The sample sizes in these trials were inadequate for statistical testing of the frequencies of rare maternal or fetal adverse effects. To test for a difference in an outcome that occurs among 0.2% to 0.4% of fetuses (with Type I error of 5% and Type II error of 20%) requires a trial with approximately 13 000 pregnancies in each group — a much larger sample than those in existing studies.[111]

Intervention

First-trimester abortion following CVS is the safest form of intervention; it has extremely few complications.[112] The complication rate in second-trimester abortion, which would be required following amniocentesis, is substantially higher (the main complication being retention of the products of conception).[113,114] Maternal death due to abortion in either the first or second trimester is extremely rare (occurring in less than 1 in 300 000 abortions).[115]

Adverse effects

The physical effects of prenatal diagnosis and intervention, which are specific to the method of diagnosis or termination, have already been discussed. There have also been investigations of the psychologic effects. Psy-

chologic effects on the mother associated with prenatal screening and testing include fear of revealing an abnormal pregnancy, fear of having to face a decision about pregnancy continuation and fear of a complication resulting from the procedure.[116] Women at a high risk of having a fetus with DS because of a previous birth of a child with DS or because of a structural chromosome rearrangement are more anxious than those at a high risk because of advanced age.[117–119] Distress among women at a high risk appears to abate rapidly if the absence of DS is confirmed by the diagnostic procedure.[120–124] Before information about the possible link between CVS and limb deficiencies was widely known, some women considered CVS preferable or less distressing than amniocentesis, presumably because it could be conducted earlier in the pregnancy.[116,120,122,125] After the association between CVS and limb deficiencies was publicized, the use of CVS appears to have decreased, although not disappeared, in some areas.[126]

Some studies have suggested that women with a positive result of a screening test involving the AFP serum marker may experience greater distress than women of an advanced age, despite the equivalent risk. However, these studies report a reduction in distress after amniocentesis.[127,128] Counselling and information may not reduce anxiety experienced after a false-positive result of a screening test.[129,130] However, in a randomized controlled trial, detailed written information about the AFP serum marker screening test given to those undergoing the test resulted in more knowledge about the test and greater satisfaction with it.[129] This effect may be generalizable to triple-marker screening; therefore, physicians offering this screening should consider the value of giving patients detailed information on the efficacy of the screening test, the implications of false-positive results and the subsequent procedures after positive results.

Women with positive results of AFP tests who do not undergo amniocentesis appear to experience more anxiety than those who undergo amniocentesis that confirms that the fetus does not have DS.[128] No study has adequately addressed possible psychologic harm to women with a positive result of a screening test who do not subsequently undergo amniocentesis.

Of women undergoing second-trimester abortion because of a fetal abnormality, 80% reported an acute grief reaction, and in some cases the grief was prolonged.[131] The grief experienced by women who have terminated a pregnancy because of genetic indications may be as intense as that felt by those who lose a fetus spontaneously.[132]

Use of prenatal diagnosis is related to views on the acceptability of pregnancy termination and to the perceived risk of abnormality in the fetus.[133] The role played by health care professionals in shaping beliefs may be important. Although most women feel that they are autonomous in their decision making, many feel there is a risk that they will be persuaded.[134] There is some evidence that individuals' perceptions of the risk of procedures and of DS may be inconsistent.[135] Some couples may accept the risk of amniocentesis even when the chance of having a fetus with DS is very low. The perception of the nature of the disability may play a greater role in the decision than its probability of occurrence.[136–138]

The psychologic implications of having no access to prenatal diagnosis or of giving birth to an infant with DS must be weighed against those of receiving false-positive results of screening tests, of undergoing the procedures and of making decisions concerning diagnosis and termination. No study has contrasted these benefits and harms directly. Although a randomized controlled trial of screening versus no screening, in which psychologic as well as physical outcomes were compared, would address these issues directly, the challenge of conducting such a trial may be onerous given the values and preferences involved. It remains to be shown whether decision analysis (such as that used to study the decisions concerning amniocentesis versus CVS[126]) or other approaches would clarify the balance of harms and benefits.

Effect of prenatal diagnosis

Crude estimates of the reduction in live births of infants with DS as a result of prenatal diagnosis offered to women 35 years and older range from 7.3% to 20%.[139–142] The reduction in birth rates of infants with DS appears to be due, at least in part, to a disproportionately higher use of pregnancy termination, without prenatal diagnosis, among older women in certain areas.[143,144] The effect of triple-marker screening has yet not been assessed widely. Attempts have been made to gauge the economic effect of prenatal screening for and diagnosis of DS.[43,145–149] Triple-marker screening is thought to be a more cost-effective approach to prevention than amniocentesis, CVS or single-marker screening.[43,147,149] However, the complex, value-laden ethical and methodologic issues underlying economic analyses in this context are beyond the scope of these guidelines.

Recommendations

The task force's recommendations, and the strength of the evidence supporting them, are summarized in Table 3.

There is fair evidence (grade B recommendation) to offer triple-marker screening to women under 35 years of age within a comprehensive screening and prenatal-diagnosis program including education, interpretation

and follow-up. However, there is concern about the limited sensitivity of the screening test, the number of women who receive false-positive results and the number of women who receive positive results but do not subsequently undergo amniocentesis. These limitations may place a heavy burden on family physicians and obstetricians to inform fully all parents interested in screening. Screening of maternal serum markers outside of a comprehensive program is not recommended.

Women provided with detailed information on serum-marker screening may demonstrate more knowledge of the procedure and more satisfaction with it. Rel-

Table 3: Summary of manoeuvres, effectiveness, levels of evidence and recommendations for prenatal screening for and diagnosis of DS

Manoeuvre	Effectiveness	Level of evidence*	Recommendation*
Offer triple-marker screening (for maternal serum levels of α-fetoprotein, chorionic gonadotropin and unconjugated estriol) to pregnant women during the second trimester, with information about the limitations and advantages of screening; offer amniocentesis to women who have a positive result of the screening test	**Screening** Among women with a low risk of having a fetus with DS (those younger than 35), this manoeuvre identifies an estimated 58% of fetuses with DS, with a rate of true-positive results of 0.1% and of false-positive results of 3.7%. The effect of false-positive results is poorly understood, and 20% of women with a positive result may decline amniocentesis. Detailed information about the screening method increases the satisfaction of women undergoing screening	Cohort studies[43-46] (II-2)	Fair evidence to include in the periodic health examination of pregnant women under 35 years of age (B) Triple-marker screening may be offered as an alternative to amniocentesis or CVS alone for women 35 years of age and older
	Among women at a higher risk of having a fetus with DS (those more than 35 years of age), an estimated 89% of fetuses with DS are identified, with an amniocentesis rate of 25%	Cross-sectional study[80] (III)	
Identify whether pregnant women have risk factors for having a fetus with DS; offer prenatal diagnosis with amniocentesis or chorionic villus sampling (CVS), with information about the limitations and advantages of each procedure, to women with risk factors	**Risk identification** The following factors indicate an increased risk of having a fetus with DS: advanced maternal age (35 years or older), a previous fetus with DS, or a family history of a known chromosome anomaly that is associated with a risk of DS in a fetus	Cohort studies[13,54-65,74-79] (II-2)	Fair evidence to include in the periodic health examination of pregnant women (B)
	Prenatal diagnosis CVS and amniocentesis provide very accurate diagnosis of DS in a fetus. Amniocentesis is associated with a higher rate of fetal loss after the procedure than the rate among women who do not undergo the procedure (1.7% v. 0.7%). CVS is associated with a greater risk of fetal loss than amniocentesis (odds ratio 1.32). An increased risk of limb deficiency has been associated with CVS	**Amniocentesis:** Randomized controlled trial[81] (I), nonrandomized controlled trial[83] (II-1) and cohort studies[82,84] (II-2) **CVS:** Cohort studies [92-97,106,107] (II-2), case–control studies[102,103] (II-2) **Amniocentesis and CVS:** Randomized controlled trials[61,105,108] (I)	

*For descriptions of the levels of evidence and classification of recommendations, see Appendix 1 in part 1 of the 1992 update (*Can Med Assoc J* 1992; 147: 443).

evant information about triple-marker screening may include (1) the limited sensitivity and specificity of screening, (2) the time sequence, nature and risks of prenatal diagnosis and second-trimester abortion, and (3) the psychologic implications of screening and diagnosis as well as the implications of having a child with DS.

There is fair evidence (grade B recommendation) to offer prenatal diagnosis with CVS or amniocentesis, accompanied by information on the limitations and advantages of each procedure, to women who are 35 years of age or over, who have had a previous fetus with DS or who are carriers of chromosome 21 rearrangements. The quality of evidence concerning the balancing of all risks with benefits among these women is limited; therefore, a grade A recommendation has not been made. However, the potential benefit in reducing distress among women who are at a high risk of having a fetus with DS is clearly substantial. Although triple-marker screening has been advocated as a more efficient method of diagnosing DS among fetuses of women at a high risk (older than 35 years of age), its value as a replacement for CVS or amniocentesis in high-risk groups has not been assessed. However, some women in this age group may see triple-marker screening as an attractive alternative that provides a chance of avoiding prenatal diagnostic procedures. Accordingly, it may be offered as an alternative to prenatal diagnosis for women 35 years or older.

There is insufficient evidence to offer testing of single maternal-serum markers (such as AFP alone) specifically for screening of DS. However, maternal serum AFP measurement may be offered to screen for neural tube defects. An abnormal AFP result, which suggests a risk of DS in the fetus, necessitates subsequent counselling and offering of prenatal diagnosis.

Ultrasonographic screening with the use of long-bone and nuchal skinfold measurements is not currently recommended as a method of screening for DS because there is insufficient evaluation of its effectiveness, insufficient comparison with triple-marker screening and concern about the reliability and generalizability of these techniques.

Validation

Several other groups have made recommendations concerning screening for and prenatal diagnosis of DS.[110,150–157] Amniocentesis and CVS have been recommended for prenatal diagnosis in high-risk groups by the US Preventive Services Task Force[152] and the Society of Obstetricians and Gynaecologists of Canada, in conjunction with the Canadian College of Medical Geneticists.[153] There have been no recommendations made concerning maternal serum triple-marker screening or ultrasonographic screening. The Cochrane Pregnancy and Childbirth Group has recently reviewed several topics in prenatal diagnosis and has made conclusions regarding amniocentesis, and transcervical and transabdominal CVS that are consistent with these recommendations.[110,154–157] The US Centers for Disease Control and Prevention have also recently published recommendations on prenatal counselling about CVS and amniocentesis that are consistent with these recommendations.[158]

Research questions

- Are tests of other maternal serum markers or other combinations of markers (e.g., AFP and hCG) more effective than triple-marker screening, or effective earlier in pregnancy?
- Is routine ultrasonographic examination to determine gestational age a necessary step in conducting triple-marker screening?
- How effective is ultrasonographic screening, in comparison with serum-marker screening, in a community setting?
- What are the outcomes among women with a positive result of a screening test who decline prenatal diagnosis?
- Are there safer, effective alternatives to CVS and to second-trimester amniocentesis (e.g., first-trimester amniocentesis)?
- What effect do prenatal screening and diagnosis have on societal perceptions of people with disabilities?
- What are the financial, emotional and social implications of having a child with DS? How effective and how widely available are interventions and community resources to improve outcomes among families with children with DS?
- Can further development and evaluation of early interventions and therapies for children with DS improve their cognitive and functional outcomes?

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Feb. 26–29, 1996: Topics in Clinical Medicine — Evidence-Based Care
Wailea, Maui, Hawaii
Melinda Arnold, Group Health Cooperative, Provider Education and Guidelines CEB-1, 201–16th Ave. E, Seattle WA 98112; tel 206 326-3934, fax 206 326-3774; marnold@accgw.ghc.org

Mar. 2–3, 1996: Violence — Implications for Clinical Practice
New Orleans
Study credits available.
Maria Gorrick, American Psychiatric Association, 1400 K St. NW, Washington DC 20005; tel 202 682-6145, fax 202 682-6102; MGORRICK@psych.org

Mar. 4–5, 1996: Evaluation and Pre-testing of Health Communication
Toronto
Health Communications Unit, Project Office, Centre for Health Promotion, 175 College St., Toronto ON M5T 1P8; tel 416 978-0522, fax 416 971-2443; hershfield.Larry@utoronto.ca; website: http://hpb1.hwc.ca:8500/syn_indx.html

Mar. 4–6, 1996: Obesity — Advances in Understanding and Treatment
Washington
International Business Communications USA Conferences Inc., 225 Turnpike Rd., Southborough MA 01772-1749; tel 508 481-6400, fax 508 481-7911

Mar. 7–8, 1996: IBC's Biennial International Conference — Mycobacterial Infection: Pathogenesis, Prevention and Strategies for New Drug and Vaccine Development
Washington
International Business Communications USA Conferences Inc., 225 Turnpike Rd., Southborough MA 01772-1749; tel 508 481-6400, fax 508 481-7911

Mar. 7–9, 1996: 1st European Forum on Quality Improvement in Health Care (sponsored by the BMJ Publishing Group and the Institute for Healthcare Improvement)
London, England
Languages: English, French, German and Spanish
Conference Unit, BMA House, Tavistock Square, London WC1H 9JP, England; tel 0171 383-6478, fax 0171 383-6663

Mar. 7–9, 1996: 12th International Seating Symposium (cosponsored by the Sunny Hill Health Centre for Children, the School of Health and Rehabilitation Sciences, University of Pittsburgh, and RESNA)
Vancouver
12th International Seating Symposium, Continuing Education in the Health Sciences, University of British Columbia, 105–2194 Health Sciences Mall, Vancouver BC V6T 1Z3; tel 604 822-4965, fax 604 822-4835

Mar. 9–10, 1996: International Psychogeriatric Association India Regional Workshop
New Delhi, India
International Psychogeriatric Association, 3127 Greenleaf Ave., Wilmette IL 60091; tel 708 966-0063, fax 708 966-9418

Mar. 14–15, 1996: Faculty Development Workshop — Executive Skills for Medical Faculty
Montreal
Study credits available.
Mrs. Jean McNab, Department of Family Medicine, McGill University, 517 Pine Ave. W, Montreal QC H2W 1S4; tel 514 398-7375

Mar. 14–15, 1996: IBC's 2nd Annual Industry Congress — Hepatitis: Latest Therapeutic Developments for Hepatitis B and C
Washington
International Business Communications USA Conferences Inc., 225 Turnpike Rd., Southborough MA 01772-1749; tel 508 481-6400, fax 508 481-7911

Mar. 14–15, 1996: IBC's 3rd Annual Conference — Therapeutic Applications of Cytokines: Control of Inflammation, Growth and Differentiatiation
Philadelphia
International Business Communications USA Conferences Inc., 225 Turnpike Rd., Southborough MA 01772-1749; tel 508 481-6400, fax 508 481-7911

Mar. 14–16, 1996: Spring in Vancouver: the Art of Emergency Medicine
Vancouver
Marion Yip or Jennie Mould, Section of Emergency Medicine, British Columbia Medical Association, 115–1665 W Broadway Ave., Vancouver BC V6J 5A4; tel 604 736-5551, fax 604 736-3987

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