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Chorionic Villus Sampling and Amniocentesis:

Recommendations for Prenatal Counseling

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Chorionic Villus Sampling and Amniocentesis: Recommendations for Prenatal Counseling

Summary

Chorionic villus sampling (CVS) and amniocentesis are prenatal diagnostic procedures that are performed to detect fetal abnormalities. In 1991, concerns about the relative safety of these procedures arose after reports were published that described a possible association between CVS and birth defects in infants. Subsequent studies support the hypothesis that CVS can cause transverse limb deficiencies. Following CVS, rates of these defects, estimated to be 0.03%–0.10% (1/3,000–1/1,000), generally have been increased over background rates. Rates and severity of limb deficiencies are associated with the timing of CVS; most of the birth defects reported after procedures that were performed at ≥70 days' gestation were limited to the fingers or toes.

The risk for either digital or limb deficiency after CVS is only one of several important factors that must be considered in making complex and personal decisions about prenatal testing. For example, CVS is generally done earlier in pregnancy than amniocentesis and is particularly advantageous for detecting certain genetic conditions. Another important factor is the risk for miscarriage, which has been attributed to 0.5%–1.0% of CVS procedures and 0.25%–0.50% of amniocentesis procedures. Prospective parents considering the use of either CVS or amniocentesis should be counseled about the benefits and risks of these procedures. The counselor should also discuss both the mother's and father's risk(s) for transmitting genetic abnormalities to the fetus.

INTRODUCTION

Chorionic villus sampling (CVS) and amniocentesis are prenatal diagnostic procedures used to detect certain fetal genetic abnormalities. Both procedures increase the risk for miscarriage (*1*). In addition, concern has been increasing among health-care providers and public health officials about the potential occurrence of birth defects resulting from CVS (*2*).

This report describes CVS and amniocentesis, provides information on indications for their use, reviews studies about the safety of the procedures, compares the benefits and risks of the two procedures (focusing particularly on the risk for limb deficiency after CVS), and provides recommendations for counseling about these issues. A public meeting was convened on March 11, 1994, to discuss the results of studies of CVS-associated limb deficiencies and preliminary counseling recommendations that had been drafted at CDC (*3*). Participants included geneticists, obstetricians, pediatricians, epidemiologists, teratologists, dysmorphologists, and genetic counselors who had a particular interest in CVS studies or who represented professional organizations and government agencies. Participants provided diverse opinions about recommendations for counseling both at the meeting and in subsequent written correspondence; input from participants has been incorporated into this document.

USE OF CVS AND AMNIOCENTESIS

CVS utilizes either a catheter or needle to biopsy placental cells that are derived from the same fertilized egg as the fetus. During amniocentesis, a small sample of the fluid that surrounds the fetus is removed. This fluid contains cells that are shed primarily from the fetal skin, bladder, gastrointestinal tract, and amnion. Typically, CVS is done at 10–12 weeks' gestation, and amniocentesis is done at 15–18 weeks' gestation. In the United States, the current standard of care in obstetrical practice is to offer either CVS or amniocentesis to women who will be ≥35 years of age when they give birth, because these women are at increased risk for giving birth to infants with Down syndrome and certain other types of aneuploidy. Karyotyping of cells obtained by either amniocentesis or CVS is the standard and definitive means of diagnosing aneuploidy in fetuses. The risk that a woman will give birth to an infant with Down syndrome increases with age. For example, for women 35 years of age, the risk is 1 per 385 births (0.3%), whereas for women 45 years of age, the risk is 1 per 30 births (3%) (*1*). The background risk for major birth defects (with or without chromosomal abnormalities) for women of all ages is approximately 3%.

Before widespread use of amniocentesis, several controlled studies were conducted to evaluate the safety of the procedure. The major finding from these studies was that amniocentesis increases the rate for miscarriage (i.e., spontaneous abortions) by approximately 0.5%. Subsequent to these studies, amniocentesis became an accepted standard of care in the 1970s. In 1990, more than 200,000 amniocentesis procedures were performed in the United States (*4*).

In the 1960s and 1970s, exploratory studies were conducted revealing that the placenta (i.e., chorionic villi) could be biopsied through a catheter and that sufficient placental cells could be obtained to permit certain genetic analyses earlier in pregnancy than through amniocentesis. In the United States, this procedure was initially evaluated in a controlled trial designed to determine the miscarriage rate (*5*). The difference in fetal-loss rate was estimated to be 0.8% higher after CVS compared with amniocentesis, although this difference was not statistically significant. Because that study was designed to determine miscarriage rates, it had limited statistical power to detect small increases in risks for individual birth defects.

CVS had become widely used worldwide by the early 1980s. The World Health Organization (WHO) sponsors an International Registry of CVS procedures; data in the International Registry probably represent less than half of all procedures performed worldwide (*6*). More than 80,000 procedures were reported to the International Registry from 1983–1992 (*6*); approximately 200,000 procedures were registered from 1983–1995 (L. Jackson, personal communication). CVS is performed in hospitals, outpatient clinics, selected obstetricians' offices, and university settings; these facilities are often collectively referred to as prenatal diagnostic centers. Some investigators have reported that the availability of CVS increased the overall utilization of prenatal diagnostic procedures among women ≥35 years of age, suggesting that access to first-trimester testing may make prenatal chromosome analysis appealing to a larger number of women (*7*). Another group of obstetricians did not see an increase in overall utilization when CVS was introduced (*8*). The increase in CVS procedures was offset by a decrease in amniocentesis, suggesting that the effect of CVS availability on the utilization of prenatal diagnostic testing depends on local factors. In the United

States, an estimated 40% of pregnant women ≥35 years of age underwent either amniocentesis or CVS in 1990 (*9*).

Although maternal age-related risk for fetal aneuploidy is the usual indication for CVS or amniocentesis, prospective mothers or fathers of any age might desire fetal testing when they are at risk for passing on certain mendelian (single-gene) conditions. In a randomized trial conducted in the United States, 19% of women who underwent CVS were <35 years of age (*10*). DNA-based diagnoses of mendelian conditions, such as cystic fibrosis, hemophilia, muscular dystrophy, and hemoglobinopathies, can be made by direct analysis of uncultured chorionic villus cells (a more efficient method than culturing amniocytes) (*11*). However, amniocentesis is particularly useful to prospective parents who have a family history of neural tube defects, because alphafetoprotein (AFP) testing can be done on amniotic fluid but cannot be done on CVS specimens.

When testing for chromosomal abnormalities resulting from advanced maternal age, CVS may be more acceptable than amniocentesis to some women because of the psychological and medical advantages provided by CVS through earlier diagnosis of abnormalities. Fetal movement is usually felt and uterine growth is visible at 17–19 weeks' gestation, the time when abnormalities are detected by amniocentesis; thus, deciding what action to take if an abnormality is detected at this time may be more difficult psychologically (*12*). Using CVS to diagnose chromosomal abnormalities during the first trimester allows a prospective parent to make this decision earlier than will amniocentesis.

Maternal morbidity and mortality associated with induced abortion increase significantly with increasing gestational age; thus, the timing of diagnosis of chromosomal abnormalities is important. Results of studies of abortion complications conducted by CDC from 1970 through 1978 indicated that the risk for major abortion complications (e.g., prolonged fever, hemorrhage necessitating blood transfusion, and injury to pelvic organs) increases with advancing gestational age. For example, from 1971 through 1974, the major complication rate was 0.8% at 11–12 weeks' gestation, compared with 2.2% at 17–20 weeks' gestation (*13*). However, the risk for developing major complications from abortion at any gestational age decreased during the 1970s. More contemporary national morbidity data based on current abortion practices are not yet available. CDC surveillance data also indicate an increase in the risk for maternal death with increasing gestation. From 1972 through 1987, the risk for abortion-related death was 1.1 deaths per 100,000 abortions performed at 11–12 weeks' gestation compared with 6.9 deaths per 100,000 abortions for procedures performed at 16–20 weeks' gestation (*14*). The lower risk associated with first-trimester abortions may be an important factor for prospective parents who are deciding between CVS and amniocentesis.

Amniocentesis is usually performed at 15–18 weeks' gestation, but more amniocentesis procedures are now being performed at 11–14 weeks' gestation. "Early" amniocentesis (defined as <15 weeks' gestation) remains investigational, because the safety of the procedure is currently being evaluated with controlled trials (*15*).

Risk estimates for miscarriage caused by either CVS or midtrimester amniocentesis have been adjusted to account for spontaneous fetal losses that occur early in pregnancy and are not procedure-related. Although one randomized trial indicated that the amniocentesis-related miscarriage rate may be as high as 1%, counselors usually cite

risks for miscarriage from other amniocentesis studies ranging from 0.25%–0.50% (1/400–1/200) (*1,15*). Rates of miscarriage after CVS vary widely by the center at which CVS was performed (*16*). Adjusting for confounding factors such as gestational age, the CVS-related miscarriage rate is approximately 0.5%–1.0% (1/200–1/100) (*1*).

Although uterine infection (i.e., chorioamnionitis) is one possible reason for miscarriage after either CVS or amniocentesis, infection has occurred rarely after either procedure. In one study, no episodes of septic shock were reported after 4,200 CVS procedures, although less severe infections may have been associated with 12 of the 89 observed fetal losses (*5*). Overall infection rates have been <0.1% after either CVS or amniocentesis (*15*).

Cytogenetically ambiguous results caused by factors such as maternal cell contamination or culture-related mosaicism are reported more often after CVS than after amniocentesis (*2*). In these instances, follow-up amniocentesis might be required to clarify results, increasing both the total cost of testing and the risk for miscarriage. However, ambiguous CVS results also may indicate a condition (e.g., confined placental mosaicism) that has been associated with adverse outcomes for the fetus (*11*). Thus, in these situations, CVS may be more informative than amniocentesis alone.

LIMB DEFICIENCIES AMONG INFANTS WHOSE MOTHERS UNDERWENT CVS

Certain congenital defects of the extremities, known as limb deficiencies or limb-reduction defects, have been reported among infants whose mothers underwent CVS. This section addresses 1) the expected frequency and classification of these birth defects, 2) the physical features of reported infants in relation to the timing of associated CVS procedures, and 3) cohort and case-control studies that have been done to systematically examine whether CVS increases the risk for limb deficiencies.

Population-Based Rates and Classification of Limb Deficiencies

Population-based studies indicate that the risk for all limb deficiencies is from 5–6 per 10,000 live births (*17*). Limb deficiencies usually are classified into distinct anatomic and pathogenetic categories. The most common subtypes are transverse terminal defects, which involve absence of distal structures with intact proximal segments, with the axis of deficiency perpendicular to the extremity. Approximately 50% of all limb deficiencies are transverse, and 50% of those defects are digital, involving the absence of parts of one or more fingers or toes. Transverse deficiencies occur as either isolated defects or with other major defects. The rare combination of transverse limb deficiencies with either absence or hypoplasia of the tongue and lower jaw—usually referred to as oromandibular-limb hypogenesis or hypoglossia/hypodactyly—occurs at a rate of approximately 1 per 200,000 births. Although the cause of many isolated limb deficiencies and multiple anomalies that include transverse deficiencies is unknown, researchers have hypothesized that these deficiencies are caused by vascular disruption either during the formation of embryonic limbs or in already-formed fetal limbs (*17,18*).

Limb Deficiencies Reported in Infants Exposed to CVS

Reports of clusters of infants born with limb deficiencies after CVS were first published in 1991 (*19*). Three studies illustrate the spectrum of CVS-associated defects (*19–21*). Data from these studies suggest that the severity of the outcome is associated with the specific time of CVS exposure. Exposure at ≥70 days' gestation has been associated with more limited defects, isolated to the distal extremities, whereas earlier exposures have been associated with more proximal limb deficiencies and orofacial defects. For example, in a study involving 14 infants exposed to CVS at 63–79 days' gestation and examined by a single pediatrician, 13 had isolated transverse digital deficiencies (*20*). In another study in Oxford of five infants exposed to CVS at 56–66 days' gestation, four had transverse deficiencies with oromandibular hypogenesis (*19*). In a review of published worldwide data, associated defects of the tongue or lower jaw were reported for 19 of 75 cases of CVS-associated limb deficiencies (*21*). Of those 19 infants with oromandibular-limb hypogenesis, 17 were exposed to CVS before 68 days' gestation. In this review, 74% of infants exposed to CVS at ≥70 days' gestation had digital deficiencies without proximal involvement.

Cohorts of CVS-Exposed Pregnancies

Cohort studies usually measure rates of a specified outcome in an exposed group compared with an unexposed group. Ideally, both groups should be selected randomly from the same study population. The three largest collaborative trials of CVS in Europe, Canada, and the United States were designed originally in this way; however, in these studies, the outcome of interest was fetal death. The report of the first U.S. collaborative trial included no mention of any structural defects; such outcomes were reported later (*5*).

After the initial case reports in 1991, neonatal outcomes from the collaborative trials were analyzed more intensively (*22*). However, rather than comparing rates for limb defects in the CVS-exposed cohorts with those of amniocentesis-exposed cohorts from the same study population, the rates in the CVS groups were compared with population-based rates. Consequently, these comparisons must be interpreted with caution because population-based rates are derived differently (i.e., usually from birth-defect registries). CVS-associated risk for limb deficiencies could be underestimated by these comparisons if follow-up of pregnancies in the exposed cohort is incomplete. Other epidemiologic issues must also be considered when interpreting comparisons of crude rates. Unless a formal meta-analysis is performed, these comparisons neither account for heterogeneity between studies nor assign individual "weights" to studies. Comparisons of crude rates also do not adjust for potential confounding variables, such as maternal age. Methods of anatomic subclassification also vary between registries and can differ from methods applied to CVS-exposed cohorts. In addition, comparing overall rates of limb deficiency in groups exposed to CVS with groups unexposed to CVS might overlook an association with a specific phenotype, such as transverse deficiency.

Published CVS cohort studies of >1,000 CVS procedures include data from 65 CVS centers (Table 1). These rates include studies that describe affected limbs in sufficient detail to exclude nontransverse defects. Rates calculated for the smaller cohorts (i.e., centers performing <3,500 procedures) are less stable, but the overall rate of nonsyndromic transverse limb deficiency from these centers was 7.4 per 10,000 procedures.

TABLE 1. Rates of transverse terminal limb-deficiencies at 65 CVS centers* — selected geographical locations, 1984–1992

Location†	No. of Centers	CVS		Rate
		No. of Cases	No. of Procedures	
U.S. (NICHD§) (*22,23*)	10	7	9,588	7.3
U.S. (*24*)	9	3	4,105	7.3
Netherlands—Rotterdam (*25*)	1	3	3,973	7.6
Italy—Sardinia (*26*)	1	3	3,082	9.7
U.S.—Beverly Hills, CA (*27*)	1	1	3,016	3.3
Germany—Münster (*28*)	1	2	2,836	7.1
Italy (GIDEF¶) (*29*)	5	3	2,759	10.9
U.S.—Philadelphia, PA (*30*)	1	1	2,710	3.7
Denmark (*31*)	2	0	2,624	0.0
Australia—Victoria (*32*)	2	3	2,071	14.5
Europe (MRC**) (*33*)	31	2	1,609	12.4
U.S.—Evanston, IL (*34*)	1	1	1,048	9.5
Total	**65**	**29**	**39,421**	**7.4**

*Per 10,000 CVS procedures.
†Excluded were centers (i.e., collaborating hospitals or other health-care facilities) reporting either ≤1,000 procedures or incomplete information about birth-defect outcomes.
§National Institute of Child Health and Human Development (combined data from two trials [*5,10*]).
¶Gruppo Italiano Diagnosi Embrio-Fetali.
**Medical Research Council, United Kingdom.

This crude rate can be compared with rates of transverse deficiencies from Victoria (Australia) and Boston, Massachusetts (United States), where cases were classified to resemble the phenotype of CVS-exposed infants with limb deficiencies, including deficiencies of single digits (Table 2). The range of rates for these two populations (1.5–2.3 per 10,000 births) is representative of rates reported for other populations. The threefold to fivefold increase in the overall rate for the 65 centers compared with the rates for Victoria or Boston is statistically significant (chi-square: $p<0.001$) (*17,32*).

Investigators participating in the International Registry also have combined birth-defect data from multiple CVS centers, including some of the 65 CVS centers (*16,35*). An abstract published in 1994 includes information about 138,000 procedures reported to the International Registry. The rate of transverse deficiencies in the reporting centers was 1.4 per 10,000 procedures, lower than most population-based rates; the distribution of limb-deficiency subtypes was similar to the results of a study of limb deficiencies in British Columbia.

The variability in limb-deficiency rates could be related to three possible explanations:

1) **Different methods of classification.** The method of classification of limb deficiencies for the International Registry resulted in a smaller proportion of transverse deficiencies (compared with all limb deficiencies) than some population-based studies (*17,32,36,37*). The reason for this smaller proportion is that the definition of "transverse terminal deficiencies" is more restrictive and includes only defects that extend across the complete width of a limb and excludes terminal deficiencies of fewer than five digits.

TABLE 2. Comparison of rates* of transverse limb deficiencies in chorionic villus sampling (CVS) cohorts and unexposed populations — selected sites and study periods

		CVS cohorts		
Location	Study Period	No. of Cases	No. of Procedures	Rate*
International Registry† (*35*)	1983–94	20	138,000	1.4 (0.9– 2.2)
Table 1 cohorts§ (*22–34*)	1984–92	29	39,421	7.4 (4.9–10.6)
		Unexposed populations		
Location	Study Period	No. of Cases	No. of Births	Rate*
Australia–Victoria (*32*)	1990–91	30	129,765	2.3 (1.6–3.3)
U.S.–Boston, MA (*17*)¶	1972–74 1979–90	18	123,489	1.5 (0.9–2.3)

*Per 10,000 procedures, 95% confidence interval.
†Method of classification of limb deficiencies differs from that in the unexposed populations listed (L. Jackson, personal communication).
§Method of classification similar to that in the unexposed populations listed.
¶Retabulated from original publication (L. Holmes, personal communication).

2) **Ascertainment of outcomes.** Ascertainment of outcomes may be incomplete in CVS registries because deliveries can occur at a hospital remote from where the CVS was performed and might not be reported back to the CVS center. The effect of this incomplete ascertainment would be to underestimate risk for adverse outcomes.
3) **Differences among centers in the performance of CVS.** Investigators have compared rates of miscarriages and rates of limb deficiencies at individual facilities. This comparison is based on the assumption that the causes of both miscarriage and limb defects might be related to particular techniques of sampling by individual obstetricians. The association between high miscarriage and limb-deficiency rates in one U.S. CVS center was cited as potential evidence of the role of surgical inexperience (*24*). A cluster of limb deficiencies in another U.S. teaching hospital (five after 507 CVS procedures) was not associated with elevated miscarriage rates; chorionic villus sample sizes were larger at this hospital than at another hospital affiliated with the same university that reported no infants with limb defects (*38*).

Case-Control Studies

Case-control approaches with a minimum of 100 case and 100 control patients have greater statistical power than cohort studies of 10,000 or fewer births to detect a fourfold increase in risk for transverse deficiencies (the degree of relative risk suggested by data from the 65 CVS centers) (*36*). Investigators participating in multicenter birth-defect studies have used this case-control approach both to measure the strength of the association between CVS and limb deficiency and to determine if a dose-response (or gradient) effect of risk exists. The latter effect would be indicated by an increased relative risk for limb deficiency after earlier procedures, suggested in case reports of CVS-associated limb deficiencies by the high frequency of early

exposures to CVS. Three case-control studies have used infants with limb deficiencies registered in surveillance systems and control infants with other birth defects to examine and compare exposure rates to CVS (*36,37,39*). The odds ratios for CVS exposure (an estimate of the relative risk for limb deficiency after CVS) are summarized in Table 3.

The U.S. Multistate Case-Control Study and the study of the Italian Multicentric Birth Defects Registry both indicated a significant association between CVS exposure and subtypes of transverse limb deficiencies (*36,37*). The EUROCAT study did not analyze risk for transverse limb deficiencies (*39*); the risk for all limb deficiencies (odds ratio [OR]=1.8, 95% confidence interval [CI]=0.7–5.0) was similar to that measured in the U.S. Multistate Case-Control Study for all limb deficiencies (OR=1.7, 95% CI=0.4–6.3) (*36*). Analysis of subtypes in the U.S. study indicated a sixfold increase in risk for transverse digital deficiencies (*36*). In the U.S. study, no association between limb deficiencies and amniocentesis was observed. In the study of the Italian Multicentric Birth Defects Registry, the association between CVS exposure and transverse limb deficiencies was stronger (Table 3) (*37*).

GESTATIONAL AGE AT CVS

The lower risk observed in the United States may be related to the later mean gestational age of exposure. Increased risk was associated with decreased gestational age at the time of exposure (Table 4). The risk for transverse deficiencies was greatest at ≤9 weeks' gestation. An analysis of cohort studies regarding the timing of CVS indicated a similar gradient with a relative risk for transverse deficiencies of 6.2 at <10 weeks' and 2.4 at ≥10 weeks' gestation (*40*). Because of reports of high rates of severe limb deficiencies after CVS at 6–7 weeks' gestation, a WHO-sponsored committee recommended that CVS be performed at 9–12 weeks after the last menstrual period (*16*).

TABLE 3. Risk for limb deficiencies and subtypes, by selected case-control studies of limb defects after chorionic villus sampling — by selected registries, 1984–1993

Registry	All limb deficiencies OR* (95% CI)†	Transverse limb deficiencies OR* (95% CI)†	Subsets of transverse deficiencies OR* (95% CI)†
U.S. Multistate Case-Control Study (*36*)	1.7 (0.4–6.3)	4.7 (0.8–28.4)	Digital: 6.4 (1.1–38.6)
EUROCAT (European Registration of Congenital Anomalies and Twins) (*39*)	1.8 (0.7–5.0)	Not subclassified	Not subclassified
IMBDR (Italian Multicentric Birth Defects Registry)** (*37*)	Not included§	12.6 (6.2–23.9)	OMLH¶:223.8 (48.9–1006.8)

*Odds ratios.
†Confidence interval.
§Case definition included only transverse limb deficiencies.
¶Oromandibular-limb hypogenesis (hypoglossia/hypodactyly) (P. Mastroiacovo, personal communication).
**IPIMC (Indagine Policentrica Italiana sulle Malformazioni Congenite).

TABLE 4. Risk for transverse limb deficiency after chorionic villus sampling (CVS), by gestational age — United States and Italy, 1988–1993

Gestational age (weeks)	United States*		Italy†	
	No. of CVS-exposed cases	OR§ (95% CI)¶	No. of CVS-exposed cases	OR§ (95% CI)¶
≤9	2	11.3 (1.0–131.6)	8	21.6 (9.0–47.7)
10	4	7.5 (1.5– 36.7)	3	14.3 (3.2–47.2)
≥11	1	5.6 (0.3– 94.7)	0	—**

*Includes transverse digital deficiencies only (*36*).
†Includes all types of transverse deficiencies (*37*).
§Odds ratio.
¶Confidence interval.
**No CVS-exposed cases.

POSSIBLE MECHANISMS OF CVS-ASSOCIATED LIMB DEFICIENCY

Several biological events have been proposed to explain the occurrence of limb deficiency after CVS, the variation in severity, and the risk associated with the timing of the procedure. These mechanisms, which include thromboembolization or fetal hypoperfusion through hypovolemia or vasoconstriction, are based on the assumption that the defects associated with CVS were caused by some form of vascular disruption. The limbs and mandible are susceptible to such disruption before 10 weeks' gestation (*17*); however, isolated transverse limb deficiencies related to fetal hypoperfusion have been reported at 11 weeks' gestation (*18*).

The rich vascular supply of chorionic villi can potentially be disrupted by instrumentation. Data from one study of embryoscopic procedures demonstrated fetal hemorrhagic lesions of the extremities following placental trauma, which produced subchorionic hematomas (*41*). Placental hemorrhage following CVS could lead to substantial fetal hypovolemia with subsequent hypoperfusion of the extremities. Because animal models show that limb deficiencies have been produced by either vasoconstrictive agents or occlusion of uterine vessels, some researchers have hypothesized that CVS-associated defects might be caused by uteroplacental insufficiency (*42*). Although the period of highest embryonic susceptibility appears to be when CVS is performed before 9 weeks' gestation (i.e., early CVS), these mechanisms also can disrupt limb structures at later gestational ages.

ABSOLUTE RISK FOR LIMB DEFICIENCY

Subtypes of limb deficiencies rarely occur in the population of infants not exposed to CVS. Thus, even a sixfold increase in risk for such types as digital defects (the finding of the U.S. Multistate Case-Control Study) is comparable to a small absolute risk (i.e., 3.46 cases per 10,000 CVS procedures [0.03%]) (*36*). The upper 95% confidence limit for this absolute risk estimate is approximately 0.1%. A range of absolute risk from 1 per 3,000 to 1 per 1,000 CVS procedures (0.03%–0.10%) for all transverse deficiencies is consistent with the overall increase in risk reported by the 65 centers (Table

1). In cohort studies that reported the timing of the CVS, the absolute risk for transverse limb deficiencies was 0.20% at ≤9 weeks, 0.10% at 10 weeks, and 0.05% at ≥11 weeks (0.07% at ≥10 weeks of gestation) (*40*).

The absolute risk for CVS-related birth defects is lower than the procedure-related risk for miscarriage that counselors usually quote to prospective parents (i.e., 0.5% to 1.0%) and also is lower than the risk for Down syndrome at age 35 (0.3%). Data from a decision analysis study supported the conclusion that, weighing a range of possible risks associated with prenatal testing, amniocentesis was preferred to CVS (*43*). This study was published in 1991 and did not consider risk for limb deficiency. Data indicate that publication of the initial case reports of limb deficiency decreased subsequent utilization of CVS (*44,45*). However, one study demonstrated that prospective parents who were provided with formal genetic counseling, including information about limb deficiencies and other risks and benefits, chose CVS at a rate similar to a group of prospective parents who were counseled before published reports of CVS-associated limb deficiencies (*44*).

RECOMMENDATIONS

An analysis of all aspects of CVS and amniocentesis indicates that the occasional occurrence of CVS-related limb defects is only one of several factors that must be considered in counseling prospective parents about prenatal testing. Factors that can influence prospective parents' choices about prenatal testing include their risk for transmitting genetic abnormalities to the fetus and their perception of potential complications and benefits of both CVS and amniocentesis. Prospective parents who are considering the use of either procedure should be provided with current data for informed decision making. Individualized counseling should address the following:

Indications for procedures and limitations of prenatal testing

- Counselors should discuss the prospective parents' degree of risk for transmitting genetic abnormalities based on factors such as maternal age, race, and family history.
- Prospective parents should be made aware of both the limitations and usefulness of either CVS or amniocentesis in detecting abnormalities.

Potential serious complications from CVS and amniocentesis

- Counselors should discuss the risk for miscarriage attributable to both procedures: the risk from amniocentesis at 15–18 weeks' gestation is approximately 0.25%–0.50% (1/400–1/200), and the miscarriage risk from CVS is approximately 0.5%–1.0% (1/200–1/100).
- Current data indicate that the overall risk for transverse limb deficiency from CVS is 0.03%–0.10% (1/3,000–1/1,000). Current data indicate no increase in risk for limb deficiency after amniocentesis at 15–18 weeks' gestation.
- The risk and severity of limb deficiency appear to be associated with the timing of CVS: the risk at <10 weeks' gestation (0.20%) is higher than the risk from CVS done at ≥10 weeks' gestation (0.07%). Most defects associated with CVS at ≥10 weeks' gestation have been limited to the digits.

Timing of procedures

- The timing of obtaining results from either CVS or amniocentesis is relevant because of the increased risks for maternal morbidity and mortality associated with terminating pregnancy during the second trimester compared with the first trimester (*13,14*).
- Many amniocentesis procedures are now done at 11–14 weeks' gestation; however, further controlled studies are necessary to fully assess the safety of early amniocentesis.

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