Invasive Prenatal Testing for Aneuploidy

Prenatal diagnosis of fetal chromosomal abnormalities is the most common indication for invasive prenatal testing. The prevalence of chromosomal abnormalities in clinically recognized early pregnancy loss is greater than 50% (1). Fetuses with aneuploidy account for 6–11% of all stillbirths and neonatal deaths (2). Chromosomal abnormalities that are compatible with life but cause considerable morbidity occur in 0.65% of newborns, and structural chromosomal rearrangements that will eventually affect reproduction occur in 0.2% of newborns (3). Consequently, screening and diagnostic programs to detect the most common autosomal trisomies in liveborn infants, including Down syndrome, are well established. The purpose of this document is to provide clinical management guidelines for the prenatal diagnosis of these aneuploidies.

Background

There are many strategies available to screen for chromosomal abnormalities (4). These incorporate maternal age and a variety of first- and second-trimester ultrasound and biochemical markers that include nuchal translucency measurement and pregnancy-associated plasma protein A, human chorionic gonadotropin, alpha-fetoprotein, estriol, and inhibin levels. All of these approaches provide an adjusted risk for Down syndrome and trisomy 18. Whereas these risk figures provide a more accurate risk for Down syndrome and trisomy 18 than maternal age alone, they do not exclude the possibility of an affected fetus because the test sensitivity is less than 100%, so not all fetuses can be identified. Studies have shown that many factors influence a woman’s decision to undergo an invasive procedure (5). These include feelings about having a child in whom a chromosomal abnormality has been diagnosed and feelings about the loss of a normal child as a result of the diagnostic procedure.
Down syndrome and other trisomies are primarily the result of meiotic nondisjunction, which increases with maternal age. Women contemplating screening versus diagnostic testing for aneuploidy may find it helpful to compare their adjusted risk after screening with their age-related risk (Table 1).

Fetuses with aneuploidy may have major anatomic malformations that often are discovered during an ultrasound examination that is performed for another indication. Abnormalities involving a major organ or structure, with a few notable exceptions, or the finding of two or more minor structural abnormalities in the same fetus indicate increased risk of fetal aneuploidy (6, 7) (Table 2). There are genetic and nongenetic causes of structural anomalies. If an aneuploidy is suspected, only a cytogenetic analysis of fetal cells can provide a definitive diagnosis. In some cases, a fetal karyotype will be sufficient but, in other situations, adjunct testing such as fluorescence in situ hybridization or other genetic testing may be required to detect chromosomal microdeletions or duplications or to further characterize marker chromosomes or chromosomal rearrangements.

**Amniocentesis**

Traditional genetic amniocentesis usually is offered between 15 weeks and 20 weeks of gestation. Many large, multicenter studies have confirmed the safety of genetic amniocentesis as well as its cytogenetic diagnostic accuracy (greater than 99%) (8). All of the large collaborative studies in which the risk of amniocentesis was evaluated were performed before the use of high-resolution concurrent ultrasonography. In more recent studies, it is suggested that the procedure-related loss rate is as low as 1 in 300–500 and may be even lower with experienced individuals or centers (9, 10). Complications, which occur infrequently, include transient vaginal spotting or amniotic fluid leakage in approximately 1–2% of all cases and chorioamnionitis in less than 1 in 1,000 cases. The perinatal survival rate in cases of amniotic fluid leakage after midtrimester amniocentesis is greater than 90% (11). Needle injuries to the fetus have been reported but are very rare when amniocentesis is performed under continuous ultrasound guidance. Amniotic fluid cell culture failure occurs in 0.1% of samples. In several studies, it has been confirmed that the incidence of pregnancy loss, blood-contaminated specimens, leaking of amniotic fluid, and the need for more than one needle puncture are related to the experience of the operator, the use of small-gauge needles, and ultrasound guidance (12–14).

Early amniocentesis performed from 11 weeks to 13 weeks of gestation has been widely studied, and the tech-

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3Risk for any chromosomal abnormality includes the risk for trisomy 21 and trisomy 18 in addition to trisomy 13, 47,XXY, 47,XYY, Turner syndrome genotype, and other clinically significant abnormalities, 47,XXX not included. Data from Hook EB. Rates of chromosome abnormalities at different maternal ages. Obstet Gynecol 1981;58:282-5.
4Data not available
technique is similar to traditional amniocentesis (15–17); however, performing early amniocentesis results in significantly higher rates of pregnancy loss and complication than performing traditional amniocentesis. In a multicenter randomized trial, the spontaneous pregnancy loss rate after early amniocentesis was 2.5%, compared with 0.7% with traditional amniocentesis (18). The overall incidence of talipes was 1.4% after the early procedure, compared with 0.1% (the same as the background rate) after traditional amniocentesis, and membrane rupture was more likely after the early procedure. Significantly more amniotic fluid culture failures occurred after the early procedure, necessitating an additional invasive procedure for diagnosis. For these reasons, early amniocentesis (at less than 14 weeks of gestation) should not be performed.

**Chorionic Villus Sampling**

Chorionic villus sampling (CVS) generally is performed after 9 completed weeks of gestation. Placental villi may be obtained through transcervical or transabdominal access to the placenta. There is no difference in fetal loss rates after transcervical or transabdominal CVS (8). The primary advantage of CVS over amniocentesis is that results are available earlier in pregnancy, which provides reassurance for parents when results are normal and, when results are abnormal, may allow for earlier and safer methods of pregnancy termination.

The overall pregnancy loss rate after CVS is greater than the rate after midtrimester amniocentesis because of the increased background rate of spontaneous pregnancy loss between 9 weeks and 16 weeks of gestation. Although recent data are limited, the procedure-related pregnancy loss rate for CVS appears to approach, and may be the same as, the rate for midtrimester amniocentesis (19–22).

In several studies, it has been shown that there is a significant learning curve associated with the safe performance of CVS (23, 24). Consequently, the pregnancy loss data described previously is only valid in experienced centers.

Although there have been reports of associations between CVS and limb reduction and oromandibular defects, the risk for these anomalies is unclear (25). In an
analysis by the World Health Organization, an incidence of limb-reduction defects of 6 per 10,000 was reported, which is not significantly different from the incidence in the general population (26). However, a workshop on CVS and limb reduction defects sponsored by the U.S. National Center for Environmental Health and the Centers for Disease Control and Prevention concluded that transverse limb deficiencies appeared to be more common after CVS. The frequency of limb reduction defects is highest when CVS is performed before 9 weeks of gestation (27, 28). In addition, a panel convened by the National Institute of Child Health and Development and the American College of Obstetricians and Gynecologists concluded that oromandibular–limb hypogenesis appeared to be more common among infants who were exposed to CVS and appeared to correlate with, but may not be limited to, CVS performed earlier than 7 weeks of gestation (25). Women considering CVS who are concerned about the possible association of CVS with limb defects can be reassured that when the procedure is performed after 9 weeks of gestation, the risk is low and probably not greater than the general population risk of limb defects.

Other complications after CVS include vaginal spotting or bleeding, which may occur in up to 32.2% of patients after transcervical CVS is performed. The incidence after transabdominal CVS is performed is less (29). The incidence of culture failure, amniotic fluid leakage, or infection after CVS is performed is less than 0.5% (29).

Cordocentesis

Cordocentesis, also known as percutaneous umbilical blood sampling, involves puncturing the umbilical vein under direct ultrasound guidance. Karyotype analysis of fetal blood usually can be accomplished within 24–48 hours. The procedure-related pregnancy loss rate has been reported to be less than 2% (30). Cordocentesis is rarely needed but may be useful to further evaluate chromosomal mosaicism discovered after CVS or amniocentesis is performed.

Clinical Considerations and Recommendations

Who should have the option of prenatal diagnosis for fetal chromosomal abnormalities?

Invasive diagnostic testing for aneuploidy should be available to all women, regardless of maternal age. Pretest counseling should include a discussion of the risks and benefits of invasive testing compared with screening tests; how many women will have a positive result (screen-positive rate) and, of those, how many will have a true positive result (detection rate); the detection rate of aneuploidies other than Down syndrome; and the type and prognosis of the aneuploidies likely to be missed by serum screening. Counseling should be provided by a practitioner familiar with these details. The differences between screening and diagnostic testing should be discussed with all women. A woman’s decision of whether to have screening, an amniocentesis, or CVS is based on many factors, including the risk that the fetus will have a chromosomal abnormality, the risk of pregnancy loss from an invasive procedure, and the consequences of having an affected child. Studies that have evaluated women’s preferences have shown that women weigh these potential outcomes differently. The decision to perform invasive testing should take into account these preferences and should not be based solely on age. Maternal age of 35 years alone should no longer be used as a threshold to determine who is offered screening versus who is offered invasive testing.

How is the risk of aneuploidy assessed?

The risk for fetal aneuploidy can be determined by referring to maternal age-specific aneuploidy risk tables or using age-adjusted risks after screening. It may be helpful to compare the patient’s individual risks with risk cutoffs used to indicate a positive screening test result. These cutoffs are based on the specific detection rate and screen-positive rate of the screening approach that is used.

Who is at increased risk for aneuploidy?

Patients with an increased risk of fetal aneuploidy include the following categories:

- Previous fetus or child with autosomal trisomy—Recently, a large collaborative study reported that the risk of trisomy recurrence is 1.6–8.2 times the maternal age risk depending on the type of trisomy, whether the index pregnancy was a spontaneous abortion, maternal age at initial occurrence, and the maternal age at subsequent prenatal diagnosis (31).
- Structural anomalies identified by ultrasonography—The presence of one major or at least two minor fetal structural abnormalities increases the likelihood of aneuploidy (6, 7). However, there are some isolated malformations that are not usually associated with aneuploidy and that may not require further testing (Table 2).
- Previous fetus or child with sex chromosome abnormality—Not all sex chromosome abnormalities have
• Parental aneuploidy or mosaicism for aneuploidy—A woman whose previous offspring had a 47,XY Y karyotype is not at increased risk of recurrence because the extra chromosome is paternal in origin. Turner syndrome (45,X) has a nominal risk of recurrence. Parents of children with 47,XY Y or 45,X karyotypes may still request prenatal diagnosis in future pregnancies for reassurance.

• Parental carrier of chromosome translocation—Women or men carrying balanced translocations, although phenotypically normal themselves, are at risk of producing unbalanced gametes, resulting in abnormal offspring. For most translocations, the observed risk of abnormal liveborn children is less than the theoretic risk because some of these gametes result in nonviable conceptions. In general, carriers of chromosome translocations that are identified after the birth of an abnormal child have a 5–30% risk of having unbalanced offspring in the future, whereas those identified for other reasons (eg, during an infertility workup) have a 0–5% risk (1). Genetic counseling may be helpful in such situations.

• Parental carrier of chromosome inversion—An inversion occurs when two breaks occur in the same chromosome and the intervening genetic material is inverted before the breaks are repaired. Although no genetic material is lost or duplicated, the rearrangement may alter gene function. Each carrier’s risk of having a liveborn abnormal child is related to the method of ascertainment, the chromosome involved, and the size of the inversion; thus, risks should be determined individually. The observed risk is approximately 5–10% if the inversion is identified after the birth of an abnormal child and 1–3% if ascertainment occurs at some other time (1). One exception is a pericentric inversion of chromosome 9, which is a common variant in the general population and of no clinical consequence.

• Parental aneuploidy or mosaicism for aneuploidy—Women with trisomy 21, although subfertile, have approximately a 50% risk of having trisomic offspring. Women with 47,XXX and men with 47,XY Y usually are fertile and have no discernible increase in risk of having trisomic offspring. In men with a normal karyotype who have oligospermia or whose partners conceive from intracytoplasmic sperm injection, there is an increased incidence of abnormal karyotype in the sperm (32).

What type of laboratory test should be performed to diagnose aneuploidy?

Metaphase analysis of cultured amniocytes or chorionic villus cells is the preferred method for karyotype analysis. This approach is highly accurate, with results typically available 1–2 weeks after the procedure. Fluorescence in situ hybridization (FISH) analysis provides a more rapid result for specific chromosomes, most commonly chromosomes 13, 18, 21, X, and Y. Whereas FISH analysis has been shown to be accurate, false-positive and false-negative results have been reported. Therefore, clinical decision making should be based on information from FISH and at least one of the following results: confirmatory traditional metaphase chromosome analysis or consistent clinical information, such as an abnormal ultrasound finding or a positive screening test result for Down syndrome or trisomy 18 (33).

Comparative genomic hybridization (CGH) is an evolving method that identifies submicroscopic chromosomal deletions and duplications. This approach has proved useful in identifying abnormalities in individuals with developmental delay and physical abnormalities when results of traditional chromosomal analysis have been normal (34). The use of CGH in prenatal diagnosis, at present, is limited because of the difficulty in interpreting which DNA alterations revealed through CGH may be normal population variants. Until there are more data available, use of CGH for routine prenatal diagnosis is not recommended.

How often does chromosomal mosaicism occur in amniocentesis or chorionic villus sampling results?

Chromosomal mosaicism, the presence of more than one cell line identified during cytogenetic analysis, occurs in approximately 0.25% of amniocentesis specimens and 1% of chorionic villus specimens. After mosaicism is found by CVS, amniocentesis typically is performed to assess whether mosaicism is present in amniocytes. In most cases, the amniocentesis result is normal, and the mosaicism is assumed to be confined to the trophoblast. Although this is unlikely to cause defects in the fetus, it may result in third-trimester growth restriction. Clinical manifestations depend on the specific mosaic cell line(s) and may range from completely normal to findings consistent with the abnormal chromosome result. Counseling following the finding of chromosomal mosaicism is complex, and referral for genetic counseling may be useful in these cases. In some instances, cordocentesis may be recommended.

A special case of mosaicism is maternal cell contamination of the fetal specimen. This can be minimized by...
discarding the first 1–2 milliliters of the amniocentesis specimen and by careful dissection of chorionic villi from maternal decidua.

How should you counsel women who have chronic infections, such as hepatitis B, hepatitis C or human immunodeficiency virus, about invasive prenatal testing?

The risk of neonatal infection through amniocentesis in women who are chronically infected with hepatitis B or hepatitis C appears to be low, although the number of exposed cases in the literature is small (35). Of 115 women reported to be positive for the hepatitis B surface antigen who underwent second-trimester amniocentesis, the rate of neonatal infection was no different than in women who did not have an amniocentesis. All of the infants received hepatitis B vaccination and immunoprophylaxis beginning at birth (36–39). There is only one series reported in the literature in which 22 women who were positive for hepatitis C underwent second-trimester amniocentesis. No infants in this series were found to be hepatitis C RNA positive on postnatal testing. This group included one woman with amniotic fluid that was hepatitis C RNA positive (40). There are insufficient data in the literature to assess the risk of CVS in these women or to estimate the risk of fetal infection among women with anterior placentas, those who are hepatitis B e antigen positive or those with high hepatitis B or hepatitis C viral loads.

Amniocentesis in women with human immunodeficiency virus (HIV) has been shown to increase the vertical transmission rate in women who do not receive retroviral therapy (41). In a recent report of a small number of cases, it is suggested that amniocentesis or CVS does not increase the neonatal infection rate in newborns of women infected with HIV who are receiving retroviral therapy (42).

Because of the limited information regarding the risk of invasive procedures in women chronically infected with hepatitis B, hepatitis C, or HIV, it would be prudent to discuss noninvasive screening options with these women.

How does prenatal diagnosis differ for women with multiple gestations?

Diagnostic options are more limited in high-order gestations (43). In women with twins, the risk of aneuploidy should be calculated by considering the maternal age-related risk of aneuploidy, population risk of dizygosity, and the probability that either one or both fetuses could be affected. Formulas and tables are available in the literature to help with these calculations (44). Counseling in this situation should include a discussion of options for pregnancy management if only one fetus is found to be affected. These options include terminating the entire pregnancy, selective second-trimester termination of the affected fetus, and continuing the pregnancy.

Scant data exist concerning fetal loss in women with twin gestation when amniocentesis or CVS is performed. According to some small series, the fetal loss rate is approximately 3.5% when amniocentesis is performed in women with multiple gestations; this was not higher than the background loss rate for twins in the second trimester in one series with a control group (30, 45, 46). There are no data concerning loss rates after amniocentesis is performed in women with high-order multiple gestations. Similar information for twin gestations from small, non-randomized series exists for CVS (46–48).

A complex counseling issue arises in the presence of a monochorionic twin gestation, in which case the likelihood of discordance in the karyotype is low, and patients may opt for having a karyotype analysis performed on a single fetus. In this situation, it is important to discuss the accuracy of determining chorionicity by ultrasonography. The determination of chorionicity is most accurate if ultrasonography is performed at or before 14 weeks of gestation. The positive predictive value of monochorionicity is 97.8% at this stage of pregnancy. This decreases to 88% if the ultrasound examination is performed after 14 weeks of gestation (49).

What information should be provided after the diagnosis of fetal aneuploidy?

After the diagnosis of a chromosomal abnormality, the patient should receive detailed information, if known, about the natural history of individuals with the specific chromosomal finding. In many cases, it may be very helpful to refer the patient to a genetic counselor or clinical geneticist and national groups such as The National Down Syndrome Society (www.ndss.org) or National Down Syndrome Congress (www.ndsscenter.org) to help the patient make an informed decision. The option of pregnancy termination also should be discussed. Patients may benefit from additional ultrasonography or fetal echocardiography and referral to appropriate obstetric and pediatric specialists or neonatologists to discuss pregnancy and neonatal management issues. Referral to parent support groups, counselors, social workers, or clergy may provide additional information and support.

Is there value in prenatal diagnosis for the patient who would decline pregnancy termination?

Prenatal diagnosis is not performed solely for assistance in the decision of pregnancy termination. It can provide
useful information for the physician and the patient. Nondirective counseling before prenatal diagnostic testing does not require a patient to commit to pregnancy termination if the result is abnormal. If it is determined that the fetus has a chromosomal abnormality, the physicians and family can plan ahead and develop a management plan for the remainder of the pregnancy, labor, and delivery (50).

Summary of Recommendations and Conclusions

The following recommendation is based on good and consistent scientific evidence (Level A):

- Early amniocentesis (at less than 15 weeks of gestation) should not be performed because of the higher risk of pregnancy loss and complications compared with traditional amniocentesis (15 weeks of gestation or later).

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

- Amniocentesis at 15 weeks of gestation or later is a safe procedure. The procedure-related loss rate after midtrimester amniocentesis is less than 1 in 300–500.
- In experienced individuals and centers, CVS procedure-related loss rates may be the same as those for amniocentesis.

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

- Invasive diagnostic testing for aneuploidy should be available to all women, regardless of maternal age.
- Patients with an increased risk of fetal aneuploidy include women with a previous fetus or child with an autosomal trisomy or sex chromosome abnormality, one major or at least two minor fetal structural defects identified by ultrasonography, either parent with a chromosomal translocation or chromosomal inversion, or parental aneuploidy.
- Nondirective counseling before prenatal diagnostic testing does not require a patient to commit to pregnancy termination if the result is abnormal.

Proposed Performance Measure

The percentage of pregnant women undergoing invasive testing who were counseled about the risks of the procedure.

References


38. Grosheide PM, Quartero HW, Schalm SW, Heijtingk RA, Christiaens GC. Early invasive prenatal diagnosis in HBsAg-positive women. Prenat Diagn 1994;14:553–8. (Level III)


The MEDLINE database, the Cochrane Library, and ACOG’s own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and June 2007. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

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

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

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

- Level A—Recommendations are based on good and consistent scientific evidence.
- Level B—Recommendations are based on limited or inconsistent scientific evidence.
- Level C—Recommendations are based primarily on consensus and expert opinion.

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