Prenatal Screening and Diagnosis for Pediatricians

ABSTRACT. The pediatrician who cares for a child with a birth defect or genetic disorder may be in the best position to alert the family to the possibility of a recurrence of the same or similar problems in future offspring. The family may wish to know about and may benefit from methods that convert probability statements about recurrence risks into more precise knowledge about a specific abnormality in the fetus. The pediatrician also may be called on to discuss abnormal prenatal test results as a way of understanding the risks and complications that the newborn infant may face. Along with the increase in knowledge brought about by the sequencing of the human genome, there has been an increase in the technical capabilities for diagnosing many chromosome abnormalities, genetic disorders, and isolated birth defects in the prenatal period. The purpose of this report is to update the pediatrician about indications for prenatal diagnosis, current techniques used for prenatal diagnosis, and the status of maternal screenings for detection of fetal abnormalities. Pediatrics 2004;114:889–994; prenatal diagnosis, amniocentesis, chorionic villus sampling, genetic screening, chromosome aberrations, prenatal ultrasonography, neural tube defects, genetic counseling, preimplantation diagnosis, α-fetoproteins.

ABBREVIATIONS. CVS, chorionic villus sampling; PGD, preimplantation genetic diagnosis; MRI, magnetic resonance imaging; NTD, neural tube defect; MSAFP, maternal serum α-fetoprotein.

INTRODUCTION

When a genetic or potentially genetic disorder is diagnosed prenatally, the pediatrician may assist the family in addressing questions about the natural history of the disorder and in planning for care of the affected newborn. The information gained from prenatal diagnosis is helpful to the obstetrician or family practitioner in the management of pregnancy, labor, and delivery and in some circumstances may improve pregnancy outcome. The availability of prenatal diagnosis gives couples options they might not have otherwise, including preparation for the birth of a child with an abnormality, termination of an affected pregnancy, or use of fetal treatment such as fetal surgery for spina bifida or use of maternal dexamethasone to prevent virilization of affected females with congenital adrenal hyperplasia. These procedures may be important to couples at increased risk of having children with genetic disorders, because without this information they might be unwilling to attempt a pregnancy.

A number of well-studied techniques are used for prenatal diagnosis. For many of these techniques, the accuracy, reliability, and safety of the procedures are positively correlated with operator experience. Procedures such as amniocentesis, chorionic villus sampling (CVS), fetal blood sampling, and preimplantation genetic diagnosis (PGD) allow analysis of embryonic or fetal cells or tissues for chromosomal, genetic, and biochemical abnormalities. Fetal imaging studies such as ultrasonography, magnetic resonance imaging (MRI), and fetal echocardiography identify structural abnormalities and provide definitive diagnostic information or suggest additional evaluation. In addition to these techniques, maternal serum screening is used to identify pregnancies that are at increased risk of adverse outcomes, such as neural tube defects (NTDs), chromosome abnormalities, and fetal abdominal wall defects. This report focuses on the techniques that are most commonly used and provides an outline of pertinent information that the practicing pediatrician may find useful. For more in-depth discussions of these techniques, a number of comprehensive texts are available.1–3 The GeneTests Web site (www.geneclinics.org) also provides extensive information about testing for many chromosomal and genetic disorders.

INDICATIONS FOR PREGNATAL DIAGNOSIS

Prenatal diagnosis is indicated whenever there is a familiar, maternal, or fetal condition that confers an increased risk of a malformation, chromosome abnormality, or genetic disorder. Some prenatal diagnostic studies are prompted by abnormal results of tests such as ultrasonographic examinations or maternal serum screening. In other circumstances, parents may be affected with a genetic disorder, may be carriers for autosomal recessive or X-linked recessive disorders, or may be a member of an ethnic group with an increased risk of a specific genetic disease.

Chromosome Analysis

The most commonly cited reason for prenatal diagnosis is advanced maternal age, which in the United States is considered to be 35 years or greater at the time of delivery. Amniocentesis or CVS is
offered to such women because of the increased risk of aneuploidy (an abnormal number of chromosomes in the fetus). Amniocentesis or CVS also is used commonly to evaluate pregnancies in which an ultrasonographic examination or a maternal serum screening result has identified a possible fetal problem. In addition to advanced maternal age or an abnormal screening result, other indications for chromosome analysis include: 1) a chromosome abnormality in a previous offspring, a parent, or a close relative; 2) a previous offspring with multiple malformations in whom no chromosomal study was obtained; and 3) fetal sex determination in pregnancies at risk of a serious X-linked disorder for which specific prenatal diagnostic tests are not available. For the child with a normal prenatal chromosome analysis but with signs of a possible chromosome abnormality such as multiple malformations, growth deficiency, or developmental disabilities, repeat testing should be considered, because the quality of a postnatal study is usually superior to one obtained prenatally, and some cases of chromosome mosaicism may only be diagnosed postnatally.

Biochemical Studies

Biochemical studies are undertaken most often when a known abnormality is present in a family and the disorder can be diagnosed by a specific biochemical test. The number of biochemical disorders that can be diagnosed prenatally is growing rapidly, so that many common inborn errors of metabolism can be diagnosed through biochemical testing for enzyme deficiency or an abnormal metabolite. Conditions such as Tay-Sachs disease, mucopolysaccharidoses, and peroxisomal diseases may be diagnosed by biochemical tests on amniotic fluid, amniocytes, or chorionic villi. Before proceeding to evaluation of the fetus, there should be biochemical confirmation of the diagnosis in the index case, one or both parents should be a confirmed carrier for an autosomal recessive or X-linked recessive disorder, or a family history of a diagnosable disorder and indeterminate carrier status should be established. In a few circumstances, biochemical testing may be used when there is no family history of a disorder but prenatal ultrasonographic findings are suggestive of a biochemical disorder. For example, in a pregnancy in which cleft palate and abnormal genital findings are identified by ultrasonography, biochemical testing for Smith-Lemli-Opitz syndrome, a disorder of cholesterol biosynthesis, should be considered, because these are characteristic features of this syndrome.

Molecular Genetic Studies

Similar to biochemical studies, molecular genetic studies almost always are undertaken because there is a positive family history of a specific genetic disease or prenatal findings point to a possible single-gene disorder that can be diagnosed by molecular techniques. The list of available molecular genetic studies has grown dramatically in the last several years, and many of the common single-gene disorders can be diagnosed rapidly and conclusively by molecular techniques. The description of the methods used to make a molecular diagnosis is beyond the scope of this report, but several useful resources are available for this purpose. Examples of disorders that are diagnosed by molecular methods include fragile X syndrome, cystic fibrosis, Duchenne and Becker muscular dystrophy, and hemophilia. In each case, it is important that the clinician first know the specific mutation that is being sought in the case of a positive family history or that the detection rate for the mutation be known if there is no family history. The consultation of a geneticist, genetic counselor, or other clinician familiar with the utility of these prenatal tests may be particularly helpful.

TECHNIQUES FOR PRENATAL DIAGNOSIS BY CELL OR TISSUE SAMPLING

Amniocentesis

Transabdominal amniocentesis is the most commonly used procedure for obtaining fetal cells that can be analyzed for cytogenetic, biochemical, or molecular abnormalities. In addition, amniotic fluid can be analyzed separately for α-fetoprotein and acetylcholinesterase concentrations associated with open NTDs and for other analytes that are diagnostic of specific genetic diseases. The procedure is most commonly performed at 15 to 18 weeks’ gestational age. Amniocentesis in the second trimester is associated with a low rate of complications and provides an accurate sample for analysis in more than 99% of cases. Fetal chromosome analysis is the most common laboratory study performed on samples obtained by amniocentesis. Results are usually available 1 to 2 weeks after the procedure and sooner in some circumstances. Fluorescence in situ hybridization studies are performed increasingly for rapid detection of fetal aneuploidy or for microdeletion syndromes such as 22q11 deletions in fetuses with congenital heart defects. Risks of amniocentesis include fetal loss, chorioamnionitis, fetal injury, and maternal Rh sensitization, each of which is very uncommon. Amniocentesis is performed under ultrasonographic guidance, which minimizes the risk of direct fetal injury. The risk of fetal loss in most large series is less than 0.5%, and many prenatal diagnostic centers have a lower loss rate. To prevent Rh isoimmunization, Rh immune globulin is administered at the time of the procedure to nonsensitized Rh-negative women.

In recent years, amniocentesis performed at 11 to 13 weeks’ gestational age has gained increasing attention. Some investigations have suggested that this technique carries similar risks to amniocentesis at 15 to 18 weeks’ gestational age. In a large multicenter randomized trial, however, investigators found a higher risk of fetal loss, a greater number of amniotic fluid culture failures, and an increased risk of talipes. Additional investigations have also identified an increased risk of foot deformities in the offspring of women who undergo early amniocentesis. Although it is desirable to complete prenatal diagnostic tests as early as possible, the American College of
Obstetricians and Gynecologists does not recommend early amniocentesis because of higher rates of pregnancy loss and other complications compared with amniocentesis after 15 weeks gestation.13

CVS

The advantage of CVS is earlier diagnosis. Earlier diagnosis provides additional time for counseling and decision-making, and in the circumstance in which termination of pregnancy is elected, termination can be performed more safely for the mother. CVS is usually performed at 10 to 12 weeks gestational age. The procedure involves transcervical placement of a catheter or transabdominal placement of a needle, under ultrasonographic guidance, into the developing placenta. The transcervical and transabdominal approaches seem to have comparable safety and accuracy.14 A sample of the chorionic villus is removed by aspiration. Once removed, the fetal villi are dissected from the maternal decidual tissue. Cytogenetic, molecular, and some biochemical studies can be performed on CVS samples, but amniotic fluid is not obtained for protein analysis. Therefore, women who have had CVS should also have maternal serum α-fetoprotein (MSAFP) screening at 15 to 20 weeks gestational age to screen for fetal NTDs.

Although CVS loss rates are slightly higher than those associated with amniocentesis in some clinical trials,15,16 other studies have suggested that the procedure-related loss rates are comparable between CVS and second-trimester amniocentesis.17,18 The success of cytogenetic diagnosis is slightly lower for CVS versus amniocentesis. In particular, CVS is associated with an increased frequency of placental mosaicism, which is a cytogenetic abnormality detected in the CVS sample but not found in the fetus or newborn. Placental mosaicism is found in approximately 1% of CVS samples,19,20 and although the fetus is chromosomally normal, placental mosaicism is associated with an increased risk of non-procedure-related, spontaneous fetal loss. An additional concern for CVS is the reported association of CVS and limb-reduction defects, especially when the procedure is performed before 10 weeks gestational age; although some investigations have shown an association21 and others have found none,22 the American College of Obstetricians and Gynecologists has recommended that CVS not be performed before 10 weeks.23

Sampling of Fetal Blood

In some circumstances, it may be useful to obtain a sample of fetal blood. This technique, referred to as cordocentesis or percutaneous umbilical blood sampling, may be used to assess fetal blood disorders, fetal infections, or isoimmunization or may be used for rapid fetal karyotyping. It also has been used to supply fetal treatment such as transfusions. Percutaneous umbilical blood sampling is usually performed with a 20- or 25-gauge spinal needle inserted into the umbilical vein or artery, preferably near the insertion of the cord into the placenta. Fetal loss or spontaneous abortion is reported in approximately 1% to 2% of cases, making the risk associated with this procedure higher than that with amniocentesis or CVS.24

PGD

In some circumstances, specific genetic diseases can be diagnosed before implantation of the blastocyst after in vitro fertilization. PGD provides prospective parents the possibility of establishing a pregnancy in which the fetus is unaffected with the disorder for which it is at risk. In this procedure, a single cell is taken from the early embryo and analyzed by molecular techniques after DNA amplification by polymerase chain reaction. For this technique to be useful, it is essential to know the precise abnormality being sought, which usually means that both the genetic locus and the mutation have been identified in a previous child or another family member. PGD is performed in a limited number of prenatal diagnostic centers, and systematic outcome analyses of large groups of patients are not available. It has been used to detect such disorders as cystic fibrosis and Tay-Sachs disease.25

TECHNIQUES FOR PRENATAL DIAGNOSIS BY FETAL VISUALIZATION

Ultrasonography

Ultrasonography has become the primary method for fetal anatomic imaging. This technique may be used in pregnancy to monitor fetal growth, movement, position, and morphology; assess amniotic fluid volume; and establish gestational age and placental location. In some countries, it has become standard practice to perform ultrasonographic examination at some time in the second trimester. In many other countries including the United States, ultrasonography is performed at some time during pregnancy for a wide range of clinical indications. During the early second trimester, ultrasonographic examination is used to date the pregnancy, identify twins, diagnose some fetal structural anomalies, and examine the placenta and the amount of amniotic fluid. Improvements in the technical quality of ultrasonographic equipment and increasing skill levels of ultrasonogram operators have led to an ever-increasing identification of fetal structural abnormalities of the genitourinary, gastrointestinal, cardiac, and central nervous systems.

Ultrasonography has become the mainstay for prenatal diagnosis of structural abnormalities, particularly when used in the mid- to late second trimester. As a modality used to follow-up on abnormal maternal screening results, ultrasonographic examination can identify most associated abnormalities such as ventral abdominal wall defects and NTDs. Almost all cases of anencephaly are detectable by ultrasonography, and more than 90% of open spina bifida is detectable when ultrasonography is used for a high-risk population such as those with abnormally high serum α-fetoprotein concentrations.26,27 With the advent of improved image quality of ultrasonographic examinations, a number of minor abnormal-
ities have been recognized. Studies of these abnormalities in high-risk populations have shown that some of these markers may be seen more commonly in pregnancies with fetal chromosome abnormalities than in unaffected pregnancies. Nuchal translucency, thickened nuchal fold or cystic hygroma, choroid plexus cysts, fetal echogenic bowel, intracardiac echogenic foci, and renal pyelectasis have all been suggested as possible markers for fetal chromosome abnormalities. Although these features are associated with increased fetal risk, they are not used as primary screening methods. When they are identified, however, additional investigation may be warranted on the basis of a number of factors such as maternal age and associated abnormalities. The pediatrician may encounter newborn infants in whom one of these markers has been detected prenatally. Because these infants have an increased risk of aneuploidy such as trisomy 13, 18, or 21, neonatal examination should be directed toward identification of clinical features associated with one of these trisomies. If the clinical examination is not suggestive of one of these conditions and there are no major anomalies, it is reasonable to observe the infant and perform no additional diagnostic testing.

MRI
MRI has received limited use, primarily because fetal movement prevents optimal resolution. Ultrafast MRI scanning has improved its utility. MRI may be especially useful for the evaluation of fetal central nervous system abnormalities, when oligohydramnios is present, or when ultrasonography is difficult. MRI generally is not recommended during the first trimester.

Fetal Echocardiography
Fetal echocardiography is usually performed after 20 weeks’ gestation. When used together with duplex and/or color-flow Doppler ultrasonography, it can identify a substantial number of major structural cardiac defects and rhythm disturbances. Fetal echocardiography is considered when there is an increased risk of congenital heart disease because: 1) there is an extracardiac malformation identified by ultrasonographic examination; 2) there has been prenatal exposure to a teratogenic agent; 3) there is a family history of congenital heart defects, especially in a parent or sibling; 4) a fetal chromosome abnormality or genetic disease associated with heart defects is suspected; 5) a maternal disease associated with fetal structural heart defects, such as diabetes or phenylketonuria, or maternal disease associated with fetal cardiac arrhythmia, such as lupus erythematosus, has been identified; 6) a cardiac defect is suspected by findings on routine ultrasonography; or 7) a fetal arrhythmia has been detected on auscultation or examination.

MATERNAL SERUM SCREENING STUDIES
Detection of NTDs
MSAFP concentrations are increased in many abnormal fetal conditions including open NTDs and defects of the genitourinary and gastrointestinal systems. MSAFP screening results are abnormal in approximately 90% of cases of anencephaly and approximately 80% of cases of open spina bifida. It is recommended that MSAFP testing be offered to all prenatal patients, and in some states it is mandated by law. Because elevated MSAFP concentrations have also been associated with adverse pregnancy outcomes such as low birth weight and stillbirth, pregnancies in which concentrations are elevated may be monitored more closely than those with normal concentrations. Most of those who have increased MSAFP concentrations even after repeat testing will have a normal outcome. When concentrations are increased, ultrasonography is used to confirm gestational age, exclude multiple gestation, and assess for recognized causes (primarily NTDs and ventral wall defects) of the increase. A normal result of an ultrasonographic examination performed in a specialized center decreases the probability of a fetal NTD by 95% or more. If ultrasonographic examination does not identify a cause, amniocentesis is offered for measurement of amniotic fluid α-fetoprotein and acetylcholinesterase concentrations, both of which are increased with open NTDs.

Detection of Chromosome Abnormalities
After the advent of MSAFP screening for NTDs, it was recognized that low second-trimester MSAFP concentrations were associated with an increased risk of Down syndrome. Since that time, additional serum markers that increase the detection rate for Down syndrome have been identified. When second-trimester MSAFP testing is combined with measurement of human chorionic gonadotropin and unconjugated estriol concentrations (these 3 proteins constitute the “triple screen” for fetal aneuploidy), up to 80% of fetuses with Down syndrome can be identified. Decreased concentrations of all 3 analytes are associated with an increased risk of fetal trisomy 18. Some screening programs have added inhibin A to the triple screen to improve the sensitivity and specificity of the test. Clinicians should be aware that MSAFP screening for Down syndrome has a positive screening rate of approximately 5% and a positive predictive value of approximately 3% to 5%, which means that the great majority of those who have a positive screening result have a normal outcome.

Over the last several years, techniques for effective first-trimester screening for Down syndrome have been explored. Although a number of concerns about the appropriateness of adopting these techniques on a population basis have been raised, many perinatologists are already using fetal ultrasonography and/or screening for maternal serum markers in clinical practice. Measurement of nuchal translucency (a sonolucent space at the back of the fetal neck) can be performed between 10 and 13 weeks’ gestation. The fetus with Down syndrome tends to have a larger area of translucency when compared with the chromosomally normal fetus. The nuchal translucency measurement is used in combination

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with 2 serum analytes, pregnancy-associated plasma protein A and the free β subunit of human chorionic gonadotropin, to adjust the risk for Down syndrome based on maternal age alone. The detection rates are comparable to second-trimester serum screening.

Detection of Other Abnormalities

There are a number of conditions associated with high or low MSAFP concentrations. In addition to abdominal wall defects such as omphalocele and gastroschisis, high concentrations are also associated with renal anomalies, congenital nephrosis, gastrointestinal tract obstruction, and low birth weight. In addition to these conditions, high MSAFP concentrations may also be seen with multifetal gestation, underestimated gestational age, and some maternal conditions such as low maternal weight. Low MSAFP concentrations are associated with adverse outcomes other than chromosomal trisomies, including fetal death and gestational trophoblastic disease. As with high MSAFP concentrations, low concentrations may be seen in nonpathologic conditions such as overestimated gestational age or high maternal weight.

CONCLUSIONS

Pediatricians may be called on to counsel a family in which prenatal diagnosis is being considered or in which there is a fetus with a genetic disorder. It is important that pediatricians involve themselves at a level appropriate to their training and experience, that they clarify their role in the prenatal diagnostic process with the family, and that they document their discussion and recommendations. In most circumstances, pediatricians will not assume a primary role in performing prenatal diagnostic procedures or counseling the family about their risks and benefits. More frequently, an obstetrician, maternal-fetal medicine specialist, clinical geneticist, and/or a genetic counselor will direct the diagnostic evaluation and provide pretest and posttest counseling. Because of a previous relationship with the family, the pediatrician may be called on to review this information and assist the family in the decision-making process. The pediatrician should be familiar with the principles of prenatal genetic diagnosis and know how to apply them to specific problems in genetic counseling, diagnosis, and management in clinical practice. Pediatricians should be familiar with resources available in their region for obtaining information about whether and how a specific disorder can be diagnosed and when and where to refer patients for prenatal genetic diagnosis. The technology of prenatal diagnosis is changing rapidly, and genetic consultants can assist pediatricians in the appropriate use and interpretation of the diagnostic tests that are available.

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