Antenatal Genetic Studies

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The Antenatal Genetic Testing Program at MCV began in 1973. The standard scheme for antenatal genetic testing involves counseling, the methods of carrier detection available, ultrasound, amniocentesis, and laboratory evaluation. Patients are referred because of a family or personal history of a genetic abnormality or because they have been evaluated in a carrier detection program like those for Tay-Sachs disease or Sickle Cell disease and are known carriers. After referral, patients are given genetic counseling by me and members of the Department of Human Genetics; if antenatal genetic testing is deemed appropriate, we obtain informed consent and proceed with an ultrasound study. The primary reason for doing an ultrasound study prior to amniocentesis is to detect twins. Twins are most likely to be in separate amniotic sacs and have different karyotypes; therefore, fluid must be obtained from each sac.

The indications for referral are listed in Table 1. The most frequent is advanced maternal age, generally considered to be 35 years or greater. If a mother is less than 35 years and pregnant, she has a 0.2% risk of having a child with Down Syndrome (about 1 in 600). Between 35 and 40 years of age the risk of having a child with Down Syndrome is between 1% and 1½% and between 40 and 45 years of age it is about 2% or about a 5 to 10 times greater risk than the general population.

Another common reason for ultrasound study is that the patient has had a previously chromosomally abnormal child. The most common abnormality is Trisomy 21 in which case risk of the recurrence is 1%. Occasionally, we find that the proband has a translocation abnormality and that one of the parents is a balanced carrier which results in a rate of recurrence of from 20% to 100%. A significant family history of chromosomally abnormal offspring (sister, brother, and their children) may also be a clue to a translocation defect. Other indications for studies include metabolic defects amenable to prenatal detection and a previous child or known carrier status for a sex-linked disease (hemophilia or Duchenne muscular dystrophy). The history of a previous child or close relative with a neural tube defect (NTD) (either anencephaly, encephalocele or meningomyelocele) is a very common reason for referral. Neural tube defects have a genetic component, so that if a couple has had an affected child, the risk of a subsequent child with a NTD is 5%, and if there have been two affected children, the risk is 10% for having a child with a NTD. Patients with close relatives with a NTD have a 1% risk of occurrence.

As mentioned, ultrasound is used primarily to diagnose twins. Once twins have been ruled out ultrasound is very useful for locating a pocket of amniotic fluid and measuring the angle and depth at which the needle has to enter the sac to withdraw fluid. The Figure is an ultrasound visualization of a uterus, with the fetus inside, at about 14 weeks gestation. The chest and head are easily identified, as is a thick anterior placenta. The amniotic fluid is the dark area and the proper needle placement is indicated.

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TABLE 1
Indications for Referral for Antenatal Genetic Testing

1. Advanced maternal age (≥ 35 years old)
2. Previous child with a chromosome abnormality
3. Parents who carry a translocation gene
4. Previous child with an inborn error of metabolism
5. Previous child with a severe X-linked disease
6. Previous child or close relative with a neural tube defect

Amniocentesis is the procedure by which amniotic fluid is obtained through the abdomen of the mother with a needle. (If we have problems obtaining fluid we can use ultrasound in conjunction with amniocentesis to see the tip of the needle.) We use a disposable kit for amniocentesis which has a 22-gauge spinal needle, local anesthesia, and Betadine swabs, which are used to prepare the abdomen after we have decided where the needle is to be inserted. After draping the abdomen with a sterile towel, the skin and subcutaneous tissue is anesthetized and the needle is inserted. The needle has a stylet which is then removed and an extension tube attached without interrupting the flow of fluid being withdrawn through the needle. Since the most common laboratory evaluation from the amniotic fluid is chromosome analysis, the fluid is processed by the cytogenetic lab in the Department of Human Genetics. It takes three to four weeks to complete the analysis with a range of about two and one half to six weeks. The fetal karyotypes are obtained from cultured fetal cells in the amniotic fluid obtained at 14 to 16 weeks gestation.

Another fairly recent and exciting area in the field of intrauterine diagnosis is that of fetal structural defects. The first group successfully diagnosed is Neural Tube Defects (NTD) with the association of elevated amniotic fluid alpha-fetoprotein in pregnancies with a NTD. In 1972, Brock and Sutcliff[1] published a series of patients in whom they had measured the amniotic fluid alpha-fetoprotein and found that there was clearly a significant difference between a group affected with NTD and a normal control group. The most accurate range of pregnancy to measure alpha-fetoprotein is 14 to 18 weeks. The diagnosis of anencephaly and large meningomyeloceles can also be made easily with modern ultrasound techniques. Because meningomyeloceles and spina bifida are more difficult to demonstrate by ultrasound, we rely mainly on alpha-fetoprotein in the amniotic fluid for their detection. In addition, with more sophisticated ultrasound equipment, we are able to diagnose other structural defects such as dwarfism (by measuring fetal limb lengths) and polycystic kidneys (Potter syndrome).

A number of questions are frequently asked about this testing. Could you accidentally hit the baby with the needle? This has certainly happened and has been reported in the literature. I reviewed one series with an intracardiac fetal puncture and death during an amniocentesis at 16 weeks. The recorded pregnancy loss rate nationwide is about 1% as a result of amniocentesis. At MCV two pregnancies have been lost in a series of 531 patients. One patient developed chorioamnionitis within 24 hours and one patient had ruptured membranes about an hour after the procedure, giving a fetal mortality of 0.4%. We have had no fetal punc-

TABLE 2
Results of Antenatal Genetic Testing
9-1-73 to 9-6-79

269	46XY (normal male)
255	46XX (normal female)
5	46XX+21 and 46XY+21 (Trisomy 21)
1	45XO (Turner syndrome)
1	47XX+18 (Trisomy 18)
1	45XY, t(18p 21p)
1	46XX 46XXr(9) (mosaic)
1	45XX, t(14q,21q)
1	46XX, 45 XO (mosaic)
1	46XX, t(6p, 14p)

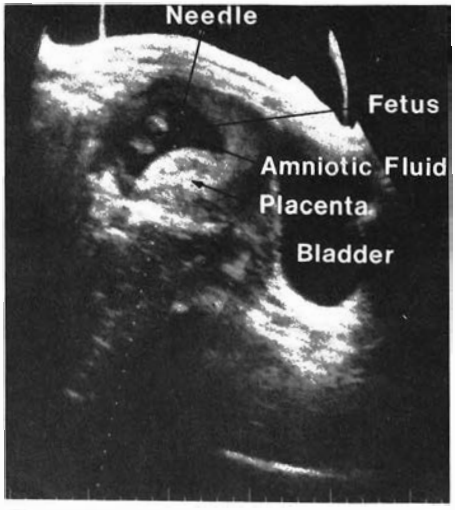

Figure.—Ultrasound visualization of a fetus in utero at 14 weeks gestation.

tures. This is an acceptable mortality rate considering that most of these patients have at least a 1% risk of having an abnormality and some as high as 5%.

Another common question is, how much does it cost to have the testing?[2] The cost varies from center to center, but the range in Virginia is $470 to $520. MCV charges $520 which includes genetic counseling, amniocentesis, ultrasound study and karyotype examination. If the patient needs only the alpha-fetoprotein determination, the cost is $175. The MCV experience with antenatal genetic studies involves 531 patients, the majority of whom were studied because of advanced maternal age. The second most common indication was a previous child with a NTD and the third was a previous child with Trisomy 21. The rest were a variety of indications; perhaps the most interesting was one patient who demanded elective sex determination. The results of chromosome analysis from our patients are presented in Table 2. Five fetuses were diagnosed as having Down Syndrome, and of seven fetuses with abnormal alpha-fetoprotein, all had a NTD. All abnormal fetuses were aborted and the diagnosis confirmed.

REFERENCE

1. Brock DJH, Sutcliff RG. Alpha-fetoprotein in the antenatal diagnosis of anencephaly and spina bifida. *Lancet* 2:197–199, 1972.