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Antenatal Genetic Studies in Twin Pregnancies

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Abstract. The diagnosis of multiple gestation at the time of genetic amniocentesis is a routine occurrence. In a combined series of 2765 patients referred for antenatal genetic studies from the Medical College of Virginia and the University of Iowa, 34 twin pregnancies were encountered (1.2%). Twenty-six of the patients with twins were referred for advanced maternal age. The other indications were previous neural tube defects (1), previous trisomy 21 (2), known carriers of Tay Sachs disease (2), previous Turner's syndrome (1), family history of trisomy 21 (1), and one pregnancy was referred because of an abnormal ultrasound. Amniocentesis procedures, outcome of the twin pregnancies, and genetic counseling issues, are discussed.

Key words: Antenatal diagnosis, Twin pregnancy, Genetic counseling

The diagnosis of multiple gestation at the time of genetic amniocentesis is a routine occurrence. The incidence of twins is approximately 1 in 80 in the general population and dizygotic twinning in women aged over 35 is more frequent. In most antenatal genetic testing programs, counseling about the risk of genetic disease and amniocentesis is performed prior to the ultrasound examination. At the time of the ultrasound examination, the diagnosis of twins is made and then the information must be imparted to the parent and counseling about amniocentesis revised. Information from the ultrasound makes it possible, in some cases, to accurately predict the zygosity of the twins. If the septum is clearly present, it is most likely a diamniotic dichorionic septum, whereas if it is extremely difficult to visualize or not visible at all, the septum is either diamniotic monochorionic, or monoamniotic monochorionic (only in MZ twins).

In most cases, however, the twins are DZ and, from the genetic counseling point of view, represent separate conceptions. For the case of advanced maternal age, where the risk at 35 is approximately 1%, the risk that one twin is affected would be approximately

2%. However, in the case of an inborn error of metabolism with a recurrence risk of 25%, the risk for one twin to be affected approaches 50%. The counseling of parents who have just learned about the presence of twins, often involves the situation of twins discordant for major genetic abnormalities and the options available in those cases. These options are termination of the pregnancy at the expense of the normal twin, continuation of the pregnancy for the life of the normal twin, or, most recently, selective birth.

After thorough counseling, the technical problems of amniocentesis in twin pregnancy is approached. The most important consideration is to assure that specimens are in fact obtained from each amniotic sac so that both fetuses are tested. Techniques to assure that separate specimens are obtained are presented in Table 1. The first is the sophisticated use of ultrasound to thoroughly map the uterine contents and identify the direction and angle of the septum. With experience, it is then possible to accurately identify the areas for amniocentesis to obtain separate specimens. This mapping is also extremely important to separately identify the fetuses, so that, if they are discordant, the affected fetus can be distinguished from the normal one. An older technique to assure separate specimens is the injection of indigo carmine dye after obtaining the first specimen. The second specimen must be clear fluid to be distinctly separate from the first. Another technique, which is not commonly employed, is the injection of radiopaque dye after the first amniocentesis followed by X-ray of the second specimen to assure that it is not radiopaque. With modern ultrasound machines and experience, the thorough mapping of the intrauterine anatomy is usually sufficient to perform the procedures.

Confirmation that cells from both fetuses have in fact been sampled can be obtained through the procedures listed in Table 2. These include obviously chromosome karyotype results which are discordant for either fetal sex or any type of marker chromosome or banding pattern. Alpha-fetoprotein can be helpful in quickly determining if the specimens are separate, in that the laboratory variation in alpha-fetoprotein should be less than 1% and a variation exceeding 1% indicates different specimens.

TABLE 1 - Techniques to Assure Separate Specimens

- Thorough intrauterine mapping with ultrasound
- Injection of indigo carmine dye after first amniocentesis
- Injection of radiopaque dye after first amniocentesis

TABLE 2 - Confirmation of Separate Amniotic Fluid Specimens

- Discordant laboratory results
- Clear fluid after dye injection
- Giemsa banding
- Quinacrine banding
- Alpha-fetoprotein

TABLE 3 - Antenatal Genetic Testing in Twin Pregnancy - Medical College of Virginia - University of Iowa

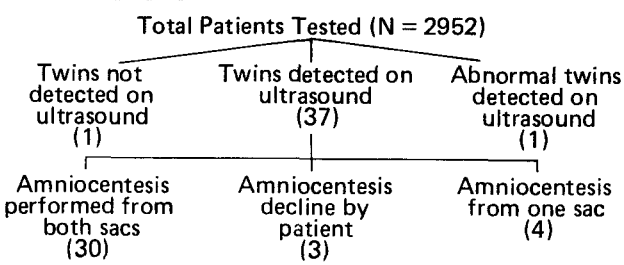

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TABLE 4. Antenatal Genetic Testing in Twin Pregnancy - Medical College of Virginia - University of Iowa

–	Total number of patients tested	2765
–	Total number of twin pregnancies	39
–	Number of twin pregnancies tested	34
–	Number of patients with twins declining testing	3
–	Number of twin pregnancies not detected	1
–	Number of abnormal fetuses detected	7

In a combined series of 2765 patients at the Medical College of Virginia and the University of Iowa (Table 3), 39 sets of twins were encountered (1.3%). Thirty-one of these patients were referred for advanced maternal age (80%). Other indications were previous neural tube defect (1), previous trisomy 21 (2), known carriers of Tay Sachs disease (2), previous Turner syndrome (1), family history of trisomy 21 (1), and one pregnancy referred because of an abnormal ultrasound. The diagnosis of pregnancy was made in 36 cases prior to the amniocentesis. In 2 cases the diagnosis was made after the first amniocentesis had been performed, and in one case the twins were not detected at the time of amniocentesis. Amniocentesis was performed in 34 cases, and in 3 cases the parents declined genetic testing after the diagnosis of twins was made because of the complexities of the decisions involving discordant twins. One pregnancy was diagnosed as twins on ultrasound at 8 weeks gestation but was a singleton at 16 weeks. In 30 cases, a clear amniotic septum could be identified between the two sacs, and specimens were obtained from both fetuses. In 4 cases, the septum was unable to be visualized on ultrasound and one amniocentesis was performed. In the 4 cases, the follow up showed that the twins were monochorionic diamniotic MZ twins, implying that the monochorionic diamniotic septum is very difficult to identify with real-time ultrasound. Of the 30 patients in which specimens were obtained, 3 patients required three to five attemps to obtain the two specimens, while 27 required two amniocenteses to obtain two specimens.

The results of the genetic studies in these 39 twin pregnancies was the detection of 7 abnormal fetuses in 5 pregnancies (Table 4). The abnormalities were as follows: MZ twins with 47,XXY; DZ twins discordant for 47,XXY; conjoined thoracopagous twins; and two pregnancies discordant for Tay Sachs disease. In addition, there was one normal twin born with a growth-retarded, stillborn cotwin, and one pregnancy lost five days following the amniocentesis due to premature labor.

The finding of twins at the time of ultrasound prior to amniocentesis for genetic studies alters the counseling for these patients and in some cases will alter the parent's wishes about the testing. With modern ultrasound equipment, the ability to diagnose twins prior to amniocentesis and to obtain separate specimens should be 100%. Extreme difficulty or inability to demonstrate the septum between the amniotic sacs implies that the pregnancy is monochorionic diamniotic or, rarely, monoamniotic. Parents must be thoroughly counseled, prior to the amniocentesis, about their options should the twins be found to be discordant for genetic disease, and the ultrasound prior to the amniocentesis must be very precise, so that separate identification of the fetuses can be made, once the results of the testing are known, and the option of selective birth will be available to the parents.

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