

Prenatal Diagnosis of Hereditary Disease and Congenital Defects

By MICHAEL M. KABACK, M.D.

Since 1966, more than 100,000 midtrimester amniocenteses have been performed throughout the world for the prenatal determination of fetal hereditary diseases or congenital defects. Recently, a growing number of pregnancies have been monitored by placental aspiration/fetoscopy or by serial ultrasonographic studies for the detection of other congenital/genetic disorders. A growing public awareness of the applicability of these technologies and their increasing availability portend a greatly increased utilization of such procedures in the coming decades.

Other, related advances also have increased the frequency with which fetal diagnostic studies are being conducted. Heterozygote-screening programs (i.e., for the identification of carriers of Tay-Sachs disease, sickle-cell anemia, and beta-thalassemia) and serum alpha-fetoprotein (AFP) screening of pregnant women (in several national and regional pilot programs) are also greatly increasing the numbers of indicated fetal diagnostic procedures that are being conducted.

The rationale for obtaining an amniotic-fluid sample is to enable study of the fluid and cellular constituents (which are of fetal origin) in order to determine whether or not the fetus in that pregnancy is afflicted with, or at high risk for, a specific hereditary disorder or developmental defect for which it is known to be at increased risk. Biochemical analyses of the fluid itself or, in most instances, cytologic (chromosomal) or biochemical determinations performed on cultivated populations of fetal cells, derived from the amniotic fluid cells, allow such determinations to be made. Results of such analyses are available generally within a few days (e.g., AFP measurement) or within two to four

weeks (chromosomal and biochemical determinations) of the procedure.

It is not the purpose of this report to review all of the sophisticated and extensive methods that have been developed for the amniocentesis-related detection of each of the hereditary diseases or developmental defects that can now be detected in the midtrimester fetus. Several hundred research articles have appeared, and pediatricians interested in learning more about these procedures are referred to the many extensive reviews that are available.¹⁻⁷

With current somatic cell tissue-culture methods, successful cultivation of amniotic fluid cells can be achieved in more than 98 percent of instances with a single sample of 10 ml. or more of amniotic fluid.⁸ Once a sufficient population of growing fetal cells is available, it is possible to thoroughly assess the chromosomal complement of the fetus and to identify virtually any fetal cytogenic abnormality. Fetal sex is established readily by karyotype assessment, nuclear chromatin-mass frequency, or Y-body analysis. A wide variety of genetically defined metabolic functions also can be assayed in such cells. In this way, the prenatal determination of about 75 serious inborn errors of metabolism, inherited as either X-linked or autosomal-recessive disorders, can be addressed in the midtrimester fetus (the metabolic function being absent, grossly deficient, or clearly abnormal in the cultivated fetal cells if the fetus is affected). Tables 1 through 5 list disorders that can now be detected in this way.

The liquid fraction of the amniotic-fluid sample, separated from the cellular component by centrifugation, also has important applications to the prenatal detection of hereditary diseases, particularly

(Continued)

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