Genetics

Update on Prenatal Screening and Diagnosis

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KEYWORDS

• Genetic disorder • Mendelian • Chromosomal • Chorionic villus sampling
• Multiple pregnancies • Fetal reduction • Pre-implantation diagnosis • Amniocentesis

KEY POINTS

- There have been tremendous advances in the ability to screen for the "odds" of having a genetic disorder (both Mendelian and chromosomal). At the same time, diagnostic capabilities have in parallel logarithmically increased as genetics advances moves from cytogenetic to molecular techniques for both chromosomes and Mendelian disorders.
- With microarray analyses on fetal tissue now showing a minimum risk for any pregnancy being at least 1 in 150 and ultimately greater than 1%, it is thought that all patients, regardless of age, should be offered chorionic villus sampling/amniocentesis and microarray analysis.
- As sequencing techniques replace other laboratory methods, the only question will be whether these tests are performed on villi, amniotic fluid cells, or maternal blood.

INTRODUCTION

Over the last past 4 decades, there have been revolutionary changes in the approach to prenatal diagnosis and screening.[1] In the 1960s and 1970s, prenatal diagnosis and screening evolved from merely wishing patients "good luck" to then asking "how old are you?" Maternal age was, and still is, a cheap screening test for aneuploidy. However, an explosion of techniques has dramatically enhanced the statistical performance of screening tests to identify high-risk patients. Biochemical and ultrasound (US) screens have gone through multiple generations with increasing sensitivities

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and specificities to the point where there has been considerable (and sometimes deliberate) confusion as to the distinction between screening and diagnosis.

A pendulum has swung back and forth between screening and testing primacy as new technologies have been developed. Overall, prenatal diagnosis has moved along 2 parallel paths (ie, imaging and tissue diagnoses) that sometimes converge. Often, clinicians are experts in one diagnostic modality or the other; there are a very limited number who are experts in both. As a result, there is often huge variability in approach to screening and diagnosis depending on by whom and where a patient is seen.

Thousands of articles and hundreds of textbooks have been written over the past decades about the subjects addressed here, but only a miniscule percentage of the available literature can be cited here. Here, the focus is on the leading edge changes in approach because a comprehensive review would go far beyond space limitations.

GENETIC COUNSELING

There has never been more need for genetic counseling for all pregnancies both to educate patients and to document that the patient was provided adequate information with which to make decisions. As the complexity of genetic information has increased massively in scope and amount, front-line obstetrician gynecologists generally have neither the time nor often the expertise to explain the nuances of new technologies. Genetic counselors are master's-trained individuals who have both an in-depth knowledge of genetic fundamentals and an understanding of screening principles and testing options. Genetic counseling as a profession emerged over the past few decades. In many settings, the counselors have far more understanding of genetic issues than do the attending physicians. It is optimum to have a coordinated team approach to patient care.

What too frequently occurs in obstetric practice is that, without adequate guidance, a "vending machine" selection of possible screening and testing options is offered to the patient. Only when there is an abnormal result does the primary medical provider first call for help to explain to an often panicked patient what the results actually mean. Thus, when possible, dedicated centers providing the continuum of genetic counseling, diagnosis, and treatment are optimal.

PRENATAL SCREENING

Mendelian Disorders

In the 1970s, prenatal screening for Mendelian disorders was simple: sickle cell for Africans, Tay-Sachs for Ashkenazi Jews, β-thalassemia for Mediterraneans, and α-thalassemia for Asians.[2] Since then, there has been an explosion of testing possibilities but also a serious disconnect between actual risks for a specific disorder and whether such risks constitute "high risk." For example, the Ashkenazi panel has increased from 1 to 3 available tests in the 1970s to 18 current "routine" test offerings,[3] and more tests are being developed. For many of the diseases tested for, the incidence in the Jewish population is actually no higher than in other ethnic groups, and the incidence of some is less than 1/100,000. Patients have been called "high risk" when a couple's risk has gone from 1 in one million to 1 in 10,000.

Several companies are now offering pan-ethnic screening for dozens of disorders.[4] Although there have been some serious problems in the implementation of these screens, including confusion regarding the actual risks of a disease for individual couples, it may ultimately prove more cost-effective to offer screening for "everything" to "everyone." However, such expansion of screening will require an increase in the