An Overview of Prenatal Genetic Screening and Diagnostic Testing

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Although prenatal genetic testing has been available for more than 3 decades, the number of conditions that can be detected has increased exponentially over the past decade. This commentary describes currently available prenatal genetic screening and diagnostic tests and explores practical and social considerations related to prenatal testing.

Prenatal testing can involve either screening or diagnostic testing: Screening tests provide only a probability that the fetus is affected, whereas prenatal diagnostic tests can determine with near certainty whether a fetus has a particular condition. In some pregnancies, family history or parental age increase the chance that the fetus has a genetic condition, but most genetic conditions occur unexpectedly.

The first congenital conditions for which routine prenatal screening became available were Down syndrome (trisomy 21) and open neural tube defects such as spina bifida. Although these conditions have different etiologies, either can occur in any pregnancy, regardless of parental age, health, environmental exposure, or family history. Each year in the United States, approximately 1 in 2,950 babies is born with spina bifida [1] and approximately 1 in 700 is born with Down syndrome [2]. Most children with Down syndrome are born to women younger than 35 years, because women in this age group have the most pregnancies, but the chance of having a child with Down syndrome gradually increases with the age of the mother. Although there are myriad other genetic conditions that arguably result in more significant medical or developmental complications, the incidence of these other conditions is much lower; for instance, the incidence of spinal muscular atrophy is 1 in 10,000 births [3], and the incidence of Smith-Magenis syndrome is 1 in 25,000 births [4].

Following the introduction of second-trimester maternal serum screening for open neural tube defects and Down syndrome, additional screening tests became available for Down syndrome and other chromosomal aneuploidies, such as trisomy 18 and trisomy 13. These newer tests include first-trimester screening and noninvasive prenatal screening.

Maternal Serum Screening and First-Trimester Screening

Second-trimester maternal serum screening is available at 15–20 completed weeks gestation. In its current form, such screening uses the levels of 4 pregnancy-related hormones found in maternal blood and other variables, such as maternal age and race, to determine the probability that a fetus has open spina bifida, Down syndrome, or trisomy 18. First-trimester screening, performed at 11–13 completed weeks gestation, uses the levels of 2 pregnancy-related hormones found in maternal blood and variables such as maternal age and measurement of fetal nuchal translucency to arrive at probabilities that the fetus has Down syndrome or trisomy 18. (One laboratory that does first-trimester screening combines risk assessment of trisomy 18 with risk assessment of trisomy 13.) In a series of about 12,000 patients screened in North Carolina from 1978 to 1982, the detection rate for open spina bifida using maternal serum screening was found to be 83% [5]. For maternal serum screening and first-trimester screening, the detection rates for Down syndrome across all maternal ages are approximately 81% and 85%, respectively [6], whereas the detection rates for trisomy 18 across all maternal ages are approximately 60% and 90%, respectively [7, 8]. The false-positive rate for either type of screening for Down syndrome and trisomy 18 is typically 5% or less.

Ultrasound, Chorionic Villus Sampling, and Amniocentesis

If first-trimester screening or maternal serum screening yields an abnormal result with a specific risk assessment (eg, 1 in 100), then further evaluation is offered. How informative further evaluation is depends on gestational age, testing methodology, and the condition itself. A detailed anatomical ultrasound (level II ultrasound) can be performed as a screening procedure at 18–20 weeks gestation to look for anatomical characteristics of the condition in question. Approximately 50%–70% of fetuses with Down syndrome will exhibit one or more sonographic markers of the condition, and approximately 80%–90% of fetuses with trisomy 18 or trisomy 13 will exhibit one or more sonographic markers.
Noninvasive Prenatal Screening

Noninvasive prenatal screening, the newest addition to the prenatal testing menu, walks the line that has long separated screening from diagnostic genetic testing. There has been an effort for more than two decades to develop a reliable noninvasive test for the prenatal detection of genetic conditions. The presence in maternal blood of fragmented, cell-free fetal DNA (cfDNA), which constitutes approximately 3%–6% of the total cfDNA present in maternal blood [13], has allowed development of noninvasive prenatal screening for trisomies 21, 18, and 13. In addition, X and Y DNA fragments can be analyzed to screen for sex chromosome conditions such as Turner syndrome (45,X); such analysis also allows for prediction of fetal sex. Noninvasive prenatal screening laboratories have validated their methodologies in high-risk pregnancies, such as those of women who are 35 years of age or older, those in which there was an abnormal result on first-trimester screening or maternal serum screening, and those in which ultrasound identified one or more anatomical abnormalities associated with trisomies 21, 18, or 13. However, noninvasive prenatal screening will not be appropriate for average-risk pregnancies until further studies have been done.

Each laboratory that performs noninvasive prenatal screening reports its results slightly differently, but all quote high detection rates (greater than 99%) and low false-positive rates (generally less than 0.1%) for Down syndrome in particular [14]. The benefits of noninvasive screening include not just its noninvasiveness, but also its increased sensitivity and specificity compared with traditional first-trimester and second-trimester screening. However, false-positive results are still possible with noninvasive prenatal screening, so confirmation of abnormal results through CVS or amniocentesis is recommended. Also, such screening is not appropriate for other types of chromosomal abnormalities nor for single-gene conditions.

It is important to consider the positive predictive value (PPV) and the negative predictive value (NPV) of prenatal screening tests. PPV and NPV are influenced not only by the sensitivity and specificity of the test but also by the prevalence of the condition in the population being screened. It follows that more fetuses will be affected by a condition as the condition becomes more prevalent in a population, whereas fewer fetuses will be affected as the condition becomes less prevalent. For example, noninvasive prenatal screening has high sensitivity (greater than 99%) for Down syndrome in the high-risk population, but what is the chance that a positive screening result means that a fetus actually has Down syndrome? Although laboratories that perform noninvasive prenatal screening have not specified PPVs, I calculate the PPV for Down syndrome to be approximately 80% for 35-year-old pregnant women and 93% for 40-year-old pregnant women; this calculation assumes approximately 100,000 annual births to 35-year-old women and 20,000 annual births to 40-year-old women, based on averages calculated from 2011 US birth data compiled by the Centers for Disease Control and Prevention [15]. The PPV would be expected to be higher in 40-year-old women than in 35-year-old women, because approximately 1 in 70 mid-second trimester pregnancies of 40-year-old women is affected by Down syndrome, whereas this rate is only 1 in 250 among 35-year-old women. In contrast, the NPV of noninvasive prenatal screening for Down syndrome is very high (99.9%), because in most pregnancies the fetus does not have Down syndrome, regardless of maternal age.

Chromosomal Microarray

When prenatal genetic testing is desired for conditions not addressed by noninvasive screening, then it is necessary to perform CVS or amniocentesis. If there is a family history of muscular dystrophy, for example, the particular disease-causing gene mutation(s) present in the family must be known before prenatal testing is done, so that the results can be interpreted accurately. In the absence of this information, the wrong genetic test could be ordered, in which case there would be little or no promise of obtaining an informative result. Also, when a fetal sample is obtained through an invasive sampling procedure, which carries a risk of pregnancy loss, it is important that it be used appropriately.

The development of prenatal chromosomal microarray analysis has enabled screening of the fetal genome at a deeper level than other tests. Chromosomal microarray analysis involves testing chorionic villi or amniocytes for submicroscopic chromosome deletions and duplications that are below the limit of resolution of routine chromosome analysis [16]. Some submicroscopic deletion/duplication conditions cause anatomical malformations, so chromosomal microarray analysis can be helpful in making a diagnosis when ultrasound abnormalities do not fit any of the
recognized patterns of features described for more common conditions, such as Down syndrome or trisomy 18. If the fetus is chromosomally normal and appears sonographically normal but microarray testing reveals a less well-described microdeletion or duplication abnormality, or a variant of uncertain significance, then it can be difficult to predict postnatal morbidity, which can cause heightened anxiety for all involved. In addition, obtaining a normal result on chromosomal microarray neither rules out all genetic conditions nor negates the presence of sonographic abnormalities.

Parental Carrier Screening

The incidence of some genetic conditions is higher in certain ethnic groups: Sickle-cell anemia is more prevalent among African Americans, cystic fibrosis is more common among whites of Northern European decent, and Tay-Sachs disease is more prevalent among Ashkenazi Jews. Because these conditions are inherited in an autosomal recessive manner, carrier screening has been routinely offered to couples with these ethnic backgrounds to provide them with more accurate information about their chances of having a fetus affected by one of these conditions. When both members of a couple are found to be carriers of the same condition(s), prenatal diagnosis through CVS or amniocentesis can be considered. Expanded carrier screening for nearly 100 conditions has become available; however, the carrier detection rate for each condition varies with ethnicity and testing methodology. Also, the conditions for which carrier screening is available vary in their severity; some conditions cause significant medical or developmental complications, but other conditions are more benign or have onset in adulthood. Couples need to be aware of these important issues before proceeding with carrier screening [17].

Decision Making

Pregnant women accept or decline prenatal genetic screening or testing for varied and multilayered reasons. Some women consider the nature of the condition(s) being tested for and their perception of, or their personal experience with, the medical and/or developmental challenges the condition presents and how it will affect quality of life. Some take into consideration the availability of prenatal treatment and/or the accessibility of pediatric specialists during the newborn period. Some women are guided by faith; by the counsel of their spouse or partner, relatives, or close friends; or both. Some women want to avoid the risk for miscarriage associated with invasive procedures, whereas others believe that this risk is low enough to be acceptable. Some want to avoid the anxiety raised by uncertain or abnormal results, and others experience heightened anxiety in the absence of information.

Currently, fetal therapy is available for only a limited number of anatomical abnormalities, such as spina bifida [18]. Down syndrome, muscular dystrophy, fragile X syndrome, and thousands of other genetic disorders have no available prenatal treatment. Nonetheless, prenatal genetic screening and testing can reassure parents that a pregnancy is at low risk of or is unaffected by a condition or set of conditions tested for—or it can give parents an opportunity to prepare (cognitively, emotionally, financially, and supportively) for the birth of a child who has a genetic condition. Whether termination of a pregnancy affected with a genetic condition is considered to be an acceptable option is a decision that ultimately rests with the pregnant woman and her family.

Understanding the benefits, risks, and limitations of prenatal genetic screening and testing is important for health care providers, laboratories, insurers, public policy professionals, and most of all, for pregnant women. Although the amount of genetic information that can be obtained about a pregnancy through screening and diagnostic testing will continue to increase, it will be up to each pregnant woman and her family to decide what they wish to learn.

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