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Changing indications for invasive testing in an era of improved screening

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ABSTRACT

Prenatal diagnostic testing is available for a growing number of disorders. The goal of prenatal diagnosis was initially focused on the identification of Down syndrome in women aged 35 years and older, but invasive prenatal genetic techniques can now detect a far broader array of conditions. The risks of invasive procedures have also decreased over time. Advances in genomic medicine allow testing for smaller but significant chromosomal abnormalities known as copy number variants, in addition to major aneuploidies and structural rearrangements. Molecular DNA techniques can detect many single-gene conditions. In the future, it is likely that whole-exome and whole-genome sequencing will be applied to prenatal genetic testing to allow identification of yet more genetic disorders. With advances in technology, the indications for testing have likewise evolved far beyond recommendations based solely on maternal age to include a more patient-centered view of the goals of prenatal testing.

Introduction

Prenatal diagnostic testing is available for an ever-increasing number of disorders. Originally focused primarily on Down syndrome, prenatal genetic testing can now detect a far broader array of conditions. Advances in genetics and genomic medicine have led to a dramatic increase in the availability of genetic testing, including in the prenatal period. At the same time, prenatal screening has also seen improvements, with development of cell-free DNA screening, as well as expanded carrier screening for a broad array of inherited conditions. This has somewhat altered the relationship between prenatal screening for the common, age-related aneuploidies, and diagnostic tests that can identify many more conditions for which the prevalence is generally independent of maternal age.

The purpose of prenatal genetic testing focuses on each individual patient's reproductive goals and preferences. Patients should have pre-test counseling to explain the benefits and limitations of invasive prenatal diagnostic testing, the conditions that will and will not be detected, and the risks of the procedures. Prenatal genetic testing has many benefits, including providing reassurance when results are normal, identifying disorders for which in utero treatment might provide benefit, optimizing neonatal outcomes by assuring the appropriate location and staffing for delivery of affected infants, and by providing the option for pregnancy termination for individual families that make that choice.

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Ultimately, whether or not a patient undergoes invasive diagnostic testing should be solely up to the patient, with input from those individuals she chooses to include in her decision-making.

Fetal genetic disorders

Fetal genetic disorders are abnormalities in structure or function caused by abnormalities or differences in the genome, as distinct from those caused by environmental or other disruptive causes. These distinctions are not always clear; a genetic predisposition may increase the susceptibility to environmental influences, and some genetic abnormalities may only under specific environmental conditions. Some disorders have an epigenetic basis; that is, genes are turned on or silenced by modification that may depend on the parent of origin or other influences. While our ability to study genetics and genomics has continued to improve, inheritance and genetics are complex and our understanding remains incomplete. Prenatal diagnosis is often complicated, and it is not always possible to predict outcome based on a prenatal genetic test. Finally, prenatal diagnostic testing is possible for many, but not all, genetic disorders.

Chromosomal abnormalities and single-gene disorders are generally detected through analysis of fetal tissue and it is these conditions that are most often the target of prenatal diagnostic testing. Chromosomal abnormalities in pregnancy are relatively common, and about 1/150 live births has a chromosomal abnormality associated with an abnormal phenotype.[1] Such aberrations are more common early in pregnancy; 50% of recognized miscarriages in the first trimester are the result of a cytogenetic abnormality, as are 5% of stillbirths.[2] An estimated 5–7% of infant and childhood deaths result from chromosomal abnormalities. Chromosomal abnormalities are also more common in the setting of multiple miscarriages and fetal structural abnormalities.[3]

Chromosomal abnormalities can be due to abnormal number or structure of one or more chromosomes. The most common abnormality of chromosome number is aneuploidy, which is the presence of an extra or missing chromosome or chromosomes. It is also possible to have one or more extra sets of chromosomes, as in triploidy or tetraploidy. Abnormalities in chromosome number can be mosaic, in which the abnormal number of chromosomes is not present in all cells. This occurs relatively commonly in the placenta and can lead to confined placental mosaicism.

In addition to abnormalities of chromosome number, structural abnormalities include deletions, duplications, translocations, and other rearrangements. In some cases, rearrangements are balanced, meaning the appropriate genomic content is present but rearranged, while in other cases, translocations or other rearrangements can result in extra or missing pieces of chromosomes. Balanced translocations most often are associated with a normal phenotype, although they can lead to recurrent miscarriage or an increased risk of abnormal offspring. Apparently balanced rearrangements that occur de novo in a fetus are associated with a small increase in risk of abnormal outcome[4]; this may occur due to a small amount of genetic material being lost or duplicated, or due to disruption of a gene or alteration of gene function. In some cases, a chromosomal microarray can identify missing or duplicated material associated with a chromosomal rearrangement that appeared balanced by karyotype. However, not all abnormalities or gene disruptions can be identified. Deletions and duplications can be quite large and easily seen by a karyotype, or these can be small microdeletions or duplications only detectable with a chromosomal microarray, fluorescence in situ hybridization, or other specialized methods.

Some genetic disorders are caused by mutations in single genes; these conditions include those that are autosomal dominant, autosomal recessive, or X-linked recessive, dominant, or semi-dominant. Diseases caused solely by abnormalities in a single gene are relatively uncommon. The phenotype of many single-gene disorders is influenced by modifying genes or by the independent actions of a combination of additional genes often with environmental influences. Examples of single-gene disorders include cystic fibrosis, hemophilia, and neurofibromatosis. Single-gene disorders can be detected through prenatal diagnosis if the disorder has been diagnosed with certainty and the particular mutation within the family has been identified. Single-gene disorders identified through carrier screening can also be diagnosed in the fetus by assessing for the mutation(s) present in the parent(s).

The most common congenital anomalies are isolated birth defects, such as congenital heart defects, neural tube defects, and facial clefts. These traits are usually determined by multiple genes and environmental factors rather than by single genes. Although they may occur in the setting of chromosomal aneuploidy or a genetic syndrome, they are most commonly seen as isolated, non-syndromic findings. Because there is a genetic component, they recur more commonly within a family. However, because they are not typically caused by a single-gene mutation but rather a complex interplay of genetic and environmental factors, prenatal diagnostic genetic testing is usually not available using specific DNA methods; rather diagnosis is usually undertaken by ultrasound or other imaging.

Finally, while most genes are encoded in the nuclear genome, mitochondria each contain their own genome. Mitochondria are all maternally inherited. Mutations can occur in mitochondrial DNA, and a number of mitochondrial diseases are due to these disorders. Because mitochondria are necessary for aerobic respiration, mitochondrial diseases commonly affect tissues with high-energy requirements, such as the central nervous system, heart, and muscle. Oxidative phosphorylation depends on factors that are encoded by both the nuclear genome and mitochondrial DNA. Prenatal diagnosis for mitochondrial diseases can be complex and clinical outcomes difficult to predict, due to variation in the number of abnormal mitochondria and the association with predicted phenotype.

Indications for prenatal diagnostic testing

Invasive diagnostic testing has traditionally been offered only to patients deemed to be at sufficiently increased risk to warrant incurring the risk of miscarriage. However, evidence