The Role of Ultrasound in Non-Invasive Prenatal Testing

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Overview

Over the past two decades, methodologies for the screening and diagnosis of fetal chromosomal abnormalities have advanced, providing the ability to screen earlier in gestation, screen for more chromosomes, and offer patients less invasive testing options. The two most common non-invasive screening tests are first-trimester nuchal translucency (NT) screening and the non-invasive prenatal test (NIPT).*

The current standard for non-invasive screening is the first-trimester screen, which is performed between 11 and 13 weeks of gestation and combines a nuchal translucency (NT) ultrasound and a maternal blood draw. A more advanced screening option, introduced in 2011, is the non-invasive prenatal test (NIPT), also referred to as a cell-free DNA screen, which can be performed as early as 10 weeks of gestation.

When presenting patients with testing options, it is important to consider a number of factors, including the patient's risk factors for fetal chromosomal and genetic abnormalities, the efficacy of each test, and the cost of the test. While the risk of chromosomal abnormalities increases with maternal age, age is not the only risk indicator. Additional factors that increase a woman's risk are a family history of chromosomal abnormalities, including a prior child or pregnancy with a chromosomal abnormality.

Genetic counseling with a maternal-fetal medicine specialist or a genetic counselor can help patients make well informed decisions about which screening test is right for them.

It is important to note that the first-trimester screening and cell-free DNA tests are indicated for screening only. They assess the patient's risk of having a baby with chromosomal abnormalities—including Down syndrome (trisomy 21), trisomy 13, and trisomy 18—but do not provide a diagnosis. If the screening test is positive or high risk, patients should follow-up with amniocentesis or chorionic villus sampling (CVS) for a confirmatory diagnosis.

First-Trimester Screening

First-trimester screening utilizes first trimester biomarkers and a measurement of the fluid at the back of the neck of the baby using ultrasound (U/S). The nuchal translucency scan is an important component of first-trimester screening because it enables us to screen for structural and/or chromosomal abnormalities that may not show up in the blood test. Certain chromosomal abnormalities can be identified by the accumulation of fluid at the back of the fetus' neck, which causes this clear space to be larger than average.

The first-trimester screening test has demonstrated a detection rate of 90% for Down syndrome, and has shown to be more accurate than the quadruple (quad) marker screen, which has 85% accuracy for the risk of Down syndrome.[1,2]

Although the first-trimester screen is still regarded as the conventional testing methodology for non-invasive testing, it may not be accessible in some geographic locations because it requires a certified sonographer to perform the NT scan. The NT scan is more difficult to perform correctly than a general ultrasound, because of the challenges inherent in accurately measuring the nuchal translucency.

NIPT Screening

Non-Invasive Prenatal Testing (NIPT) consists of a maternal blood draw to test cell-free fetal DNA circulating in the patient's plasma. Available as early as 10 weeks' gestation, cfDNA testing offers tremendous potential as a screening method for fetal aneuploidy and the blood draw can be performed by OB/GYNs as well as maternal-fetal physicians.

NIPT technology analyzes free-floating fetal DNA for a number of chromosomal conditions, including trisomy 13, trisomy 18, and trisomy 21 (Down syndrome). In high-risk patients, NIPT has shown to have a screening accuracy of 99% for Down syndrome.

I recommend NIPT for high-risk patients who do not want an invasive procedure: patients who are at advanced maternal age or have ultrasound markers or findings suggestive of a chromosome abnormality like Down syndrome, a family history or prior child with Down syndrome, or a previous fetal chromosomal abnormality. NIPT currently is not recommended as a routine screening test by the Society for Maternal-Fetal Medicine for low-risk patients or patients with multiples.[3]

The Complementary Roles of NIPT and Ultrasound

While NIPT screening offers significant benefits, it does have limitations. The blood test does not look at every chromosome in detail, so even if the cfDNA test is negative or low risk, there still could be fetal abnormalities. If a patient has an issue with additional chromosomal material that is not included in NIPT screening or a family history of a birth defect such as a cardiac anomaly, it may not be detected on the NIPT test. NIPT has shown a high degree of accuracy for the chromosome abnormalities it screens for, but it is important to counsel patients that NIPT is not an all-inclusive test.

In my experience, the closest thing to a gold standard for prenatal testing is the NIPT screen combined with NT ultrasound at 12 weeks, early genetic U/S and an alpha-fetoprotein (AFP) screen for spina bifida at 16 weeks, and targeted U/S at 20 weeks. For high-risk patients who do not want an invasive diagnostic test, I recommend the NIPT screen, the AFP screen at 16 weeks, and the three ultrasound evaluations. This is the most comprehensive, non-invasive testing method that achieves a high detection rate with low false negatives and false positives. This

is consistent with recommendations from the American College of Obstetricians and Gynecologists (ACOG).[4]

If I counsel a patient who is at low risk for fetal chromosomal abnormalities, but who has had an NIPT test performed by their OB/GYN, I would still recommend an ultrasound scan at 12, 16 and 20 weeks. It is a reasonable approach for most patients.

Counseling Patients to Determine the Best Testing Approach

Non-invasive prenatal testing may not be the right approach for all patients. It is critical to understand the patient's family history, genetic history, and ultrasound findings to determine what type of testing is appropriate. I may counsel patients to have an invasive diagnostic test for a number of reasons. Did a prior ultrasound show an abnormality, such as cystic hygroma? If so, the non-invasive test might be helpful, but Iwould recommend a full invasive test to check full chromosomes in this type of patient.

Even when patients choose non-invasive cfDNA testing, if they have risk factors in their family or genetic history, I would recommend that they be referred to a maternal-fetal medicine specialist for counseling. While it has become routine to test for Down syndrome if a patient is 35 or older, it is also important to offer genetic counseling and testing for other potential genetic abnormalities, including cystic fibrosis, spinal muscular atrophy, and fragile X syndrome.

NIPT is part of the puzzle, but it is not the whole picture. A comprehensive approach that combines NIPT with a series of ultrasounds and other screening tests based on the patient's risk factors can provide the optimal combination of effective prenatal care and patient peace of mind.

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References

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3 Cell-free DNA screening for fetal aneuploidy. Committee Opinion No. 640. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;126:e31-7.)

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*NIPTs are lab-developed tests that are not reviewed or approved by the FDA.

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