Seminars in Perinatology ▮ (2015) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

Seminars in Perinatology

www.seminperinat.com

Screening for fetal aneuploidy

Britton D. Rink, MD, MS[a],*, *and Mary E. Norton, MD*[b]

[a]*Department of Maternal Fetal Medicine, Mount Carmel Health Systems, 6001 East Broad St, Office 3044, Columbus, OH 43213-1502*

[b]*Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, CA*

ARTICLE INFO

Keywords:
prenatal screening
chromosomal aneuploidy
genetic testing
cell-free fetal DNA
prenatal ultrasound
prenatal genetic counseling

ABSTRACT

Screening is currently recommended in pregnancy for a number of genetic disorders, chromosomal aneuploidy, and structural birth defects in the fetus regardless of maternal age or family history. There is an overwhelming array of sonographic and maternal serum-based options available for carrying out aneuploidy risk assessment in the first and/or second trimester. As with any screening test, the patient should be made aware that a "negative" test or "normal" ultrasound does not guarantee a healthy baby and a "positive" test does not mean the fetus has the condition. The woman should have both pre- and post-test counseling to discuss the benefits, limitations, and options for additional testing. Rapid advancements of genetic technologies have made it possible to screen for the common aneuploidies traditionally associated with advanced maternal age with improved levels of accuracy beyond serum and ultrasound based testing. Prenatal screening for fetal genetic disorders with cell-free DNA has transformed prenatal care with yet unanswered questions related to the financial, ethical, and appropriate application in the provision of prenatal risk assessment.

Prenatal screening for fetal chromosomal aneuploidy

Screening is the process of surveying a population with identified markers and defined cut-off levels to identify those individuals with a higher risk for a particular disorder. Screening programs are applicable to a population whereas diagnostic testing is applicable to the individual. The goal of any screening program is the use of markers with sufficient sensitivity to identify a significant portion of affected individuals or pregnancies while minimizing false-positive results. A successful screening program should have an accurate diagnostic test to identify those who are truly affected with consideration of the financial and ethical implications for the population.

Screening for chromosomal aneuploidy in pregnancy began in the 1960s with maternal age as the only available marker. As maternal age increases, the chance of delivering a child with Down syndrome (DS) increases from about 1/1000 at 30 years of age, to almost 1/400 at 35 years of age, and 1/100 at 40 years of age.[1] In contrast, paternal age does not affect aneuploidy risk. This clinical observation is consistent with studies demonstrating that greater than 90% of trisomy 21 results from non-disjunction in the oocyte, most commonly during meiosis I.[2] The mechanism of the non-disjunction event related to maternal age is not known. Because of the association of advancing maternal age with non-disjunction predisposing to aneuploidy, prenatal diagnosis has traditionally been offered to women aged 35 years or older. At 35 years of age, the chance of identifying a fetus with DS approximately equals the chance of miscarriage because of the amniocentesis procedure. Although antiquated, maternal age remains the most frequent method for identifying

Dr. Norton has received research funding from Ariosa Diagnostics and Natera. Dr. Rink has no disclosures.

*Corresponding author.
E-mail address: Britton.Rink@mchs.com (B.D. Rink).

http://dx.doi.org/10.1053/j.semperi.2015.11.006
0146-0005/

women at increased risk for fetal chromosome abnormalities and remains a determinant of who should be offered prenatal diagnostic testing.

Recent decades have seen the development of screening approaches using multiple biochemical and/or ultrasound markers in the first and second trimesters. In 2007, the American College of Obstetricians and Gynecologists (ACOG) recommended that screening and the option of diagnostic testing be offered to all women regardless of age or a-priori risk status.[3] They recommended as an alternative to traditional second trimester testing, the use of first trimester measurement of the fetal nuchal translucency plus serum markers. Combining first and second trimester screening results was also suggested to optimize detection rates. This was a dramatic shift from the concept of diagnostic procedures being reserved for women of advanced maternal age and focused on the concept of improved individual risk to reduce the need for invasive testing. The next step in the evolution of prenatal screening was the identification of cell-free fetal DNA (cffDNA) in maternal blood leading to the development of noninvasive prenatal testing (NIPT). The superior accuracy of cell-free fetal DNA for trisomy 21 screening, when compared with conventional screening options, has had a profound influence on the field of prenatal screening and diagnosis. Although there have been significant decreases in the number of patients undergoing invasive testing, there remain unique medical, ethical and financial challenges related to the implementation of cell-free DNA screening in the general obstetric population.[4]

First trimester risk assessment

The nuchal space is a normal and identifiable fluid-filled space behind the fetal neck that is present in all fetuses between 11 and 14 weeks of gestation. In 1992, Nicolaides et al.[5] reported the association between an increased measurement of the nuchal translucency (NT) and trisomy 21. As that original report, multiple other investigators have reported a similar association between the NT and fetal trisomy 21. When combined with the maternal age risk there is a 69–75% detection rate and a 5–8.1% false-positive rate for trisomy 21.[6–8]

There is no one single mechanism leading to an increased nuchal translucency, but it is hypothesized to be a complex, multifactorial process linked to one or more abnormalities in embryonic development. Available literature suggests a measurement greater than or equal to 3.5 mm (99th percentile) should be considered abnormal.[3] An increased nuchal translucency over 3.5 mm is an indication for further testing that may include diagnostic testing for aneuploidy, a detailed fetal anatomic survey by ultrasound, and/or fetal echocardiogram. The risk for aneuploidy, structural abnormality, and fetal demise increases as the nuchal translucency thickness increases.

A cystic hygroma is a single or septated fluid-filled cavity often involving the nuchal region that is the result of a lymphatic malformation and subsequent lymph accumulation. Approximately 50% of cystic hygromas identified in the first trimester are associated with chromosomal aneuploidy, the majority of which are fetuses affected with Down syndrome.[9] It remains unknown whether a cystic hygroma represents the severe end of the same processes that result in an increased nuchal translucency, or represents a separate entity. The management is similar irrespective of any distinction between the two entities.[10]

An increased NT measurement is not uniquely associated with Down syndrome. It is also often increased in fetuses with a variety of other genetic conditions, including trisomy 13, 18, Turner syndrome, and triploidy, as well as structural birth defects including congenital heart defects, and gastrointestinal, genitourinary, and musculoskeletal abnormalities.[7,11] Makrydimas et al.[12] reported that 1 in 16 fetuses with a nuchal measurement greater than or equal to 3.5 mm had a structural cardiac abnormality. A population-level study of singleton live births in California showed that fetuses with a nuchal translucency measurement $\geq$3.5 mm were 12 times as likely to have a critical congenital heart defect as compared to those fetuses with a normal nuchal measurement.[13] Post-test genetic counseling should therefore include discussion of these other possible genetic and structural abnormalities that may be identified with diagnostic testing and detailed ultrasound evaluation.

Presently, first trimester aneuploidy risk assessment combines nuchal translucency and two maternal serum biomarkers as a reliable and effective screening test for common aneuploidies. This has been validated by several multicenter trials.[6,7,14] First trimester screening (FTS) typically occurs between 9 and 14 weeks of gestation, depending on which markers are used, and provides risk assessment for trisomies 21 and 18 primarily, as well as for trisomy 13 in some laboratories. FTS generally includes ultrasound measurement of the nuchal translucency at a crown rump length between 38 and 84 mm as well as biochemical measurements of the free beta subunit or total human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A). PAPP-A is lower and free beta hCG is generally elevated in pregnancies affected with trisomy 21. Alone, the two biochemical markers have a 61% detection rate for DS at a 5% false-positive rate.[15] However, when combined with NT measurement and maternal age, the test has an 85% detection rate for Down syndrome at a 5% false-positive rate.[15–17]

The management of a structurally normal, euploid fetus with increased nuchal translucency represents a counseling challenge. Providers may consider advanced genetic testing options including microarray and sequencing for specific conditions such as Noonan syndrome. A study of 675 fetuses with increased NT, and karyotype and pregnancy outcome information available reported an extremely high chance of a favorable outcome in fetuses with initial NT $<$ 4 mm and a normal karyotype. In those fetuses with a normal mid-trimester ultrasound, the residual chance for an adverse outcome including developmental delay was not increased above the general population.[18] In approximately 3% of fetuses with an increased nuchal translucency, the finding will persist at the time of the mid-trimester anatomic survey. For those fetuses, there is a 10% chance of evolution to hydrops and therefore continued ultrasound surveillance is indicated.[19]

Because the nuchal translucency measurement is very precise, often challenging to obtain, and known to be