EDITORIAL

Nuchal Translucency and First-Trimester Screening

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First-trimester screening for Down syndrome has become a commonly used approach in prenatal genetic diagnosis. The drive behind the development of earlier, reliable methods of genetic screening and risk assessment is the ability to provide the parents with more options at an earlier gestational age. Currently, this involves the sonographic evaluation of fetal nuchal translucency (NT) in combination with maternal serum levels of free beta-hCG and PAPP-A to provide a risk assessment for Down syndrome.[1,2] This is referred to as combined first-trimester screening. Based on a survey of US maternal-fetal medicine specialists in 2001, of the 543 respondents, 46% used NT sonography and 27% used first-trimester maternal serum screening for Down syndrome.[3]

The term "nuchal translucency" refers to the fluid-filled space between the back of the fetal neck and the overlying skin.[4] It has been noted that fetuses with Down syndrome, as well as other forms of aneuploidy, have increased edema in this area, resulting in an increased NT measurement.[4] Based on seminal work by Nicolaides and others, measurement of NT in fetuses between 11 and 14 weeks has been used since the early 1990's to provide earlier risk assessment of fetuses with aneuploidy.[5] Initial results indicated detection rates comparable to second-trimester maternal serum screening.[5] However, three recent large trials, including the US-based First- and Second-Trimester Evaluation of Risk (FASTER) trial, the North American-based First Trimester Maternal Serum Biochemistry and Ultrasound Fetal Nuchal Translucency Screening (BUN) Study, and the European-based Serum, Urine, and Ultrasound Screening Study (SURUSS) Trial have demonstrated that combined screening in the first trimester outperforms both NT and first-trimester serum screening when performed separately, with detection rates for Down syndrome ranging from 79%-87% at a false positive rate of 5%.[6–8] This compares favorably with performance of second-trimester serum screening, also referred to as the "quad" screen, which utilizes maternal serum levels of unconjugated estriol, free human chorionic gonadotropin, alpha-fetoprotein, and inhibin A, with a detection rate of 81%.[7] Furthermore, the detection rate for trisomy 18 with the combined screen was comparable to the quad screen.[8]

There are still a number of issues which limit the use of NT. The technical expertise required to obtain reliable and reproducible images has proven challenging. Furthermore, patients must have access to providers who are capable of performing first-trimester chorionic villus sampling when a patient screens positive. There is still no consensus as to the most efficient or cost-effective schema for risk assessment. Patients and their providers must face this very personalized decision of whether to perform first- or second-trimester screening, a combination of the two as an "integrated" or "sequential" screen, or none at all. Integrated screening has been shown to provide the highest detection rate for Down syndrome by combining NT with first and second-trimester maternal serum screening. This higher detection rate involves a delay until the second-trimester for the completed results.[7] Sequential screening, which uses the same data as integrated screening, provides a preliminary result from the first-trimester component, then calculates a final risk estimate based on the addition of second-trimester maternal serum screening results. This method has a similar detection rate, at the expense of a higher false positive rate. Patients who opt for first-trimester screening alone may still wish to have a maternal serum alpha-fetoprotein and detailed ultrasound performed in the second-trimester to screen for neural tube defects. A mid-trimester ultrasound can also screen for numerous anatomic defects.

Any review of prenatal genetic risk assessment must also mention exciting developments in the area of noninvasive fetal diagnosis. Using powerful techniques such as polymerase chain reaction, analysis of free fetal DNA found in maternal serum will allow the prenatal diagnosis of many diseases as early as the first-trimester.[9] Newer technologies such as genomics, proteomics, and metabolomics are also likely to find critical applications in both invasive and noninvasive prenatal diagnosis. With these advances, it is clear that ethical dilemmas will become more prevalent. As such, guidelines regarding their application will need to keep pace with the advances themselves.

Efforts to improve genetic screening and diagnosis must be coordinated to ensure adequate quality assurance and to provide a mechanism for making interventions when issues arise at an individual or group level. Two such organizations, the Fetal Medicine Foundation in London and the US-based Maternal-Fetal Medicine Foundation, are currently in existence and will play key roles in making first-trimester risk assessment reliable and more available to patients who desire it. Agreement on a single effective approach to prenatal diagnosis will require more studies, experience, and expertise.

The pathophysiologic basis of nuchal edema leading to an increased NT has been postulated to result from a number of causes. These include cardiac failure, alterations of the dermal cellular matrix, and abnormal lymphatic development.[4] In this issue of the *Journal*, Bekker et al provide new information supporting one of these mechanisms. They hypothesize that in Down syndrome, abnormal differentiation of blood vascular endothelium into lymphatic endothelial cells causes enlargement of the jugular lymphatic sacs, leading to the accumulation

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of nuchal edema and resultant increased NT. This is one of the first reports detailing the relationship of an abnormal phenotype of the lymphatic system to the development of nuchal edema. Although the specific cause remains a topic of further investigation, this work represents a step towards a more thorough understanding of the pathophysiology of increased NT, as well as other developmental abnormalities associated with Down syndrome and other aneuploidies.

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