Second-Trimester Ultrasound for Adjusting Patient's Risk for Down Syndrome

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Screening for Down syndrome (DS) has changed dramatically in the last decade. General screening of pregnant women in the first trimester (between 11 and 13 gestational weeks) currently combines ultrasound measurement of fetal nuchal translucency in millimeters with two biochemical markers: human chorionic gonadotropins and pregnancy-associated plasma protein A. This enables detection of 90% of affected fetuses, with a false positive rate of only 5% [1]. At this stage, the vast majority, about 95%, are screened negative and reassured, while those screened with a high risk benefit from an early workup, and if diagnosed positive for DS are offered early termination of pregnancy. This important information, which categorizes the patient as high, low or intermediate risk for DS in the first trimester, is now provided to clinicians before performance of genetic sonography in the second trimester.

Second-trimester genetic sonography remains the primary method for assessment of fetal anatomy. The detection of structural abnormality and fetal malformations during ultrasound examination should be followed by genetic testing, not only for DS and not only by karyotype. The additional information provided by chromosomal microarray analysis, now routinely performed in these cases, enables identification of clinically significant chromosomal abnormalities in approximately 6% of fetuses with normal karyotype [2].

"Soft markers" such as increased nuchal fold thickness, intracardiac hyperechoic foci, hyperechogenic bowel, mild hydronephrosis, shortened extremities and mild ventriculomegaly, detected during fetal sonography, are more commonly detected than structural malformations. These markers are insignificant as "stand-alones" with regard to neonatal outcomes, but are informative to substantiate the patient's baseline risk for DS. They are often transient and have a variable impact on risk assessment.

A recent study of 72,000 fetuses that underwent genetic sonography, reported by Bronshtein et al. in this issue of *IMAJ* [3], shows a 90% detection rate of DS. This high rate concurs with studies that included echocardiogram as part of the ultrasound examination [4]. Isolated malformations that were found to indicate an increased risk for DS were common atrioventricular septal canal and duodenal atresia, each with an odds ratio of 88. Of the soft markers evaluated, nuchal edema was found to be a high risk marker, with an odds ratio of 39. Interestingly, 14% of all DS cases had completely normal first-trimester screening prior to the abnormal thickening observed on the 14–17 week scan.

Bromley and colleagues [5] recently addressed the importance of second-trimester soft markers for detection of DS after a normal first-trimester nuchal translucency. In their study, 33% of DS cases were detected using second-trimester scans, of which 36% had congenital malformations. Cardiac defects were the most common malformation. Soft markers were detected in all cases, thick nuchal fold being the most common soft marker. Increased nuchal fold was identified in 54% of fetuses with DS that had a normal nuchal translucency in the first trimester and no malformation detected. This surprising finding of a lack of association between nuchal translucency at 11–13 weeks gestation and a thick nuchal fold was reported in three published studies [6-8]. Thus, an abnormal nuchal thickness in the second trimester can evolve from a normal first-trimester nuchal translucency, with the same impact for further adjusting a patient's risk for DS.

Following their meta-analysis of 48 studies, Agathokleous and fellow researchers [9] concluded that the incidence of each of the selected second-trimester sonographic markers is higher in trisomy 21 than in euploid fetuses. Calculation of the likelihood ratio (LR) for each sonographic marker indicated only a small effect on modifying the pre-test odds for trisomy 21 for most markers, including intracardiac echogenic focus, echogenic bowel, mild hydronephrosis and short femur. On the other hand, for detecting ventriculomegaly, nuchal fold thickness and aberrant right subclavian artery, the increased risk is three- to fourfold higher. The demonstration of the hypoplastic nasal bone was associated with a six- to sevenfold increased risk of DS. This finding of a strongly associated marker describing a fetal profile is not surprising, as the obvious flat profile of DS newborns, created in part by the small nose, contributes to the mid-face hypoplasia, as reported by J.L.H. Down in 1866 [10].

The described meta-analysis estimated the LR of isolated markers by multiplying the positive LR for a given marker by the negative LR of each of the other markers. Surprisingly, intracardiac echogenic focus, a soft marker found in 5% of the normal population of patients who elected to undergo invasive testing in the past [11,12],

was calculated with a LR of 0.95, indicating a slight decrease in the risk for DS. This reduced risk is reported here by Bronstein et al. [3], with an odds ratio of 0.1.

An important finding of the described meta-analysis is the calculated 7.7-fold maternal baseline reduction in the risk for DS, when all markers are absent. As the vast majority of second-trimester ultrasound examinations do not detect positive markers, this modifies a patient's risk based on second-trimester ultrasound. It incorporates the ultrasound findings into the screening algorithm and may provide practical quantitative data for patient counseling with regard to further DS evaluation. On the other hand, detection of any one of the markers during the scan should stimulate a meticulous examination by the sonographer to look for all other markers of defects.

Advanced and highly skilled ultrasonography has been implemented for the assessment of new sonographic markers for DS. Odeh et al., also in the current issue of *IMAJ* [13], retrospectively assessed the presence of fetal salivary glands in DS and normal fetuses between 14 and 16 weeks of gestation. In the DS group, 33% had congenital absence of one or more salivary glands compared to 6% of the normal fetuses. Although the study was conducted in a small number of patients, they concluded that, due to its high specificity, a congenital absence of salivary glands may aid in the assessment of DS.

Our group has described several markers for the assessment of DS. In one study, we reported an odds ratio of 107 for abnormal umbilical vein anatomy in fetuses with DS compared with normal fetuses [14]. Subsequent to these findings, our genetic sonography includes routine assessment of the umbilical vein and the ductus venosus in the longitudinal plane. Any abnormality in these veins is recorded and a genetic consultation is carried out. Another marker, an aberrant right subclavian artery (ARSA) [15], was detected in 13 fetuses (1.4%) with a normal karyotype; 37.5% of fetuses with DS were found to have an ARSA. The odds ratio for ARSA in DS compared with normal fetuses was 42. A recent meta-analysis reported a 23.6% prevalence of ARSA in the DS population (95% confidence interval 19.4–27.9%) and 1.02% in euploid fetuses (95%CI 0.86–1.10%), resulting in a pooled LR+=26 [16]. Although the meta-analysis showed ARSA to be a significant risk factor for DS, the evidence is still insufficient to recommend fetal karyotyping in cases of isolated ARSA. As in all cases of soft markers, a mathematical risk model should be conducted for individual risk assessment.

Although fetal loss due to invasive testing is reportedly decreasing, healthy fetuses still die due to complications of unnecessary interventions [17]. Non-invasive prenatal testing for the detection of DS has profoundly affected the practice of fetal medicine worldwide [18], yet for many women the expense is still too high. Thus, until the situation changes, the need remains to perform highly skilled prenatal ultrasound for reassessment of patients' risk for DS, the most common intellectual disability in children and adults.

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"Being deeply loved by someone gives you strength, while loving someone deeply gives you courage"

Lao Tzu (6th Century BC), Chinese philosopher and writer, known as the reputed author of the *Tao Te Ching* and the founder of philosophical Taoism