New mixture models of first trimester screening for trisomy markers

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Introduction
The importance of the fetal biometry reference normograms during the screening for trisomy is well-known and some preliminary studies have been highlighted the importance of local normal curves and charts. To our knowledge, there was no study to establish the Central European normograms.

The aim of the study: was to establish the local fetal growth charts and normograms of fetal biparietal diameter, femur and humeral length, nuchal translucency, prenasal thickness, nasal bone length, ductus venosus PI, and PT-to-NBL and NBL-to-PT ratio from about 10 weeks and fetal heart rate and CRL from the 37 days of gestation to the midtrimester. The secondary aim was to improve efficacy of screening for chromosomal abnormalities at the first trimester ultrasound screening.

Results: Normograms were created for Fetal Heart Rate (FHR), Femur Length (FL), Biparietal Diameter (BPD), Nasal Bone Length (NBL), Prenasal Thickness (PT), NBL/PT ratio, PT/NBL ratio, Nuchal Translucency (NT), Ductus Venous flow Pulsatility Index (DVPI), DVPI+NT, DVPI-NT+PT/NBL ratio, NT/DVPI-to-PT/NBL ratios and DVPI/NT-to-PT/NBL ratios. The specific sensitivity, specificity and likely-hood ratios were determined for trisomies to FHR, FL, BPD, NBL, PT, NBL/PT, PT:NBL, NT, DVPI and their combinations. DVPI/NT-to-PT/NBL ratios were reached best efficacy with 100% sensitivity and 99.47% of specificity at 188.50 positive likelihood ratio.

Significant differences were observed between euploid and trisomy group from the aspect of nuchal translucency, fetal heart rate, nasal bone length, prenasal thickness, ductus venosus PI, prenasal thickness-to-nasal bone length and ductus venosus-to-nuchal translucency to prenasal thickness-to-nasal bone length ratios. (p < 0.001)

However, during the second trimester NBL-to-PT was better than the PT-to-NBL, although PT-to-NBL was better in the first trimester. The problem with this ratio is the zero division so if there is no nasal bone, it is unable to use for risk estimation.

Materials: This prospective observational study has been designed to measure, and describe the normal biometric parameters. All included 4321 cases scans have been performed from January, 2008 to February, 2014 in the MEDISONO Fetal and Maternal Health Research Centre and the Department of Medical Genetics, University of Szeged, Szeged, Hungary.

This study contains for (both low- and high) mixed-risk obstetric populations, and ethnically over 99.8% of pregnancies were a Caucasian population of Hungary. The study protocol was approved by the Regional Ethics Committee of the University of Szeged and all procedures were in full accordance with the Helsinki Declarations.

Methods: All measurements were repeated for 3 times and the best one was selected. Measurements of fetal biometry parameters were followed the FMRM measurement criterias and INTERGROWTH-21 standardizations for ultra-sonographers. CRL was measured in the mid-sagittal section, a neutral horizontal position, using the optimal magnification with the correct calliper position. NT and DVPI measurements were fully followed the FMRM criteria. DVPI-NT and NT-to-DVPI were established by the division NT and DVPI. Measurements of BPD were obtained from a transverse axial plane of the fetal head showing a central midline echo broken in the anterior third by the cavum septi pellucidi, if already present. BPD was measured from the outer border of the skull. The femur length (FL) was measured from the greater trochanter to the lateral condyle if it was eviscerated and shown, as if on the two ossification border of the bone. To measure the FHR, M-Mode was used in acquiring volume with automatic calculation. The NBL and PT were measured using the same view. If it was possible NT, NBL and PT were measured on the same plane. PT-to-NBL and NBL-to-PT were established by the division of NBL and PT. Statistical evaluation has been performed with SPSS 22.

Conclusions: Local normograms and the most sensitive ultrasound screening model for trisomy 21, and 18 were introduced. Using these ratios could be comparable to the efficacy of NIPT and provides successful pre-risk. These measurements and methods should be incorporated into first trimester screening for trisomy. Further investigation will be necessary to observe these findings on different population and also in the second and third trimester.

Clinical applications:
The increasing geographical inequalities in screening effectiveness demonstrated the existence of non-exploited opportunities in certain (non-properly managed) areas but 2D ultrasound is commonly used in the obstetries and these markers could be easily measured in 5-15 minutes.

Prenatal screening could show a significant improvement year by year if correct (local) normogram and protocol could be introduced and used. Using the correct protocol cost-benefit ratio could be increased. Parental stress and false-positive/negative rate could be decreased, while unnecessary NIPTs and invasive procedures could be limited to real cases.