

International gestational age-specific centiles for umbilical artery Doppler indices: a longitudinal prospective cohort study of the INTERGROWTH-21st Project

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Abstract

Background

Reference values for umbilical artery Doppler indices are used clinically to assess fetal well-being. However, many studies that have produced reference charts have important methodologic limitations, and these result in significant heterogeneity of reported reference ranges.

Objectives

To produce international gestational age-specific centiles for umbilical artery Doppler indices based on longitudinal data and the same rigorous

methodology used in the original Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project.

Study Design

In Phase II of the INTERGROWTH-21st Project (the INTERBIO-21st Study), we prospectively continued enrolling pregnant women according to the same protocol from 3 of the original populations in Pelotas (Brazil), Nairobi (Kenya), and Oxford (United Kingdom) that had participated in the Fetal Growth Longitudinal Study. Women with a singleton pregnancy were recruited at <14 weeks' gestation, confirmed by ultrasound measurement of crown–rump length, and then underwent standardized ultrasound every 5±1 weeks until delivery. From 22 weeks of gestation umbilical artery indices (pulsatility index, resistance index, and systolic/diastolic ratio) were measured in a blinded fashion, using identical equipment and a rigorously standardized protocol. Newborn size at birth was assessed using the international INTERGROWTH-21st Standards, and infants had detailed assessment of growth, nutrition, morbidity, and motor development at 1 and 2 years of age. The appropriateness of pooling data from the 3 study sites was assessed using variance component analysis and standardized site differences. Umbilical artery indices were modeled as functions of the gestational age using an exponential, normal distribution with second-degree fractional polynomial smoothing; goodness of fit for the overall models was assessed.

Results

Of the women enrolled at the 3 sites, 1629 were eligible for this study; 431 (27%) met the entry criteria for the construction of normative centiles, similar to the proportion seen in the original fetal growth longitudinal study. They contributed a total of 1243 Doppler measures to the analysis; 74% had 3 measures or more. The healthy low-risk status of the population was confirmed by the low rates of preterm birth (4.9%) and preeclampsia (0.7%). There were no neonatal deaths and satisfactory growth, health, and motor development of the infants at 1 and 2 years of age were documented. Only a very small proportion (2.8%–6.5%) of the variance of Doppler indices was due to between-site differences; in addition, standardized site difference estimates were marginally outside this threshold in only 1 of 27 comparisons, and this supported the decision to pool data from the 3 study sites. All 3 Doppler indices decreased with advancing gestational age. The 3rd, 5th, 10th, 50th, 90th, 95th, and 97th centiles according to gestational age for each of the 3 indices are provided, as well as equations to allow calculation of any value as a centile and z scores. The mean pulsatility index according to gestational age = $1.02944 + 77.7456 * (\text{gestational age})^{-2} - 0.000004455 * \text{gestational age}^3$.

Conclusion

We present here international gestational age-specific normative centiles for umbilical artery Doppler indices produced by studying healthy, low-risk pregnant women living in environments with minimal constraints on fetal growth. The centiles complement the existing INTERGROWTH-21st

Standards for assessment of fetal well-being.

Key words: antepartum testing, Doppler, fetal growth restriction, fetal well-being, INTERBIO, INTERGROWTH-21st ultrasound, longitudinal study, multinational study, perinatal morbidity, perinatal mortality, placenta, pulsatility index, reference ranges, resistance index, systolic/diastolic ratio, umbilical artery

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The umbilical artery waveform, obtained using Doppler ultrasonography, reflects the impedance to blood flow in the fetal compartment of the placenta.^{1,2} The ability to assess the umbilical artery waveform using Doppler was first described in 1977³; just a few years later, Trudinger and Cook⁴ first showed that in normally grown fetuses the impedance decreased with advancing gestation, whereas the impedance increased in growth restricted fetuses. The clinical value of measuring the umbilical artery Doppler is now well-established in high-risk pregnancy as one of the few interventions that reduce perinatal mortality but not in low-risk pregnancies.^{5,6}