OBSTETRICS

A fetal cardiovascular score to predict infant hypertension and arterial remodeling in intrauterine growth restriction

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OBJECTIVE: Intrauterine growth restricted (IUGR) fetuses experience cardiovascular remodeling that persists into infancy and has been related to cardiovascular outcomes in adulthood. Hypertension in infancy has been demonstrated to be a strong risk factor for later cardiovascular disease. Close monitoring together with dietary interventions have shown to improve cardiovascular health in hypertensive children; however, not all IUGR infants show increased blood pressure. We evaluated the potential of fetal echocardiography for predicting hypertension and arterial remodeling in 6-month-old IUGR infants.

STUDY DESIGN: One hundred consecutive IUGR and 100 control fetuses were observed into infancy. Fetal assessment included perinatal Doppler imaging, cardiac morphometry, ejection fraction, cardiac output, isovolumic relaxation time (IVRT), tricuspid annular-plane systolic excursion (TAPSE), and tissue Doppler imaging. *Infant hypertension* and *arterial remodeling* were defined as mean blood pressure of >95th percentile together with aortic intima-media thickness of >75th percentile at 6 months of age. Odds ratio were obtained for fetal parameters that were associated with infant outcomes.

RESULTS: Fetal TAPSE, right sphericity index, IVRT, and cerebroplacental ratio were the strongest predictors for postnatal vascular remodeling. A cardiovascular risk score that was based on fetal TAPSE, cerebroplacental ratio, right sphericity index, and IVRT was highly predictive of infant hypertension and arterial remodeling (area under the curve, 0.87; 95% confidence interval, 0.79—0.93; $P < .001$).

CONCLUSION: Fetal echocardiographic parameters identify a high-risk group within the IUGR fetuses who could be targeted for early screening of blood pressure and other cardiovascular risk factors and for promoting healthy diet and physical exercise.

Key words: cardiovascular risk, fetal echocardiography, hypertension, intrauterine growth restriction, programming

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Intrauterine growth restriction (IUGR) is defined as an estimated fetal weight below the 10th percentile for gestational age. Evidence from large epidemiologic studies has long suggested a strong association between IUGR and increased cardiovascular mortality rates in adulthood.[1] Recent prospective studies have described that fetuses with IUGR have cardiac remodeling and dysfunction that persists into infancy in the form of remodeled hearts, hypertension, and increased intima-media thickness.[2-5] Hypertension in childhood is a strong risk factor for later cardiovascular disease[6,7] and is considered an indication for lifestyle modifications.[7,8] Detection of IUGR may constitute an opportunity

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to apply preventive cardiovascular interventions from early life.[9] However, IUGR may affect up to 5-10% of the whole population, and only a fraction will display the cardiovascular features described earlier during childhood. Therefore, personalized medicine approaches are required to allow selection of subjects who are at high risk.

Perinatal selection of cases that are at risk would allow an efficient approach to detect fetuses who may later benefit from early screening and intervention in infancy.[7,9] Perinatal criteria that are used conventionally to establish the severity of IUGR, such as gestational age at onset or fetoplacental Doppler changes, have shown a weak association with postnatal cardiovascular findings. Thus, a remarkable proportion of fetuses with relatively benign forms of IUGR may still experience hypertension and cardiovascular remodeling in childhood.[4,10,11] Fetal echocardiography is a potential and so far unexplored approach to achieve prenatal detection of cardiovascular remodeling that persists into childhood. Several functional and morphometric echocardiographic parameters show remarkable differences in IUGR with respect to normally grown fetuses.[2,4,5,11,12] However, the relationship of these changes with cardiovascular findings in childhood has not been determined. It is unknown to what extent prenatal changes are only a direct reflection of fetal deterioration because of hypoxia and undernutrition that occurs in IUGR.[3] In addition, events during the neonatal period might exert influences in later cardiovascular function.

We conducted a prospective cohort study that included 100 IUGR fetuses and 100 normally grown fetuses. Subjects were evaluated prenatally with comprehensive echocardiography and followed into 6 months of age to assess blood pressure and aortic intima-media thickness (aIMT). We evaluated the correlation of fetal echocardiographic parameters with postnatal cardiovascular features and explored whether a cardiovascular score was predictive of infant hypertension and arterial remodeling.

Materials and Methods

Study population

The study design was a prospective cohort study that included fetuses with IUGR and control subjects who were identified in utero and followed into infancy. The source population comprised women who were pregnant from April 2010 to September 2012 who attended the Department of Maternal–Fetal Medicine at Hospital Clínic in Barcelona, Spain. Pregnancies with structural/chromosomal anomalies, multiple pregnancies, or evidence of fetal infection or that were achieved by assisted reproduction technologies were excluded from the study. *IUGR* was defined as an estimated fetal weight and (later) confirmed birthweight of <10th percentile according to local reference curves.[13] In total, 132 IUGR fetuses were included for the study in prenatal life; 4 fetuses were later excluded because of Down's syndrome (2 fetuses) and pulmonary stenosis (2 fetuses); 5 fetuses died before delivery, and 11 fetuses died in the neonatal period. From the remaining 112 patients, 12 were lost on follow up, which left us with 100 IUGR cases. The reference cohort of fetuses with normal estimated fetal weight and birthweight (10th-90th percentile) were sampled randomly from pregnancies at our institution and paired with IUGR cases by gestational age at scan (±1 week). The study was approved by our institution's Ethics Committee, and written parental consent was obtained for all study participants. The study protocol included fetal standard obstetric assessment and echocardiography, record of delivery data, and postnatal vascular assessment at 6 months of corrected age.

Baseline and perinatal characteristics

At fetal examination, maternal characteristics such as height, weight, body mass index, smoking during pregnancy, and parity were recorded. Gestational age at scan was calculated based on the crown-rump length that had been obtained at the first-trimester screening. All women underwent ultrasonographic examination with a Siemens Sonoline Antares machine (Siemens Medical Systems, Malvern, PA) that included estimation of fetal weight and standard obstetric Doppler evaluation that comprised measurement of the pulsatility index (PI) for the uterine arteries, umbilical artery, middle cerebral artery, ductus venosus, and aortic isthmus. Both estimated fetal weight and birthweight percentile were calculated with local reference curves.[13] Uterine artery evaluation was performed with the probe placed on the lower quadrant of the abdomen, angled medially, with identification by color Doppler imaging of the apparent crossover with the external iliac artery. Mean uterine artery PI was calculated as the average PI of right and left arteries.[14] Umbilical artery was evaluated in a free loop of the umbilical cord; middle cerebral artery was measured in a transverse view of the fetal skull at the level of its origin from the circle of Willis.[15] Cerebroplacental ratio was calculated by division of middle cerebral artery and umbilical artery PI.[16] Ductus venosus was obtained from a mid-sagittal or alternatively a transverse section of the fetal abdomen before its entrance into the inferior vena cava, with the Doppler gate positioned at the isthmic portion.[17] The aortic isthmus was obtained either in a sagittal view of the fetal thorax with a clear visualization of the aortic arch by placement of the Doppler sample volume between the origin of the left subclavian artery and the confluence of the ductus arteriosus or in a cross section of the fetal thorax at the level of the 3-vessel and trachea view, with the Doppler gate placed in the aorta just before the convergence of the arterial duct.[18] On delivery, gestational age, birthweight, birthweight percentile, mode of delivery, Apgar scores, presence of preeclampsia, and length of stay at the neonatal intensive care unit were recorded.

Fetal echocardiography

On IUGR diagnosis, a complete 2-dimensional echocardiographic examination was performed initially to assess structural heart integrity with a Siemens Sonoline Antares machine (Siemens Medical Systems). Cardiovascular evaluation was performed with a curved-array 2-6 MHz transducer (with the