IMAGING

The fetal cardiovascular response to increased placental vascular impedance to flow determined with 4-dimensional ultrasound using spatiotemporal image correlation and virtual organ computer-aided analysis

Neil Hamill, MD; Roberto Romero, MD, D Med Sci; Sonia Hassan, MD; Wesley Lee, MD; Stephen A. Myers, DO; Pooja Mittal, MD; Juan Pedro Kusanovic, MD; Mamtha Balasubramaniam, MS; Tinnakorn Chaiworapongsa, MD; Edi Vaisbuch, MD; Jimmy Espinoza, MD; Francesca Gotsch, MD; Luis F. Goncalves, MD; Shali Mazaki-Tovi, MD; Offer Erez, MD; Edgar Hernandez-Andrade, MD; Lami Yeo, MD

OBJECTIVE: We sought to determine if increased placental vascular impedance to flow is associated with changes in fetal cardiac function using spatiotemporal image correlation and virtual organ computer-aided analysis.

STUDY DESIGN: A cross-sectional study was performed in fetuses with umbilical artery pulsatility index >95th percentile (abnormal [ABN]). Ventricular volume (end-systole, end-diastole), stroke volume, cardiac output (CO), adjusted CO, and ejection fraction were compared to those of 184 normal fetuses.

RESULTS: A total of 34 fetuses were evaluated at a median gestational age of 28.3 (range, 20.6–36.9) weeks. Mean ventricular volumes were lower for ABN than normal cases (end-systole, end-diastole) with a proportionally greater decrease for left ventricular volume (vs right). Mean left and right stroke volume, CO, and adjusted CO were lower for ABN (vs normal) cases. Right ventricular volume, stroke volume, CO, and adjusted CO exceeded the left in ABN fetuses. Mean ejection fraction was greater for ABN than normal cases. Median left ejection fraction was greater (vs right) in ABN fetuses.

CONCLUSION: Increased placental vascular impedance to flow is associated with changes in fetal cardiac function.

Key words: cardiac function, cardiac output, contour finder, ejection fraction, fetal echocardiography, fetus, 4-dimensional, intrauterine growth restriction, prenatal diagnosis, sonography, spatiotemporal image correlation, STIC, stroke volume, 3-dimensional, umbilical artery Doppler, ventricular volume, virtual organ computer-aided analysis, VOCAL

Cite this article as: Hamill N, Romero R, Hassan S, et al. The fetal cardiovascular response to increased placental vascular impedance to flow determined with 4-dimensional ultrasound using spatiotemporal image correlation and virtual organ computer-aided analysis. Am J Obstet Gynecol 2013;208:153.e1-13.

Abnormal umbilical artery (UA) Doppler velocimetry reflects increased impedance to blood flow in the placenta.[1-4] Mathematical modeling of the placental circulation shows that initially, placental resistance and pulsatility index (PI) increase very slowly with fractional terminal vessel obliteration.[5] However, there is a steep increase of the PI after 60-90% of vessels are obliterated.[5]

In human pregnancies, structural heart disease,[6-8] small for gestational age with normal UA Doppler velocimetry,[9,10] intrauterine growth restriction (IUGR),[11-15] twin-to-twin transfusion syndrome,[16-18] and intraamniotic infection[19,20] (reported in animal models also[21,22]) can result in fetal cardiac dysfunction. The heart is a

From the Perinatology Research Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, and Detroit, MI (Drs Hamill, Romero, Hassan, Mittal, Kusanovic, Chaiworapongsa, Vaisbuch, Espinoza, Gotsch, Goncalves, Mazaki-Tovi, Erez, Hernandez-Andrade, Yeo); the Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI (Drs Hamill, Hassan, Mittal, Kusanovic, Chaiworapongsa, Vaisbuch, Espinoza, Goncalves, Mazaki-Tovi, Erez, Hernandez-Andrade, and Yeo); the Division of Fetal Imaging, Department of Obstetrics and Gynecology, William Beaumont Hospital, Royal Oak, MI (Dr Lee and Ms Balasubramaniam); and Case-MetroHealth, Cleveland, OH (Dr Myers).

Received June 28, 2012; revised Oct. 5, 2012; accepted Nov. 5, 2012.

This research was supported, in part, by the Perinatology Research Branch, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services.

Dr Romero has contributed to this work as part of his official duties as an employee of the US Federal Government. The authors report no conflict of interest.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Federal Government.

Presented at the 19th World Congress on Ultrasound in Obstetrics and Gynecology (International Society of Ultrasound in Obstetrics and Gynecology), Hamburg, Germany, Sept. 13-17, 2009.

Reprints not available from the authors.

0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2012.11.043

central organ in the fetal adaptive mechanisms to placental insufficiency and hypoxia.[23] Therefore, it follows that placental insufficiency with increased placental vascular resistance may lead to fetal cardiovascular compromise,[24] and even fetal metabolic acidosis and death.[25] Indeed, severe IUGR due to placental insufficiency contributes to 30% of total perinatal loss and severe morbidity.[26] Monitoring of fetal cardiac function has been proposed as an adjunct to current methods to predict adverse outcome and death in IUGR.[27] Fetuses with abnormal UA Doppler velocimetry have been shown to have similar changes to those observed in adults with atherosclerosis. This may be important in relating placental vascular disease (detected by UA Doppler velocimetry) to the risk for adult cardiovascular disease.[28] Studies report that fetuses with abnormal UA Doppler velocimetry have evidence of higher red blood cell count and hemoglobin concentration,[29] endothelium activation,[28] platelet activation (which promotes thrombosis),[30] platelet consumption,[31] an atherogenic lipoprotein profile,[32] and evidence of intravascular inflammation.[33] Epidemiologic studies and animal models have also established that low-birthweight babies have an increased risk of cardiovascular disease later in life.[34,35] Thus, the condition that is the focus of our study is the in utero equivalent to fetal atherosclerosis, and this, along with fetal cardiac dysfunction, may have important consequences in fetal programming of cardiac disease and the early onset of disease.[23] Examining fetal cardiovascular parameters is required to gain an understanding of the hemodynamic changes occurring in the setting of increased placental vascular impedance to flow.

However, the repeatability and reproducibility of most fetal echocardiographic measurements determined using 2-dimensional (2D) sonography is poor, particularly for ventricular volume and volume flow estimations.[36] This has been attributed to measurement variation in the atrioventricular (AV) and semilunar valves, which can lead to large differences in the estimated cardiac output (CO).[36,37] Errors in measuring velocity-time integral or valve area will greatly influence volume flow measurements, particularly because the valve area is related to the square of the radius, thus accentuating any errors.[38] Moreover, the use of 2D measurements to estimate ventricular volume requires assumptions about the 3-dimensional (3D) geometry of the heart that may be invalid, leading to inaccuracy in estimations of CO.[36,37]

Both 3D[39] and 4-dimensional (4D) sonography have the potential to minimize the limitations inherent in 2D estimations of fetal cardiovascular parameters because: (1) geometric assumptions are not made when assessing ventricular volumes; (2) neither small outflow tract diameters nor angle-dependent Doppler measurements are required for calculation; and (3) from a single cardiac dataset obtained using spatiotemporal image correlation (STIC), all parameters required for calculation (left and right ventricular volumes) are present in the same volume, reducing the risk inherent in measuring 2 chambers at different times when using 2D ultrasound.[40] Indeed, 3D[41-46] and 4D[47-57] echocardiography have been used to evaluate cardiovascular parameters in normal fetuses.

Yet, there are insufficient data regarding the fetal cardiovascular response to increased placental vascular impedance to flow determined using 4D sonography. We have previously described a repeatable and reproducible technique to quantify ventricular volume calculations using STIC and virtual organ computer-aided analysis (VOCAL).[58] Subsequently, we quantified fetal cardiovascular parameters (ventricular volume, stroke volume, CO, and ejection fraction) in a group of 184 normal fetuses over a range of gestational ages.[40] Therefore, the objective of this study was to use the same technique to determine if increased placental vascular impedance to flow is associated with changes in fetal cardiac function.

MATERIALS AND METHODS

Study population

A cross-sectional study was conducted to include pregnancies with increased placental vascular impedance to flow (UA PI >95th percentile[59]) by searching our database of women enrolled into research protocols that included examination of the fetal heart by 3D and 4D ultrasound. Women were eligible for inclusion if gestational age was determined by either a first- or second-trimester sonographic examination and there was a singleton fetus (>19 weeks of gestation). Women were excluded in the presence of fetal hydrops or chromosomal or congenital abnormalities. A control group, consisting of 184 normal fetuses whose cardiovascular parameters had been previously reported,[40] was used for comparison.

IUGR was defined as an abdominal circumference (AC) <5th percentile for gestational age[60,61] with UA PI >95th percentile.[59] Estimated fetal weight (EFW) was not used to determine the presence of IUGR. Fetal Doppler recordings were obtained from the UA (free loop of cord), middle cerebral artery, and ductus venosus when possible. Preeclampsia was defined as the presence of systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, and proteinuria of 300 mg/24 hours or ≥+2 (dipstick) on 2 occasions 6 hours apart. All women provided written informed consent prior to undergoing sonographic examination. Participation was approved by the institutional review board of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and by the Human Investigation Committee of Wayne State University.

Examination technique

Ultrasound examinations were performed by 8 experienced sonographers using systems with STIC capability (Voluson 730 Expert, Voluson E8 Expert; GE Medical Systems, Kretztechnik GmbH, Zipf, Austria) and utilizing a motorized curved-array transabdominal transducer (2-5 or 4-8 MHz). Tissue harmonic imaging was used for each examination, and compound resolution imaging was used at the sonographer's discretion. A transverse view of the fetal chest at the level of the 4-chamber view was obtained, from which STIC datasets were acquired. The transducer was oriented such that the fetal spine was located posteriorly for each acquisition. Acquisition time was 10 seconds with a sweep angle that was sufficient to encom-