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Reduced fetal growth velocity precedes antepartum fetal death

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KEYWORDS: abdominal circumference; biparietal diameter; customized growth standard; head circumference; small-for-gestational age; stillbirth

CONTRIBUTION

What are the novel findings of this work?
Pregnancies that resulted in antepartum fetal death had significantly lower growth velocities of fetal head circumference, biparietal diameter, abdominal circumference, femur length and estimated fetal weight (EFW) compared to pregnancies that delivered a liveborn neonate, according to the Perinatology Research Branch/Eunice Kennedy Shriver National Institute of Child Health and Human Development (PRB/NICHD) and the Hadlock fetal growth standards.

What are the clinical implications of this work?
Assessment of fetal growth velocity doubles the detection rate of antepartum fetal death compared to a single EFW measurement at the last available ultrasound scan before diagnosis of demise. Fetuses with EFW growth velocity $< 10^{th}$ percentile value of pregnancies with a live birth had a 9.4-fold and 11.2-fold increased risk of antepartum death, based on the Hadlock and PRB/NICHD growth standards, respectively.

ABSTRACT

Objectives *To determine whether decreased fetal growth velocity precedes antepartum fetal death and to evaluate whether fetal growth velocity is a better predictor of antepartum fetal death compared to a single fetal biometric measurement at the last available ultrasound scan prior to diagnosis of demise.*

Methods *This was a retrospective, longitudinal study of 4285 singleton pregnancies in African-American women who underwent at least two fetal ultrasound examinations between 14 and 32 weeks of gestation and delivered a liveborn neonate (controls; $n = 4262$) or experienced antepartum fetal death (cases; $n = 23$). Fetal death was defined as death diagnosed at ≥ 20 weeks of gestation and confirmed by ultrasound examination. Exclusion criteria included congenital anomaly, birth at < 20 weeks of gestation, multiple gestation and intrapartum fetal death. The ultrasound examination performed at the time of fetal demise was not included in the analysis. Percentiles for estimated fetal weight (EFW) and individual biometric parameters were determined according to the Hadlock and Perinatology Research Branch/Eunice Kennedy Shriver National Institute of Child Health and Human Development (PRB/NICHD) fetal growth standards. Fetal growth velocity was defined as the slope of the regression line of the measurement percentiles as a function of gestational age based on two or more measurements in each pregnancy.*

Results *Cases had significantly lower growth velocities of EFW ($P < 0.001$) and of fetal head circumference, biparietal diameter, abdominal circumference and femur length (all $P < 0.05$) compared to controls, according to the PRB/NICHD and Hadlock growth standards. Fetuses with EFW growth velocity $< 10^{th}$ percentile of the controls had a 9.4-fold and an 11.2-fold increased risk of antepartum death, based on the Hadlock and*

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customized PRB/NICHD standards, respectively. At a 10% false-positive rate, the sensitivity of EFW growth velocity for predicting antepartum fetal death was 56.5%, compared to 26.1% for a single EFW percentile evaluation at the last available ultrasound examination, according to the customized PRB/NICHD standard.

***Conclusions** Given that 74% of antepartum fetal death cases were not diagnosed as small-for-gestational age (EFW < 10th percentile) at the last ultrasound examination when the fetuses were alive, alternative approaches are needed to improve detection of fetuses at risk of fetal death. Longitudinal sonographic evaluation to determine growth velocity doubles the sensitivity for prediction of antepartum fetal death compared to a single EFW measurement at the last available ultrasound examination, yet the performance is still suboptimal.*

INTRODUCTION

Fetal death diagnosed after 20 weeks of gestation occurs in 6 per 1000 deliveries and accounts for more than one-half of annual infant deaths in the USA[1]. More than 80% of fetal deaths occur prior to the onset of labor[2–5].

Since birth weight is considered to be a surrogate for fetal growth, and a small-for-gestational-age (SGA) neonate is associated with an increased risk of stillbirth[6–10], fetal growth restriction (FGR) is frequently cited as an antecedent of antepartum stillbirth[7, 11–14].

The relationship between fetal growth and stillbirth is poorly understood for several reasons. First, the exact timing of death is unknown and an overestimation of the gestational age leads to increased frequency of SGA among stillbirths[6,10,14–18]. Second, although most cases of FGR and fetal overgrowth result in live birth[11,19–21], abnormal fetal growth may still be a cause of fetal death[6,10,14,15,22–24]. Third, it is unclear whether impaired fetal growth is a cause of fetal death[2] or a result of placental dysfunction. Fourth, maternal characteristics affecting growth of normal liveborn neonates are also risk factors for stillbirth[25]. Finally, given that most reports examine maternal and fetal conditions present at the time of or after fetal death, longitudinal studies are needed to gain insight into causality[7,19,26–29].

Although improvement in prediction of SGA at birth by serial ultrasound examinations compared to a single last available estimated fetal weight (EFW) measurement is controversial[30–32], the assessment of fetal growth velocity has been proposed to improve the detection of growth-restricted fetuses at increased risk of adverse perinatal outcome[33–36]. Studies conducted in Sweden[37], Norway[38] and Denmark[22,23] have reported that impairment of fetal growth was associated with fetal and/or neonatal death; yet, the association between growth velocity and fetal death was not assessed. Although Hirst *et al.*[4] reported that a reduced fetal size doubled the risk of fetal death, the authors did not find evidence of decreased growth velocity of either head circumference (HC) or abdominal circumference (AC) among cases with antepartum fetal death.

We therefore aimed to determine whether fetal growth velocity is decreased in pregnancies that experience antepartum fetal death compared to those that deliver a liveborn neonate, and to evaluate whether growth velocity is a better predictor of antepartum fetal death when compared to a single EFW measurement at the last available ultrasound scan prior to diagnosis of demise.

METHODS

Study population

This was a retrospective study of 5846 singleton pregnancies enrolled between August 2006 and April 2017 at the Center for Advanced Obstetrical Care and Research of Hutzel Women's Hospital, affiliated with the Wayne State University School of Medicine and the Detroit Medical Center, Detroit, MI, USA. The clinical database is housed by the Perinatology Research Branch (PRB), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health, US Department of Health and Human Services, Detroit, MI, USA. All study participants had provided written informed consent for their data to be used in future research, prior to the collection of demographic or clinical information, images and samples. The use of demographic, clinical and ultrasound data for research purposes was approved by the Human Investigation Committee of Wayne State University and the Institutional Review Board of the NICHD.

Given that most of the study participants self-reported as African-American (92%) and that we aimed to compare growth velocity based on changes in growth percentiles obtained not only with the Hadlock standard but also with the customized PRB/NICHD standard, which was established in an African-American population, we restricted our analysis to the African-American population.

A retrospective, longitudinal study was designed based on the following inclusion criteria: (1) singleton pregnancy; (2) African-American maternal ethnicity; (3) at least two fetal ultrasound examinations performed between 14 and 32 weeks of gestation; and (4) availability of relevant perinatal information. Participants were classified according to pregnancy outcome as controls, if pregnancy resulted in delivery of a liveborn neonate, or as cases, if antepartum fetal death occurred. Antepartum fetal death was defined as death diagnosed at ≥ 20 weeks of gestation and confirmed by ultrasound examination prior to the onset of labor[39]. Pregnancies with congenital anomalies, intrapartum fetal death or birth at < 20 weeks of gestation and cases that were lost to follow-up were not included in the study. Detailed data on demographic characteristics, medical history and pregnancy outcome were extracted from the electronic medical records of the patients.

Ultrasound examination

Transabdominal ultrasound examinations were performed to obtain the fetal biometric parameters by using methods described previously by Chitty and Altman and colleagues[40–42] and Altman and Chitty[43], which are consistent with recommendations of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[44] and the American Institute of Ultrasound in Medicine (AIUM)[45]. Fetal biometric parameters included (1) biparietal diameter (BPD), outer edge to inner edge of the calvarium; (2) HC, ellipse placed around the outside of the calvarium; (3) AC, ellipse placed at the outer surface of the skin; and (4) femur length (FL), calipers placed at the ends of the ossified diaphysis.

Clinical definitions

Risk factors associated with fetal death[2,4] that were considered in this study included maternal chronic medical conditions, pregnancy complications and maternal age > 35 years or < 20 years. Obesity was defined as a prepregnancy body mass index of > 30 kg/m^2. Maternal chronic medical conditions included obesity, hypertension, diabetes mellitus, asthma, anemia, thyroid disease, epilepsy, liver disease, kidney disease, neurologic or psychiatric disease and syphilis. Pregnancy complications included any of the following conditions: pre-eclampsia; eclampsia; gestational hypertension; hemolysis, elevated liver enzymes and low platelet count syndrome; cervical insufficiency; placental abruption; preterm labor; preterm prelabor rupture of the membranes; clinical chorioamnionitis; and preterm delivery. Medically indicated preterm delivery was defined as birth at < 37 weeks of gestation as a consequence of a medical intervention indicated to end the pregnancy in the presence of serious maternal or fetal compromise[46].

Statistical analysis

Demographic data were compared between cases and controls using the Wilcoxon signed-rank test for continuous variables and the Fisher's exact test for categorical variables. EFW was calculated from fetal AC, FL and HC using Hadlock's formula[47]. The EFW percentiles were computed according to the PRB/NICHD[48] and Hadlock[49] fetal growth standards. The INTERGROWTH-21st growth standard[50] was also considered, but was not included since percentiles could not be derived for scans obtained prior to 22 weeks of gestation. EFW percentiles for both standards were obtained using the fetal growth percentile software calculator[51]. Growth velocity was defined as the change in the percentile of EFW or individual fetal parameters per week of gestation and was expressed as the linear regression slope of measurement percentiles as a function of gestational age from all measurements between 14 and 32 weeks of gestation, unless otherwise specified (see spreadsheet calculator in Appendix S1). The upper limit of gestational age corresponded to the highest gestational age at the last scan among cases before diagnosis of fetal death. Growth velocity below zero represents deceleration, while positive values represent acceleration, with zero denoting no change in the percentile with gestational age.

Receiver-operating-characteristics (ROC) curves were used to compare prediction of fetal death based on the following parameters: (1) growth velocity of EFW percentiles according to the PRB/NICHD and Hadlock standards; (2) growth velocity of percentiles for HC, BPD, AC and FL based on the non-customized PRB/NICHD and Hadlock standards; and (3) EFW percentile at the last available scan based on the customized PRB/NICHD and Hadlock standards in cases and matched controls.

A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using the R programming language, version 3.5.1 (https://www.r-project.org).

RESULTS

Among 5846 participants with a singleton pregnancy enrolled during the study period, 5375 (91.9%) were of African-American ethnicity. Of these, 4290 underwent two or more ultrasound examinations between 14 and 32 weeks of gestation. Among these pregnancies, 28 cases had antepartum fetal death and 4262 delivered a liveborn neonate.

Of the 28 cases of antepartum fetal death, only 28.6% (8/28) had an EFW < 10th percentile at the last ultrasound examination, according to either of the two standards considered. Figure 1 depicts the longitudinal EFW percentiles of the 28 cases according to the two standards; a downward trend with gestational age was observed, suggesting a decline in EFW percentile with each advancing gestational week. Five of the 28 cases with antepartum fetal death were excluded from further analysis because they had only two ultrasound examinations, of which the latter was performed after fetal demise was diagnosed. The clinical characteristics of the study group (4262 controls and 23 cases) are shown in Table 1. The median gestational age at delivery and neonatal weight were lower in cases compared to those in controls ($P < 0.001$, for both). Compared to controls, cases had a higher rate of induction of labor ($P < 0.001$) and a lower rate of spontaneous vaginal delivery ($P < 0.001$). There were no differences in maternal age, maternal height, body mass index, parity, smoking status, rate of Cesarean delivery and fetal sex between cases and controls. Cases had a significantly higher rate of placental abruption (relative risk (RR), 16.4 (95% CI, 5.4–49.5); $P = 0.001$), preterm delivery (RR, 7.1 (95% CI, 6.1–8.2); $P < 0.001$) and indicated preterm delivery (RR, 10.6 (95% CI, 8.3–13.4); $P < 0.001$) compared to controls.

An EFW < 50th percentile at the last scan before diagnosis of fetal death carried a 3-fold increase in the risk of fetal death using the PRB/NICHD standard ($P < 0.05$), yet it did not reach significance according to the Hadlock standard ($P = 0.08$).

EFW percentiles at first and last ultrasound examinations

The EFW percentiles were compared between cases and controls in two gestational-age intervals corresponding to the range of gestational age at the first (14.1–26.6 weeks) and last (19.4–30.6 weeks) ultrasound examination of the cases ($n = 23$). There were 4115 controls matched with cases at the first ultrasound examination and 2634 controls matched with cases at the last ultrasound examination. The median gestational age at the first ultrasound examination was 17.4 (interquartile range

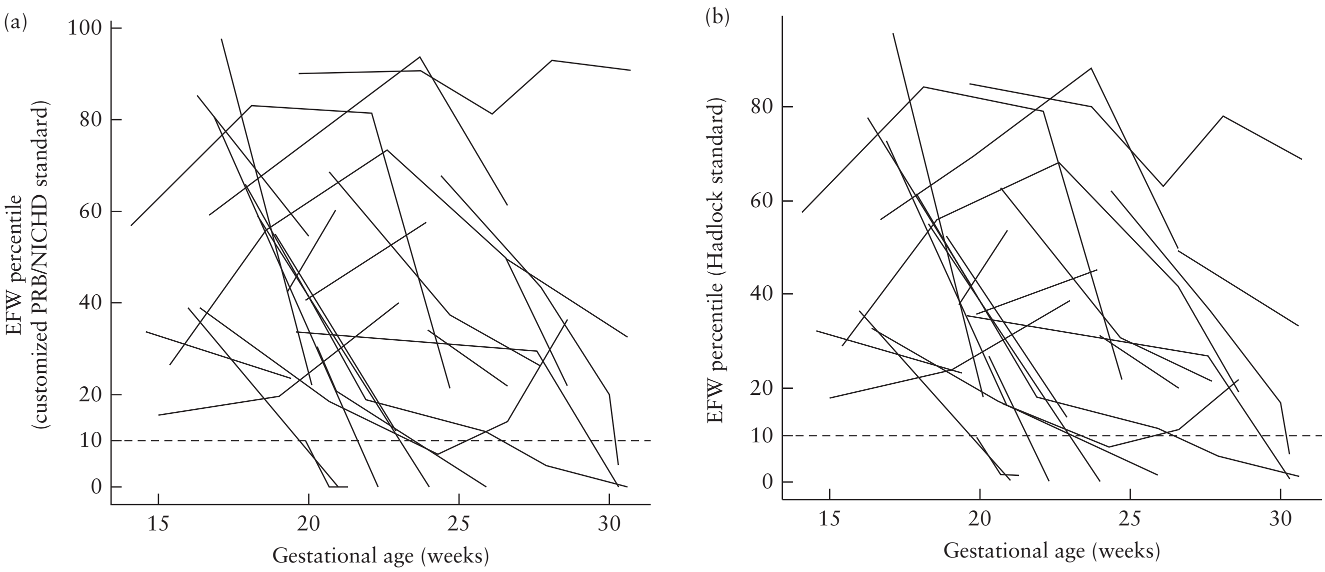

Figure 1 Longitudinal estimated fetal weight (EFW) percentiles of 28 cases of antepartum fetal death, showing downward trend with advancing gestational age, according to the customized Perinatology Research Branch/Eunice Kennedy Shriver National Institute of Child Health and Human Development (PRB/NICHD) (a) and the Hadlock (b) fetal growth standards. Only 28.6% (8/28) of cases had an EFW < 10th percentile at the last scan, according to both standards. Dashed line represents 10th percentile.

Table 1 Clinical characteristics of 4285 study participants, according to pregnancy outcome

Characteristic	*Live birth* (n = 4262)	*Fetal death* (n = 23)	P
Maternal age (years)	23 (20–27)	20 (19–29)	0.23
Maternal height (cm)	162.56 (157.48–167.64)	160.02 (157.48–170.18)	0.92
Maternal weight at enrolment (kg)	73.03 (60.78–89.81)	77.11 (62.37–90.72)	0.77
Maternal body mass index (kg/m^2)	27.4 (22.9–33.6)	30.5 (22.0–35.8)	0.9
Parous	2683 (63.0)	12 (52.2)	0.29
Gestational age at delivery (weeks)	39.1 (38.0–40.1)	28.6 (23.7–30.4)	< 0.001
Neonatal weight (g)	3155 (2811–3475)	930 (409–1295)	< 0.001
Cesarean delivery	1326 (31.1)	3 (13.0)	0.07
Spontaneous labor	2425/4261 (56.9)	4 (17.4)	< 0.001
Induction of labor	1401 (32.9)	18 (78.3)	< 0.001
Male fetal sex	2181 (51.2)	14 (60.9)	0.41
Chronic medical condition	2732 (64.1)	17 (73.9)	0.39
Smoker	764 (17.9)	4 (17.4)	1.00
Drug abuse	1153 (27.1)	7 (30.4)	0.81
Alcohol abuse	133 (3.1)	1 (4.3)	0.52
Chronic hypertension	255 (6.0)	2 (8.7)	0.65
Gestational diabetes	165 (3.9)	2 (8.7)	0.23
Pre-eclampsia	260 (6.1)	3 (13.0)	0.16
Chronic hypertension with pre-eclampsia	120 (2.8)	2 (8.7)	0.14
Gestational hypertension	521 (12.2)	3 (13.0)	0.76
Placental abruption	34 (0.8)	3 (13.0)	0.001
Preterm labor	278 (6.5)	3 (13.0)	0.19
Preterm prelabor rupture of membranes	140 (3.3)	1 (4.3)	0.54
Clinical chorioamnionitis	257 (6.0)	2 (8.7)	0.65
Preterm delivery	552 (13.0)	21 (91.3)	< 0.001
Medically indicated preterm delivery	316 (7.4)	18 (78.3)	< 0.001
Spontaneous preterm labor with preterm delivery	236 (5.5)	3 (13.0)	0.13

Data are given as median (interquartile range), *n* (%) or *n*/*N*.

(IQR), 15.9 – 19.9) weeks, and the median gestational age at the last ultrasound examination was 28.9 (IQR, 26.9–30.1) weeks. At the first ultrasound examination, there were no differences in the median EFW percentile between cases and controls, regardless of the growth standard (PRB/NICHD: 49.61 (IQR, 33.8–66.84) *vs* 49.12 (IQR, 25.18–72.86); $P = 0.709$ (Figure 2a) and Hadlock: 49.3 (IQR, 32.45–61.65) *vs* 43.4 (IQR, 24.3–67.2); $P = 0.556$ (Figure 2b)). The median EFW at the first ultrasound examination was close to the 50th percentile according to both standards in cases and controls (Figure 2). However, the median EFW percentile at the last ultrasound examination was lower in cases compared to gestational age-matched controls according to both standards (PRB/NICHD: 22.22 (IQR, 6.12–38.14) *vs* 46.02 (IQR, 22.41–71.25); $P = 0.002$ (Figure 2a) and Hadlock: 21.5 (IQR, 7.55–35.85) *vs* 32.5 (IQR, 16.8–54.7); $P = 0.015$ (Figure 2b)). Of note, at the last scan before 30.6 weeks, the median EFW of controls using the PRB/NICHD standard was on the 46th (and not the 50th) percentile because the control group included all pregnancies, with or without complications, in which a live birth occurred. In addition, the median EFW percentile at the last examination among controls according to the Hadlock standard was even lower (33rd) compared to that obtained with the PRB/NICHD standard (46th), which is in agreement with previous reports on disparity between the study population (African-American) and the population used to derive the Hadlock standard (Caucasian)[48,52].

Association between EFW growth velocity and fetal death based on two or more longitudinal scans

The EFW growth velocity was analyzed for all available ultrasound examinations performed before 32 weeks of gestation in each pregnancy. The distributions of EFW growth velocities in cases and controls are shown in Figure 3. The median EFW growth velocity was −0.14 (IQR, −1.66 to 1.23) percentiles/week in controls and −4.53 (IQR, −8.56 to −0.38) percentiles/week in cases ($P < 0.001$), according to the customized PRB/NICHD standard (Figure 3a). The growth deceleration among controls was expected given the cross-sectional EFW percentile results described above (median EFW was on the 49th percentile at the first scan and decreased to the 46th percentile at the last scan before 31 weeks of gestation). Similarly, when EFW percentiles were derived using the Hadlock standard, the median EFW growth velocity was −0.8 (IQR, −2.28 to 0.39) percentiles/week in controls and −4.27 (IQR, −8.82 to −1.13) percentiles/week in cases ($P < 0.001$) (Figure 3b). Overall, these results suggest that a reduced EFW growth velocity precedes diagnosis of fetal death according to both fetal growth standards. For example, the median EFW growth velocity of cases (about −4.5 percentiles/week) would correspond with a pregnancy outcome of fetal death in a pregnancy that had an

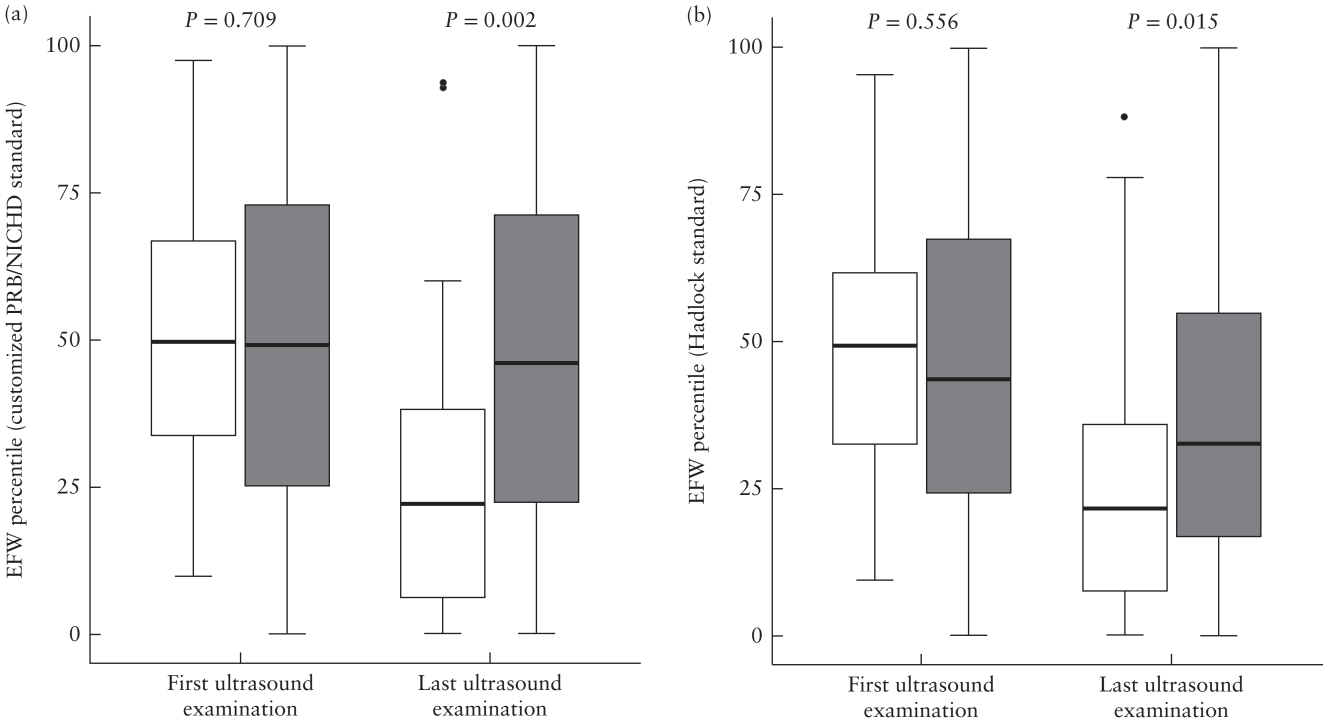

Figure 2 Box-and-whiskers plots of estimated fetal weight (EFW) percentiles in cases of antepartum fetal death (□) and liveborn controls (■) at the first and last ultrasound examinations, performed before 31 weeks' gestation, according to the customized Perinatology Research Branch/Eunice Kennedy Shriver National Institute of Child Health and Human Development (PRB/NICHD) (a) and the Hadlock (b) fetal growth standards. Boxes show median and interquartile range (IQR), and whiskers are range excluding outliers more than 1.5 × IQR from upper or lower quartile. Circles are outliers.

EFW on the 50th percentile at 20 weeks of gestation, which decreased to the 5th percentile at 30 weeks of gestation.

Although the analyses presented above were based on data collected in women who self-identified as African-American, the decline in EFW growth velocity preceding fetal death is likely not to be unique to this ethnic group. Expanding the analysis to include data from 379 additional women (148 Caucasian, 28 Hispanic, 20 Asian and 183 other), with one additional case of fetal death, resulted in similar results. According to the Hadlock standard, while the median EFW growth velocity of African-American controls was declining by 0.8 percentiles/week, it was declining slightly less steeply (0.5 percentiles/week) in all other pregnancies ($P = 0.002$); yet, the decline in EFW growth velocity among the cases remained substantially steeper (4.15 percentiles/week; $P < 0.001$; Figure S1).

Association between growth velocity of individual fetal biometric parameters and fetal death based on two or more longitudinal scans

The differences in EFW growth velocity between cases and controls according to the customized PRB/NICHD and non-customized Hadlock standards have been presented above. To assess the differences in growth velocity of individual fetal biometric parameters, we used the Hadlock standard and PRB/NICHD African-American standards that were not customized for additional maternal characteristics and fetal sex.

The medians of fetal HC, BPD, AC and FL growth velocities calculated by using the non-customized PRB/NICHD standard were significantly lower in cases compared to those in controls ($P < 0.05$ for all). Similarly, medians of fetal HC, BPD, AC and FL growth velocities calculated using the Hadlock standard were significantly lower in cases compared to those in controls ($P < 0.05$ for all).

Prediction of antepartum fetal death by fetal growth velocity

The area under the ROC curves (AUC) for prediction of fetal death by EFW growth velocity was similar for the two growth standards (PRB/NICHD: 0.74 (95% CI, 0.57–0.85) and Hadlock: 0.73 (95% CI, 0.57–0.85); Figure 4). At a 10% false-positive rate, the sensitivity of EFW growth velocity for prediction of antepartum fetal death, using the customized PRB/NICHD and Hadlock standards, was 56.5% (95% CI, 34.8–78.3%) for both. When the EFW growth velocity was calculated by using only the first and last available scans from 14–32 weeks' gestation, as opposed to two or more scans, the AUC for prediction of fetal death, using the PRB/NICHD standard, decreased slightly from 0.74 (95% CI, 0.57–0.85) to 0.73 (95% CI, 0.59–0.86). When utilizing the same two scans from each patient to calculate the EFW velocity percentile using the NICHD calculator (https://www.nichd.nih.gov/fetalvelocitycalculator)[32], as opposed to the EFW growth percentile velocity based on the customized PRB/NICHD standard, the point estimate of AUC for prediction of fetal death decreased further to 0.70 (95% CI, 0.56–0.82), although not significantly (Figure S2).

The performance of prediction of antepartum fetal death based on different EFW growth velocity cut-offs for the PRB/NICHD and Hadlock growth standards is displayed in Table 2. Fetuses with growth velocity < 50th percentile of the control group had a 4.7-fold increased risk of antepartum fetal death according to both growth

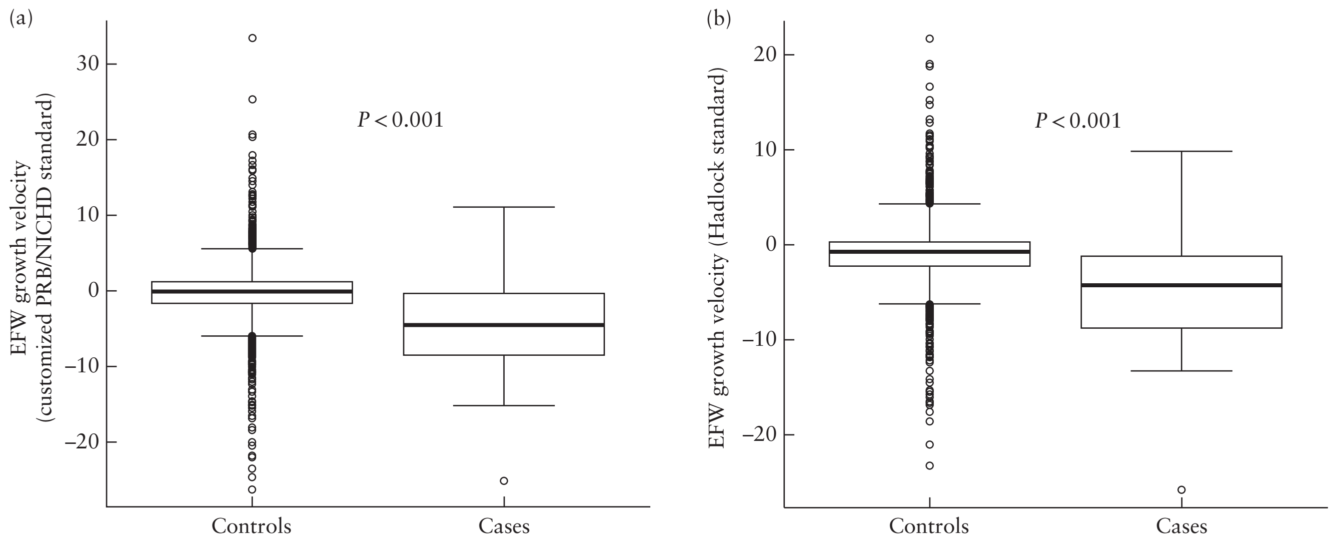

Figure 3 Box-and-whiskers plots of estimated fetal weight (EFW) growth velocities in cases of antepartum fetal death ($n = 23$) and liveborn controls ($n = 4262$), according to the customized Perinatology Research Branch/Eunice Kennedy Shriver National Institute of Child Health and Human Development (PRB/NICHD) (a) and the Hadlock (b) fetal growth standards. EFW growth velocity was calculated as the change in the EFW percentile/week by fitting a linear regression model to the percentile values of each patient. Boxes show median and interquartile range (IQR), and whiskers are range excluding outliers more than 1.5 × IQR from upper or lower quartile. Circles are outliers.

standards. According to the PRB/NICHD standard, an EFW growth velocity below the 40th, 30th, 20th, 10th and 5th percentiles carried a 3.4-, 4.3-, 6.1-, 11.2- and 13.6-fold increased risk of antepartum death, respectively. Similarly, according to the Hadlock standard, an EFW growth velocity below the 40th, 30th, 20th, 10th and 5th percentiles carried a 3.4-, 3.6-, 5.1-, 9.4- and 13.6-fold increased risk of antepartum death, respectively (Table 2).

The ROC curves for prediction of antepartum fetal death by the growth velocities of HC, BPD, AC, FL and EFW based on the non-customized PRB/NICHD and Hadlock charts are displayed in Figure 5. Regardless of the non-customized standard considered, low growth velocities of HC and EFW predicted antepartum fetal death with AUCs of 0.74 and 0.73, respectively, which were higher compared to those for BPD, AC or FL. Among the latter parameters, BPD growth velocity also predicted antepartum fetal death (AUC, 0.67 (95% CI, 0.51–0.80)) based on the PRB/NICHD standard (Figure 5a), while AC growth velocity also predicted fetal death (AUC, 0.70 (95% CI, 0.54–0.84)) based on the Hadlock standard (Figure 5b).

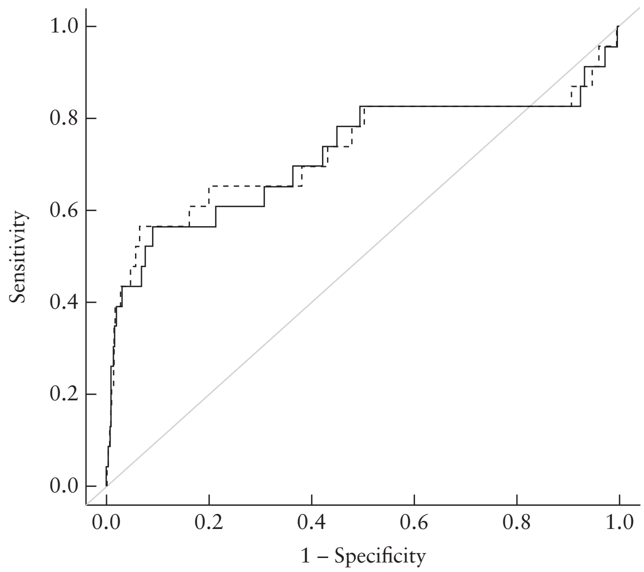

Figure 4 Receiver-operating-characteristics curves for the prediction of antepartum fetal death by estimated fetal weight growth velocity, based on the customized Perinatology Research Branch/Eunice Kennedy Shriver National Institute of Child Health and Human Development (- - - -) and the Hadlock (——) fetal growth standards.

Comparison of predictive performance for antepartum fetal death between EFW growth velocity and EFW percentile at the last scan

To assess the benefit of EFW growth velocity relative to a single EFW measurement for the prediction of fetal death, we amended the analysis described in the subsection above, thus retaining the last ultrasound examination of controls within the same range of gestational age as the last available scan in cases (19.4–30.6 weeks). The AUC of EFW growth velocity for prediction of fetal death was slightly higher compared to that of the EFW percentile at the last scan for both standards, although the difference did not reach statistical significance (PRB/NICHD: 0.72 (95% CI, 0.57–0.86) *vs* 0.69 (95% CI, 0.58–0.79), $P = 0.46$; Hadlock: 0.71 (95% CI, 0.56–0.85) *vs* 0.65 (95% CI, 0.53–0.76), $P = 0.16$). However, for both standards, the sensitivity (at a 10% false-positive rate) of EFW growth velocity was two-times higher compared to that of the EFW percentile at the last ultrasound examination (PRB/NICHD: 56.5% (95% CI, 34.8–76.2%) *vs* 26.1% (95% CI, 8.7–43.5%), $P = 0.02$; Hadlock: 52.2% (30.4–69.6%) *vs* 26.1% (8.7–43.5%), $P = 0.03$).

Table 2 Predictive performance of estimated fetal weight (EFW) growth velocity for antepartum fetal death, according to the Perinatology Research Branch/Eunice Kennedy Shriver National Institute of Child Health and Human Development (PRB/NICHD) and Hadlock fetal growth standards

Standard/ cut-off	*EFW growth velocity (controls) (percentiles/week)*	*Relative risk*	*Sensitivity*	*Specificity*	*Positive likelihood ratio*	*Negative likelihood ratio*
PRB/NICHD						
50th percentile	−0.115	4.70 (1.60–13.77)	0.83 (0.61–0.95)	0.50 (0.48–0.52)	1.65 (1.36–2.00)	0.35 (0.14–0.85)
40th percentile	−0.712	3.39 (1.40–8.21)	0.70 (0.47–0.87)	0.60 (0.58–0.62)	1.74 (1.32–2.29)	0.51 (0.27–0.94)
30th percentile	−1.395	4.31 (1.84–10.13)	0.65 (0.43–0.84)	0.70 (0.68–0.72)	2.17 (1.60–2.95)	0.50 (0.28–0.87)
20th percentile	−2.291	6.08 (2.65–13.98)	0.61 (0.39–0.80)	0.80 (0.78–0.82)	3.04 (2.17–4.26)	0.49 (0.29–0.81)
10th percentile	−3.662	11.17 (4.94–25.23)	0.57 (0.34–0.77)	0.90 (0.89–0.91)	5.64 (3.87–8.22)	0.48 (0.30–0.77)
5th percentile	−5.223	13.62 (6.08–30.53)	0.43 (0.23–0.66)	0.95 (0.94–0.96)	8.68 (5.29–14.23)	0.60 (0.42–0.85)
Hadlock						
50th percentile	−0.765	4.70 (1.60–13.77)	0.83 (0.61–0.95)	0.50 (0.48–0.52)	1.65 (1.36–2.00)	0.35 (0.14–0.85)
40th percentile	−1.330	3.39 (1.40–8.21)	0.70 (0.47–0.87)	0.60 (0.58–0.62)	1.74 (1.32–2.29)	0.51 (0.27–0.94)
30th percentile	−1.989	3.59 (1.56–8.25)	0.61 (0.39–0.80)	0.70 (0.68–0.72)	2.03 (1.45–2.83)	0.56 (0.34–0.93)
20th percentile	−2.881	5.10 (2.25–11.56)	0.57 (0.34–0.77)	0.80 (0.78–0.82)	2.83 (1.96–4.08)	0.54 (0.34–0.87)
10th percentile	−4.139	9.41 (4.19–21.13)	0.52 (0.31–0.73)	0.90 (0.89–0.91)	5.21 (3.46–7.83)	0.53 (0.35–0.81)
5th percentile	−5.467	13.62 (6.08–30.53)	0.43 (0.23–0.66)	0.95 (0.94–0.96)	8.68 (5.29–14.23)	0.60 (0.42–0.85)

Values in parentheses are 95% CI. Test positive is defined as EFW growth velocity of cases < nth percentile of EFW growth velocity of controls.

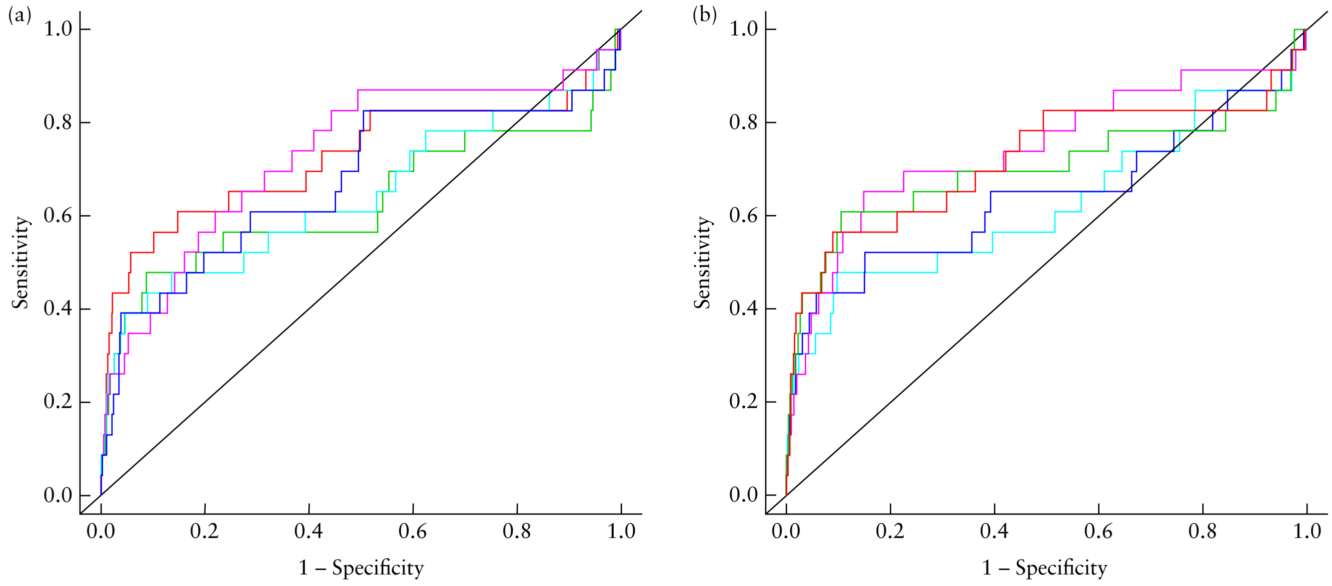

Figure 5 Receiver-operating-characteristics (ROC) curves for the prediction of antepartum fetal death by growth velocities of estimated fetal weight (EFW, ——), fetal head circumference (HC, ——), biparietal diameter (BPD, ——), abdominal circumference (AC, ——) and femur length (FL, ——), based on non-customized Perinatology Research Branch/Eunice Kennedy Shriver National Institute of Child Health and Human Development (PRB/NICHD) (a) and Hadlock (b) fetal growth standards. Areas under the ROC curves for each predictor using PRB/NICHD and Hadlock standards, respectively, were: EFW, 0.73 (95% CI, 0.57–0.85) *vs* 0.73 (95% CI, 0.57–0.85); HC, 0.74 (95% CI, 0.60–0.84) *vs* 0.74 (95% CI, 0.61–0.87); BPD, 0.67 (95% CI, 0.51–0.80) *vs* 0.63 (95% CI, 0.48–0.77); AC, 0.63 (95% CI, 0.47–0.76) *vs* 0.70 (95% CI, 0.54–0.84); FL, 0.64 (95% CI, 0.49–0.79) *vs* 0.62 (95% CI, 0.46–0.76).

DISCUSSION

The current study demonstrates, for the first time, that a reduced fetal growth velocity, expressed as change in the measurement percentile/week for individual fetal biometric parameters (HC, BPD, AC and FL) and EFW, precedes antepartum fetal death. These findings complement those of four previous studies[22,23,37,38] which reported that impaired fetal growth was associated with perinatal death; however, none of these studies evaluated the growth velocities of EFW and fetal biometric parameters. Of note, when data from only two scans were analyzed, the measurement-percentile regression slope was the same as the difference in percentiles between scans divided by the difference in gestational ages. For the purpose of ranking fetuses from the lowest to the highest growth velocity based on two scans, our approach is equivalent to the one based on the difference in *Z*-scores[34,53].

Most cases of antepartum fetal death are not SGA fetuses

Only 26% (6/23) of cases of fetal death herein were SGA (EFW $< 10^{th}$ percentile) at the last scan prior to the diagnosis of fetal demise. Moreover, an EFW $< 50^{th}$ percentile at the last available examination carried a 3-fold increased risk of antepartum fetal death, using the PRB/NICHD growth standard, which is consistent with the results of Williams *et al.*[54], who found that birth weight $< 50^{th}$ or $> 90^{th}$ percentile was associated with fetal death. Other studies have reported that stillbirth was associated with birth weight $< 40^{th}$ or $\geq 95^{th}$ percentile[55], $< 75^{th}$ or $\geq 95^{th}$ percentile[56] and $< 80^{th}$ or $> 95^{th}$ percentile[57].

Customized *vs* non-customized fetal growth standards for the prediction of antepartum fetal death

Sovio *et al.*[34] found that the association between birth-weight percentile and adverse neonatal outcome was similar when customized or non-customized birth-weight or fetal growth standards were applied in nulliparous women. Similarly, others observed no improvements in the prediction of neonatal morbidity[58–60] and stillbirth[59,60] by customized fetal growth standards when compared to non-customized charts. However, we have demonstrated recently that there was a modest benefit in the customized evaluation of fetal growth for prediction of perinatal mortality, yet the choice of the customized and non-customized standards being compared can also have an effect[58].

Although the PRB/NICHD standard has been found to be superior to the Hadlock standard when a single ultrasound scan was considered for prediction of perinatal death[58], the two standards performed similarly for the prediction of fetal death when the velocity of the percentiles was evaluated in the current study. Possible explanations include the following: (1) the evaluation of fetal growth velocity accounts for some of the effects of maternal factors on fetal growth; and (2) the current study involved growth evaluation at earlier gestational ages compared to those in the previous report[58].

Clinical implications

In the current study, 74% of cases of antepartum death occurred in fetuses that were not SGA. Given that a meta-analysis of randomized controlled trials reported no reduction of perinatal death or perinatal morbidity associated with routine ultrasound examination in late pregnancy[61], and given that the routine ultrasound examination is associated with a high iatrogenic prematurity rate among pregnancies incorrectly suspected prenatally of FGR[62], the strategy to prevent antepartum fetal death should change. Hence, the use of fetal growth velocity can be a useful tool for the detection and prevention of this complication.

We found that fetuses with EFW growth velocity $< 50^{th}$ percentile of the control group had a 4.7-fold increased risk of antepartum death, using the Hadlock or PRB/NICHD growth standard. These findings are in line with a recent definition of late FGR by 56 participating experts[63], which considered a decline of more than two quartiles in a growth chart to be a criterion for late FGR. Previous studies have demonstrated that a decline in fetal growth velocity is a major determinant of adverse perinatal outcome both in SGA[31,34,53] and appropriately grown[64–67] fetuses. According to Chatzakis *et al.*[67], a fetal growth deceleration $\geq 50^{th}$ percentile in non-SGA fetuses was associated with an increased risk of neonatal intensive care unit (NICU) admission (odds ratio (OR), 1.8) and perinatal death (OR, 3.8).

The result of the current study is also in line with the reported relationship between low growth velocity and intrapartum operative delivery and admission to the NICU in both low-risk[33] and high-risk populations[53,64,68–70]. In addition, growth velocity of the fetal AC in the lowest decile distinguished SGA newborns who experienced increased morbidity[71]. These observations indicate that fetal growth velocity has more clinical utility for identifying adverse perinatal outcomes or neonatal anthropometric features of FGR[32,36,72].

Research implications

The current study strengthens the importance of considering reduction in fetal growth velocity as a herald of antepartum fetal death. Given the moderate sensitivity (57% at 10% false-positive rate) and low prevalence of fetal death, the predictive performance based on ultrasound alone is suboptimal; hence, additional biochemical markers are needed to improve the prediction of fetal death. For instance, an abnormal low maternal plasma angiogenic index-1 (ratio of placental growth factor to soluble fms-like tyrosine kinase-1) determined at 24–28 weeks[29] or 30–34 weeks[28] of gestation carries a 29-fold or 23-fold increased risk for stillbirth, respectively. Doppler uterine velocimetry[73] and maternal serum alpha-fetoprotein/pregnancy-associated plasma protein-A ratio[74] during the first trimester of pregnancy have also been proposed as potential predictors of stillbirth. Future studies that combine maternal risk factors, placental biomarkers and fetal growth velocity in pregnancy to predict stillbirth are warranted.

Strengths and limitations

The current study has a number of strengths: (1) this was the largest study evaluating the relationship between fetal growth velocity and fetal death in an African-American population; (2) patient enrolment took place at a single ultrasound unit in which a consistent protocol was implemented to acquire ultrasound data by sonographers who were blinded to the clinical information; and (3) the use of both customized and non-customized standards to determine percentile velocity provided additional generalization to the findings. Since fetal growth velocity was expressed as the slope of the regression line of measurement percentiles as a function of gestational age based on two or more serial measurements prior to 32 weeks, a possible limitation of this study is the irregularity of the distribution of gestational ages.

Conclusions

Antepartum fetal death is preceded by a significant decrease in fetal growth velocity. Given that three of four antepartum fetal death cases had an EFW $> 10^{th}$ percentile at the last scan when the fetus was alive, the fetal growth velocity percentile may be a useful tool for improving the detection of pregnancies at risk of antepartum fetal death. Longitudinal sonographic evaluation to determine fetal growth velocity doubles the sensitivity for predicting antepartum fetal death compared to a single ultrasound examination.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Box-and-whiskers plots of estimated fetal weight (EFW) percentile velocities between cases and controls by ethnicity, according to the Hadlock standard. EFW velocity was calculated as the change in the EFW percentile/week by fitting a linear regression model to the percentile values of each patient. Note, the only non-African-American case shown in the figure had two scans at 15 and 19 weeks' gestation, and hence the velocity calculation was likely less reliable. AA, African-American.

Figure S2 Receiver-operating-characteristics (ROC) curves for the prediction of antepartum fetal death by growth velocity of estimated fetal weight (EFW) (Perinatology Research Branch/Eunice Kennedy Shriver National Institute of Child Health and Human Development (PRB/NICHD)) and velocity percentile (NICHD standard). EFW velocity was calculated based on first and last scan in the interval from 14 to 32 weeks' gestation (PRB/NICHD). The same data were used as input in the NICHD velocity percentile calculator for African-American women (https://www.nichd.nih.gov/fetalvelocitycalculator). Values in parentheses are 95% CI. AUC, area under the ROC curve.

Appendix S1 Spreadsheet calculator showing an example of growth velocity determination based on two or more percentile values

