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Prediction of Neonatal Growth Restriction in Fetuses With Gastroschisis by Early Third Trimester Ultrasonography Utilizing Contemporary Birth Weight Percentiles

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Abbreviations

AC, abdominal circumference; AGA, appropriate for gestational age; AUC, area under the curve; BPD, biparietal diameter; EDD, estimated date of delivery; EFW, estimated fetal weight; FGR, fetal growth restriction; FL, femur length; HC, head circumference; OFD, occipitofrontal diameter; ROC, Receiver operating characteristic; SGA, small for gestational age

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Objective—To identify the estimated fetal weight (EFW) formula and threshold for the optimal prediction of fetal growth restriction (FGR) at 26–34 weeks' in fetuses with gastroschisis.

Methods—Late second and third trimester ultrasound data were used to calculate the EFW utilizing eight different formulas: Hadlock I-IV, Honarvar, Shepard, Siemer, and Warsof. EFW and birth weight percentiles were assigned from US population growth curves. FGR and small for gestational age (SGA) were defined as EFW and birth weight less than the tenth percentile for gestational age; Receiver operating characteristic (ROC) curves were used to compare formula performance for FGR diagnosis at 26–34 weeks' to identify an SGA birth weight.

Results—There were 170 newborns with gastroschisis; 46 (27%) were SGA. The mean gestational age at the time of ultrasound was 30.8 ± 1.7 weeks. The mean gestational age at birth was 36.3 ± 1.7 weeks. ROC curve analysis found the Hadlock III formula had the largest area under the curve (AUC) of 0.813 closely followed by Hadlock IV (AUC = 0.811) and Hadlock II (AUC = 0.808) for diagnosis of FGR correlating to neonatal SGA diagnosis. Hadlock II, Hadlock III, and Hadlock IV had the highest diagnostic accuracies when compared to the other EFW formulas.

Conclusions—The Hadlock II, Hadlock III, and Hadlock IV formulas have comparable predictive performance in the optimal identification of FGR in fetuses with gastroschisis at 26–34 weeks'. A threshold of an EFW less than the 25.2th percentile is suggested.

Key Words—estimated fetal weight; gastroschisis; growth restriction

Introduction

Gastroschisis is a congenital defect in the abdominal wall. Between 2006 and 2012, the estimated birth prevalence in the United States was 4.9 cases per 10,000 live births, which is a 30% increase from 1995 to 2005.[1] This anomaly is characterized by an intact umbilical cord insertion and a defect in the abdominal wall, which is usually located to the right of the cord insertion. The bowel protrudes through this aperture and floats in the amniotic fluid without a covering membrane.[2] The contemporary mortality rate for neonates with gastroschisis is about 6%. Infants born at <34 weeks' gestation, or with low birth weight (<2500 g) are at highest risk for mortality.[3]

Sonographic assessment of the fetus generally includes an estimation of fetal weight (EFW) by measurement of standard biometric parameters such as head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL). The EFW is then calculated using one of several logarithmic regression models utilizing the individual fetal biometric measurements, and a weight percentile is assigned utilizing the best gestational age and a selected birth weight table. In the United States many obstetrical ultrasound units utilize the Hadlock IV EFW equation and a selected birth weight percentile table which may or may not be contemporary or reflective of their population (e.g., Brenner et al utilizes almost 50-year-old data from Ohio and North Carolina).[4] Due to bowel herniation, fetuses with gastroschisis often have smaller abdominal circumferences which may result in EFW underestimation.[5,6] This has prompted investigation of alternative EFW equations which do not include the AC measurement.[5,7,8]

Fetuses with gastroschisis have a higher incidence of fetal growth restriction (FGR) compared with those without abdominal wall defects.[6] Infants with gastroschisis whose birth weights are less than the tenth percentile fare worse than those with higher birth weight.[9,10] An absolute birth weight >2500 g is associated with a better post-natal course for infants with gastroschisis.[3] The timing and type of antenatal testing employed in fetuses with gastroschisis is highly variable.[11] ACOG guidelines do not generally recommend a specific antenatal testing protocol for fetuses with anomalies but do recommend testing for fetuses with FGR commencing at the time of diagnosis.[12] For fetuses with anomalies, an individualized approach to antenatal testing is recommended.

Growth restriction in a fetus with gastroschisis may start as early as the second trimester. Clinical decisions regarding antenatal testing and indicated preterm delivery may need to be made as early as in the beginning of the third trimester. It is critical to identify fetuses at risk while limiting unnecessary testing and potentially unindicated preterm births. Therefore, the objective of this study was to evaluate the predictive accuracy of different sonographic EFW formulas for birth weight less than the 10th percentile using biometry obtained from fetuses with gastroschisis in the late second and third trimesters. We sought to identify the EFW formula and threshold with the optimal prediction of FGR utilizing a contemporary birthweight reference.

Material and Methods

The study was approved for an exempted review by the Institutional Review Board of the associated hospitals. We queried the obstetric ultrasound database for the term "gastroschisis" from 1995 to 2021 in a single institution with AIUM accreditation for standard obstetrics with an adjunct in detailed fetal anatomic ultrasound examinations. RDMS-certified sonographers performed all ultrasounds, which were then reviewed by Maternal–Fetal Medicine specialists. During the 26-year study period, ultrasound machines from Siemens, GE, Philips, and Acuson were used. The prenatal diagnosis of gastroschisis was confirmed at subsequent ultrasound and at birth. Data from ultrasound studies performed at 26w0d to 34w6d weeks' gestation was collected. If there was more than one ultrasound during this period, then the first one was used. All studies measured the following fetal biometrics: head circumference, femur length, biparietal diameter, and abdominal circumference. The AC was measured in a transverse view through the fetal abdomen with an ellipse around the fetal skin at the level of the fetal stomach and the confluence of the right and left portal veins. The portion of the eviscerated fetal abdominal contents was not included in the AC measurement. The EFW was calculated in grams according to eight formulas: Hadlock I, Hadlock II, Hadlock III, Hadlock IV, Honavar, Shepard, Siemer, and Warsof; the formulas are included in the Appendix A.[5,7,13–15] These values are subsequently referred to as calculated EFW. The EFW percentiles were determined from contemporary sex-specific birthweight-for-gestational age references derived from over 3.2 million singleton births that occurred in the United States in 2017.[16] These are referred to as EFW percentiles. All the calculated EFW formulas utilize the AC except for Honarver (FL only) and Siemer (FL, BPD, and occipital frontal diameter). Occipitofrontal diameter (OFD) was not routinely measured and was calculated (OFD = [(2 * HC)/π] − BPD) for use in the Siemer formula. In addition, two routinely calculated reported biometric ratios HC/AC and FL/AC, and the abdominal circumference (AC) measurement and percentile were assessed for accuracy for predicting small for gestational age (SGA) at delivery.[17]

Eligibility criteria consisted of isolated gastroschisis confirmed at delivery, at least one obstetrical ultrasound examination at 26w0d to 34w6d, and known neonatal outcome. This range of gestation age was chosen a priori as it represents the earliest point at which decisions regarding antenatal testing and other interventions for FGR are typically made. Exclusion criteria consisted of fetuses with major anomalies other than gastroschisis, no ultrasound from 26w0d to 34w6d, multiple gestations, and incomplete ultrasound or neonatal outcome data. Perinatal deaths were not excluded, as these cases were delivered proximate to the diagnosis of fetal death. Maternal age and delivery route were recorded. Birth weight (BW), delivery method, and fetal sex assigned at birth were recorded. The best obstetrical estimated date of delivery (EDD) was assigned by the physicians performing the ultrasound utilizing established ultrasound dating criteria.[18] Gestational age at delivery was calculated from the assigned EDD and the date of birth. Neonates were separated into two groups based upon their birthweight. Infants were classified as SGA when their birth weights were less than the 10th percentile for singletons as established by Aris et al, and the remainder was categorized as appropriate for gestational age (AGA).[16]

Data analysis was by Analyze-It v 5.51 (Leeds, UK) for Microsoft Excel (Redmond, WA). Receiver operating curves (ROC) were constructed to assess the ability of each calculated EFW formula, biometric ratio, and AC percentile to diagnose an SGA birthweight. The area under the curve (AUC) for each ROC curve was compared using the method described by Delong, with $P < .01$ for significance.[19] The Youden method was additionally used to define the optimal cutoff point for a formula's EFW.[20] For each calculated EFW formula, biometric ratio, and AC percentile diagnostic indices were calculated for the 10th percentile for the gestational age, the percentile which yielded 100% sensitivity, and the percentile for optimal accuracy (defined as [True Positives + True Negatives]/total n). Sensitivity, specificity, true positive rate, and false positive rate were calculated. When the optimal accuracy was achieved at more than one threshold, the one with the highest sensitivity was reported. Categorical variables were reported as n (percentile) and compared utilizing Fisher's exact test. Continuous variables were reported as mean ± standard deviation and compared with Student's *t*-tests when the distribution was normal and by Wilcoxon rank sum for non-parametric distributions.

Results

One hundred and seventy infants met the inclusion criteria. The incidence of SGA at birth was 27% (46/170). Three pregnancies resulted in fetal demise at 32, 34, and 37-weeks' gestation, and all three fetuses were found to be SGA at delivery.

The mean gestational age at ultrasound used in this study was 30.8 ± 1.7 weeks. Table 1 contains the maternal and neonatal demographic data. There was not a significant difference in maternal age, gestational age at ultrasound, gestational age at birth, or route of delivery between the AGA and SGA groups. The mean birth weight for the SGA infants was significantly less than the AGA infants ($P < .0001$, Student's *t*-test). There was not a significant difference in birth weights by sex for the AGA infants. There was a greater percentage of male infants in the SGA group compared to SGA female infants. Approximately two-thirds of infants were delivered by cesarean and the rates were comparable between groups.

Figure 1 contains the mean EFW percentiles for the AGA and SGA neonatal birth weights obtained by the different calculated EFW formulas. The mean EFW percentiles for the Honarvar formula were significantly greater for both AGA and SGA fetuses compared to all the other formulas ($P < .01$, one-way ANOVA with post hoc Tukey HSD). The Hadlock I mean EFW percentiles were significantly less for both AGA and SGA fetuses ($P < .01$, one-way ANOVA

TABLE 1. Demographic Information From Third Trimester Ultrasound

Parameter	AGA (n = 124)	SGA (n = 46)	
Maternal age (years)	22.2 ± 3.9	20.8 ± 3.6	*P* = .04
Gestational age at ultrasound (weeks)	30.8 ± 1.7	31.0 ± 1.8	*P* = .50
Gestational age at birth (weeks)	36.2 ± 1.8	36.5 ± 1.5	*P* = .39
Birth weight (g)	2619 ± 491	2125 ± 334	
Sex			
Female	65 (52.4%)	16 (34.8%)	
Male	59 (47.6%)	30 (65.2%)	
Delivery route			*P* = .78
Vaginal	43 (34.7%)	17 (37.0%)	
Cesarean	81 (65.3%)	29 (63.0%)	

Values are mean ± SD. *P* values calculated with Student's *t*-test, $\alpha = 0.01$; AGA, appropriate for gestational age; SGA, small for gestational age.

with post hoc Tukey HSD). The remainder of the formulas' mean EFW percentiles were not significantly different for AGA or SGA fetuses.

Figure 2 displays the ROC curves for each calculated EFW formula as a predictive test for SGA at delivery at the time of the 3rd trimester US examination. The AUCs were the largest for the Hadlock II, Hadlock III, and Hadlock IV formulas. The AUCs for the Hadlock II, Hadlock III, and Hadlock IV, Siemer, Warsof and Shepard were not significantly different. The AUCs for the Hadlock II, Hadlock III, and Hadlock IV were significantly larger than the Hadlock I and Honarvar formulas. The biometric ratios FL/AC and HC/AC and the AC measurement and percentile were poor discriminators with low sensitivities at the maximum accuracy, ranging from zero (AC percentile, and FL/AC) to 0.239 (HC/AC).

The predictive performance of each formula was then compared utilizing the traditional EFW of <10th percentile calculated in the early third trimester for the diagnosis of an SGA birth weight, Table 2. The accuracies ranged from 0.465 (Hadlock I) to 0.782 (Hadlock III); all formulas except Hadlock I had low sensitivity (range 0.174–0.304) at the 10th percentile.

Figure 1. Mean EFW percentiles for AGA and SGA neonatal birth weights obtained by eight different calculated EFW formulas.

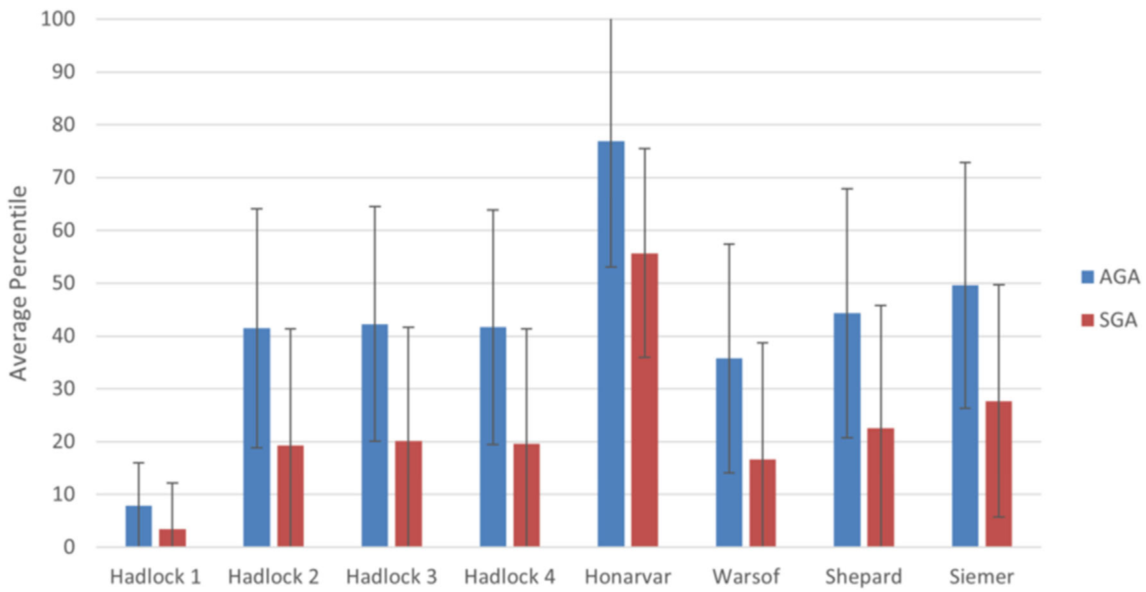
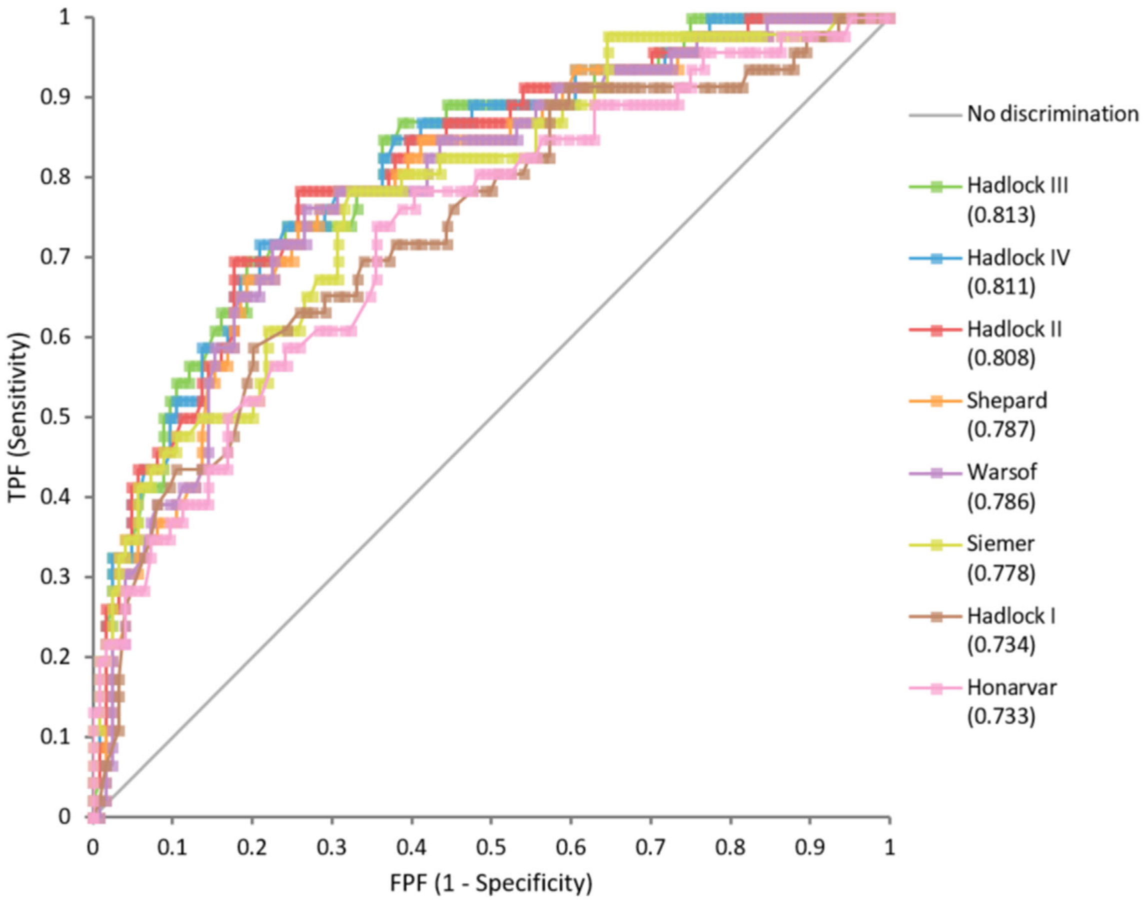


Figure 2. Receiver Operating Characteristic (ROC) curves for each calculated EFW formula as a diagnostic test for SGA at delivery at the time of the 3rd trimester ultrasound examination. Hadlock II, Hadlock III, and Hadlock IV AUCs were not significantly different, and were significantly larger than the Hadlock I and Honarvar formulas (*P* < .01).



The Hadlock I sensitivity was 0.913, but this was at the expense of high false positive rates (specificity of 0.298). The thresholds for 100% sensitivity were then evaluated, and it was found this results in high numbers of false positives and low specificities (range 0.048–0.331) for all formulas (Table 3).

TABLE 2. Diagnostic Performances Utilizing Calculated Estimated Fetal Weight <10th Percentile

Formula	Accuracy	Sens	Spec	PPV	NPV
Hadlock I	0.465	0.913	0.298	0.326	0.902
Hadlock II	0.776	0.261	0.968	0.75	0.779
Hadlock III	0.782	0.261	0.976	0.8	0.781
Hadlock IV	0.776	0.261	0.976	0.8	0.781
Honarvar	0.735	0.022	1.0	1.0	0.734
Shepard	0.765	0.196	0.976	0.75	0.766
Siemer	0.771	0.174	0.992	0.889	0.764
Warsof	0.776	0.304	0.952	0.7	0.787

NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

Table 4 contains the ROC characteristics and the diagnostic indices for each calculated EFW formula at the threshold with the highest accuracy. The AUC's ranged from 0.73 (Hadlock I and Honaver) to 0.81 (Hadlock III and Hadlock IV). The maximum accuracy (0.806) was obtained with the Hadlock II. Hadlock III, Hadlock IV, and Siemer accuracies were 0.8. The Hadlock III formula had the highest sensitivity (0.543) of the four most accurate at a threshold of 18.1%. Hadlock III had more false positives (specificity 0.895) compared to the other three highest and had the highest negative predictive value (0.841).

Finally, the Youden index was used to determine the maximal potential effective formula and the

Table 3. Calculated Estimated Fetal Weight (EFW) Thresholds for 100% Sensitivity

Formula	Threshold (EFW %)	PPV	Specificity	True Negatives	False Positives
Hadlock I	21.2	0.284	0.065	8	116
Hadlock II	63.1	0.311	0.177	22	102
Hadlock III	58.5	0.331	0.25	31	93
Hadlock IV	59.5	0.324	0.226	28	96
Honarvar	99.7	0.281	0.048	6	118
Shepard	77.1	0.305	0.153	19	105
Siemer	85.3	0.284	0.065	8	116
Warsof	60.0	0.305	0.153	19	105

PPV, positive predictive value.

Table 4. Receiver Operating Characteristics and Highest Accuracy with Thresholds for Calculated EFW Formulas at 26–34 weeks

Formula	AUC	Accuracy	Sens	Spec	PPV	NPV
Hadlock I	0.734	0.776 at 1.0%	0.391	0.919	0.643	0.803
Hadlock II	0.808	0.806 at 13.5%	0.435	0.944	0.741	0.818
Hadlock III	0.813	0.80 at 18.1%	0.543	0.895	0.658	0.841
Hadlock IV	0.811	0.80 at 14.2%	0.435	0.935	0.714	0.817
Honarvar	0.733	0.776 at 38.9%	0.283	0.960	0.722	0.783
Shepard	0.787	0.782 at 15.4%	0.348	0.944	0.696	0.796
Siemer	0.778	0.80 at 17.6%	0.413	0.944	0.731	0.813
Warsof	0.786	0.782 at 9.3%	0.304	0.960	0.737	0.788

AUC, area under curve; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

optimal cut off, Table 5. The Youden Index was maximal for the Hadlock II at a threshold of 25.2% with a sensitivity of 0.783 and specificity 0.742.

Discussion

The accurate identification of fetuses with gastroschisis in the late second and early third trimester who will be SGA at delivery allows for the benefits of selective antenatal testing and indicated delivery for abnormal testing. Screening for these fetuses is typically performed by serial calculation of the EFW. An ideal screening test would detect 100% of the fetuses with gastroschisis who would be SGA at birth, while minimizing false positives (high positive predictive value). This focuses antenatal testing on the fetuses who need it while minimizing unnecessary antenatal testing, false positive antenatal tests, and potentially non-indicated preterm birth.

We evaluated eight different formulas for calculation of the EFW in the early third trimester in a large population of fetuses with gastroschisis. The traditional threshold of EFW less than the 10th percentile

Table 5. Youden Indices to Determine Optimal Cutoff Point

Formula	Sens	Spec	Youden Index	Threshold EFW %
Hadlock I	0.587	0.798	0.385	2.4
Hadlock II	0.783	0.742	0.525	25.2
Hadlock III	0.696	0.806	0.502	22.4
Hadlock IV	0.717	0.790	0.508	23.2
Honarvar	0.739	0.645	0.384	74.7
Shepard	0.739	0.742	0.481	27.1
Siemer	0.783	0.677	0.46	37.2
Warsof	0.761	0.734	0.495	20.5

EFW, estimated fetal weight; Sens, sensitivity, Spec, specificity.

has low sensitivity and accuracy. The 100% sensitivity was only achievable with unacceptably high false positive rates. The highest accuracy and sensitivity in identifying the SGA neonates at 26–34 weeks was with the Hadlock III equation (54.3%) utilizing a threshold for calculated EFW of 18.1%. The other calculated EFW equations and biometric ratios had sensitivities <50% at their maximum accuracy. All but the Honarvar and Siemer formulas include the AC measurement in the calculation. The Honarver formula (FL only), calculated considerably higher EFWs for both AGA and SGA fetuses compared to the Hadlock II, III, and IV formulas. The Siemer formula (FL, BPD, and OFD) performed better than the Honarver, but not as well as other formulas that included the AC (Hadlock II, III, and IV).

Previous studies evaluating ultrasound prediction of FGR in fetuses with gastroschisis have focused on EFW obtained as close to delivery as possible compared to actual birth weights, and some included fetuses with omphalocele.[8,9,21–25] Nicholas et al found the Hadlock I formula to be the best screening test for FGR. In their study, the Hadlock formula had better specificity when compared to the Siemer formula, which excluded the abdominal circumference (AC) in its calculations.[5,22] In a similar comparison, Chaudhury et al found the Shepard and Siemer formulas both to be good predictors of fetal growth restriction at the 5th and 10th percentiles when used within 14 days of delivery, with the Shepard formula slightly more accurate at 82% compared to Siemer's formula at 80%.[5,14,25] Our study evaluated late second and early third-trimester biometric measurements to diagnose a contemporary definition of SGA at term. We specifically chose ultrasounds at these gestational ages as it is at this point that prenatal fetal testing might reasonably be initiated.

We found that the Hadlock II, III, and IV formulas did a better job in predicting the SGA diagnosis when the fetus was estimated to have FGR. We did not find an advantage to the two formulas that excluded the AC, Honavar, and Siemer. The Hadlock formulations are commonly used, and therefore our findings will be applicable and useful to other ultrasound units. Identification of FGR in the third trimester would assist in identifying the fetuses at most risk for morbidity and mortality earlier. An approach utilizing Hadlock II to identify which fetuses with gastroschisis will be SGA at birth, would identify about three-quarters (78.3%) in the early third trimester. Antenatal testing could be initiated at the time of the diagnosis of FGR with an acceptable false positive rate (1-specificity = 0.258). The remaining quarter would need to be identified by traditional serial ultrasound screening. Practically, any one of the Hadlock II, Hadlock III, or Hadlock IV formulas could be used with comparable overall clinical performance (Tables 4 and 5).

An alternative approach would be to test all fetuses at a predetermined gestational age. Towers et al suggest that testing be considered at 28 weeks' gestation based on the experience of a cohort of 84 fetuses with gastroschisis.[26] Of the fetuses that underwent antenatal testing, 38% were delivered based upon abnormal testing. A recent survey of Maternal–Fetal Medicine specialists reported that 68% of these physicians initiated antepartum testing for fetuses with gastroschisis at 32 weeks.[11] However, both approaches increase the risk for unindicated preterm birth from false positive antenatal testing. This is an undesired outcome, as preterm birth at <34 weeks increases the risk of mortality.[3] Our unit's approach is to initiate testing at the time of the diagnosis of FGR in fetuses with gastroschisis, and to start testing all fetuses at 34 weeks, when the implications of a false positive diagnosis are less grave.

Limitations of our study include a study population spanning 26 years during which time management and antepartum surveillance have changed and focus solely on ultrasound parameters. Including other potentially confounding variables such as maternal BMI, substance use, parity, and obstetrical history might improve the accuracy of the diagnosis of FGR, and a multivariate model would be a sound direction for future research. Also, owing to the retrospective nature of our study, neonatal outcomes were limited to the presence of SGA at birth and Apgar scores, which are surrogates for morbidity and mortality. Due to the dispersion of the infants after birth, we were not able to follow the infants' neonatal and surgical courses. Therefore, our study was limited to the correlation of fetal size estimated prenatally by ultrasound and neonatal birthweights.

The study strengths include the large population of fetuses with gastroschisis, number of EFW formulas compared, an incidence of 27% SGA at delivery of fetuses with gastroschisis (which is consistent with the current literature), and updated sex-specific neonatal birth weight definitions.[9,16,25] The birth weight definitions reflect contemporary sociodemographics of the United States, were collected prospectively, and utilize the most reliable estimate of gestational age, the obstetrical best estimate, which is more accurate than older last menstrual period-based references. As the birth weight definitions are descriptive, the median birthweight will tend to be lower than the EFW.[27] This may decrease the sensitivity and increase the specificity for FGR. Finally, our core physicians have remained the same during the study period, and image acquisition and quality have been consistent.

Antepartum management of fetuses with gastroschisis provides unique challenges as conventional methods of monitoring fetal growth is compromised by the fetus' evisceration. We suggest that, utilizing one of the Hadlock II, Hadlock III, or Hadlock IV formulas for estimation of fetal weight and a calculated EFW threshold less than the 25.2th percentile to achieve the optimal diagnosis of FGR in fetuses with gastroschisis in the early third trimester and subsequent SGA at delivery.

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APPENDIX

A.1. Eight formulas used to calculate the estimated fetal weight.[5,7,13–15]

Hadlock et al I (1985)	$\log_{10} EFW = 1.304 + 0.05281(AC) + 0.1938(FL) - 0.004(AC \times FL)$
Hadlock et al II (1985)	$\log_{10} EFW = 1.335 - 0.0034(AC \times FL) + 0.0316(BPD) + 0.0457(AC) + 0.1623(FL)$
Hadlock et al III (1985)	$\log_{10} EFW = 1.326 - 0.00326(AC \times FL) + 0.0107(HC) + 0.0438(AC) + 0.158(FL)$
Hadlock et al IV (1985)	$\log_{10} EFW = 1.3596 + 0.0064(HC) + 0.424(AC) + 0.174(FL) + 0.00061(BPD \times AC) - 0.00386(AC \times FL)$
Honarvar (2001)	$EFW = 0042\left(FL^2\right) + 0.32(FL) - 1.36$
Shepard (1982)	$\log_{10} EFW = -1.7492 + 0.166(BPD) + 0.046(AC) - 0.002646(AC \times BPD)$
Siemer et al (2008)	$EFW = -145.577 + 23.724\left(FL^2\right) + 1.255\left(BPD^3\right) + 0.001\left(e^{OFD}\right) - 0.0000406\left(10^{FL}\right) + 1.03\left(e^{FL}\right)$
Warsof et al (1977)	$\log_{10} EFW = 1.599 + 0.144(BPD) + 0.032(AC) - 0.000111\left(AC \times BPD^2\right)$