

ORIGINAL ARTICLE

Utility of third trimester sonographic measurements for predicting SGA in cases of fetal gastroschisis

YJ Blumenfeld^{1,2}, S Do¹, Al Girsan¹, AS Davis^{2,3}, SR Hintz^{2,3}, AK Desai⁴, T Mansour⁴, TA Merritt⁵, BT Oshiro⁴, YY El-Sayed^{1,2}, AA Shamshirsaz⁶ and HC Lee³

OBJECTIVE: To assess the accuracy of different sonographic estimated fetal weight (EFW) cutoffs, and combinations of EFW and biometric measurements for predicting small for gestational age (SGA) in fetal gastroschisis.

STUDY DESIGN: Gastroschisis cases from two centers were included. The sensitivity, specificity, positive and negative predictive values (PPV and NPV) were calculated for different EFW cutoffs, as well as EFW and biometric measurement combinations.

RESULTS: Seventy gastroschisis cases were analyzed. An EFW < 10% had 94% sensitivity, 43% specificity, 33% PPV and 96% NPV for SGA at delivery. Using an EFW cutoff of < 5% improved the specificity to 63% and PPV to 41%, but decreased the sensitivity to 88%. Combining an abdominal circumference (AC) or femur length (FL) z-score less than -2 with the total EFW improved the specificity and PPV but decreased the sensitivity.

CONCLUSION: A combination of a small AC or FL along with EFW increases the specificity and PPV, but decreases the sensitivity of predicting SGA.

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INTRODUCTION

Gastroschisis is a severe paraumbilical abdominal wall defect that occurs in approximately one to five cases per 10 000 live births.¹ Fetal gastroschisis is commonly diagnosed *in utero* by routine ultrasound starting as early as the first trimester. Approximately 15 to 30% of fetal gastroschisis cases are born small for gestational age (SGA) less than 10% for gestational age.^{2–7} Although the etiology of SGA among gastroschisis cases remains unclear, it may be an intrinsic part of gastroschisis physiology with some investigators suggesting involvement of the vascular endothelial growth factor–nitric oxide synthase 3 pathway.^{3,8} SGA is associated with adverse neonatal outcomes including prolonged neonatal intensive care unit length of stay, and surgical complications including perioperative infections and delayed closure of the abdominal wall defect.^{2,4,9} Therefore, accurately predicting SGA prenatally is important for patient counseling and delivery planning.

The incidence of suspected intrauterine growth restriction (IUGR) less than 10% by prenatal ultrasound in gastroschisis cases is found in 50 to 75% of pregnancies, higher than the incidence of SGA at birth.^{2,10} Intrauterine growth restriction often begins in the second trimester, and is driven largely by the fact that the herniated viscera lead to decreased abdominal circumference (AC), which is one of the major component of different estimated fetal weight ultrasound formulas.^{4,11–14} Numerous studies, including a recent study by our group, have assessed the predictive utility of the total estimated fetal weight (EFW) in predicting SGA at birth in gastroschisis cases.^{2,4,10,11} Most have shown that prenatal ultrasound generally underestimates the actual birth

weight, especially when the common Hadlock formula is used, resulting in high false-positive rates.^{4,10–12} Given the high sensitivity but more modest specificity of prenatal ultrasound, improving the accuracy of SGA prediction in these cases is warranted. The aim of our study was to assess the accuracy of different EFW cutoffs, and combinations of EFW and biometric measurements for predicting SGA in gastroschisis cases.

METHODS

Study population

This was a retrospective study of all infants with prenatally diagnosed gastroschisis whose mothers received prenatal care at Loma Linda University Medical Center and Lucile Packard Children's Hospital Stanford between 2008 and 2013. Both institutions are tertiary care referral centers in California with maternal–fetal medicine, prenatal ultrasound, level IV neonatal intensive care units and pediatric surgical expertise in the management of gastroschisis.

Gastroschisis cases were identified from separate institutional databases in which pregnancies with fetal anomalies are prospectively entered. Only cases with information on SGA diagnosis were included in the current analysis. Pregnancies complicated by fetal gastroschisis are managed in outpatient high-risk pregnancy clinics in both centers, with serial ultrasound surveillance and antenatal non-stress testing. Indications for iatrogenic preterm delivery include severe maternal medical or obstetric complications, or non-reassuring fetal status including suspected IUGR or abnormal antenatal testing. In the absence of associated fetal or maternal morbidity, delivery for gastroschisis cases is typically recommended between 36 0/7 and 37 6/7 weeks in both institutions in order to avoid term stillbirth, although the precise timing of which is left to the discretion

¹Department of Obstetrics & Gynecology, Stanford University School of Medicine, Stanford, CA, USA; ²The Fetal and Pregnancy Health Program, Lucile Packard Children's Hospital Stanford, Palo Alto, CA, USA; ³Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, Stanford, CA, USA; ⁴Department of Obstetrics and Gynecology, Loma Linda University School of Medicine, Loma Linda, CA, USA; ⁵Department of Pediatrics, Division of Neonatology, Loma Linda University School of Medicine, Loma Linda, CA, USA and ⁶Department of Obstetrics & Gynecology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA. Correspondence: Dr YJ Blumenfeld, Department of Obstetrics & Gynecology, Stanford University, 300 Pasteur Drive, Room HH333, Stanford, CA 94305, USA. E-mail: yairb@stanford.edu

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of the primary care provider. A trial of labor is preferred over cesarean delivery in the absence of obstetric contraindications.

Study data from both institutions were collected and managed using Research Electronic Data Capture (REDCap), a secure, web-based application designed to support data capture for research studies. Institutional review board approvals from both Loma Linda University and Stanford University were obtained prior to initiation of the study.

Study definitions

Detailed perinatal, intrapartum and neonatal variables were collected from electronic medical records. In addition, ultrasound reports and stored ultrasound images were reviewed by trained research nurses and physicians. The prenatal EFW was assessed using a Hadlock formula incorporating the biparietal diameter (BPD), head circumference (HC), AC and femur length (FL) ($\text{Log}_{10}(\text{weight}) = 1.3596 - 0.00386 \times \text{AC} \times \text{FL} + 0.0064 \times \text{HC} + 0.00061 \times \text{BPD} \times \text{AC} + 0.0424 \times \text{AC} + 0.174 \times \text{FL}$).¹⁴ The EFW percentile for a given gestational age was then estimated using a Hadlock EFW percentile calculator.^{12,13} Only cases with ultrasound assessment 2 weeks prior to delivery were included in the analysis. Doppler studies of the ductus venosus, umbilical vein or middle cerebral artery are not routinely performed in prenatally diagnosed cases of fetal gastroschisis in either center, and umbilical artery Doppler assessment is only performed in cases of suspected IUGR (EFW < 10%). Maternal pre-pregnancy body mass index was calculated as (body mass index = weight in kilograms/height² in meters) using height and documented weight at pre-pregnancy. SGA was defined by a birth weight less than 10th percentile at delivery using gender-specific Fenton growth charts for infants.¹⁵

Statistical analysis

To account for differences in the gestational age at the last scan between the patients, Z-scores were calculated for the different biometric measurements. Z-scores (assessment of the standard deviation from the expected mean for gestational age) for individual sonographic parameters were calculated based on published formulas incorporating the gestational age at the time of the ultrasound exam.¹² Statistical analysis was performed using Stata/SE 14.1 (Stata Corp. College Station, TX, USA). Unadjusted analyses were performed using χ^2 test for categorical variables, and Student's *t*-test for continuous variables. Receiver operating characteristic curves, sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated for the total EFW and individual biometric parameters. EFW less than the 5th and 10th percentiles were considered as cutoffs for estimating diagnostic parameters. The level of significance was set at $P < 0.05$. Area under the curve was estimated using logistic regression with individual or combination of biometric parameters as predictor variables.

RESULTS

Of 178 total gastroschisis cases managed in our centers during the time period, we excluded 108 cases that did not have an ultrasound performed within 2 weeks of delivery, yielding a total of 70 cases for analysis. Of those, 16 infants (23%) were determined to be SGA at birth. When comparing baseline demographic data between the SGA and appropriate for gestational age (AGA) groups, there was no difference in mean maternal age (21.2 vs 21.6 years, $P = 0.78$), the gestational age of the last ultrasound exam (35.9 vs 35.2 weeks, $P = 0.14$), days between the last ultrasound exam and delivery (6.0 vs 5.8, $P = 0.91$), or the gestational age of delivery (36.8 vs 36.0 weeks, $P = 0.12$) between those with and without SGA. Women with and without SGA neonates had similar pre-pregnancy body mass index (22.5 vs 27.4, $P = 0.30$) (Table 1).

The mean EFW and individual biometric parameters were compared between those with and without SGA at delivery (Table 2). There was a statistically significant difference between the mean AC in the SGA group when compared with the AGA group (27.0 vs 28.9 cm, $P = 0.020$). All of the other parameters, including the mean EFW were found to be similar between the groups. When considering EFW percentile, SGA neonates had significantly lower EFW percentile (3.8 percentile) compared with AGA neonates (16.5 percentile, $P = 0.021$). Gestational age-specific Z-scores for the individual sonographic parameters were

Table 1. Maternal demographic and obstetric factors in SGA and AGA gastroschisis cases

	SGA (n = 16)	AGA (n = 54)	P-value
Maternal age (years)	21.2 (4.2)	21.6 (4.2)	0.78
Race			0.45
White	44%	46%	
Asian	6%	4%	
American Indian/Alaska Native	6%	0	
Other	25%	30%	
Unknown	19%	20%	
Ethnicity—Hispanic	88%	70%	0.17
Nulliparity	75%	68%	0.59
BMI (pre-pregnancy)*	22.5 (3.9)	23.0 (3.4)	0.57
Maternal weight gain (kg)*	27.8 (10.2)	35.7 (15.4)	0.057
Smoking*	19%	11%	0.44
GA of last US exam (weeks)	35.9 (1.4)	35.2 (1.8)	0.14
Days between last US exam and delivery	6.0 (4.3)	5.8 (5.1)	0.91
GA at delivery (weeks)	36.8 (1.3)	36.0 (1.8)	0.12

Abbreviations: AGA, appropriate for gestational age; BMI, body mass index; GA, gestational age; SGA, small for gestational age; US, ultrasound. Means (standard deviation) or column %'s are shown. *Missing variables—BMI $n = 3$, smoking $n = 1$, maternal weight gain $n = 1$.

Table 2. Total estimated fetal weight (EFW), head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), femur length (FL) at the last ultrasound before delivery

	SGA (n = 16)	AGA (n = 54)	P-value
EFW at last US, g	1940 (376)	2178 (453)	0.059
HC, cm	30.5 (1.1)	30.6 (1.7)	0.80
BPD, cm	8.4 (0.5)	8.4 (0.6)	0.94
AC, cm	27.0 (2.3)	28.9 (2.8)	0.020
FL, cm ^a	6.3 (0.4)	6.4 (0.4)	0.48

Abbreviation: AGA, appropriate for gestational age. Means (s.d.) are shown. ^aFemur length was missing for one AGA patient.

Table 3. Mean z-scores for individual sonographic biometric parameters and risk of small for gestational age (SGA)

	SGA (n = 19)	AGA (n = 49)	P-value	Odds ratio for SGA status ^a	95% CI
HC	-2.2	-1.6	0.11	0.70	0.44, 1.09
BPD	-1.5	-1.0	0.15	0.71	0.45, 1.13
AC	-3.4	-1.6	< 0.0001	0.46	0.29, 0.72
FL	-2.3	-1.6	0.013	0.50	0.28, 0.89

Abbreviations: AC, abdominal circumference; AGA, appropriate for gestational age; BPD, biparietal diameter; FL, femur length; HC, head circumference. ^aOdds ratios with 95% CI estimated per increase in z-score of 1. Femur length not known for one AGA patient.

compared between SGA and AGA neonates (Table 3). There was a statistically significant difference between the z-score of the AC (-3.4 vs -1.6, $P < 0.0001$) and FL (-2.3 vs -1.6, $P = 0.013$) between the groups. The other parameters, HC and BPD, were similar between groups.

Prediction of SGA was assessed using receiver operating characteristic analysis along with the sensitivity, specificity, PPV and NPV of the total EFW and individual parameters using z-scores less than -2, which is consistent with less than 5% for gestational age (Table 4 and Figure 1). An EFW less than 10% had 94% sensitivity, 43% specificity, 33% PPV and 96% NPV for SGA at

Table 4. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the total estimated fetal weight (EFW) and individual sonographic parameters and combination of parameters for prediction of small for gestational age

	Sensitivity	Specificity	PPV	NPV
EFW < 5%	88%	63%	41%	94%
EFW < 10%	94%	43%	33%	96%
HC z-score ≤ -2	63%	67%	36%	86%
BPD z-score ≤ -2	38%	80%	35%	81%
AC z-score ≤ -2	88%	61%	40%	94%
FL z-score ≤ -2	56%	70%	36%	84%
EFW < 5%+AC z-score ≤ -2	81%	72%	46%	93%
EFW < 5%+FL z-score ≤ -2	56%	77%	43%	85%
EFW < 5%+AC z-score ≤ -2+FL z-score ≤ -2	25%	91%	44%	80%
EFW < 10%+AC z-score ≤ -2	88%	63%	41%	94%
EFW < 10%+FL z-score ≤ -2	56%	70%	36%	84%
EFW < 10%+AC z-score ≤ -2+FL z-score ≤ -2	31%	83%	36%	80%

Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; FL, femur length; HC, head circumference; US, ultrasound. EFW at last US considered as percentile; other parameters based on z-score according to gestational age.

	AUC	95% CI	
EFW at last US (percentile)	0.832	0.716	0.949
HC	0.660	0.517	0.802
BPD	0.632	0.481	0.783
AC	0.833	0.706	0.960
FL	0.697	0.548	0.846
EFW + AC	0.833	0.706	0.960
EFW + FL	0.798	0.670	0.926
EFW + AC + FL	0.835	0.706	0.964

US=ultrasound; HC=head circumference; BPD=biparietal diameter; AC=abdominal circumference; FL=femur length

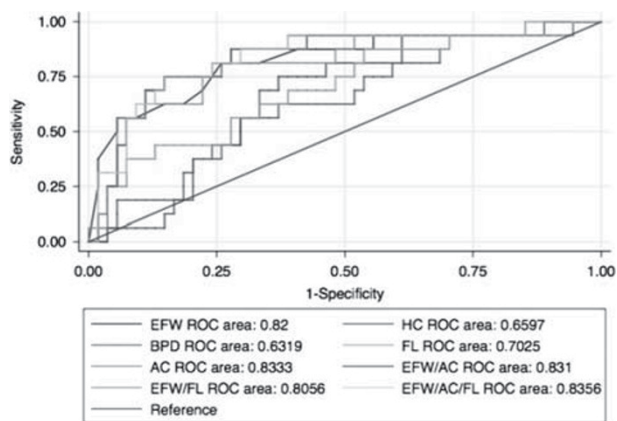


Figure 1. Prediction of SGA at delivery among fetuses with gastroschisis using the third trimester estimated fetal weight (EFW) and biometric measurements (AC, FL, BPD, HS). AC, abdominal circumference; BPD, biparietal diameter; FL, femur length; HC, head circumference; ROC, receiver operating characteristic; US, ultrasound.

delivery. Thirty-four cases had a prenatal sonographic EFW less than 5% for gestational age, 14 of whom were born SGA. Using an EFW cutoff of < 5% improved the specificity to 63% and PPV to 41% but decreased the sensitivity to 88%. The only individual parameter with similar area under the curve was an AC z-score less than -2.

In order to study the predictive utility of biometric measurements, we then analyzed different combinations of EFW cutoffs

and parameters with a z-score less than -2. Combining an EFW less than 5% and AC z-score less than -2 (requiring both to be true to predict SGA) increased the specificity from 61–63 to 72%, with a decrease in sensitivity from 88 to 81% when compared with the EFW less than 5% alone. The combination of EFW less than 5% and AC z-score less than -2 also yielded a higher PPV (46%) and similar NPV (93%) compared with the EFW alone. Adding an FL z-score less than -2 to the EFW less than 5% (requiring both to be true to predict SGA) increased specificity to 77%, but dramatically decreased the sensitivity to 56% and NPV to 85% when compared with the EFW less than 5% alone. A combination of EFW less than 5%+AC z-score less than -2+FL z-score less than -2 (requiring all three to predict SGA) increased specificity to 91%, but decreased the sensitivity to 25% and the NPV to 80% when compared with the total EFW less than 5% alone.

DISCUSSION

In this multi-institutional cohort of gastroschisis cases we found differences in sonographic AC and FL z-scores within 2 weeks of delivery between SGA and AGA infants. However, the addition of a very short AC or FL with a z-score less than -2 to the overall EFW increased the specificity and PPV of prenatal ultrasound, but decreased the sensitivity compared with the EFW alone.

Our findings have several important contributions to the existing literature and potential clinical implications. First, our data showing a smaller FL in addition to the expected smaller AC support the theory that prenatal IUGR may be an intrinsic part of gastroschisis physiology. In their study of 70 gastroschisis cases, Centofanti *et al.*¹⁶ found that fetal measurements of HC, AC and FL were all smaller during the second half of the pregnancy in fetuses with gastroschisis compared with normal controls. The etiology for SGA in gastroschisis cases deserves further research, but the mechanism is likely intrinsic to the fetus rather than placental since prior studies found similar rates of oligohydramnios and umbilical artery Doppler flow abnormalities between SGA and AGA cases.² In their study of 42 gastroschisis cases undergoing long-term follow-up (median age 9), Harris *et al.*¹⁷ described significant catch up growth between birth and follow-up for the majority of children; however, those with complex gastroschisis (bowel complications such as atresia and volvulus) at birth had a significantly lower median body mass index and weight z-scores at follow-up.

Second, our data provide clinicians comprehensive data about the predictive utility of different EFW cutoffs, and combinations of EFW and small biometric measurements in predicting SGA at delivery. Multiple studies have shown the relatively poor accuracy of prenatal ultrasound in predicting SGA irrespective of EFW formulas.^{6,11} In their study of 53 gastroschisis cases, Nicholas *et al.*¹¹ compared the Honarvar, Siemer and Hadlock formulas for EFW. While none of the three formulas met the criteria for ideal formula (low systematic error and high precision) the authors found the Hadlock formula to have the best bias and precision combination. In a similar study of 62 gastroschisis cases with an ultrasound performed within 2 weeks of delivery, Chaudhury *et al.*⁶ compared the accuracy of five different EFW formulas. They found similar accuracy rates using the Hadlock formula (89% sensitivity and 68 to 70% specificity) but higher specificity (up to 86%) and positive predictive value (67%) when using either the Shepard or Siemer formulas. In our study, we showed increased specificity and PPV with using an EFW cutoff less than 5% compared with < 10% although at a slightly decreased sensitivity. We also showed that adding an AC or FL z-score less than -2 to the overall EFW irrespective of cutoff using a Hadlock formula may improve the specificity and positive predictive rate as well but at a cost of decreasing the sensitivity. It is unclear if a similar effect can be seen by using the Shepard or Siemer formulas.

Whether improving SGA prediction in the late preterm period will improve prenatal management and neonatal outcomes warrants further investigation. In a recently published study analyzing prenatal, intrapartum and neonatal differences between SGA and AGA gastroschisis cases, we found no difference in preterm premature membrane rupture rates, preterm delivery rates, meconium staining, or mode of delivery between SGA and AGA cases.² That being said, it is plausible that prenatal providers suspecting IUGR at later preterm gestational ages may iatrogenically induce gastroschisis pregnancies prematurely in order to avoid stillbirth. Several studies have correlated earlier gestational age at delivery with adverse neonatal outcomes among gastroschisis cases, but prospective implementation of our findings is warranted to assess whether a later gestational age of delivery can be achieved by optimizing the accuracy of prenatal ultrasound.^{18–20}

Our study is not without limitations. This was a retrospective study utilizing existing records, and the protocol for ultrasound surveillance was not standardized across both institutions. Thus, it is possible that selection bias exists in our data set since providers concerned about IUGR may have been more likely to perform an ultrasound at late preterm gestational ages. That being said the rate of SGA seen in our cohort is consistent with other published cohorts, and at worst this bias may have affected the PPV and NPV, but not the sensitivity and specificity. Moreover, while other studies have suggested that the Hadlock formula may not be the ideal formula for IUGR determination in gastroschisis cases, given its wide prevalence in many prenatal diagnostic centers and prior gastroschisis studies we specifically targeted this formula.^{4,6,10,16} Additional studies would be needed to study our approach using additional EFW formulas. Finally, we assessed different methods of predicting SGA at delivery and not necessarily additional neonatal morbidity. The predictive utility of sonographic assessments for adverse neonatal outcomes will be the topic of future analyses.

Despite these limitations, it is important to note the strengths of our study. First, given the relatively low incidence of gastroschisis (1 in 2000 to 1 in 3000 pregnancies) we provided data from a robust cohort analyzing both the accuracy of the total EFW and individual ultrasound parameters within 2 weeks of delivery. In fact, the average days from ultrasound to delivery in our cohort was less than 7 days. Second, we used a commonly used gender-specific neonatal weight nomogram (the Fenton curve) to diagnose SGA, and used calculations provided by Hadlock and colleagues to determine the z-scores of individual biometric parameters. This allowed us to present the accuracy of individual parameters, the total EFW, and a combination of the EFW and individual parameters. Finally, combining data from two separate institutions makes our findings generalizable to other sites using the Hadlock formula to determine the EFW.

In conclusion, adding third trimester AC or FL with a z-score less than -2 to the total EFW improves the specificity and PPV for suspected SGA in gastroschisis cases, but lowers the overall sensitivity. Our data can assist providers suspecting IUGR in the third trimester in pregnancies complicated by fetal gastroschisis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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