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ORIGINAL ARTICLE

Predicting birth weight in fetuses with gastroschisis

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OBJECTIVE: To determine the accuracy of commonly utilized ultrasound formulas for estimating birth weight (BW) in fetuses with gastroschisis.

STUDY DESIGN: A retrospective review was conducted of all inborn pregnancies with gastroschisis within the five institutions of the University of California Fetal Consortium (UCfC) between 2007 and 2012. Infants delivered at $\geqslant 28$ weeks who had an ultrasound within 21 days before delivery were included. Prediction of BW was evaluated for each of the five ultrasound formulas: Hadlock 1 (abdominal circumference (AC), biparietal diameter (BPD), femur length (FL) and head circumference (HC)) and Hadlock 2 (AC, BPD and FL), Shepard (AC and BPD), Honarvar (FL) and Siemer (BPD, occipitofrontal diameter (OFD), and FL) using Pearson's correlation, mean difference and percent error and Bland–Altman analysis. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the ultrasound diagnosis of intrauterine growth restriction (IUGR) were assessed.

RESULTS: We identified 191 neonates born with gastroschisis within the UCfC, with 111 neonates meeting the inclusion criteria. The mean gestational age at delivery was 36.3 ± 1.7 weeks and the mean BW was 2448 ± 460 g. Hadlock (1) formula was found to have the best correlation ($r = 0.81$), the lowest mean difference (8 ± 306 g) and the lowest mean percent error (1.4 ± 13%). The Honarvar and Siemer formulas performed significantly worse when compared with Hadlock 1, with a 13.7% ($P < 0.001$) and 3.9% ($P = 0.03$) difference, respectively, between estimated and actual BW. This was supported by Bland–Altman plots. For Hadlock 1 and 2, sensitivity was 80% with a NPV of 91%.

CONCLUSION: The widely used Hadlock (1) and (2) formulas provided the best estimated BW in infants with gastroschisis despite its inclusion of abdominal circumference. Furthermore, this formula performs well with diagnosis of IUGR.

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INTRODUCTION

Gastroschisis is a congenital abdominal wall defect that results in herniation of bowel and other abdominal contents. In the United States, the prevalence of gastroschisis has increased by 30%, to 4.9 per 10 000 live births between 2006 and 2012, compared with 3.6 per 10 000 live births between 1995 and 2005.[1–4] Fetal growth restriction is common in fetuses with gastroschisis and is estimated to be as high as 60%.[5,6] Antenatal surveillance of fetal growth in this population has traditionally been difficult and many have argued against its accuracy because of the spillage of the abdominal contents outside of the abdomen, thereby rendering the abdominal circumference component of the biometric measurements imprecise. Therefore, the diagnosis of growth restriction in fetuses with gastroschisis is often questioned because of the inability to accurately estimate fetal weight as a result of the imprecise abdominal circumference measurement.[5,6]

Raynor and Richards[7] described a 50% overestimation of growth restriction, with 43% carrying this diagnosis prenatally, and with only 23% actually demonstrating growth restriction after birth. They attributed the overdiagnosis to smaller than average abdominal circumference measurements. Fetal growth restriction and gastroschisis are independent risk factors for perinatal morbidity, as well as for intrauterine fetal death, and therefore practitioners often elect to deliver fetuses preterm to avoid these outcomes. The decision and timing of delivery is often undertaken based on ultrasound prediction of fetal growth restriction despite its potential imprecision.

Over the past 30 years, many ultrasound formulas have been established for estimating fetal weight based on multiple fetal biometric parameters. These formulas include those of Hadlock *et al.*[8] (1) and (2), Shepard *et al.*,[9] Honarvar *et al.*,[10] Siemer *et al.*,[11] Warsof *et al.*,[12] and many more. The majority of these formulas, with the exception of the Siemer *et al.*[11] formula, include abdominal measurements and were derived from structurally normal fetuses in which the abdominal shape resembles a circle in the appropriate transverse ultrasound plane (Figure 1). However, fetuses with gastroschisis have an abnormally shaped abdominal plane because of the extrusion of abdominal visceral contents (Figure 2), thereby precluding accurate measurement of the abdominal circumference and potentially resulting in an underestimation of the abdominal circumference and overall estimated fetal weight (EFW). The Siemer *et al.*[11] formula was first published in 2008 specifically for estimation of fetal weight in fetuses with abdominal wall defects without use of an abdominal measurement.

Therefore, the aim of this study was to compare the accuracy of the most commonly utilized ultrasound formulas for estimating birth weight (BW) in gastroschisis, and to identify the optimal formula to be utilized in these high-risk pregnancies.

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METHODS

We performed a retrospective review of all inborn pregnancies complicated by gastroschisis within the five institutions of the University of California Fetal Consortium (UCfC) from 2007 to 2012. The UCfC is a multi-institutional collaboration of the five University of California medical centers: including University of California Davis, University of California Irvine, University of California Los Angeles, University of California San Diego and University of California San Francisco. All institutions participating in the University of California Fetal Consortium are tertiary academic medical centers with a full complement of perinatal, neonatal and surgical services. A multi-institutional review board reliance registry approved the study (Institutional Review Board No. 10-04093, approved on 4 January 2017).

Figure 1. Abdominal circumference of normal fetus.

Figure 2. Abdominal circumference with fetal gastroschisis.

Cases of gastroschisis were identified by International Classification of Diseases, 9th Revision codes. Maternal and neonatal variables were abstracted through an individual chart review at each institution. All patients included in the analysis received prenatal and postnatal care within the same institution. Neonates who were transferred into a UCfC institution after delivery for postnatal care were excluded. We included pregnancies delivered at $\geqslant 28$ weeks and limited our analysis to cases with an ultrasound examination within 21 days of delivery.

Variables collected from hospital charts included maternal age, parity, smoking, drug use, gestational age at last ultrasound, gestational age at delivery and BW. Ultrasound reports were abstracted for fetal biometry at the five institutions that included biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL). Measurements of the herniated bowel was not included in the analysis. The occipitofrontal diameter (OFD) was calculated based on the following formula: $\text{OFD} = 0.6369 \times \text{HC} - \text{BPD}$. This is not a biometry that is routinely measured, but it is included in the Siemer *et al.*[11] formula. Ultrasound estimated fetal weight was calculated *post hoc* for the last ultrasound evaluation before delivery with the equations of Hadlock *et al.* (1) and (2),[8] Shepard *et al.*,[9] Honarvar *et al.*[10] and Siemer *et al.*[11] (Table 1). Interval growth between time of ultrasound to birth was corrected for by adding a standard expected weight of 30 g per day.[13] For all infants, estimated weight percentile was determined based on the EFW from each formula using the Hadlock fetal weight curves for estimating percentiles. In addition, BW percentile was determined using Fenton growth curves for preterm infants, based on gestational age, gender and weight.[13] Intrauterine growth restriction (IUGR) was defined as an EFW of less than the 10th percentile.[14,15]

Pearson's correlation coefficient was calculated to determine correlation between EFW for each formula and BW. This was done for all infants as well as the subgroup of infants < 2500 g. The mean difference between EFW and BW was calculated to assess for bias in EFW measurements by formula in the estimation of BW. Mean percent errors for each formula were calculated (percent error $= (\text{EFW} - \text{BW/BW}) \times 100$) for all infants as well as the subgroup of infants < 2500 g. To assess agreement between EFWs and BWs for each formula, Bland–Altman plots were created by plotting the mean of EFW and BW against the difference in measurement between EFW and BW. A regression line was overlaid to assess for varying trends in agreement across the range of birth weights. As part of the Bland–Altman analysis, 95% limits of agreement were

Table 1. Ultrasound formulas for estimating fetal weight

Formula	Biometric Measurements	Equation
Hadlock et al. (1) [8]	AC, BPD, FL, HC	Log10 EFW = 1.3596 + 0.0064 (HC) + 0.0424 (AC) + 0.174 (FL) + 0.00061 (BPD x AC) – 0.00386 (AC x FL)
Hadlock et al. (2) [8]	AC, BPD, FL	Log10 EFW = 1.335 – 0.0034 (AC x FL) + 0.0316 (BPD) + 0.0457 (AC) + 0.1623 (FL)
Honarvar et al. [10]	FL	EFW = 0.042 FL^2 (cm) + 0.32 (FL) – 1.36
Shepard et al.[9]	AC, BPD	Log10 EFW = –1.7492 + 0.166 (BPD) + 0.046 (AC) – 0.002546 (AC)
Siemer et al.[11]	BPD, OFD, FL	$\text{EFW} = -145.577 + 23.724 \times \text{FL}^2 + 1.255 \times \text{BPD}^3 + 0.001 \times e^{\text{OFD}} - 0.0000406 \times 10^{\text{FL}} + 1.03 \times e^{\text{FL}}$

Abbreviations: AC- abdominal circumference; BPD- biparietal diameter; FL- femur length; HC- head circumference; OFD- occipitofrontal diameter; EFW- estimated fetal weight determined (values within which 95% of differences exist between EFW and BW). Sensitivity, specificity, PPV and negative predictive value (NPV) were used to assess the diagnostic utility of determining IUGR for each formula (Stata 12.0; StataCorp, College Station, TX, USA).

RESULTS

We identified 191 neonates born with gastroschisis within the UCfC during the study period. Eighty patients were excluded for incomplete ultrasound reports or because the last ultrasound was more than 21 days before delivery: 47 and 33, respectively. The remaining 111 cases were included for analysis. The mean maternal age was 22 ± 4 years. The mean gestational age at delivery was 36.3 ± 1.7 weeks and mean BW was 2448 ± 460 g (Table 2).

For all formulas, there was a significant correlation between EFW and BW ($P < 0.001$) (Table 3). The Hadlock *et al.*[8] (1) formula had the best correlation ($r = 0.81$), lowest mean difference (8.0 ± 306 g) and the lowest mean % error (1.4 ± 13%), and was used as the referent to determine whether other equations had significantly worse error. The Hadlock *et al.*[8] (2) formula performed very similar to Hadlock *et al.*[8] (1) with a low mean difference (9.5 ± 306 g) and no significant difference in mean percent error (1.4 ± 13%; $P = 0.7$). The Shepard *et al.* formula had a relatively low mean difference (20.7 ± 326 g) and no significant difference in mean percent error (1.8 ± 14%; $P = 0.4$) from Hadlock *et al.*[8] (1) (Table 3).

The Honarvar *et al.*[10] formula performed the poorest with a correlation coefficient of 0.72, a mean difference of 271.2 ± 352 g and a mean percent error that was significantly worse than Hadlock *et al.*[8] (1) (13.7 ± 17%; $P < 0.001$). The Siemer *et al.*[11] formula performed slightly better than the Honarvar *et al.*[10] formula but still lagged behind the Hadlock *et al.*[8] (1) and (2) formulas in accuracy. Trends in formula performance were similar among the subset of infants < 2500 g with an overall slight decrease in accuracy across all formulas (Table 4).

Sensitivity was highest for Hadlock *et al.*[8] (1) and (2) (80%) in the diagnosis of BW less than the 10th percentile based on EFW (Table 5). Specificity was highest for Honarvar *et al.*[10] (98%) and Siemer *et al.*[11,16] (82%), though sensitivity was extremely low (23%) for the Honarvar *et al.*[10] formula. PPV was highest for the Honarvar *et al.*[10] formula (78%), with all others in the 50% range. NPV was highest for Hadlock *et al.*[8] (1) and (2) (91%). Measurements performed at either 1 week or 3 weeks before delivery performed similarly to the overall data presented in Table 5. Those measured at 2 weeks before delivery had a lower sensitivity, specificity and PPV, but this variation is likely because of the small sample size of the subgroups. NPV remained consistent. The overall diagnostic accuracy (receiver operating characteristic curve) for the diagnosis of BW less than the 10th percentile was similarly fair among all five equations (0.70 to 0.74) (Table 5).

DISCUSSION

Among infants with gastroschisis, IUGR is a common occurrence leading to interventions such as iatrogenic preterm deliveries. Prematurity often increases the morbidity in these already high-risk pregnancies. Previous studies have suggested that ultrasound formulas that incorporate abdominal circumference into the biometric measurements may underestimate true fetal weight because abdominal contents do not reside within the actual abdominal cavity being measured. In our study, which is one of the largest contemporary cohorts of fetuses with gastroschisis, we compared the accuracy of five common formulas for estimating fetal weight by ultrasound. Using a large multicenter cohort, we demonstrated that the Hadlock *et al.*[8] (1) and (2) ultrasound formulas were most accurate in predicting BW in these infants. Furthermore, these formulas performed well in the evaluation of fetuses with EFW less than the 10th percentile and actual BW of < 2500 g, essential in determining timing of delivery. All five equations performed similarly fair in the diagnosis of BW less than the 10th percentile.

Table 2. Patient characteristics for 111 infants with gastroschisis

Characteristic	*Mean ± s.d. or* N *(%)*
Maternal age (years)	22 ± 4.0
Gestational age at last ultrasound (weeks)	34.8 ± 1.9
Gestation age at delivery (weeks)	36.3 ± 1.7
Days between last ultrasound and delivery	9.7 ± 7.0
Birth weight (g)	2448 ± 460
Birth weight < 10th percentile	30 (27%)

Two previous papers have examined the accuracy of different sonographic formulas for estimating fetal weight in a mixed abdominal wall defect population, including both gastroschisis and omphalocele.[11,16] Siemer *et al.*[11] found their formula (designed without the use of abdominal circumference for use in this population) provided a more accurate estimate of fetal weight than the Hadlock *et al.*[8] (1) and (2) formulas that underestimated fetal weight. Alternatively, we have demonstrated the Hadlock *et al.*[8] formulas to be more accurate and the Siemer *et al.*[11,16] formula tends to overestimate the weight. This may be explained by the lack of adjustment for interval fetal weight gain between last ultrasound and birth in the Siemer *et al.*[11,16] study that was up to 7 days.

Using a mixed abdominal wall defect cohort, Nicholas *et al.*[16] similarly compared the formulas of Hadlock *et al.*,[8] Honarvar *et al.*[10] and Siemer *et al.*;[11,16] however, they adjusted for interval fetal weight gain between last ultrasound and birth.[16] The Siemer *et al.*[11] formula produced the lowest mean percent error; however, similar to our study, they found Honarvar *et al.*[10] and Siemer *et al.*[11,16] had very poor sensitivities (24% and 64%, respectively) for the diagnosis of IUGR. They also demonstrated a high sensitivity of 91% and NPV of 94% for Hadlock *et al.*[8] formula. It is difficult to ascertain the full implications of including both gastroschisis and omphalocele patients on the generalizability to infants with gastroschisis as frequent liver involvement in omphalocele likely leads to a different impact on abdominal circumference than may be seen for gastroschisis alone.

More recently, Chaudhury *et al.*[17] performed a similar assessment in a population of 62 fetuses with gastroschisis alone. This study, like that of Siemer *et al.*,[11,16] suggests that Hadlock *et al.*[8] underestimated birth weight, though similarly no adjustments were made for interval growth. Furthermore, for all formulas assessed, there were large negative mean differences with much wider 95% limits of agreement than were seen in our current study. This may be a reflection of a smaller sample size. However, similar to Siemer *et al.*,[11,16] Nicholas *et al.*[16] and our current study, Chaudhury *et al.*[17] report the highest sensitivities and NPVs among the Hadlock *et al.*[8] formulas (89% and 94%). Alternatively, the PPV was found to be disappointingly low for all formulas, in alignment with previously published literature. Although unclear why, it is important to keep this in mind as the misdiagnosis and overdiagnosis of growth restriction also has very important implications on delivery timing and neonatal outcomes.

It has been shown that both infants with gastroschisis and infants with IUGR are at increased risk of intrauterine fetal demise. As a result, infants with gastroschisis who are also IUGR are often delivered early in the setting of IUGR. Recent national data by Sparks *et al.*[18] demonstrated an increased risk of stillbirth with expectant management over delivery after 37 weeks of gestation. Because of this risk, we must be certain that our fetal measurements are (1) capturing the maximum number of infants with true IUGR (high sensitivity) and (2) that infants with true IUGR are not misclassified as weight greater than the 10th percentile (high NPV) and allowed to remain pregnant with potentially

Table 3. Correlation, mean difference and 95% limits of agreement between ultrasound estimated fetal weight and actual birth weight

Formula	*Correlation (r)*		*Mean difference (g ± s.d.)*	*95% Limits of agreement (g)*
	All infants (n = *111*)	*< 2500 g* (n = *31*)	*All infants* (n = *111*)	*All infants* (n = *111*)
Hadlock *et al.* (1)[8]	0.81*	0.72*	8.0 (±306)	− 604 to 620
Hadlock *et al.* (2)[8]	0.81*	0.72*	9.5 (±306)	− 602 to 621
Honarvar *et al.*[10]	0.72*	0.62*	271.2 (±352)	− 432 to 974
Shepard *et al.*[9]	0.79*	0.71*	20.7 (±326)	− 631 to 672
Siemer *et al.*[11]	0.77*	0.68*	53.8 (±328)	− 601 to 709

**P* < 0.001.

Table 4. Mean percent error between ultrasound estimated fetal weight and actual birth weight in all infants and those < 2500 g

Formula	*Mean % error (% ± s.d.)*			
	All infants		*< 2500 g*	
	(n = *111*)	P	(n = *30*)	P
Hadlock *et al.* (1)[8]	1.4% (±13%)	Reference	3.9% (±14%)	Reference
Hadlock *et al.* (2)[8]	1.4% (±13%)	0.7	3.8% (±14%)	0.5
Honarvar *et al.*[10]	13.7% (±17%)	< 0.001	21.7% (±16%)	< 0.001
Shepard *et al.*[9]	1.8% (±14%)	0.4	3.9% (±16%)	0.9
Siemer *et al.*[11]	3.9% (±14%)	0.003	8.9% (±14%)	< 0.001

P < 0.001.

Table 5. Diagnostic tests for prediction of birth weight < 10th percentile

Formula	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Accuracy (ROC)*
Hadlock *et al.* (1) [8]	80%	73%	53%	91%	0.72
Hadlock *et al.* (2) [8]	80%	73%	52%	91%	0.71
Honarvar *et al.* [10]	23%	98%	78%	77%	0.74
Shepard *et al.* [9]	77%	72%	50%	89%	0.70
Siemer *et al.*[11]	73%	82%	59%	89%	0.74

Abbreviation: ROC, receiver operating characteristic curve.

increased risk of demise. The commonly used Hadlock *et al.*[8] (1) and (2) formulas demonstrate the best sensitivity and NPV in the diagnosis of IUGR.

This study has demonstrated that the commonly used Hadlock *et al.*[8] (1) and (2) formulas perform better than other formulas in the estimation of fetal weight and the diagnosis of IUGR in gastroschisis. However, it is worth noting that no formula is perfect. The 95% limits of agreement demonstrate that although the mean difference and mean % error values are within the range of what is seen for normal infants without abdominal wall defects, there is still a large range within which 95% of the true values lie. For all formulas the 95% limits of agreement are in the range of 600 g that could be potentially clinically relevant particularly in small fetuses.

Although this is a large study assessing the estimation of fetal weight and IUGR in infants with gastroschisis, it is not without limitations. Limitations to this study include the need for calculation of OFD as this is not a biometric measurement routinely performed at all UCfC sites. In addition, although the multisite study design adds strength to the study in terms of generalizability, it can also be a limitation as it can create variance among sites in the techniques used to perform the biometric measurements. Finally, this is a retrospective review and therefore carries its own inherent flaws including misclassification, selection and information bias.

In conclusion, the commonly used Hadlock *et al.*[8] formulas for ultrasound estimation of fetal weight perform well in fetuses with gastroschisis. Use of specific formulas without abdominal circumference are not necessary and may have less utility in the diagnosis of IUGR necessary for helping clinicians determine timing of delivery.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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