OBSTETRICS

Sonographic markers associated with adverse neonatal outcomes among fetuses with gastroschisis: an 11-year, single-center review

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BACKGROUND: Gastroschisis complicates 1 in 2000 births and is readily identifiable during prenatal ultrasound scans. Outcomes in fetuses that are affected by gastroschisis vary widely from stillbirth or neonatal death to uncomplicated surgical correction, which makes prenatal counseling challenging.

OBJECTIVE: The goal of our study was to identify sonographic markers that are associated with perinatal death and morbidity that include significant bowel injury, necrotizing enterocolitis, and the need for bowel resection in fetuses with gastroschisis.

STUDY DESIGN: We identified a cohort of fetuses that were diagnosed with gastroschisis from 2003-2014. Sonographic markers that were reviewed included growth restriction, abdominal circumference, oligohydramnios, bowel dilation, and gastric bubble characteristics. We evaluated these markers both at diagnosis and near delivery. Four adverse perinatal outcomes were assessed: perinatal death, necrotizing enterocolitis, need for bowel resection, and a composite of significant bowel injury, which included a diagnosis of bowel atresia or necrosis at the time of surgical exploration. Logistic regression was performed to calculate odds ratios and 95% confidence intervals for each marker and outcome.

RESULTS: One hundred seventy-seven patients were identified, and 154 of these patients met inclusion criteria after exclusions for delivery <24 weeks gestation, other associated anomalies, lethal karyotype, or lost to follow-up evaluation. Markers at the time of diagnosis (median gestational age, 21 weeks [25th,75th interquartile range, 19, 24 weeks]) that were associated with perinatal death were abdominal circumference <5th percentile (odds ratio, 5.56; 95% confidence interval, 1.25—24.76), abnormal gastric bubble (odds ratio, 11.20; 95% confidence interval, 2.15—58.33), and abnormal stomach location (odds ratio, 17.1; 95% confidence interval, 2.99—97.85). An abnormal stomach location (odds ratio, 5.53; 95% confidence interval, 1.03—29.72) before delivery was associated with perinatal death. Gastric dilation before delivery (odds ratio, 4.36; 95% confidence interval, 1.10—17.34)] was associated with the need for bowel resection.

CONCLUSION: Early sonographic markers of increased perinatal mortality rates include abdominal circumference <5th percentile and an abnormal gastric bubble.

Key words: bowel dilation, diagnosis, dilated stomach, gastric bubble, gastroschisis, prenatal, ultrasound scan

Gastroschisis is a congenital anomaly in which an abdominal wall defect facilitates extrusion of the intestines into the amniotic cavity in utero. The incidence of gastroschisis is increasing, with recent estimates at >4 per 10,000 live births.[1] Although considered a treatable condition, a recent metaanalysis suggests that 4-5% of gastroschisis pregnancies end in intrauterine fetal demise and that fetuses that are live-born have a postnatal mortality rate of 5-10%.[2]

The incorporation of ultrasound scanning into the antepartum treatment of fetuses with gastroschisis has grown since initial reports of prenatal diagnosis of gastroschisis from the 1970s.[3,4] The prognostic ability of various sonographic markers in infants with gastroschisis has been studied previously. However, the existing data are inconclusive regarding the utility of prenatal ultrasound scans in the identification of infants who are most likely to experience adverse outcomes. In the 1980s the proposal was that patients should be delivered if there was fetal bowel dilation.[5] However, this subsequently was called into question by Sipes et al[6] in 1990. Some authors have questioned the clinical importance of antenatal bowel dilation entirely[7]; others acknowledge associated morbidity but concede that it might not be an indication for obstetric intervention.[8] Similarly, there is not a consensus on the importance of the stomach bubble among fetuses with prenatally diagnosed gastroschisis. Some authors report that a dilated stomach is associated with worse neonatal outcomes[9]; other authors did not find an association.[10]

This study was conducted to evaluate whether we could identify sonographic markers, both at the time of diagnosis and proximal to delivery, that are associated with increased perinatal mortality and morbidity rates in fetuses with gastroschisis. If such markers are identified, this could improve prenatal counseling, obstetric management, and timing of delivery to prevent adverse perinatal outcomes.

Materials and Methods

We conducted a retrospective cohort study of all patients who received a diagnosis of gastroschisis prenatally who delivered at 1 of the medical centers that comprise the Cincinnati Fetal Center (TriHealth Hospital or University of Cincinnati Medical Center). Subjects included mothers who were evaluated in

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the Cincinnati Fetal Center between January 2003 and May 2014. Exclusion criteria included delivery at <24 weeks gestation, other associated anomalies, lethal karyotype, or lost to follow-up evaluation. The study was approved by the institutional review boards at Cincinnati Children's Hospital Medical Center, the University of Cincinnati Medical Center, and TriHealth Hospital.

Subjects were identified by querying a database that is maintained by the Cincinnati Fetal Center. The database includes prenatal and postnatal diagnoses for all mothers who are seen in consultation. Data regarding maternal demographics, obstetric and medical complications, delivery details, and maternal medical record were collected. In addition, in-utero sonograms were reviewed at 2 time points: the initial ultrasound scan at 1 of the 2 tertiary referral perinatal centers (University of Cincinnati Medical Center or TriHealth Hospital) and the ultrasound scans that were performed closest to delivery. All sonograms were performed by the Registered Diagnostic Medical Sonographers in an American Institute of Ultrasound in Medicine–accredited perinatal ultrasound unit.

Although markers have not been defined uniformly in previous studies, for the purposes of our evaluation, sonographic markers that were evaluated included (1) *oligohydramnios* defined as an amniotic fluid index <5 cm,[11] (2) the presence of *intrauterine growth restriction* defined as an estimated fetal weight at <10th percentile defined by the Hadlock Curve,[12] (3) abdominal circumference <10th percentile and <5th percentile,[13] (4) the presence of *intraabdominal*, *extraabdominal*, or *any bowel dilation* defined as dilation >1 cm (Figure 1, A), and (5) abnormal gastric bubble, which included either an abnormally dilated stomach or an abnormally positioned stomach (Figure 1, B and C).[14] An abnormal stomach bubble was determined by the interpreting maternal-fetal medicine specialist as previously reported in the literature that included subjective stomach dilation and/or malposition.[15] We assessed the presence of bowel dilation using an objective cut-off of 1 cm, as previously reported as a cut-off for normality[15] acknowledging that there is not a consensus in the literature. Subjects were categorized according to the diagnosis that was made at the time of imaging when possible and when not possible by annotated review of the archived imaging. Four perinatal outcomes were assessed: perinatal death,[16] necrotizing enterocolitis, need for bowel resection within 48 hours of delivery, and a composite of significant bowel injury that included a diagnosis of bowel atresia or necrosis at the time of initial surgical exploration. *Atresia* was defined as an anatomic narrowing through which no stool could be passed; *necrosis* was defined as nonviable tissue found at time of surgical exploration.

Patients who were referred to the Cincinnati Fetal Center were followed with ultrasound scans for fetal growth every 3-4 weeks and twice weekly antenatal testing in the third trimester. Cesarean delivery was recommended for obstetric indications and not solely for the finding of gastroschisis, unless there was liver herniation. Timing of delivery was based on recommendations from the managing maternal-fetal medicine physician. A subanalysis that compared trial of labor vs elective cesarean and the primary perinatal outcomes was performed.

Chi-square analysis was used to analyze categoric variables. Logistic regression was performed to calculate odds ratios (OR) and 95% confidence intervals (CIs) for each sonographic marker for the adverse outcomes: perinatal loss, need for bowel resection, and presence of our composite for significant bowel injury. ORs were considered significant if the 95% CI did not include the null value of 1.0. All data analysis was performed with IBM SPSS statistical software (version 22; IBM Corporation, Armonk, NY).

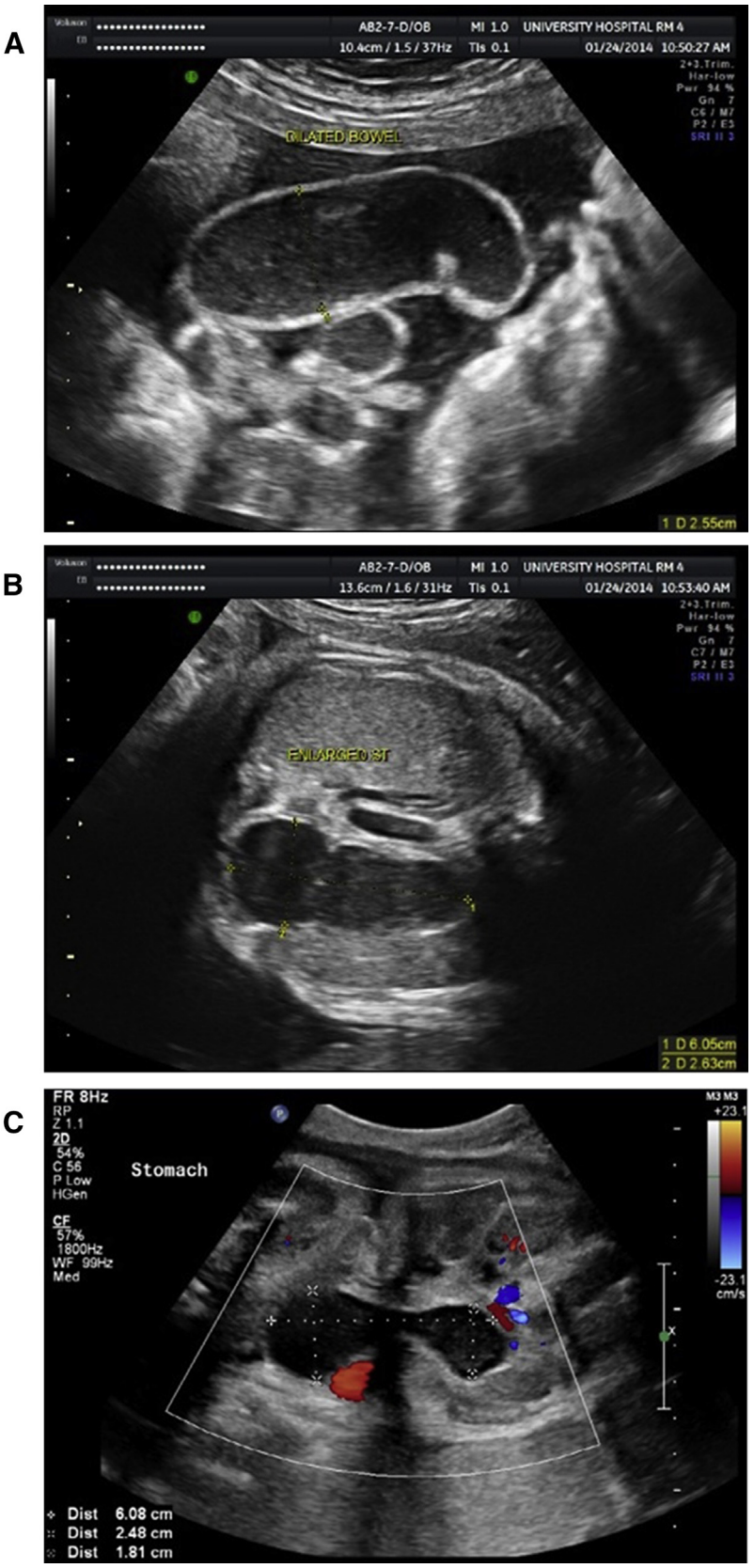
Results

We identified 177 patients who delivered a fetus with gastroschisis at a study center during the study period. After consideration of the inclusion/exclusion criteria, 154 were eligible for analysis (Figure 2). The demographic characteristics of our population are outlined in Table 1. The cohort had a mean maternal age of 21.9 ± 4.1 years, median gravidity of 1, and a mean body mass index of 28.8 ± 6.6 kg/m^2. Body mass index range extended from 17.3-57.1 kg/m^2. Tobacco use complicated 29.9% of cases. Median gestational age at delivery was 36 weeks with 7.8% (12/154) delivered at <34 weeks gestation, 68.6% (106/154) delivered at 34-37 weeks gestation, and 23.4% (36/154) delivered at ≥37 weeks gestation. The perinatal mortality rate was 5.8%, which included 4 cases of intrauterine fetal death (2.6%) at 33, 34, 36, and 38 weeks gestational age and 5 cases of neonatal death (3.2%).

Delivery outcomes are summarized in Table 1. The cesarean delivery rate was 42.7% (64/150), 20.3% (13/64) of whom were delivered electively via cesarean, with gastroschisis as the sole indication for their cesarean delivery. Among the women who attempted a vaginal delivery, the vaginal delivery rate was 79%. Mode of delivery was not associated with increased perinatal deaths ($P > .999$), need for bowel resection ($P > .999$), our bowel injury composite ($P = .8$), or necrotizing enterocolitis ($P = .4$).

The ultrasound scan at diagnosis was performed at a median gestational age of 21 weeks (interquartile range, 19–24 weeks; Table 2). The ultrasound scan before delivery was performed a median of 1 week (interquartile range, 1–2 weeks) before delivery (Table 3). Perinatal loss was the first adverse perinatal outcome examined (n = 9; 5.8%). Markers that were associated with perinatal loss at the diagnostic ultrasound scan were abdominal circumference <5th percentile (OR, 5.56; 95% CI, 1.25–24.76), an abnormal gastric bubble (OR, 11.20; 95% CI, 2.1 –58.33), and abnormal stomach location (OR, 17.1; 95% CI, 2.99–97.85). One sonographic marker before delivery that was associated with perinatal death was an abnormal stomach bubble (OR, 5.53; 95% CI, 1.03–29.72). The second adverse perinatal outcome examined was necrotizing enterocolitis (n = 8; 5.2%). Oligohydramnios (n = 2) that was noted on the diagnostic ultrasound scan was associated with necrotizing enterocolitis of the neonate (OR, 26.25;

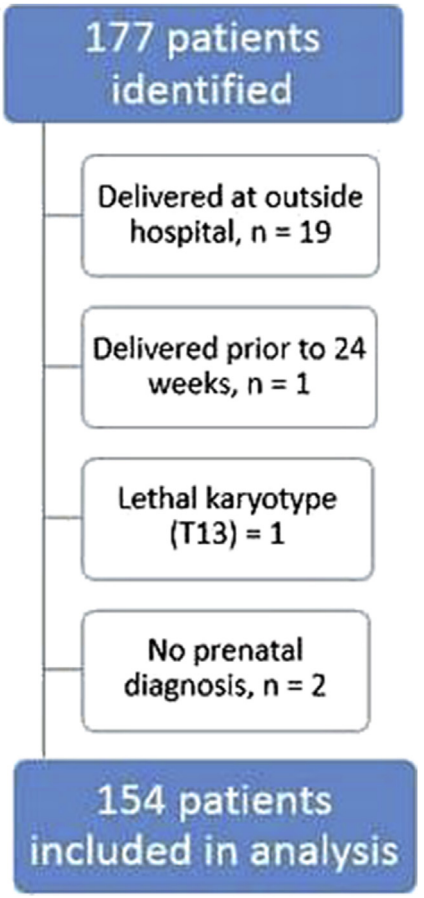
FIGURE 1
Sonographic markers of interest evaluated in this analysis



A. Dilated bowel measuring 2.55 cm, marked by calipers **B.** An abnormal appearing, enlarged, and elongated stomach. **C.** An enlarged and displaced stomach being pulled through the site of the abdominal cord insertion of the umbilical cord.

Sinkey et al. Sonographic markers of gastroschisis. Am J Obstet Gynecol 2016.

FIGURE 2
Flowchart of patients included/ excluded from analysis



One hundred seventy seven patients were originally identified. After applying inclusion/ exclusion criteria, patients were included in the analysis.

Sinkey et al. Sonographic markers of gastroschisis. Am J Obstet Gynecol 2016.

95% CI, 1.38–499.61). The third adverse perinatal outcome that was examined was the need for bowel resection (n = 16; 10.4%). No sonographic markers at the time of diagnosis were associated with this outcome. Gastric

TABLE 1
Demographic information[a] (n = 154)

Variable	Measure
Demographic factor	
Age, mean ± SD	21.9 ± 4.1
Age, range	13-39
Race, n (%)	
African American	28 (18.2)
Asian	2 (1.3)
White	86 (55.8)
Hispanic	2 (1.3)
Unknown	35 (22.7)
Gravidity, median (interquartile range)	1 (1–2)
Parity, median (interquartile range)	0 (0–1)
Body mass index, kg/m^2	
Mean ± SD	28.8 ± 6.6
Range	17.3–57.1
Tobacco use, n/N (%)	44/147 (29.9)
Delivery information	
Gestational age at delivery, median (interquartile range)	36 (35, 37)
Delivery, n (%)	
<34 Weeks gestation	12 (7.8)
34-37 Weeks gestation	106 (68.8)
≥37 Weeks gestation	36 (23.4)
Cesarean delivery, n (%)	64/150 (42.7)
Perinatal death, n (%)	
Intrauterine growth restriction	4 (2.6)
Neonatal mortality	5 (3.2)

[a] Because of retrospective nature of review, some patient information and outcomes are missing. Denominator is listed for variables where N is less than the total number of participants

Sinkey et al. Sonographic markers of gastroschisis. Am J Obstet Gynecol 2016.

dilation (n = 16) that was noted on the ultrasound scan before delivery was associated with the need for bowel resection (OR, 4.36; 95% CI, 1.10–17.34). The fourth adverse perinatal outcome that was examined was a composite of significant bowel injury (n = 18; 11.7%) that included atresia and necrosis. Bowel dilation that was noted on the diagnostic ultrasound scan (OR, 9.28; 95% CI, 1.76–48.88) and on the sonogram before delivery (OR, 3.83; 95% CI, 1.1–12.39), specifically extra-abdominal dilation (OR, 12.14; 95% CI, 2.82–52.27), was associated with the bowel composite.

Next, birthweight as a continuous variable and birthweight <10th percentile as a categoric variable were analyzed for the 4 adverse perinatal outcomes as mentioned earlier (perinatal loss, bowel injury composite, necrotizing enterocolitis, and need for bowel resection). No significant associations were found between birthweight and adverse perinatal outcomes (Table 2).

Comment

In this large, cohort of 154 fetuses with prenatally diagnosed gastroschisis that were treated in a single Fetal Center, we identified several sonographic markers that were associated significantly with perinatal outcomes that included perinatal death, a composite for bowel injury, necrotizing enterocolitis, and the need for bowel resection. These findings differ from a recently published review.[17] These data add to the current body of literature, can help guide counseling for families with affected pregnancies, and highlight areas that would benefit from further research.

Our most striking finding was the association of an abnormal stomach bubble at the time of diagnosis (OR, 11.20; 95% CI, 2.15–58.33) and abnormal stomach location before delivery (OR, 5.53; 95% CI, 1.03–29.72) with perinatal loss. This finding aligns with conclusions drawn by Aina-Mumuney et al.[9] Among their cohort of 34 fetuses with prenatally diagnosed gastroschisis with a dilated stomach bubble, fetuses with a dilated stomach had higher rates of neonatal death compared with fetuses without a dilated stomach ($P = .48$). Our findings differ from other reports that did not find an association between an abnormal stomach bubble and perinatal loss.[15,18-20] There are several reasons that could explain this discrepancy. Our contrasting conclusions could be due to our larger total sample size (66 cases,[18] 80 cases,[15] 98 cases,[20] and 105 cases[21] vs our 154 cases). Additionally, the differing conclusions are likely due to varying definitions of a dilated stomach bubble and various obstetric managements of these findings. This finding does have biologic plausibility because prenatally diagnosed stomach bubble abnormalities suggest downstream obstruction or intrinsic dysmotility and therefore warrants further investigation.

In addition to the significance of the gastric bubble among fetuses with prenatally diagnosed gastroschisis, the significance of dilated bowel in a fetus with gastroschisis is often debated in the literature. We found dilated bowel at both the diagnostic ultrasound scanning and the ultrasound scanning before delivery to be associated with the composite of significant bowel injury that included atresia and necrosis, but not perinatal loss or the need for bowel

TABLE 2
Prognostic indicators of adverse perinatal outcomes at ultrasound scan performed at initial diagnosis[a]

Indicator	Perinatal loss	Composite of significant bowel injury	Necrotizing enterocolitis	Need for bowel resection
Sonographic marker, n (%)	9 (5.8)	18 (11.7)	8 (5.2)	16 (10.4)
Intrauterine growth restriction[b] (n = 12)	1.51 (0.17–13.21)	—[c]	1.91 (0.21–17.23)	0.80 (0.10–6.70)
Abdominal circumference <10th (n = 47)	2.98 (0.68–13.08)	0.83 (0.24–2.95)	0.43 (0.05–4.03)	1.58 (0.49–5.03)
Abdominal circumference <5th (n = 32)	5.56 (1.25–24.76)	0.60 (0.12–2.92)	2.49 (0.39–15.80)	0.96 (0.25–3.76)
Oligohydramnios (n = 2)	—[c]	—[c]	26.25 (1.38–499.61)	—[c]
Bowel dilation (n = 7)	—[c]	9.28 (1.76–48.88)	4.04 (0.39–42.01)	1.35 (0.15–12.16)
Intraabdominal dilation (n = 2)	—[c]	—[c]	—[c]	—[c]
Extraabdominal dilation (n =5)	—[c]	3.59 (0.34–38.20)	—[c]	2.94 (0.28–30.74)
Abnormal gastric bubble (n = 9)	11.20 (2.15–58.33)	1.41 (0.16–12.69)	—[c]	3.03 (0.54–16.88)
Abnormal stomach location (n = 7)	17.1 (2.99–97.85)	2.02 (0.21–19.04)	—[c]	1.68 (0.18–15.64)
Gastric dilation (n = 3)	8.29 (0.67–102.85)	—[c]	—[c]	4.43 (0.67–51.42)

[a] The ultrasound scan at diagnosis was performed at a median (25th–75th interquartile range) of 21 (range, 19-24) weeks gestation; [b] Defined as estimated fetal weight <10th percentile; [c] No cases among exposed group.

Sinkey et al. Sonographic markers of gastroschisis. Am J Obstet Gynecol 2016.

resection. Our findings differ from Long et al[21]; among their cohort of 170 infants with gastroschisis and dilated bowel (which they defined as 20 mm), they found that dilated bowel was associated with perinatal death. Our findings also differ from publications that used 17 mm as a cutoff that concluded that bowel dilation was not associated with adverse outcomes.[22-24] The conflicting reports in the literature are likely due to varying definitions of bowel dilation

TABLE 3
Prognostic indicators of adverse perinatal outcomes at sonogram proximal to delivery[a]

Indicator	Perinatal loss	Composite of significant bowel injury	Necrotizing enterocolitis	Need for bowel resection
Intrauterine growth restriction (n = 39)	1.89 (0.36 – 9.84)	0.15 (0.01 – 1.18)	0.64 (0.06 – 6.36)	0.61 (0.15-2.40)
Abdominal circumference				
<10th (n = 62)	1.46 (0.33–6.43)	0.90 (0.28–2.89)	0.90 (0.12–6.67)	1.99 (0.57–6.89)
<5th (n = 46)	0.89 (0.20–3.93)	0.60 (0.17–2.09)	0.52 (0.05–5.16)	0.91 (0.28–3.00)
Oligohydramnios (n = 8)	2.16 (0.23–20.13)	—[b]	—[b]	1.33 (0.15–12.04)
Bowel dilation (n = 43)	3.69 (0.65–21.07)	3.83 (1.19–12.39)	5.58 (0.56–55.64)	1.66 (0.52–5.34)
Intraabdominal dilation (n = 11)	1.84 (0.20–17.35)	1.53 (0.46–5.09)	3.11 (0.29–33.12)	2.10 (0.39–11.30)
Extraabdominal dilation (n = 34)	1.56 (0.25–9.80)	12.14 (2.82–52.27)	2.35 (0.32–17.46)	1.21 (0.34–4.36)
Abnormal gastric bubble (n = 28)	4.80 (0.86–30.37)	2.86 (0.79–10.30)	1.09 (0.11–11.02)	2.94 (0.82–10.58)
Abnormal stomach location (n = 20)	5.53 (1.03–29.72)	2.46 (0.67–9.02)	1.77 (0.17–18.12)	1.58 (0.39–6.37)
Gastric dilation (n = 16)	1.50 (0.16–14.35)	2.53 (0.59–10.89)	—[b]	4.36 (1.10–17.34)
Birth				
Birthweight	0.999 (0.997–1.00)	1.000 (0.999–1.00)	0.999 (0.997–1.00)	0.999 (0.998–1.00)
Birthweight <10% (n = 32)	2.26 (0.51–10.00)	1.54 (0.50–4.76)	2.35 (0.53–10.51)	3.03 (0.96–9.53)

[a] Sonogram performed closest to delivery, median (25th–75th interquartile range) of 1 (range, 1-2) weeks before delivery; [b] No cases among exposed group.

Sinkey et al. Sonographic markers of gastroschisis. Am J Obstet Gynecol 2016.

(from 6-25 mm), the varied location of the measured bowel (intra- vs extra-abdominal), and the gestational age at the time of the ultrasound scan. The outcomes that are experienced after these sonographic findings may differ from author to author based on geographic antenatal treatment of these fetuses as well.

We found the presence of an abdominal circumference <5th percentile at the time of diagnosis, but not before delivery, to be associated with perinatal loss. Our findings differ from those reported by Ajayi et al.[25] Their cohort consisted of 74 fetuses, so it is possible that their study was not powered to detect a difference. Additionally, they used an abdominal circumference cutoff of <2.5 percentile, which leads to a lower detection rate. Our populations seem homogenous in that our rates of bowel resection were almost identical (10.4% vs 10.8%); however, our neonatal mortality rate was slightly higher than their rate (3.2 % vs 1.4%). More studies are needed to clarify the role of the abdominal circumference in the prediction of outcomes of fetuses with gastroschisis.

Birthweight was not correlated with perinatal death nor the other adverse perinatal outcomes studied. Our series included 4 stillbirths at 33, 34, 36, and 38 weeks gestation in addition to 5 neonatal deaths after delivery at 36, 39, 28, 33, and 37 weeks gestation. Given the lack of protective effect that was seen in term deliveries, especially on mortality rates, we did not find birthweight to be associated with this outcome nor with the other morbidities that were studied.

This study has several strengths. First is the relatively large sample size of 154 fetuses with prenatally diagnosed gastroschisis. Second, all ultrasound scans were performed in highly specialized obstetric imaging centers, which likely improved homogeneity for the identification of the markers that were studied. Third, the sonographic and outcome associations have biologic plausibility.

There are several limitations to this study. First, because of its retrospective nature, 1 weakness is variance in practice, especially given the lengthy duration of our study period. Second, the large CIs are a function of studying more rare outcomes and a limitation in studies of this nature and topic. Authors have proposed that associations that are found in observational studies might not be credible if the ORs do not exceed 3 or 4.[26] Our lowest significant OR was 3.83 and ranged to 26.25. Although the CIs are indeed large, the ORs exceed previously reported thresholds for significance in observational studies. Third, we did not evaluate any novel markers in this study, and even with this contribution to the available evidence in the literature, prenatal prediction of likelihood of neonatal complications from gastroschisis remains a challenge to those who treat these patients. Finally, our study does not address the ongoing debate over timing and mode of delivery. In spite of recent reviews by Grant et al[27] and large (n = 519 patients) prospective multicentered studies, there is no international standard for the management of gastroschisis. Because timing and/or mode of delivery could impact perinatal outcomes, the sensitivity, specificity, and positive and negative predictive values of these ultrasound markers may not be generalizable to other populations with different management protocols.[28,29]

Additional research in this area may help to determine whether these markers or other novel sonographic markers or diagnostic tests may be useful in the prediction of adverse perinatal outcomes, short-term and long-term, in fetuses that are diagnosed with gastroschisis. Although it is useful to know sonographic markers that predict perinatal death and bowel injury, more research is needed to know how to optimize delivery strategies when these sonographic markers are identified to balance the risks and benefits of avoiding perinatal death while minimizing the adverse effects of prematurity. ■

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