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Sonographic predictors of postnatal bowel atresia in fetal gastroschisis

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Abstract

Objective—To estimate the association between antenatal bowel dilation and postnatal small bowel atresia in fetal gastroschisis and to establish a threshold at which the risk of adverse neonatal outcome increases.

Methods—A retrospective cohort study of singleton gestations with an antenatal diagnosis of gastroschisis seen in our ultrasound unit from 2001–2010. Stored images were reviewed, blind to postnatal diagnoses and outcomes, from the last ultrasound exam before delivery. Fetal intra- and extra-abdominal bowel dilation as well as bowel wall thickness was measured. Previously published definitions of bowel dilation including >6mm, >10mm, >14mm and >18mm were evaluated for association with the primary outcome of bowel atresia. The optimal threshold to define fetal bowel dilation was determined by evaluating the significance of association as well as test performance characteristics.

Results—Of 109 consecutive patients with fetal gastroschisis, there were 4 cases of intrauterine fetal demise and 3 neonatal deaths. Of the 94 live births with complete outcome data, 39 (41.5%) had measurable intra-abdominal bowel dilation (IABD). There were 14 (14.9%) cases of bowel atresia. Using a threshold of >14mm, IABD was significantly associated with an increased risk for bowel atresia (RR 3.1, 95% CI 1.2–8.2) with a sensitivity of 57.1%, specificity of 75.0%, positive predictive value of 28.6% and negative predictive value of 90.9%. IABD >14mm was also associated with a significantly longer neonatal intensive care unit length of stay. There was no significant association between extra-abdominal bowel dilation and bowel atresia at any of the thresholds evaluated.

Conclusion—IABD >14mm is associated with an increased risk for postnatal bowel atresia in fetal gastroschisis. This finding may be useful in counseling patients regarding the anticipated postnatal course for their neonate.

Keywords

abdominal wall defect; bowel atresia; bowel dilation; bowel wall thickening; gastroschisis

Introduction

Gastroschisis is a congenital full-thickness paramedian abdominal wall defect that occurs in approximately 3 to 5 per 10,000 births, with an increasing incidence documented over recent

decades.¹⁻³ Whilst prognosis is generally favorable, there is a significant disparity in neonatal morbidity and mortality rates based on the presence or absence of associated intestinal abnormalities at birth, such as atresia, necrosis, or perforation. These patients with “complex gastroschisis” have mortality rates ranging between 28-50% compared to those with “simple gastroschisis” who have documented survival rates approaching 100%.⁴⁻⁶ The ability to predict which fetuses are at increased risk for these postnatal complications would significantly aid in the counseling of parents in the prenatal period regarding the anticipated postnatal course for their neonate, as well as the need for referral to a tertiary care center for delivery and specialized pediatric services.

In cases of bowel atresia, it is hypothesized that there is an accumulation of fluid in the bowel lumen proximal to the site of obstruction, resulting in the sonographic appearance of bowel dilation. Prior studies have generated conflicting results regarding the association of antenatal bowel dilation and postnatal bowel atresia; however, the majority are limited by small sample size and the use of varying thresholds to define bowel dilation.⁷⁻¹² Furthermore, many of these reports have limited their investigation to a single sonographic predictor and have relied on retrospective ultrasound reporting to obtain information regarding the appearance of the fetal bowel, thus introducing the possibility for significant ascertainment bias. A recent meta-analysis by Tower et al concluded that fetuses with isolated gastroschisis and antenatal bowel dilation are not at increased risk for adverse perinatal outcome; however, that analysis did not differentiate between intra-abdominal and extra-abdominal bowel dilation and did not perform subgroup analyses based on the threshold used to define dilated bowel.¹³ The objective of this study was to comprehensively evaluate the association between antenatal bowel dilation and postnatal small bowel atresia in fetal gastroschisis and to estimate the threshold at which the risk of adverse neonatal outcomes significantly increases.

Methods

This was a retrospective cohort study of all consecutive patients carrying singleton gestations diagnosed with fetal gastroschisis who were evaluated at Washington University Medical Center Division of Ultrasound and Genetics from 2001-2010. Patients with chromosomal abnormalities, multiple anomalies or incomplete neonatal medical records were excluded. Institutional review board approval from Washington University was obtained. Patients with fetal gastroschisis were identified using an established perinatal database in the institution. Maternal demographic information, maternal medical and obstetrical history, indication for ultrasound, ultrasound findings and any genetic screening or diagnostic testing results were entered into this database at the time of the ultrasound visit for all patients seen in our center. Pregnancy complications and delivery outcome data as well as neonatal outcome data were also routinely obtained and entered into this database by a dedicated nurse outcome coordinator.

It is standard practice for ultrasound evaluation of patients with fetal gastroschisis seen in the unit to include serial assessment of fetal position, biometric measurements, amniotic fluid volume measurement and evaluation for any intra-abdominal or extra-abdominal bowel dilation. Stored ultrasound images from the last ultrasound exam prior to delivery were reviewed for each patient. The ultrasound exam closest to delivery was chosen, as it was hypothesized that the appearance of the bowel at this exam would be most representative of bowel pathology at the time of delivery. The transverse diameter of the largest dilated loop of both intra-abdominal and extra-abdominal small bowel was measured from inner wall to inner wall (i.e., endoluminal diameter, figures 1A and 1B). Additionally, maximum bowel wall thickness was measured from the inner wall to the outer wall of the thickest portion of small bowel visualized, either intra- or extra-abdominal in location (Figure 1C). All

sonographic bowel measurements were taken posthoc by a single author, blind to neonatal outcomes, in order to limit both ascertainment bias and inter-observer measurement variability. Detailed neonatal outcome information was then extracted from medical records by an examiner who was blind to the antenatal sonographic findings.

The primary exposure in the study was the presence of intra-abdominal bowel dilation (IABD) on antenatal ultrasound evaluation. Previously defined thresholds of bowel dilation in the published literature, including >6 mm, >10 mm, >14 mm and >18 mm were evaluated.^{9,12,14,15} Secondary exposures included extra-abdominal bowel dilation (EABD) and bowel wall thickness >3 mm.^{15,16} The primary outcome was postnatal small bowel atresia requiring surgical intervention. Secondary outcomes included necrotizing enterocolitis (NEC), bowel necrosis, bowel perforation, complex gastroschisis, neonatal intensive care unit (NICU) length of stay, time to abdominal wall closure, time on ventilator support, time on total parenteral nutrition (TPN), time to initial enteral feedings, time to full enteral feedings and neonatal death.

Baseline characteristics as well as the incidence of the primary and secondary outcomes were compared between patients with and without any measurable fetal IABD. Normality of distribution was tested using the Kolmogorov-Smirnov test. Student's t-tests and Mann-Whitney U tests were used to compare continuous variables, and Chi-square and Fisher's exact tests were used to compare dichotomous variables, as appropriate. Incidences, relative risks (RR) and 95% confidence intervals (CI) were then calculated for the association of each pre-defined threshold of bowel dilation and bowel atresia. In addition, test performance characteristics including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for bowel atresia were calculated. The optimal threshold of bowel dilation for predicting postnatal atresia was determined by evaluating the significance of association, as well as the test performance characteristic which would provide the optimal trade-off between sensitivity and specificity. Incidences of the secondary outcomes were then compared between patients with fetal dilated bowel and those without. Similar analyses were then performed for EABD and thickened bowel wall. P-values <0.05 were considered statistically significant. All statistical analyses were performed using STATA 12.1, Special Edition (College Station, TX).

Results

Of 109 patients with fetal gastroschisis diagnosed antenatally and confirmed at birth, there were 4 (3.7%) cases of intrauterine fetal death. Of the remaining 105 live births, complete neonatal records were available for 94 (89.5%) patients, comprising the final study cohort. There were 14 cases of postnatal bowel atresia (14.9%). The mean gestational age at the time of the ultrasound exam prior to the time of delivery was 33.7 ± 2.6 weeks, which was 2.4 ± 2.1 weeks from delivery, on average. The mean gestational age at the time of delivery was 36.1 ± 1.8 weeks. On average, patients with any measurable fetal IABD were similar in baseline demographics and pregnancy characteristics to those without any measurable fetal IABD. In addition, there were no significant differences in gestational age at delivery or birth weight between the study groups (Table 1).

The range of measurable IABD was 7.0 mm - 75.0 mm. Of the various tested thresholds used to define bowel dilation, IABD > 14 mm was the only threshold which was significantly associated with the primary outcome of postnatal bowel atresia (28.6% vs. 9.1%; RR 3.1, 95% CI 1.2-8.2). IABD >14 mm also demonstrated the most discriminatory test performance characteristics for the prediction of postnatal bowel atresia with a sensitivity of 57.1%, specificity of 75.0%, PPV of 28.6% and NPV of 90.9%. In contrast, EABD was a very common finding, with measurable extra-abdominal bowel loops observed

in 88.3% of the study cohort. The range of measurable EABD was 3.9 mm - 32.0 mm. There was no significant association between any of the thresholds used to define EABD and the postnatal finding of bowel atresia (Table 2). Trends in the incidence of postnatal bowel atresia across the varying thresholds of intra- and extra-abdominal bowel dilation are shown in Figures 2A and B.

Given the association identified between IABD >14 mm and postnatal bowel atresia, secondary neonatal adverse outcomes were evaluated with respect to this threshold. There was no difference in the incidence of NEC, bowel perforation, bowel necrosis, or complex gastroschisis between fetuses with IABD >14 mm and those with IABD ≤14 mm. Although, on average, neonates with IABD >14 mm had longer NICU stays (80.5 days vs. 47.5 days), there was no difference in time to abdominal wall closure, time on TPN and time to initial and full enteral feeding (Table 3).

The range of measurable bowel wall thickness was 1.0 mm - 3.8 mm. There were six cases of thickened bowel wall >3 mm in the study cohort. All cases of thickened bowel wall occurred in fetuses with IABD >14 mm. Fetuses with thickened bowel wall had a four-fold increased risk of postnatal bowel atresia compared to those with normal bowel wall thickness (50.0% vs. 12.5%; RR 4.0, 95% CI 1.5-10.6). Test performance characteristics for the prediction of postnatal bowel atresia were as follows: sensitivity 21.4%, specificity 96.3%, PPV 50.0% and NPV 87.5%. Fetuses with thickened bowel wall also had an increased risk for developing NEC compared to those with normal bowel wall thickness (50.0% vs. 10.2%; RR 4.8, 95% CI 1.8-13.4). There was a trend toward an increasing incidence of bowel necrosis and complex gastroschisis in fetuses with thickened bowel wall; however, these values did not reach statistical significance. Similar to fetuses with IABD, fetuses with thickened bowel wall also had significantly longer NICU stays (100.5 days vs. 48.5 days; $p=0.03$, table 4).

There were three neonatal deaths in the cohort, with gestational age at delivery ranging from 33 1/7 to 38 1/7 weeks. Only one neonatal death occurred in a fetus with IABD >14 mm, who was subsequently diagnosed with a small bowel atresia at birth. The remaining two neonatal deaths also occurred in cases of complex gastroschisis (one case of bowel perforation and one case of bowel necrosis). None of the three neonatal deaths occurred in fetuses with sonographic evidence of thickened bowel wall. Given the small number of cases, a definitive trend cannot be established; however, it is plausible that neonatal death may be related to the diagnosis of complex gastroschisis and not necessarily related to any pattern of antenatal sonographic findings.

Discussion

Findings from our study demonstrate a significant association between fetal IABD and the diagnosis of postnatal small bowel atresia in cases of isolated gastroschisis; however, this association did not reach significance until a threshold of 14 mm of bowel dilation was reached. Fetal IABD >14 mm also was associated with a prolonged NICU length of stay, consistent with the projected need for surgical intervention and extended post-operative recovery time in gastroschisis infants with bowel atresia. In contrast, fetal EABD was not associated with postnatal bowel atresia at any of the thresholds evaluated, consistent with the hypothesis that dilation of the herniated portion of fetal bowel may be more reflective of impaired peristalsis rather than true obstruction.

Our findings are similar to those of Contro et al who demonstrated a four-fold increased risk of small bowel obstruction in fetuses with IABD, but not in fetuses with EABD. However, in contrast to our study, these authors used a threshold of >6 mm to define bowel dilation.¹¹

In a cohort study of 43 patients, Huh et al also demonstrated an increased risk for postnatal bowel complications in fetuses with IABD, but only in those fetuses with multiple loops of dilated bowel.¹⁰ In a more recent cohort study of 130 infants with gastroschisis, Ghionzoli et al again observed an increased risk of bowel atresia in fetuses with bowel dilation; however, in their study the location of bowel dilation (intra- vs. extra-abdominal) was not predictive when using a more conservative threshold of >18 mm of dilation.⁹

Other studies have not confirmed these associations. In a retrospective cohort study of 64 fetuses with gastroschisis, Badillo et al identified no correlation between antenatal bowel dilation and adverse postnatal outcome.¹⁷ Similarly, Long et al observed no significant association between IABD >20 mm and postnatal bowel atresia; yet, they did observe that fetuses with IABD had a significantly longer length of time on TPN, a potential surrogate marker for postnatal complications.⁸ Our study did not demonstrate a significantly longer length of time on TPN in fetuses with IABD; however, this may be reflective of heterogeneous practice patterns in newborn feeding strategies.

The significance of sonographic bowel wall thickening in gastroschisis fetuses has been studied less extensively. In a 1988 report of 11 infants with gastroschisis, Bond et al first demonstrated a significant association between thickened bowel wall and poor neonatal outcome; however, subsequent studies have not confirmed this association^{12,16,18}. It is postulated that prolonged exposure of the fetal bowel to the harsh amniotic fluid environment results in progressive bowel injury over time, leading to sonographic changes in the appearance of the bowel wall. Our study demonstrated an increased risk for both bowel atresia and NEC in fetuses with thickened bowel wall. It is important to note that all cases of thickened bowel wall occurred in fetuses that also had IABD >14 mm; therefore, it remains unclear whether thickened bowel wall is an independent predictor of postnatal bowel atresia.

Strengths of our study include our relatively large cohort of gastroschisis fetuses with extensive and complete neonatal outcome information. This allowed for a rigorous evaluation of postnatal outcomes. We also chose an objectively measurable primary outcome of bowel atresia requiring surgical intervention, thereby limiting subjectivity in provider diagnosis and outcome extraction from the medical record. In contrast to many prior studies, we were also able to retrospectively review stored ultrasound images, as it is standard practice at our institution for sonographers to record images of the most dilated loops of both intra- and extra-abdominal bowel at each exam. This permitted a single examiner, blind to neonatal outcomes, to take all measurements of bowel dilation and thickening, thus eliminating ascertainment and misclassification bias. This approach also allowed for a uniform measurement technique in this research setting. Another strength is that we were able to evaluate multiple thresholds of bowel dilation to determine which had the most favorable test performance characteristics. Evaluating this trade-off of sensitivity and specificity is especially useful when using any measurement tool to counsel patients. Although we would have expected to observe a dose-response relationship with increasing thresholds of bowel dilation and risk of atresia, it is likely that the non-significant association observed at these higher thresholds was due to the small number of patients with such degrees of bowel dilation.

Our study is not without limitations. We were unable to control for antenatal management strategies such as frequency of ultrasound evaluation and timing of delivery; however, these factors are unlikely to have a significant impact on the majority of our outcomes of interest. Additionally, while our primary outcome was objective, many of our secondary outcomes such as time to abdominal wall closure, days on ventilatory support and time to enteral feeding varied based on pediatric practice patterns. We would argue that this range in

practice actually makes our study more generalizable to neonates who are cared for at a variety of institutions with a wide range of practice patterns. Furthermore, while we were able to extensively evaluate many neonatal outcomes we were unable to thoroughly evaluate rare outcomes such as neonatal mortality, nor identify long-term complications which may have a significant impact on quality of life.

In conclusion, fetal IABD >14 mm is significantly associated with an increased risk of postnatal bowel atresia in cases of isolated gastroschisis. A threshold of 14 mm to define fetal bowel dilation results in favorable test performance characteristics as well as a modest predictive efficacy for bowel atresia. Although fetal IABD <14mm does not completely exclude the possibility for postnatal bowel atresia, the high NPV of 90.9% may be particularly useful in reassuring parents that the risk for postnatal bowel atresia is extremely low in these cases. In contrast, fetal EABD is a very common sonographic finding in fetal gastroschisis and not associated with significant bowel pathology at the time of delivery. Although we do not suggest that the presence or absence of these sonographic findings should alter antenatal surveillance or timing of delivery, these findings may be very useful adjuncts in counseling parents in the prenatal period about the projected hospital course for their neonate with gastroschisis.

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Figure 1. Third-trimester sonographic evaluation of fetal bowel. (a) Intra-abdominal bowel dilation, (b) extra-abdominal bowel dilation and (c) bowel wall thickening.

Figure 2. Incidence of postnatal bowel atresia across varying thresholds of (a) intra-abdominal bowel dilation and (b) extra-abdominal bowel dilation.

Table 1

Maternal demographics and pregnancy characteristics comparing patients with any measurable fetal intra-abdominal bowel dilation (IABD) and those without measurable IABD in gastroschisis pregnancies

<i>Characteristic</i>	<i>Any measurable IABD (n=39)</i>	<i>No IABD (n=55)</i>	<i>P-value</i>
Mean maternal age (years)	21.5 ± 2.6	22.1 ± 3.9	0.36
Mean GA at ultrasound (weeks)	33.5 ± 3.9	33.9 ± 2.4	0.67
Mean gravidity	2.0 ± 1.4	1.8 ± 1.1	0.34
Mean parity	0.6 ± 1.0	0.6 ± 1.1	0.83
Caucasian	76.2%	73.3%	0.82
African-American	14.3%	13.3%	0.92
Tobacco exposure	30.3%	19.6%	0.26
Alcohol exposure	6.0%	15.6%	0.15
Mean GA at delivery (weeks)	36.1 ± 1.5	36.0 ± 2.0	0.60
Birth weight (g)	2435 ± 496	2438 ± 659	0.98

GA, gestational age.

Table 2

Relative risks and test performance characteristics of various thresholds of antenatal intra- and extra-abdominal bowel dilation (IABD and EABD) for the prediction of postnatal bowel atresia

<i>Intra-abdominal bowel dilation</i>							
<i>Threshold</i>	<i>Incidence in IABD group</i>	<i>Incidence in non-IABD group</i>	<i>Relative risk (95% CI)</i>	<i>Sensitivity (%)</i>	<i>Specificity (%)</i>	<i>PPV</i>	<i>NPV</i>
>6 mm (n=39)	23.1% (9/39)	9.1% (5/55)	2.5 (0.9-7.0)	64.3	62.5	23.1%	90.9%
>10 mm (n=35)	22.9% (8/35)	10.2% (6/59)	2.2 (0.8-5.9)	57.1	66.3	22.9%	89.8%
>14 mm (n=28)	28.6% (8/28)	9.1% (6/66)	3.1 (1.2-8.2)	57.1	75.0	28.6%	90.9%
>18 mm (n=19)	26.3% (5/19)	12.0% (9/75)	2.2 (0.8-5.8)	35.7	82.5	26.3%	88.0%
<i>Extra-abdominal bowel dilation</i>							
<i>Threshold</i>	<i>Incidence in EABD group</i>	<i>Incidence in Non-EABD group</i>	<i>Relative risk (95% CI)</i>	<i>Sensitivity (%)</i>	<i>Specificity (%)</i>	<i>PPV</i>	<i>NPV</i>
>6 mm (n=78)	14.1% (11/78)	18.7% (3/16)	0.7 (0.2-2.4)	78.6	16.3	14.1%	81.3%
>10 mm (n=61)	14.7% (9/61)	15.1% (7/47)	0.9 (0.3-2.7)	64.3	35.0	14.8%	84.8%
>14 mm (n=47)	14.9% (7/47)	14.9% (7/47)	1.0 (0.4-2.6)	50.0	50.0	14.9%	85.1%
>18 mm (n=34)	17.6% (6/34)	13.3% (8/60)	1.3 (0.5-3.5)	42.9	65.0	17.6%	86.7%

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table 3

Association of intra-abdominal bowel dilation (IABD) >14 mm with adverse neonatal outcomes in gastroschisis

<i>Outcome</i>	<i>IABD >14 mm (n=28)</i>	<i>IABD 14 mm (n=66)</i>	<i>P-value</i>
Bowel atresia (n=14)	28.6%	9.1%	0.01
Necrotizing enterocolitis (n=12)	17.9%	10.6%	0.33
Bowel perforation (n=4)	4.5%	3.5%	0.83
Bowel necrosis (n=6)	10.7%	4.5%	0.35
Complex gastroschisis (n=18)	28.6%	15.1%	0.13
Neonatal death (n=3)	3.6%	3.0%	0.89
NICU length of stay (days)	80.5 (34.5-136.5)	47.5 (31.0-78.0)	0.02
Time on ventilator (days)	2.0 (0-6.0)	2.0 (0-5.0)	0.91
Time to abdominal wall closure (days)	5.0 (1.5-6.0)	6.0 (3.5-8.0)	0.05
Time on TPN (days)	33.0 (22.0-72.0)	36.0 (20.0-55.0)	0.52
Time to initial enteral feeds (days)	17.5 (12.5-22.5)	16.0 (12.0-21.0)	0.93
Time to full enteral feeds (days)	36.0 (25.0-52.0)	38.5 (21.5-65.5)	0.92

Data expressed as % or median (interquartile range).

Table 4

Association of bowel wall thickness >3 mm with adverse neonatal outcomes in gastroschisis

<i>Outcome</i>	<i>Thickened bowel wall (n=6)</i>	<i>Normal thickness bowel wall (n=88)</i>	<i>P-value</i>
Bowel atresia (n=14)	50.0%	12.5%	0.04
Necrotizing enterocolitis (n=12)	50.0%	10.2%	0.03
Bowel perforation (n=4)	16.7%	3.4%	0.23
Bowel necrosis (n=6)	33.3%	4.5%	0.05
Complex gastroschisis (n=18)	50.0%	17.1%	0.08
NICU length of stay (days)	100.5 (82.0-196.0)	48.5 (31.0-81.5)	0.03
Time on ventilator (days)	6.0 (2.0-14.0)	1 (0-5.0)	0.17
Time to abdominal wall closure (days)	1.5 (1.0-3.0)	6.0 (4.0-7.0)	0.02
Time on TPN (days)	45.5 (19.0-72.0)	35.5 (21.0-55.5)	0.91
Time to initial enteral feeds (days)	16.5 (11.0-22.0)	17.0 (12.0-21.0)	0.95
Time to full enteral feeds (days)	49.5 (23.0-76.0)	38.0 (25.0-60.0)	0.78

* Data expressed as % or median (interquartile range).