It's Complex: Predicting Gastroschisis Outcomes Using Prenatal Imaging

Short Title: Prenatal imaging predicts gastroschisis outcomes

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ABSTRACT

Introduction: Gastroschisis occurs in 1 out of 2,000 births with survival rates partially contingent on intestinal complications and time to establishing feeding. Enhancements in prenatal imaging have given better insight into postnatal outcomes. The goal of this study was to examine the gastroschisis patient population at a single children's hospital in the modern era and to utilize prenatal ultrasound to develop new prenatal prognostic indicators.

Methods: We performed a retrospective review of gastroschisis patients at a quaternary care referral children's hospital from 2010 through 2018. We recorded demographics, prenatal data and imaging, early postnatal data, operative data, and patient outcomes. We compared patients within our cohort born with complex gastroschisis (bowel atresia/ perforation) to uncomplicated gastroschisis patients. Second trimester and third trimester prenatal ultrasounds (US) were evaluated for changes in amniotic fluid level, amount of external bowel, bowel dilatation, and bowel wall edema to identify prognostic indicators of the status of the bowel at birth. For categorical variables, Chi-square tests were used to assess for significance. Univariate and multivariable analyses were used to asses significance between categorical and continuous variables using medians and interquartile ranges or means.

Results: 134 patients were included in the study: complex (24), uncomplicated (110). Compared to uncomplicated gastroschisis, complex patients required longer median days to feeding initiation (44 vs 10, $p<0.001$), full feeding (80 vs 23, $p<0.001$), length of stay (LOS) (83 vs 33, $p<0.001$), and TPN at discharge ($p=0.004$). Full US data was available on 81% of patients, and partial data was identified on 19%. Prenatal US analysis showed significantly more complex patients had polyhydramnios on third trimester US (4.3% to 23.5%, $p=0.018$). US analysis between complex and uncomplicated patients showed large amount of external bowel (41.2% vs 22.3%, $p=0.129$) and prevalence of internal bowel dilation (29.4% vs 10.6%, $p=0.053$) on third trimester US and increase in bowel edema (29.4% vs 13.8%, $p=0.148$) and external bowel dilation (64.7% vs 51.1%, $p=0.429$) from second to third trimester US. Multiple multivariable logistic regression analyses revealed amniotic fluid on third trimester US to be the most significant predictor of complex gastroschisis. However, there were no differences in perioperative or long-term complications in the complex group when compared to the group with uncomplicated gastroschisis.

Conclusions: Markers on prenatal ultrasound can predict intestinal complications at birth. Complex gastroschisis is associated with increased time to feeds and LOS.

Key words: Gastroschisis, complex, prenatal imaging, prognostic factors, ultrasound

INTRODUCTION

Gastroschisis is an anterior abdominal wall defect that occurs in 1 out of every 2000 births with varying outcomes based on intestinal complications [1]. Two of the most important variables in the care of gastroschisis patients include timing of reduction of the bowel back into the abdominal cavity and establishment of full enteral feeding. A patient with complex gastroschisis is diagnosed based on bowel complications present at birth, including intestinal atresia, perforation, or both [Figure 1]. Complex gastroschisis patients experience higher mortality and morbidities, including increased infections and functional bowel deficits, such as short bowel syndrome [2]. Complex and uncomplicated gastroschisis patients experience a significant difference in outcomes, making prenatal identification of complex gastroschisis imperative for parental counseling and perinatal management.

Gastroschisis is often diagnosed on prenatal ultrasound (US) in the second trimester [3]. However, complex gastroschisis is only definitively diagnosed postnatally. Enhanced prenatal imaging has driven studies to identify prognostic factors for complex gastroschisis. Three-dimensional ultrasound has been used to evaluate fetal stomach volume and stomach-bladder distance as prognostic indicators. However, no significant difference was found in these variables between complex and uncomplicated patients [4]. A meta-analysis showed intra-abdominal bowel dilation, polyhydramnios, and gastric dilation could be used to identify a high-risk group more likely to experience post-natal complications [5]. More recently, Dewberry and colleagues identified internal bowel dilation on prenatal ultrasound as a significant predictor of complex gastroschisis and increased time to full enteral feeding [6]. Despite these findings, the prenatal indices identified to date have been mostly subjective and difficult to translate between institutions. The goals of this study were to identify novel indices on serial prenatal ultrasound that can help prognosticate complex gastroschisis and adverse outcomes, and to characterize complex and uncomplicated gastroschisis within our patient population. Our hypothesis was that there are identifiable objective differences between these two groups that can be delineated on prenatal US.

METHODS

This study retrospectively evaluated 134 patients with surgically-repaired gastroschisis at a quaternary-care referral children's hospital from 2010 to 2018. Following consent-exempt approval by the Indiana University Institutional Review Board, records of patients admitted with gastroschisis were queried using hospital and surgical billing records. Newborns with gastroschisis and other major comorbidities, such as complex congenital heart disease, lethal genetic conditions (trisomy 9, 13, 18), major central nervous system abnormalities, and infants who died on transport prior to arrival at the Riley Hospital NICU were excluded. All data was collected and stored in a secure online REDCap database. Birth weight, presence of complex gastroschisis (atresia, perforation), day of life (DOL) of abdominal closure, type of closure (primary closure or use of a silo), presence of infection or sepsis, days until feeding initiation, days until full feeding, requirement for total parenteral nutrition (TPN) at discharge, length of hospital stay, and long-term intestinal complications (dysmotility, volvulus, NEC, adhesive bowel obstruction) were collected for each patient to identify complex patients and evaluate outcomes between complex and uncomplicated patients. Complex gastroschisis was diagnosed based on clinical determination of an atresia, perforation, or both present in the bowel at birth. In patients with matted bowel, the determination was made at a later time. Sepsis was defined as documented or suspected sepsis from any source.

119 patients had either complete or partial prenatal data. 15 patients had no available prenatal medical record. US images were evaluated for bowel wall dilation (internal and external), bowel wall edema, and amount of external bowel (small($<40mm^2$), moderate($40\text{-}70mm^2$), or large($>70mm^2$)). The first prenatal US was generally in the second trimester (median EGA 20 weeks [IQR 17.5-22.5 weeks]), and we defined this study as "second trimester" for the remainder fo the manuscript. Similarly, the final prenatal US was generally in the third trimester (35 weeks [IQR 33.5-36.5 weeks]) and was defined as such for consistency in the manuscript. Measurements of bowel wall thickness [Figure 2] and total area of herniated abdominal contents were obtained using sonographic PACS software measuring tools (GE

Viewpoint). The "area of external defect" was defined as the point of ventral wall defect to the farthest extending loop of bowel in the horizontal plane, and from cranial to caudal extension in the vertical plane [Figure 3]. Additional prenatal information included quantity of amniotic fluid (normal, polyhydramnios or oligohydramnios), as well as estimated fetal weight (EFW) determined from abdominal circumference (AC) for gestational age at time of scan. Any genetic anomalies or major comorbidities seen on US were noted. Finally, second and third trimester US measurements of bowel wall thickness, area of external defect, and wall edema were compared, and any progression or reduction of disease was correlated with outcomes to identify prenatal US prognosticators.

Data from the REDCap database was exported to IBM SPSS Statistics 24 software, which was used to complete Chi-square tests (Fisher's exact or Pearson chi-square) for categorical variables and univariate analyses of continuous variables. Univariate and multivariable analyses were used to asses significance between categorical and continuous variables using medians or means. Univariate analyses were completed for several grouped cohorts using the nonparametric independent-samples median test. Multivariate logistic regression analyses were used to assess the significance of prenatal US factors as predictors of complex gastroschisis. A reduced model multivariate logistic regression analysis was performed on significant prenatal US factors. Sensitivity and specificity analyses were completed on these significant prenatal US factors and positive and negative predictive values were evaluated.

RESULTS

Complex vs Uncomplicated Gastroschisis Outcomes

Of the 134 patients included in this study, 24 (17.9%) had a complex gastroschisis, and 110 (82.0%) were uncomplicated. There was 100% survival in the complex group and a 99.1% survival in the uncomplicated group. The sole mortality in the uncomplicated group was a result of acute NEC totalis that proceeded to septic shock. The patient was progressing well on full feeds before abruptly becoming ill. This patient was born prematurely at 33 weeks EGA, which could have contributed to the development of NEC. Of the complex patients, 3 presented with both atresia and perforation, 16 presented with atresia only, 3 presented with perforation only, and 2 presented with other indications of complex gastroschisis (matted bowel, primary bowel dysfunction). Table 1a shows a comparison of patient characteristics and Tables 1b-1c show a comparison of outcomes for complex vs uncomplicated patients.

There were no significant differences in rates of adhesive bowel obstruction, dysmotility, postoperative infection, and ventral hernia between complex and uncomplicated patients. 16.7% (p=0.02) of complex patients had a central line infection and 20.8% (p=0.02) suffered documented or suspected sepsis in the first 30 days postop, compared to 2.7% and 4.8%, respectively, of uncomplicated patients. [Table 1c]

Prenatal Ultrasound Indices

Median EGA for second trimester US was 20 weeks (IQR 17.5-22.5 weeks) and 35 weeks (IQR 33.5-36.5 weeks) for third trimester US. Median EGA for second trimester US was 20 and 21 weeks for uncomplicated and complex patients respectively and 35 and 34.5 weeks respectively on third trimester US. Complex patients had a mean defect area of 932.25 mm^2 on second trimester US and 4918.88 mm^2 on third trimester US. In contrast, uncomplicated patients had a mean defect area of 996.62 mm^2 on second trimester US and 3920.62 mm^2 on third trimester US. Pearson chi-square and Fishers Exact tests revealed polyhydramnios was significantly increased in complex patients from second to third trimester US (4.3% to 23.5%). Though not statistically significant, other differences in groups were noted, including increased amount of external bowel (p=0.129) and increased internal bowel dilation (0.053) among complex patients on third trimester US. From second to third trimester US, complex patients had an increase in external bowel dilation (51.1% to 64.7%, p=0.429) and an increase in bowel edema (13.8% to 29.4%, p=0.148). Mean defect area, bowel thickness, and abdominal circumference were evaluated

between complex and uncomplicated patients on second and third trimester US without a significant difference between groups. [Tables 2-3]

All factors on third trimester US and change in external bowel, bowel edema, and bowel dilation from second to third trimester US were assessed as predictors for complex gastroschisis using multivariate logistic regression models. In a multivariable regression model including all US factors, amount of external bowel ($p=0.031$), amniotic fluid ($p=0.011$), change in external bowel ($p=0.044$), and change in bowel edema ($p=0.032$) were found to be significant both alone and in the full model. In a multivariable regression model including only these four factors, polyhydramnios amniotic fluid was found to be the only factor significantly associated with complex gastroschisis at birth ($p=0.011$) [Table 4]. Sensitivity and specificity analyses were completed for these four factors, where an increased amount of external bowel on third trimester US compared to second trimester US showed the highest sensitivity (58.8%) and polyhydramnios amniotic fluid on third trimester US showed the highest specificity (95.7%) [Table 5].

DISCUSSION

The goal of this study was to compare complex and uncomplicated gastroschisis patients in a large single institution cohort and use serial prenatal US to identify new prenatal markers to predict complex disease. Since this study was done at a single institution, characterization of the patient population was important. Our comparison of uncomplicated and complex gastroschisis patients showed increased morbidities in complex patients including more post-operative days to initiate enteral nutrition, wean TPN, and achieve full enteral nutrition. Complex patients had a significantly higher rate of central line infections and documented or suspected sepsis, including line, intra-abdominal, urologic, and unknown source, in the first 30 days post-operation, anticipated by increased days with a central or PICC in place for parenteral nutrition. Similarly, a previous study comparing outcomes for complex and uncomplicated patients showed complex patients also had more days to enteral feeding initiation and full enteral feeds, a longer LOS, prolonged parenteral nutrition, and increased rates of sepsis [2]. Previous studies, one of which was conducted at the same institution as this study, also showed an increase in mortality for complex patients, which differed from our study, in which the mortality in the complex group was zero [2,7]. A more recent study from the Children's Hospital of Pennsylvania showed no increase in mortality for complex gastroschisis, similar to the results of this study [8]. Interestingly, there were no significant differences in many long-term complications between complex and uncomplicated patients. Trends showed an increased percentage of complex patients had an adhesive bowel obstruction, dysmotility, and post-operative infections. However, these differences were not significant. A previous study showed a significant increase in NEC in complex patients, which was predictive of poor outcomes, however, we did not see NEC complications among complex patients in this study [8]. Similar data for increased rates of surgical re-intervention for adhesive bowel obstruction in complex patients was demonstrated in another previous study [9]. Overall, however, other studies confirmed our data that high rates of dysmotility and hernia repair occur in both complex and uncomplicated patients [9]. These findings could indicate complex patients experience more short-term complications after birth and during their significantly increased hospital stay. However, having complex gastroschisis did not appear to influence long-term outcomes and intestinal function.

On prenatal US, patients with complex gastroschisis were more likely to have polyhydramnios on third trimester US. Interestingly, there were no significant differences between patients who eventually had complex vs uncomplicated gastroschisis on second trimester US. Polyhydramnios amniotic fluid on third trimester US was the most predictive factor for complex gastroschisis. Trends showed more complex patients had an increase in both external bowel and bowel edema from second to third trimester US and an increased amount of external bowel on third trimester US, but these values were not statistically significant. These findings make physiologic sense, as threatened bowel can be expected to become more edematous over time, even in relation to the amount of bowel injury normally expected with the exposure to amniotic fluid in gastroschisis. While the initial second trimester US itself may not

be helpful to predict complex gastroschisis, third trimester US and change over time may be more useful in prenatal counseling, thus serial US into the third trimester is valuable. This data validates previous studies showing polyhydramnios [5] on prenatal US is predictive of complex gastroschisis and adds additional factors predictive of complex gastroschisis.

Large amount of external bowel on third trimester US, polyhydramnios on third trimester US, and an increase in bowel edema from second to third trimester US all had a high specificity, which makes identification of these factors on prenatal US useful in identification of patients that may be more likely to be born with a complex gastroschisis. All three of these factors also had a high negative predictive value making patients without these factors on prenatal US less likely to be born with a complex gastroschisis. These results indicate evaluation of third trimester US and trends from second to third trimester US are valuable in identification of factors related to complex gastroschisis at birth. These factors can be used to plan for delivery, help with team readiness for what to expect at birth, and to inform family of LOS and complications they can expect for their baby.

Limitations of this study include a small sample size, specifically of complex patients, due to the rare nature of these intestinal complications. The single institution nature of this study also introduced institutional bias of particular methods to treat gastroschisis patients, whereas patients with the same presentation may be treated differently at other institutions. The solution to both of these challenges would be to expand this study to a multi-institutional cohort to increase the patient number and level out treatment biases of a particular institution. Other limitations in evaluation of prenatal data include missing prenatal US data for 15 patients in the study. The sample size of 119 patients, however, showed significant predictive value of complex gastroschisis from US factors.

CONCLUSION

Not surprisingly, complex gastroschisis patients had a significantly longer LOS, time to initiation of enteral nutrition, and time to full enteral nutrition postnatally. We were able to identify polyhydramnios in third trimester US as a strong predictor of complex gastroschisis at birth, and several other ultrasound factors, including a large amount of external bowel on third trimester US and an increase in bowel edema from second to third trimester US, had high specificity and negative predictive value. Using these prenatal markers to prognosticate which patients will fall into the complex gastroschisis category can inform prenatal family counseling and immediate postnatal care. Future studies will work to validate these prenatal markers in a larger multi-institutional cohort.

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Figure Legend

Figure 1. Patient with complex gastroschisis, including small bowel necrosis, small bowel atresia, and colonic atresia

Figure 2. Measurement of bowel wall thickness

Figure 3. Measurement of area of external defect

Table 1a. Patient characteristics for complex vs uncomplicated gastroschisis

Table 1b. Comparison of outcome data for complex vs uncomplicated gastroschisis

Table 1c. Frequency of postnatal complications for complex vs uncomplicated gastroschisis

Table 2. Comparison of US factors from second trimester (2^{nd} tri) US and third trimester (3^{rd} tri) US for complex and uncomplicated patients

Table 3. Comparison of prenatal US measurments for complex and uncomplicated gastroschisis patients

Table 4. Multivariate logistic regression analysis of predictors of complex gastroschisis on third trimester (3^{rd} tri) US

Table 5. Sensitivity and specificity for US predictors of complex gastroschsis

Figure 1. Patient with complex gastroschisis, including small bowel necrosis, small bowel atresia, and colonic atresia

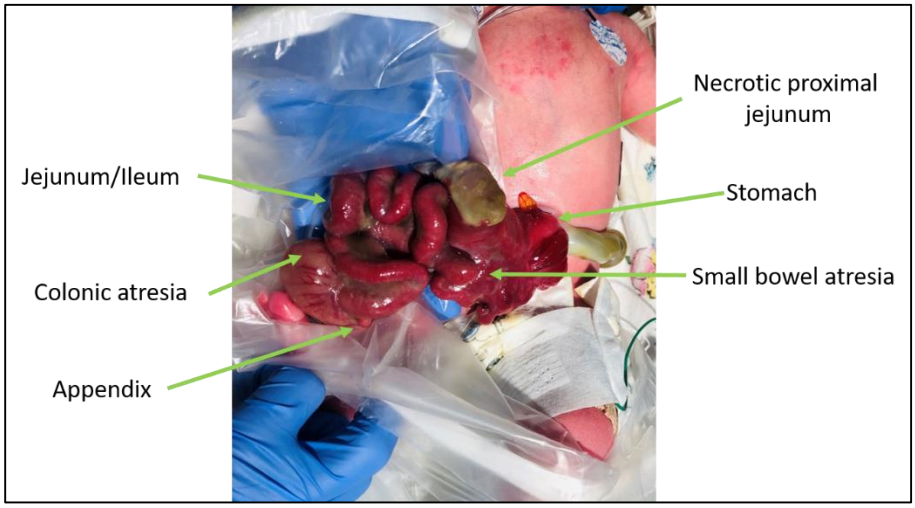


Figure 2. Measurement of bowel wall thickness

Figure 3. Measurement of area of external defect

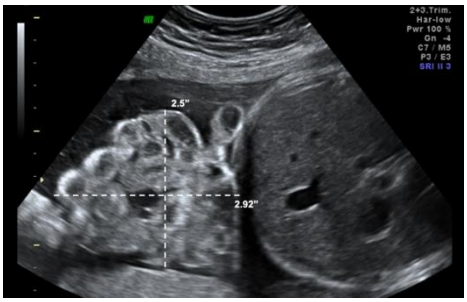


Table 1a. Patient characteristics for complex vs uncomplicated gastroschisis

Table 1a Patient characteristics for complex vs uncomplicated

	Complex (n=24)	Uncomplicated (n=110)	P
Sex	13 (54.2%) male 11 (45.8%) female	49 (44.5%) male 61 (55.5%) female	0.499
C-section	5 (20.8%)	39 (35.5%)	0.231
Silo placement	18 (75%)	97 (88.2%)	0.110
*EGA at birth	35.4±2.9	36.5±1.5	0.087
*Birth weight (grams)	2369.1±685.2	2496.7±517.9	0.397
*APGAR 1 minute	6.5±2.6	6.4±2.5	0.936
*APGAR 5 minutes	7.8±1.5	7.8±1.7	0.890

*Values represent means +/- standard deviation.

Table 1b. Comparison of outcome data for complex vs uncomplicated gastroschisis

Table 1b Comparison of outcome data for complex vs uncomplicated

	Complex (n=24)	Uncomplicated (n=110)	P
Days intubated in first 30 days of life (DOL)	9 (3-30)	5 (0-18)	0.074
DOL abdominal closure	7 (1-20)	5 (1-20)	0.054
Days to feeding initiation	**44 (5-92)**	**10 (3-71)**	**0.001**
Days to full feeding	**80 (17-356, n=23)**	**23 (10-179, n=109)**	**< 0.001**
Length of stay	**83 (28-263)**	**33 (16-113, n=109)**	**< 0.001**

Values represent medians and range.

Table 1c. Frequency of postnatal complications for complex vs uncomplicated gastroschisis

Table 1c Postnatal complications for complex vs uncomplicated

	Complex (n=24)	Uncomplicated (n=110)	P
TPN required at discharge	**7 (29.2%)**	**7 (6.4%, (n=109))**	**0.004**
NEC	1 (4.2%)	2 (1.8%)	0.450
Adhesive bowel obstruction	3 (12.5%)	5 (4.5%)	0.153
Dysmotility	7 (29.2%)	23 (20.9%)	0.420
Central line infection	**4 (16.7%)**	**3 (2.7%)**	**0.020**
Postoperative infection	7 (29.2%)	18 (17.1% (n=105))	0.250
Sepsis in first 30 days post-op	**5 (20.8%)**	**5 (4.8% (n=105))**	**0.020**
Ventral hernia	3 (12.5%)	21 (19.1%)	0.566

Table 2. Comparison of US factors from second trimester (2nd tri) US and third trimester (3rd tri) US for complex and uncomplicated patients

Table 2 Comparison of US factors				
		Complex (n=24)	Uncomplicated (n=110)	p
Amount of external bowel (2nd tri US)				
	Small/moderate	22 (100%, n=22)	96 (98%, n=98)	1.000
	Large	0 (0%)	2 (2%, n=98)	
Amount of external bowel (3rd tri US)				
	Small/ moderate	10 (58.8%, n=17)	73 (77.7%, n=94)	0.129
	Large	7 (41.2%)	21 (22.3%)	
Amniotic fluid (2nd tri US)				
	Normal/ oligohydramnios	22 (100%, n=22)	96 (98%, n=98)	1.000
	Polyhydramnios	0 (0%)	2 (2%)	
Amniotic fluid (3rd tri US)				
	Normal/ oligohydramnios	**13 (76.5%, n=17)**	**90 (95.7%, n=94)**	**0.018**
	Polyhydramnios	**4 (23.5%)**	**4 (4.3%)**	
Internal bowel dilation (2nd tri US)				
		2 (9%, n=22)	2 (2%, n=97)	0.155
Internal bowel dilation (3rd tri US)				
		5 (29.4%, n=17)	10 (10.6%, n=94)	0.053
External bowel dilation (2nd tri US)				
		2 (9%, n=22)	2 (2%, n=98)	0.153
External bowel dilation (3rd tri US)				
		10 (58.8%, n=17)	47 (50%, n=94)	0.602
Bowel edema (2nd tri US)				
		0 (0%, n=22)	1 (1%, n=98)	1.000
Bowel edema (3rd tri US)				
		4 (23.5%, n=17)	17 (18.1%, n=94)	0.736
Change in bowel edema (2nd tri to 3rd tri US)				
	Same	12 (70.6%, n=17)	81 (86.2%, n=94)	0.148
	More	5 (29.4%)	13 (13.8%)	
Change in amount of external bowel (2nd tri to 3rd tri US)				
	Same	7 (41.2%, n=17)	32 (34%, n=94)	0.590
	More	10 (58.8%)	62 (66%)	
Change in bowel dilation (2nd tri to 3rd tri US)				
	Less/ same	6 (35.3%, n=17)	46 (48.9%, n=94)	0.429
	More	11 (64.7%)	48 (51.1%)	

Table 3. Comparison of prenatal US measurments between complex and uncomplicated gastroschsis patients

Table 3 Comparison of prenatal US measurements between complex and uncomplicated gastroschisis patients

Ultrasound Factor		Complex	Uncomplicated	P
Defect area (mm^2)				
	2nd Trimester US	1003.8±787.3 (n=12)	1094.4±891.5 (n=60)	0.214
	3rd Trimester US	3937.9±2377.6 (n=15)	3584.9±1712.2 (n=81)	0.792
Bowel Thickness (mm)				
	2nd Trimester US	2.3±0.4 (n=12)	2.1±0.6 (n=62)	0.726
	3rd Trimester US	3.3±1.5 (n=15)	3.4±1.3 (n=82)	0.590
Abdominal Circumference (cm)				
	2nd Trimester US	16.4±4.4 (n=22)	15.1±3.5 (n=96)	0.210
	3rd Trimester US	26.3±3.3 (n=14)	27.0±3.0 (n=86)	0.473

Values represent means +/- standard deviation.

Table 4. Multivariate logistic regression analysis of predictors of complex gastroschisis on third trimester (3rd tri) US

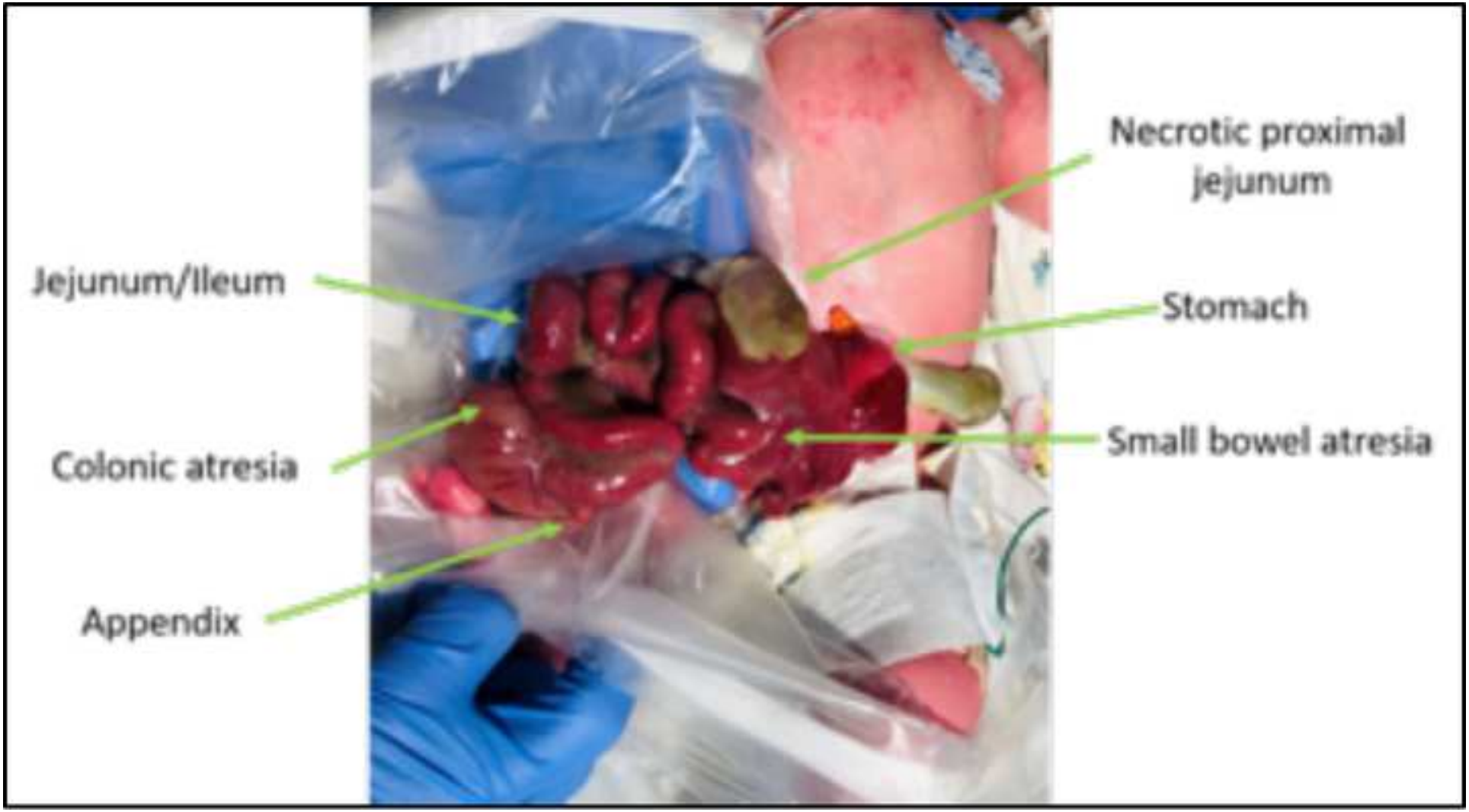
Table 4 Multivariable logistic regression of US factors			
Ultrasound Factor	Reduced model (p-value)	Full model Odds ratio [CI] (p-value)	
Amount of external bowel on 3rd tri US	0.054	Large	3.586 [0.980-13.123] (0.054)
		Small or moderate	Reference
Amniotic fluid on 3rd tri US	**0.013**	**Polyhydramnios**	8.754 [1.646-46.548] **(0.011)**
		Normal or oligohydramnios	Reference
Change in external bowl	0.092	Large	0.291 [0.077-1.102] (0.069)
		Small or moderate	Reference
Change in bowel edema	0.064	More	3.320 [0.857-12.858] (0.082)
		Same	Reference

Table 5. Sensitivity and specificity for US predictors of complex gastroschisis

Table 5 Sensitivity and specificity tests for US predictors of complex gastroschisis				
Predictor of complex gastroschisis on 3rd trimester (tri) prenatal US	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Large amount of external bowel	41.2%	77.7%	25%	88%
Polyhydramnios amniotic fluid	23.5%	95.7%	50%	87.4%
More external bowel compared to 2nd tri US	58.8%	34%	13.8%	82%
More bowel edema compared to 2nd tri US	29.4%	86.2%	27.8%	87.1%

Figure

Click here to access/download;Figure;Figure 1.tiff



Figure

Click here to access/download;Figure;Figure 2.tiff

Figure

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