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The significance of organ prolapse in gastroschisis ☆

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ABSTRACT

Purpose: The aim of this study was to evaluate the incidence and importance of organ prolapse (stomach, bladder, reproductive organs) in gastroschisis.
Methods: This is a retrospective review of gastroschisis patients from 2000 to 2014 at a single tertiary institution. Statistical analysis was performed using a chi-square test, Student's *t* test, log-rank test, or Cox regression analysis models. All tests were conducted as two-tailed tests, and p-values < 0.05 were considered statistically significant.
Results: One hundred seventy-one gastroschisis patients were identified. Sixty-nine (40.6%) had at least one prolapsed organ besides bowel. The most commonly prolapsed organs were stomach (n = 45, 26.3%), reproductive organs (n = 34, 19.9%), and bladder (n = 15, 8.8%). Patients with prolapsed organs were more likely to have simple gastroschisis with significant decreases in the rate of atresia and necrosis/perforation. They progressed to earlier enteral feeds, discontinuation of parenteral nutrition, and discharge. Likewise, these patients were less likely to have complications such as central line infections, sepsis, and short gut syndrome.
Conclusions: Gastroschisis is typically described as isolated bowel herniation, but a large portion have prolapse of other organs. Prolapsed organs are associated with simple gastroschisis, and improved outcomes most likely due to a larger fascial defect. This may be useful for prenatal and postnatal counseling of families.
Type of study: Case Control/Retrospective Comparative Study.
Level of evidence: Level III.

Gastroschisis is a congenital anterior abdominal wall defect typically located to the right of the umbilicus which results in herniation of the small bowel into the amniotic cavity. The etiology of gastroschisis is largely unknown. Several risk factors have been linked to gastroschisis including young maternal age, low maternal BMI, maternal smoking and maternal infection to name a few. Pregnancies complicated with gastroschisis have a variable prenatal course with up to 10% ending in unexpected fetal demise. Additionally, a subset of fetuses with gastroschisis have other complications, including intrauterine growth restriction (IUGR) or decreased mesenteric blood flow. Fortunately, sonographic diagnosis of gastroschisis can be made between 11 and 14 weeks gestation and upwards of 90% of pregnancies are diagnosed prenatally [1,2]. Early identification permits monitoring for IUGR as well as intra-abdominal bowel dilatation (IABD), polyhydramnios, and gastric dilatation which are markers for postnatal complications.

Postnatally, gastroschisis is often divided into simple and complex subgroups. Approximately 80–90% of cases of gastroschisis are simple or isolated gastroschisis [2–4]. The remaining 10–20% of patients have complex gastroschisis which is typically defined as complicated by intestinal perforation, stenosis, volvulus, atresia or necrotizing enterocolitis (NEC) [2–5]. Gastroschisis is generally considered to have good outcomes because, unlike patients with omphalocele, gastroschisis is typically not associated with other congenital abnormalities. However, those patients with complex gastroschisis may suffer extensive bowel loss, liver failure, sepsis, and early childhood death [5].

Further research regarding the natural history of gastroschisis is essential as the global and national incidence has risen in the recent decades and is currently 2–5 per 10,000 live births [1–3,6,7,2,8,9]. Early identification of factors which may predict complex gastroschisis would aid in prenatal counseling of patients.

1. Materials and methods

This is an IRB approved retrospective case series. Patients were identified in one of two ways. (1) All inborn cases of antenatally diagnosed

Abbreviations: IUGR, intrauterine growth restriction; IABD, intraabdominal bowel dilation; NEC, necrotizing enterocolitis; QoL, quality of life; BP%, biparietal diameter percentile; FL%, femur length percentile; AC%, abdominal circumference percentile; TPN, total parenteral nutrition.

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gastroschisis from September 1, 2000 to December 31, 2011 at the Medical College of Wisconsin and Children's Hospital of Wisconsin. Neonates were excluded if they were born at an outside institution, had incomplete records, or if a diagnosis of ruptured omphalocele were made immediately after delivery. (2) The Children's Hospital of Wisconsin has a Clinical Outcomes Registry which is a prospectively consented registry used to acquire medical and quality of life (QoL) data concurrently in pediatric patients across multiple specialties. Patients in this registry born between 2002 and 2014 with the diagnosis of gastroschisis were identified. The two databases were combined and duplicate records removed. A total of 171 unique patients were identified. One patient did not have data available regarding organ prolapse and was excluded from that portion of the analysis.

A chart review was performed to obtain demographic and clinical data. Maternal data included age at delivery, gravidity, parity, and smoking status.

Fetal data included estimated weight percentile, biparietal diameter percentile (BP%), femur length percentile (FL%), and abdominal circumference percentile (AC%). Fetuses were noted to have IUGR if the femur length/abdominal circumference was >23.5 on ultrasound or if IUGR was recorded in the mother's chart.

Neonatal data included estimated gestational age at delivery, birth weight percentile and sex. Gestational age was based on the best available estimated date of confinement (last menstrual period or ultrasound derived). The type of gastroschisis was categorized as simple or complex. Complex gastroschisis was defined as that complicated by intestinal perforation, stenosis, volvulus, atresia or NEC. NEC was identified surgically or by pneumatosis intestinalis on imaging.

Outcomes recorded included length of ventilator support, time to initiate enteral feedings, length of total parenteral nutrition (TPN), and length of stay. Other outcomes included central line infections, sepsis, wound infections/dehiscence, and death. Sepsis was defined as culture proven cases only. Charts were also analyzed for subsequent operations. Subsequent operations excluded line placements, line repairs, line removals, and silo reductions.

The type of abdominal closure was recorded and defined as primary or delayed with silo placement.

Fetal, maternal and neonatal charts were also analyzed for the presence of other prolapsed organs besides bowel. Prolapse was defined as any organ outside the fascial defect other than bowel (small bowel, large bowel or duodenum). Prolapse was recorded as present if it was identified on prenatal ultrasound, the physical exam of the history and physical note, or if it was noted in the operative report. The type of organ prolapsed was also recorded. The prolapsed reproductive organs group included ovaries, fallopian tubes, uterus or testes or a combination of the aforementioned categories. The prolapsed organ was categorized as other if it was not a stomach, bladder or reproductive organ. The “other” organs included liver and omentum.

Cases were grouped based on sex and presence or absence of prolapsed organs. Data were first analyzed using descriptive statistics. Categorical variables were summarized with percentages in each category, and compared using a Chi-square test, with exact p-values whenever a cell had fewer than 5 subjects. Normally distributed continuous data was summarized using mean and standard deviation, and compared using a *t* test. Time-to-event outcomes were summarized using median and quartiles, and log-rank test was used for comparisons. For these outcomes, patients who died were censored at the day of death. Logistic regression was used to assess the predictors of prolapsed organs. Cox regression analysis models were used to compare outcomes for patients with and without prolapse adjusting for sex, maternal age, tobacco use, gestational age at delivery, and birthweight percentile. In a follow-up analysis, indictor variables for the prolapse of individual organs were used instead of an overall indicator of any prolapsed organ. All tests were conducted as two-tailed tests and p-values <0.05 will be considered statistically significant. SAS 9.4 (SAS Institute, Cary, NC) was the primary analysis software.

2. Results

Maternal, fetal and neonatal characteristics of the patient population are presented in Table 1 along with stratified data on patients with and without prolapse. There were statistically significant differences in the patient population with prolapse compared to those without any organs prolapsed besides bowel. Mothers of patients with prolapse had statistically less previous pregnancies than those without prolapse. Fetuses with prolapse had similar biparietal diameter percentiles and femur length percentiles but had significantly higher femur length to abdominal circumference percentiles and were more likely to have IUGR. Neonatal characteristics of the two groups were similar for gestational age at delivery and birth weight percentile, however males were less likely to have prolapse. Likewise, patients with prolapse were more likely to have simple gastroschisis.

Given the above difference, patient data was then stratified by sex (Table 2). Male gastroschisis patients had larger biparietal diameter percentiles and were less likely to have prolapsed organs.

Outcomes were then evaluated for all patients and compared between those with and without prolapse (Table 3). Patients with prolapse were less likely to have complex gastroschisis and this difference was continued in two of the defined categories of complex gastroschisis: atresia and necrosis/perforation. Patients with prolapse also had a shorter time to beginning enteral feeds, shorter time to stopping total parenteral nutrition and shorter lengths of stay. Likewise,

Table 1
Maternal, fetal and neonatal characteristics for the entire patient cohort as well as stratified by no prolapse or prolapsed organs. Data are reported as mean ± SD for continuous variables and number (percentile) for binary variables. Statistical differences were calculated between the no prolapse and prolapse groups. Parameters in bold are statistically different.

	All, N = 170 (%)	No prolapse, N = 101 (%)	Prolapse, N = 69 (%)	p-Value
Maternal Characteristics				
Maternal Age (years)	22.2 ± 4.6	22.7 ± 4.6	21.4 ± 4.4	0.069
Gravida	2.0 ± 1.4	**2.2 ± 1.6**	**1.7 ± 1.0**	**0.031**
Primipara	87 (50.9)	47 (54.7)	39 (45.3)	0.201
Tobacco Use	54 (32.1)	35 (64.8)	19 (35.2)	0.368
Fetal Characteristics				
Biparietal Diameter Percentile	37.1 ± 21.6	39.8 ± 21.6	33.5 ± 21.3	0.076
Femur Length Percentile	20.2 ± 18.9	19.5 ± 17.3	21.4 ± 21.0	0.535
FL/AC Percentile	22.8 ± 1.6	**22.5 ± 1.3**	**23.2 ± 1.8**	**0.007**
IUGR	63 (39.1)	**24 (38.7)**	**38 (61.3)**	**<0.001**
Neonatal Characteristics				
Gender				
Male	86 (50.3)	**61 (71.8)**	**24 (28.2)**	**0.001**
Female	85 (49.7)	**40 (47.1)**	**45 (52.9)**	
Gestational Age at Delivery (weeks)	35.5 ± 1.7	35.4 ± 1.9	35.7 ± 1.3	0.163
Birth Weight Percentile	27.1 ± 21.7	29.1 ± 21.4	24.5 ± 22.1	0.181
Simple Gastroschisis	149 (87.1)	**81 (54.7)**	**67 (45.3)**	**0.001**

Table 2
Maternal, fetal and neonatal characteristics for the entire patient cohort as well as stratified by male or female. Data are reported as mean ± standard deviation for continuous variables and number (percentile) for binary variables. Statistical differences were calculated between the no prolapse and prolapse groups. Parameters in bold are statistically different.

	All, N = 171 (%)	Male, N = 86 (%)	Female, N = 85 (%)	p-Value
Maternal Characteristics				
Maternal Age (years)	22.2 ± 4.6	21.8 ± 4.4	22.6 ± 4.7	0.219
Gravida	2.0 ± 1.4	1.9 ± 1.5	2.0 ± 1.4	0.831
Primipara	87 (50.9)	45 (52.3)	42 (49.4)	0.703
Tobacco Use	54 (32.1)	26 (31.0)	28 (33.3)	0.741
Fetal Characteristics				
Biparietal Diameter Percentile	37.1 ± 21.6	**40.9 ± 21.9**	**33.1 ± 20.7**	**0.023**
Femur Length Percentile	20.2 ± 18.9	21.9 ± 19.4	18.5 ± 18.4	0.259
FL/AC Percentile	22.8 ± 1.6	22.8 ± 1.4	22.9 ± 1.7	0.817
IUGR	63 (39.1)	28 (34.1)	35 (44.3)	0.187
Neonatal Characteristics				
Gestational Age at Delivery (weeks)	35.5 ± 1.7	35.6 ± 1.9	35.5 ± 1.5	0.801
Birth Weight Percentile	27.1 ± 21.7	25.6 ± 21.8	28.5 ± 21.6	0.396
Simple Gastroschisis	149 (87.1)	72 (83.7)	77 (90.6)	0.180
Prolapsed Organs	**69 (40.6)**	**24 (28.2)**	**45 (52.9)**	**0.001**
Stomach	**45 (26.3)**	**15 (17.4)**	**30 (35.3)**	**0.008**
Reproductive Organs	**34 (19.9)**	**8 (9.3)**	**26 (30.6)**	**<0.001**
Bladder	**15 (8.8)**	**2 (2.3)**	**13 (15.3)**	**0.003**
Other	3 (1.8)	1 (1.2)	2 (2.4)	0.621

prolapse patients had less complications related to line infections, sepsis and short gut syndrome. When comparing patients with bladder prolapse to those without, no statistical differences were noted in outcomes (Table 4).

Cox regression analysis models were used to determine hazard ratios for the continuous outcomes adjusting for gender, maternal age, maternal tobacco use, gestational age at delivery, and birthweight percentile. Patients with prolapse began enteral feeds earlier (hazard ratio 1.3, p-value 0.126), stopped TPN earlier (hazard ratio 1.4, p-value 0.053) and had shorter lengths of stay (hazard ratio 1.4, p-value 0.056), but none of these values reached statistical significance. In this model, patients with prolapse had similar lengths of intubation (hazard ratio 0.93, p-value 0.674).

3. Discussion

Gastroschisis and omphalocele are the two most common abdominal wall defects. The severity of the omphalocele is often described by the presence of liver herniation, however, gastroschisis is generally described as containing only bowel. Indeed, this is often cited as one of the main differences between gastroschisis and omphalocele, along with location of the defect, and associated anomalies [10]. Yet, when the literature is evaluated, several gastroschisis studies document the presence of other prolapsed organs [11–20]. These studies rarely comment on outcomes in patients with prolapsed organs, and those that do focus on patients with bladder prolapse [12,17–20]. The aim of this study was to evaluate the incidence and importance of organ prolapse in gastroschisis.

Patient characteristics were compared based on the presence or absence of prolapse and this revealed several interesting differences in maternal, fetal and neonatal parameters. Mothers of patients with prolapse had less previous pregnancies but the two patient populations had similar numbers of first time mothers. It has been established that multigravidas, particularly those whom have changed partners, have the higher risk than primigravidas for having a child with gastroschisis [21]. The pathophysiology of this finding has not been established. This data set is similarly unable to explain the discrepancy in the number of previous pregnancies between the groups.

Fetal characteristics which were different between patients with prolapse and those without included FL/AC% and presence of IUGR. These two parameters are related and the presence of statistical differences in these attributes between patients with and without visceral herniation highlights a known problem in documentation of growth in fetuses with gastroschisis. Patients with gastroschisis have bowel outside their abdomen, thus their abdominal circumference is abnormally small. Theoretically, the larger the fascial defect, the smaller the abdominal circumference. Yet, one definition of IUGR is FL/AC greater than 23.5. Thus, many have argued that these measurements are not appropriate to define IUGR in this patient population. To further this point, when one looks at the neonatal characteristics, there was no difference

Table 3
Outcomes data for the entire patient cohort as well as stratified by no prolapse or prolapsed organs. Data are reported as median (1st quartile – 3rd quartile) for continuous variables and number (percentile) for binary variables. Statistical differences were calculated between the no prolapse and prolapse groups. Parameters in bold are statistically different.

	All, N = 170 (Q_1–Q_3)	No prolapsed organs, N = 101 (Q_1–Q_3)	Prolapsed organs, N = 69 (Q_1–Q_3)	p-Value
Complex	22 (12.9%)	**20 (19.8%)**	**2 (2.9%)**	**0.001**
Bowel Atresia	13 (7.6%)	**12 (11.9%)**	**1(1.4%)**	**0.012**
Necrosis/Perf	10 (5.9%)	**9 (8.9%)**	**1(1.4%)**	**0.050**
Volvulus	6 (3.5%)	6 (5.9%)	0 (0%)	0.082
NEC	14 (8.2%)	10 (9.9%)	4 (5.8%)	0.339
Ventilator Days	4.0 (2.0–9.0)	4.0 (2.0–10.0)	4.0 (3.0–9.0)	0.644
Other Related Operations	0.0 (0.0–1.0)	0.0 (0.0–2.0)	1.0 (0.0–1.0)	0.740
Days to Initiate Feeds	15.0 (11.0–23.0)	**17.0 (12.0–25.0)**	**14.0 (11.0–20.0)**	**0.038**
Days to Stop TPN	23.0 (18.0–35.0)	**25.0 (19.0–41.0)**	**21.0 (17.0–30.0)**	**0.005**
Length of Stay	29.0 (23.0–44.0)	**30.0 (23.0–58.0)**	**27.0 (22.0–36.5)**	**0.006**
Wound Breakdown	30 (17.9%)	15 (15.2%)	15 (21.7%)	0.273
Central Line Infection	14 (8.2%)	**13 (13.0%)**	**1 (1.4%)**	**0.007**
Sepsis	12 (7.1%)	**11 (11.1%)**	**1 (1.4%)**	**0.029**
Short Gut Syndrome	7 (4.1%)	**7 (6.9%)**	**0 (0.0%)**	**0.042**
Death	9 (5.3%)	8 (7.9%)	1 (1.4%)	0.085

Table 4
Outcomes data for the entire patient cohort as well as stratified by no bladder prolapse or prolapsed bladder. Data are reported as median (1st quartile – 3rd quartile) for continuous variables and number (percentile) for binary variables. Statistical differences were calculated between the no bladder prolapse and bladder prolapse groups. Parameters in bold are statistically different.

	All, N = 170 (Q_1–Q_3)	No bladder prolapse, N = 156 (Q_1–Q_3)	Bladder prolapse, N = 15 (Q_1–Q_3)	p-Value
Complex Gastroschisis	22 (12.9%)	22 (14.2%)	0 (0.0%)	0.223
Bowel Atresia	13 (7.6%)	13 (8.4%)	0 (0.0%)	0.380
Necrosis/Perf	10 (5.9%)	10 (6.5%)	0 (0.0%)	0.603
Volvulus	6 (3.5%)	6 (3.9%)	0 (0.0%)	0.658
NEC	14 (8.2%)	14 (9.0%)	0 (0.0%)	0.371
Ventilator days	4.0 (2.0–9.0)	4.0 (2.0–9.0)	4.0 (4.0–11.0)	0.925
Other Related Operations	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.5 (0.0–1.0)	0.681
Days to Initiate Feeds	15.0 (11.0–23.0)	15.0 (11.0–23.0)	15.0 (11.0–21.0)	0.265
Days to Stop TPN	23.0 (18.0–35.0)	23.0 (18.0–36.0)	22.0 (17.0–28.0)	0.121
Length of Stay	29.0 (23.0–44.0)	28.0 (23.0–48.0)	30.0 (24.0–36.0)	0.209
Wound Breakdown	30 (17.9%)	27 (17.6%)	3 (20.0%)	1.000
Central Line Infection	14 (8.3%)	14 (9.1%)	0 (0.0%)	0.371
Sepsis	12 (7.1%)	12 (7.8%)	0 (0.0%)	0.390
Short Gut Syndrome	7 (4.1%)	7 (4.5%)	0 (0.0%)	0.635
Death	9 (5.3%)	9 (5.8%)	0 (0.0%)	0.608

in birth weight percentile in patients with and without prolapse. This exemplifies the erroneous nature of the definition of IUGR for patients with gastroschisis.

While FL/AC% and IUGR defined as FL/AC greater than 23.5 may not be useful measures of fetal growth in gastroschisis, the discrepancy in FL/AC% between patients with and without prolapse still offers valuable information. Patients with prolapse had higher FL/AC% with similar FL%. The only way to have a larger FL/AC% with a similar numerator is to have a smaller denominator. Thus, the abdominal circumference must be smaller in the prolapsed group. This supports our theory that patients with prolapse have a larger fascial defect. The larger fascial defect allows prolapse of more bowel and even herniation of other viscera. And despite the fact that more viscera are outside the abdomen, the fascial defect is large enough that there is no impingement of mesenteric blood supply. The robust blood supply through the wide fascial opening leads to intact bowel without atresias or necrosis/perforation. Therefore, these patients would have a lower likelihood of complex gastroschisis. Thus, prolapsed organs may be a marker of a larger fascial defect and a decreased risk of complex gastroschisis, particularly complex gastroschisis due to atresias or necrosis/perforation.

Interestingly, while the overall cohort had nearly identical numbers of male and female patients, males were much less likely to have prolapsed organs. Initially, one may think this difference is simply because the testes have migrated to the scrotum and are thus not in a location permitting prolapse. However, when the data were reanalyzed dividing the cohort by sex there were statistical differences not just in prolapsed reproductive organs, but also in stomach and bladder prolapse. Thus, the disparity in the rate of organ prolapse by sex is not simply due to the location of the reproductive organs.

It was also interesting to note that male and females had a similar incidence of simple and complex gastroschisis. This may imply that organ prolapse is a more reliable indicator of outcomes in females, however a larger cohort will be necessary to verify this theory. The only other statistical difference noted between males and females was a larger biparietal diameter percentile but previous studies have shown that males have larger biparietal diameters measurements than females [22].

After defining differences in patient characteristics with and without prolapse, patient outcomes were then evaluated. Prolapse patients are less likely to have complex gastroschisis. It is, therefore, not surprising that this patient population has improved outcomes. Similar to what is seen in the literature comparing simple and complex gastroschisis, prolapse patients have shorter times to initiate enteral feed and to discontinue total parenteral nutrition. They have shorter lengths of stay. Likewise, prolapse patients have less complications such as central line infections, sepsis and short gut syndrome. No difference was noted in mortality between gastroschisis patients with and without prolapsed, but may be a result of an insufficient sample size.

In an attempt to control for confounders, continuous outcomes were evaluated with a Cox regression model to adjust for gender, maternal age, maternal tobacco use, estimated gestational age and birth weight percentile. When analyzed in this manner, there were no statistical differences in days to initiate feeds, days to stop TPN, length of intubation or length of stay. A larger cohort may alter these results and allow adjusted outcomes to be calculated for binary parameters such as central line infections or sepsis.

As mentioned above, previous studies have investigated the presence of bladder herniation and outcomes in gastroschisis patients. In 2010, Werner reviewed the 11 cases of bladder herniation in gastroschisis patients reported in the literature prior to that time [17]. Despite the fact that five of these patients had prenatal hydronephrosis or hydroureter, only one patient suffered significant morbidity or mortality [17]. This patient's death was attributed delivery at a community hospital which was a substantial distance from a tertiary center [17]. Subsequent to this article, Mousty et al. described six patients with bladder herniation out of 105 gastroschisis patients [12]. Five of these patients were female and one was male. The single male patient died at 36 weeks in utero. All of the female patients survived to delivery and discharge. One patient had complex gastroschisis and the median length of stay for these patients was 89 days (Q1 = 40, Q3 = 98). None of the bladder prolapse patients in this cohort had complex gastroschisis and the median length of stay was 30 days (Q1 = 24, Q3 = 36). No other outcome data is recorded in the paper. Similar to our data, Werner and Mousty found that bladder herniation was more common in females. Mousty suggests that with gastroschisis and bladder prolapse have poorer outcomes and require close observation. It is further suggested that male gastroschisis patients with bladder prolapse are noted to have a poorer outcome. Unfortunately, this conclusion is based off two subjects. In our cohort, there was no difference in patient outcomes in patients with or without bladder prolapse (Table 4). There were only 2 male patients with bladder herniation in our patient population. Both had simple gastroschisis, underwent primary repair and were discharged home in 20 and 27 days. More data is necessary to determine if male gastroschisis patients with bladder prolapse portend worse outcomes.

4. Conclusions

In conclusion, the presence of organs prolapsed in gastroschisis in addition to bowel (bladder, stomach, liver, omentum, or reproductive organs) appears to be predictive of improved outcomes. This may be a marker of a larger fascial defect allowing for better mesenteric blood supply. Patients with prolapsed organs were more likely to have simple gastroschisis with significant decreases in the rate of atresia and necrosis/perforation. They progressed to earlier initiation of enteral feeds, discontinuation of parenteral nutrition and discharge. Likewise, these patients were less likely to have complications such as central line infections, sepsis and short gut syndrome.

A multicenter study is underway to further elucidate the prognostic value of organ prolapse in gastroschisis patients. A larger cohort would allow statistical analysis that controls for confounders and would permit further characterization of outcomes based on the particular organ prolapsed and sex of the patient. This may improve the quality of prenatal counseling in gastroschisis patients as the presence of a prolapsed organ on prenatal ultrasound may be indicative of improved outcomes.

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