Review Article
Gastroschisis: Antenatal Sonographic Predictors of Adverse Neonatal Outcome

Rachael Page, Zachary Michael Ferraro, Felipe Moretti, and Karen Fung Kee Fung

Division of Maternal-Fetal Medicine, The Ottawa Hospital, General Campus, 501 Smyth Road, Room 8472, Ottawa, ON, Canada K1H 8L6

Correspondence should be addressed to Karen Fung Kee Fung; kfung@ottawahospital.on.ca

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Objectives. The aim of this review was to identify clinically significant ultrasound predictors of adverse neonatal outcome in fetal gastroschisis. Methods. A quasi-systematic review was conducted in PubMed and Ovid using the key terms “gastroschisis,” “predictors,” “outcome,” and “ultrasound.” Results. A total of 18 papers were included. The most common sonographic predictors were intra-abdominal bowel dilatation (IABD), intrauterine growth restriction (IUGR), and bowel dilatation not otherwise specified (NOS). Three ultrasound markers were consistently found to be statistically insignificant with respect to predicting adverse outcome including abdominal circumference, stomach herniation and dilatation, and extra-abdominal bowel dilatation (EABD). Conclusions. Gastroschisis is associated with several comorbidities, yet there is much discrepancy in the literature regarding which specific ultrasound markers best predict adverse neonatal outcomes. Future research should include prospective trials with larger sample sizes and use well-defined and consistent definitions of the adverse outcomes investigated with consideration given to IABD.

1. Introduction

Gastroschisis is a congenital abdominal wall defect occurring in approximately 5 in 10,000 live births [1]. As a full thickness defect in the anterior abdominal wall gastroschisis is almost invariably located to the right of the umbilical ring and is characterized by the extrusion of the midgut from the coelom with the absence of a membranous covering (Figure 1) [2]. The pathophysiology of gastroschisis continues to elude clinicians and researchers although risk factors that are consistently associated with the development of this defect include young maternal age, low BMI, race, smoking, low socioeconomic status, recreational drug use, and alcohol consumption during pregnancy [3]. Although the survival rate for infants born with gastroschisis is approximately 90% it is associated with significant morbidity resulting from prolonged hospital stay, delay in time to start oral feeding, time on ventilator, long-term use of total parenteral nutrition (TPN), multiple surgical interventions, and neonatal complications including sepsis, necrotizing enterocolitis, and short bowel syndrome [4, 5].

The condition of the bowel at birth is an important prognostic factor for neonatal comorbidities. Neonates with gastroschisis can be divided into two groups, which have distinct and unique outcomes, based on the presence or absence of associated bowel complications including atresia, necrosis, volvulus, perforation, and ischemia [6]. Optimal management for neonates with gastroschisis is unclear given the controversy in literature regarding which factors most accurately predict neonatal outcomes [7]. As such, this review aims to highlight sonographic predictors of neonatal outcome most commonly reported in the literature including bowel thickness, bowel dilatation, stomach dilatation, stomach herniation, bladder herniation, intruterine growth restriction (IUGR), abdominal circumference, hyperperistalsis, being small for gestational age (SGA), amniotic fluid index (e.g., polyhydramnios, oligohydramnios, and meconium-stained amniotic fluid), and liver herniation. An improved ability to predict which fetuses are at an increased risk for neonatal complications may assist with appropriate triage, aid in prenatal counseling/medical management of gastroschisis,
and encourage multisystem neonatal support to minimize postnatal complications [8, 9].

2. Methods

2.1. Search Strategy. PubMed and Ovid were queried to identify relevant literature pertaining to antenatal ultrasound predictors of adverse outcome in gastroschisis. To complement the comprehensive Ovid search, a PubMed search was conducted using the search terms “gastroschisis and predictors and outcome” with no filters applied. This yielded 15 papers that were included if they met the following inclusion criteria:

(1) antenatal gastroschisis diagnosis,
(2) predictors of adverse outcome being the primary focus of study.

All abstracts were reviewed for content relevance and 2 papers were excluded as they were out of scope and focused on the effects of maternal factors and colonic atresia on adverse outcomes. The remaining 13 papers were read in detail and eliminated if the primary outcome of the study was not specifically ultrasound predictors of adverse neonatal outcome; this left four papers for review.

Two additional Ovid searches were conducted to ensure completeness using the Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R), 1946 to present. The first search used the terms “gastroschisis” and “predictors of outcome.” Each of the terms was searched independently and then combined to generate the new combined search term of “Gastroschisis AND predictors of outcome” which yielded a total of 2 results. One of the two was a duplicate from the previous PubMed search and the other was read and excluded as it failed to satisfy the aforementioned inclusion criteria. The second Ovid search used the key words “gastroschisis” and “ultrasound.” Similar to the first Ovid search, the terms were searched separately and then combined to generate the new search term of “Gastroschisis and Ultrasound” which yielded a total of 91 results. The following limits were then applied:

(1) English,
(2) humans,
(3) publication year: 2009-current.

The publication year limits were set in order to ensure that studies captured were relevant to modern clinical practice. A total of 34 search results remained. All papers were reviewed and 20 were omitted (duplicates or failed to meet inclusion criteria) (see the Appendix). The remaining 12 were then comprehensively reviewed and included. Lastly, reference lists of the included studies were searched for original articles that may meet inclusion criteria. Two papers were retrieved using this method leaving a total of 18 papers included in this review.

2.2. Synthesis Strategy. Key details pertaining to our objectives and inclusion criteria were extracted from the 18 papers and tabulated (Table 1). The data extracted included descriptive information including patient characteristics, sample size, study design and analytical methods, prenatal ultrasound markers evaluated, adverse outcomes reported, statistically significant prenatal ultrasound markers predictive of outcome, odds ratios and 95% confidence intervals (OR 95% CI), and $P$ values.

3. Prenatal Ultrasound Markers and Identification of Adverse Outcomes

3.1. Intra-Abdominal Bowel Dilatation (IABD). Several studies report IABD (Figure 2) as a significant predictor of various adverse outcomes in cases presenting with gastroschisis [1, 10–13]. However, heterogeneity among included studies with respect to methodology and diagnostic thresholds for IABD has resulted in contradictory results (Table 1). For instance, Nick et al. [10] completed a single-centre retrospective chart review and report that IABD in the second trimester is a statistically significant predictor of bowel atresia as all infants in this study that presented with IABD were diagnosed with
Table 1: Summary of prenatal ultrasound markers predictive of adverse outcome in the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study characteristics</th>
<th>Sample size [n]</th>
<th>Methods</th>
<th>Prenatal UM evaluated</th>
<th>Adverse outcome</th>
<th>Prenatal UM predictive of outcome</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puliganda et al., 2004 [16]</td>
<td>Retrospective analysis. Infants born with GS between 1990 and 2000</td>
<td>113</td>
<td>Analysis of variance (ANOVA), Student's t-test, and Fisher's exact tests and linear and logistic regression used for statistical analysis; ( P &lt; 0.05 ) = significant</td>
<td>IUGR</td>
<td>Number of surgeries Days on TPN Days to full PO Days NPO Length of stay (days)</td>
<td>None</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Nick et al., 2006 [10]</td>
<td>Retrospective review from January 1998 to August 2004. All neonates delivered with GS and admitted to Vanderbilt University Medical Centre</td>
<td>72</td>
<td>Binary variables analyzed with Fisher's exact test; continuous variables analyzed by logistic regression; Wilcoxon's rank sum test determined if the number of days to complete closure and LOS was different between neonates with and without atresia; ( P &lt; 0.05 ) = significant</td>
<td>IABD (no threshold) IUGR &lt;10th percentile Abnormal umbilical artery Doppler velocimetry</td>
<td>Small-bowel atresia IUGR LOS in NICU LOS in hospital Time to complete closure Discharge status of infant</td>
<td>IABD</td>
<td>&lt;0.0001</td>
<td>0.0199</td>
</tr>
<tr>
<td>Davis et al., 2009 [9]</td>
<td>Retrospective analysis of neonates with GS at a single institution between June 1998 and March 2007</td>
<td>46</td>
<td>Comparisons made using Fisher's exact test, Pearson's test, Student's t-test for continuous variables, or ANOVA; ( P &lt; 0.05 ) = significant</td>
<td>Bowel dilatation (&gt;10, &gt;17, &gt;20mm) Bowel wall thickness (&gt;3, &gt;4mm) A(H)</td>
<td>Bowel atresia Necrotic bowel Bowel stenosis In utero volvulus Other outcomes explored but all NS</td>
<td>None</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Houben et al., 2009 [13]</td>
<td>Retrospective review of all infants born with GS at King's College Hospital (UK) from August 1994 to December 2007</td>
<td>46</td>
<td>Data quoted as median (range)</td>
<td>IABD &gt; 10mm Growth restrictions Hyperperistalsis</td>
<td>Closing gastrochisis (defined as circumferential or partial closure of the ring around protruding bowel associated with intestinal atresia, bowel ischemia, bowel necrosis, or viable intestine)</td>
<td>IABD</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Payne et al., 2009 [22]</td>
<td>Retrospective analysis of all GS patients born between January 1990 and December 2007 admitted at NICU of the Children's Hospitals and Clinics of Minnesota, Minneapolis Campus</td>
<td>155</td>
<td>Normality of data examined using Shapiro-Wilk test; nonnormal distributed variables were summarized as median and range; univariate analyses performed using Wilcoxon's rank-sum or Fisher's exact tests; linear regression used to determine association between parenteral nutrition and LOS; variables associated with LOS at ( P &lt; 0.10 ) were included in multiple regression; ( P &lt; 0.05 ) = significant</td>
<td>( A )H &lt; 5th percentile AC &lt;5th percentile Dilated intestine (&gt;10 mm, &gt;18 mm)</td>
<td>GI complication Requiring a silo Primary repair</td>
<td>Dilated intestine (&gt;10 mm) Dilated intestine (&gt;18 mm) None</td>
<td>NR</td>
<td>0.01</td>
</tr>
<tr>
<td>Study</td>
<td>Study characteristics</td>
<td>Sample size</td>
<td>Methods</td>
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<td>Nicholas et al., 2009 [17]</td>
<td>Retrospective cohort study at Washington University Medical Center from 1991 to 2006</td>
<td>80</td>
<td>Multivariable and univariable statistical analysis, backward stepwise logistic regression used to identify variables in final prediction model; ( P &lt; 0.10 ) = significant in univariate analysis; predictive effectiveness of final model evaluated using area under receiver operating characteristic curve (AUC-ROC)</td>
<td>Dilated bowel &gt;10 mm</td>
<td>Composite death, prolonged hospital stay, &gt;2 surgeries, feeding difficulties, sepsis, atresia</td>
<td>IUGR</td>
<td>2.7 (1.0–73)</td>
<td>0.05</td>
</tr>
<tr>
<td>Ajayi et al., 2011 [18]</td>
<td>Retrospective review of pregnancies complicated by GS between 2000 and 2008</td>
<td>74</td>
<td>Multivariable and univariable statistical analysis, backward stepwise logistic regression used to identify variables in final prediction model; ( P &lt; 0.10 ) = significant in univariate analysis; predictive effectiveness of final model evaluated using area under receiver operating characteristic curve (AUC-ROC)</td>
<td>AC &lt;25th percentile</td>
<td>Mortality</td>
<td>None</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Alfaraj et al., 2011 [23]</td>
<td>Retrospective study of singleton neonates with GS delivered at Mount Sinai Hospital with postnatal care at the Hospital for Sick Kids in Toronto, Canada, from January 2001 to February 2010</td>
<td>98</td>
<td>Multivariable and univariable statistical analysis, backward stepwise logistic regression used to identify variables in final prediction model; ( P &lt; 0.10 ) = significant in univariate analysis; predictive effectiveness of final model evaluated using area under receiver operating characteristic curve (AUC-ROC)</td>
<td>Gastric dilatation &gt;2 SD above normal value</td>
<td>Meconium stained amniotic fluid, intestinal atresia, necrosis, or perforation</td>
<td>Gastric dilatation</td>
<td>None</td>
<td>NR</td>
</tr>
<tr>
<td>Contro et al., 2010 [12]</td>
<td>Retrospective study of all GS cases between November 1998 and September 2008</td>
<td>48</td>
<td>Multivariable and univariable statistical analysis, backward stepwise logistic regression used to identify variables in final prediction model; ( P &lt; 0.10 ) = significant in univariate analysis; predictive effectiveness of final model evaluated using area under receiver operating characteristic curve (AUC-ROC)</td>
<td>IABD &gt; 6 mm</td>
<td>Bowel obstruction, bowel resection, sepsis, atresia</td>
<td>IABD</td>
<td>4.05</td>
<td>0.037</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>EABD &gt; 6 mm</td>
<td>Time in NICU (days)</td>
<td>None</td>
<td>NR</td>
<td>0.062</td>
</tr>
<tr>
<td>Study</td>
<td>Study characteristics</td>
<td>Sample size</td>
<td>Methods</td>
<td>Prenatal UM evaluated</td>
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<td>Garcia et al., 2010[4]</td>
<td>Retrospective study of singletons with a prenatal diagnosis of GS at a tertiary center for fetal medicine in Brazil from January 1997 to August 2009</td>
<td>94</td>
<td>Cut-off value for prediction determined in ROC curve; cases grouped according to bowel dilatation and compared with chi-square and Fisher's exact test and Mann-Whitney U test</td>
<td>Bowel dilatation &gt; 25 mm</td>
<td>Intrauterine fetal death (IUD)</td>
<td>None</td>
<td>NR</td>
<td>0.003</td>
</tr>
<tr>
<td>Mears et al., 2010[24]</td>
<td>Retrospective study of all cases of isolated GS diagnosed antenatally from 2004 to 2008</td>
<td>47</td>
<td>Spearman correlations used to explore relationships between antenatal findings and outcome measurements. Differences between groups examined with Kruskal-Wallis and Mann-Whitney U tests; P-value &lt;0.05 = significant</td>
<td>IABD &gt; 10 mm</td>
<td>Type of surgical repair (primary, silo, patch, or stoma)</td>
<td>EABD predicted primary closure</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Kuleva et al., 2012[11]</td>
<td>Retrospective case-control study of all antenatal diagnoses of isolated GS from 1999 to 2010</td>
<td>105</td>
<td>Normality of continuous data tested using Kolmogorov-Smirnoff test; between group comparisons using Fisher's exact test; Mann-Whitney U test or Student's t-test; relationship between prenatal ultrasound markers, complex GS and adverse outcome tested by chi-square test and logistic univariate and multivariate regression; all P values &lt;0.05 = significant</td>
<td>Thickered intestinal wall</td>
<td>CGS</td>
<td>IABD</td>
<td>4.13 (1.32–12.90)</td>
<td>0.048</td>
</tr>
<tr>
<td>Long et al., 2011[19]</td>
<td>Cases of antenatally diagnosed GS were identified from an in-house database of antenatal ultrasound scans performed in the Fetal Management Unit at St Mary's Hospital, Manchester, from January 1998 to December 2007</td>
<td>170</td>
<td>Chi-square test used to compare categorical outcomes and Fisher exact test used where numbers of included individuals were &lt;10, Mann-Whitney U test used for nonparametric data. P-value &lt;0.05 = significant</td>
<td>Bowel dilatation &gt; 20 mm</td>
<td>GA at delivery</td>
<td>Bowel dilatation</td>
<td>NR</td>
<td>0.02</td>
</tr>
<tr>
<td>McClellan et al., 2011[20]</td>
<td>Retrospective review of patients undergoing surgery for GS at the University of California Los Angeles Medical Center from 1995 to 2010</td>
<td>117</td>
<td>Logistic regression used to compare association between mortality of gastroschisis patients with liver herniation with those without</td>
<td>Liver herniation</td>
<td>Mortality</td>
<td>Liver herniation</td>
<td>NR</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Study</td>
<td>Study characteristics</td>
<td>Sample size ([n])</td>
<td>Methods</td>
<td>Prenatal UM evaluated</td>
<td>Adverse outcome</td>
<td>Prenatal UM predictive of outcome</td>
<td>OR (95% CI)</td>
<td>(P) value</td>
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<tr>
<td>Mousty et al., 2012 [21]</td>
<td>Retrospective cohort study of six singletons with GS associated with secondary fetal bladder herniation managed at a tertiary referral center between 2001 and 2010</td>
<td>6</td>
<td>No statistics presented</td>
<td>Bladder herniation</td>
<td>Mortality</td>
<td>Bladder herniation</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Wilson et al., 2012 [5]</td>
<td>Retrospective review of all cases of GS evaluated prenatally at the Center for Advanced Maternal Fetal Care, September 2007–June 2010</td>
<td>89</td>
<td>Categorical data compared with chi-square test, Student’s (t)-test; (P &lt; 0.05) = significant; linear regression used to estimate association between days in NICU and presence of any bowel dilatation</td>
<td>Bowel dilatation (IABD, EABD, or both) (&gt;10) mm</td>
<td>Gestational age at birth Birth weight at delivery Length of NICU admission Number of surgeries</td>
<td>None</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Janoo et al., 2013 [6]</td>
<td>Retrospective cohort study, all cases of GS managed at West Virginia University Hospital Morgantown 1998–2002</td>
<td>19</td>
<td>(P) value below 0.05 = significant</td>
<td>Bowel thickness Final bowel dilatation Delta dilatation</td>
<td>Time to feeding Final bowel dilatation Delta dilatation Number of days on ventilator Number of days in hospital</td>
<td>None</td>
<td>NR</td>
<td>0.023 0.007 NS NS</td>
</tr>
<tr>
<td>Goetzinger et al., 2014 [1]</td>
<td>Retrospective cohort study; patients carrying singletons diagnosed with GS, at Washington University Medical Center Division of Ultrasound and Genetics from 2001 to 2010</td>
<td>94</td>
<td>Normality tested using Kolmogorov-Smirnov test; Student’s (t)-tests and Mann Whitney (U) tests used to compare continuous variables; chi-square and Fisher’s exact test used to compare dichotomous categorical variables</td>
<td>IABD (&lt;6, &gt;10, &gt;14, and &gt;18 mm) EABD Bowel-wall thickening ((&gt;3) mm)</td>
<td>Bowel atresia NICU length of stay (days) Bowel atresia NICU length of stay (days)</td>
<td>IABD &gt; 14 mm Thickened bowel wall</td>
<td>0.01 0.02 0.04 0.03</td>
<td></td>
</tr>
</tbody>
</table>

GS: gastroschisis; IUGR: intrauterine growth restriction; TPN: total parenteral nutrition; PO: time to full enteral feedings; NPO: total number of days feeding was held; IABD: intra-abdominal bowel dilatation; NICU: neonatal intensive care unit; AFI: amniotic fluid index; AC: abdominal circumference; GI: gastrointestinal; LOS: length of stay; SGA: small for gestational age; EABD: extra-abdominal bowel dilatation; CGS: complex gastroschisis; IUDF: intrauterine fetal demise; ND: neonatal death; GA: gestational age; IF: intestinal failure; BW: birth weight; NE: necrotizing enterocolitis.

\*\* Denotes explanation that follows.
bowel atresia after birth. However, a threshold was not used to identify the presence of IABD and results may vary if only severe dilatation was included. Moreover, IABD in the second trimester was associated with prolonged NICU length of stay (57 days versus 29 days for those without IABD).

Similar results were reported in a single-centre retrospective cohort study by Goetzinger et al. [1] such that patients with IABD >14 mm had 3-fold greater likelihood of bowel atresia (3.1 OR (95% CI: 1.2–8.2)) in comparison to those without IABD (<14 mm). Prolonged stay in the neonatal intensive care unit (NICU) (81 versus 48 days) was also greater for those with IABD. In a single-centre retrospective case-control study by Kuleva et al. [11], it was demonstrated that infants with IABD (>6 mm) were four times more likely compared to those with IABD (<6 mm) to have complex gastroschisis, which they defined as gastroschisis with associated bowel-related complications (e.g., intestinal atresia, perforations, necrosis, and volvulus). In this study subcategorizing cases into “complex” and “simple” gastroschisis aided in predicting morbidity as the infants that were classified as complex gastroschisis required multiple interventions and stoma placement, with a longer time on parenteral nutrition and a prolonged hospital stay [11]. Likewise, Contro et al. [12] reported that infants with IABD (>6 mm) had a fourfold increased risk of presenting with postnatal bowel obstruction. In this same study, IABD was predictive of the need for bowel resections and a second laparotomy, although no odds ratios were reported. Yet, contrary to the other reports, this single-centre retrospective chart review failed to find a significant association between IABD and NICU length of stay [12]. Finally, with respect to adverse outcomes, Houben et al. [13] focused specifically on closing gastroschisis which they defined as the circumferential or partial closure of the ring around the protruding bowel associated with intestinal atresia, bowel ischemia, bowel necrosis, or viable intestine. Similar to the aforementioned studies, this retrospective chart review reports an association between IABD (>10 mm) and closing gastroschisis with associated intestinal atresia. However, these results must be interpreted with caution as they failed to report odds ratios or P values.

Only three of the studies reported maternal characteristics, albeit to a limited degree. Furthermore, no statistical tests were completed to determine if there were significant relationships between maternal characteristics and adverse outcome [1, 11, 12]. Maternal prepregnancy weight, body mass index (BMI), and nutrition/lifestyle issues were not reported in any of the five studies and are factors known to influence fetal growth [14, 15]. Collectively, the definition of IABD is inconsistent and diagnostic thresholds varied between studies. Standardized measures are of utmost importance to reliably define a threshold for severe IABD. Only then can consensus be reached in terms of its true clinical significance in predicting adverse outcome. If no or low thresholds are used the prevalence of adverse outcomes is likely overestimated and modifications to current practice may not be warranted. Goetzinger et al. [1] concluded that despite the presence or absence of sonographic findings such as IABD, EABD, and bowel wall thickness, they do not advocate a change in antenatal surveillance or timing of delivery. In contrast, Houben et al. [13] highlighted the importance of early delivery if closing gastroschisis was suspected. In light of these discrepancies it is evident that further research is required in order to reconcile variation in clinical recommendations with respect to timing of delivery and other surgical intervention in fetal gastroschisis.

3.2. Intrauterine Growth Restriction (IUGR). Puligandla et al. [16] define IUGR as insufficient in utero fetal growth based on ultrasound examinations, Doppler flow assessments, and biophysical profiles. Many clinicians support preterm birth for infants with significant IUGR, which is a topic of controversy for infants with gastroschisis [16]. For instance, a retrospective chart review by Nick et al. [10] reviewed several antenatal variables to assess their ability to predict the presence of neonatal bowel atresia. IUGR, defined as birth weight for gestational age of less than the 10th percentile, was found to be a significant predictor as six of ten newborns with atresia presented with IUGR (60%), compared with ten of forty-eight without atresia (21%) [8]. Similarly, in a large retrospective cohort study, Nicholas et al. [17] confirmed a high incidence of IUGR in gastroschisis and an increased risk for adverse neonatal outcomes. In this study, they used a composite definition for adverse neonatal outcome which included neonatal death, prolonged hospital stay, > two surgeries, feeding difficulties, sepsis, and gastrointestinal atresia [17]. Conversely, Puligandla et al. [16] demonstrated that IUGR infants with gastroschisis had equivalent outcomes to infants without IUGR. Furthermore, there was no difference between the two groups regarding the number of surgeries required, days on TPN, days to full enteral feeding (PO), total number of days oral feeding was held (NPO), and the length of hospital stay.

Although several studies have indicated IUGR as a significant predictor [10, 16, 17], others have suggested that the prevalence of IUGR is overestimated up to twofold when compared to the diagnosis of SGA at birth [18]. Reasons for this observation may include the fact that sonographic estimated fetal weight (EFW) calculations heavily rely on abdominal circumference which has been found to be smaller in fetal gastroschisis given that the fetal intestines are protruding through the intestinal wall [18].

Nicholas et al. [17] evaluated a collection of maternal characteristics and lifestyle factors and failed to detect any association with adverse outcome. However, Nick et al. [10] and Puligandla et al. [16] did not report any maternal characteristics or lifestyle factors. Puligandla et al. [16] concluded that, in the context of IUGR, routine premature delivery (<36 weeks) was not advocated. In their retrospective chart review, infants born at less than 37 weeks of gestation had more surgeries, longer time on TPN, longer times to full enteral feeding, and longer lengths of stay, despite excluding those with atresia. Although the findings of this single study are not supportive of elective preterm birth in IUGR the results must be interpreted with caution.

3.3. Bowel Wall Thickness. It has been proposed that bowel exposure to amniotic fluid results in progressive bowel injury
over time, resulting in a sonographic change in the bowel wall’s appearance [1]. Bowel wall thickness as a sonographic predictor for adverse neonatal outcome has been studied less extensively and produced discrepant findings. For instance, Goetzinger et al. [1] suggested prolonged exposure of the fetal bowel to the amniotic fluid results in progressive bowel injury over time and consequently changes the bowel wall appearance. In a retrospective study, Goetzinger et al. [1] demonstrated an increased risk for bowel atresia, necrotizing enterocolitis (NEC), prolonged NICU length of stay, and prolonged time to abdominal wall closure in fetuses with thickened bowel wall greater than 3 mm. Despite reaching statistical significance, it was noted that all cases of thickened bowel wall occurred in fetuses with IABD greater than 14 mm. Thus, it is difficult to interpret what factor independently predicts these outcomes [1]. In contrast, Kuleva et al. [11] examined the difference in prevalence of thickened intestinal wall between cases complicated with simple and complex gastroschisis. Of interest, they reported no significant differences between groups. However, one cannot rule out the possibility that differences may have been observed if a continuous threshold was used for determining the presence or absence of thickened intestinal wall as opposed to simple dichotomous categorization. Similarly, in a separate retrospective cohort study, Janoo et al. [6] did not observe any between-group differences in neonatal outcomes with respect to bowel thickness, although a trend emerged suggesting that an adverse event was more likely with a progressively thicker bowel. Lastly, Davis et al. [9] evaluated the clinical significance of bowel wall thickening of >3 and >4 mm but found no relationship between bowel wall thickness and bowel condition at birth or with poor clinical outcomes.

Although Goetzinger et al. [1] reported maternal characteristics, the study was limited as they only looked at a comparison between fetuses with IABD and those without and bowel wall thickness was not included in the analysis. On the other hand, the remaining three studies failed to comprehensively report maternal characteristics and demographics and did not look at the potential association between these factors and adverse outcomes in fetal gastroschisis [6, 9, 11].

With respect to timing of delivery and bowel thickness, Goetzinger et al. [1] did not support a change in the timing of delivery or antenatal surveillance despite ultrasound findings of EABD, IABD, and bowel wall thickness. Likewise, Janoo et al. [6] found no relationship between gestational age and time to feeding, length of hospital stay, or number of days on ventilator indicating their findings do not suggest elective preterm birth. Despite the agreement between these two studies, properly designed trials are needed prior to making clinical recommendations regarding timing of delivery.

3.4. Bowel Dilatation: NOS. Bowel dilatation, not otherwise specified (NOS), refers to the studies that did not differentiate between intra-abdominal bowel dilatation and extra-abdominal bowel dilatation when doing their analyses. For instance, in a retrospective chart review, Garcia et al. [4] reported a significant association between bowel dilatation greater than 25 mm and intestinal abnormalities, lower rate of primary surgical closure, longer periods to achieve full oral feeding, and a prolonged hospital stay. In fact, bowel transverse diameter (BTD) > 25 mm yielded a sensitivity of 38%, a specificity of 87%, a positive predictive value (PPV) of 38%, and a negative predictive value (NPV) of 87%. Similar results were observed in another retrospective chart review by Long et al. [19] who reported that bowel dilatation greater than 20 mm was predictive of a higher infant mortality rate and a prolonged time on parenteral nutrition (PN). Although infants with bowel dilatation spent an average longer time on PN the median number of days between the two groups was not different [19]. In a secondary analysis evaluating the effect of atresia on the number of days spent on PN, independent of bowel dilatation, a significant difference was found between those without atresia (median 20 days) versus those with atresia (median 65 days) [19]. These findings illustrate the significant effect that adverse outcomes, such as bowel atresia, can have on secondary neonatal outcomes. In contrast to the studies by Garcia et al. [4] and Long et al. [19], the retrospective chart review done by Wilson et al. [5] reported no significant association between bowel dilatation (IABD, EABD, or both) greater than 20 mm and adverse outcome. This discrepancy may be due to smaller sizes and inadequate power to detect change (e.g., n = 87 cases [5] versus n = 170 [19] and n = 94 [4] cases). Similarly, Davis et al. [9] failed to find a significant relationship between bowel dilatation and adverse neonatal outcomes and should be carefully interpreted as the lack of availability of ultrasound records (n = 25) may have attenuated a potential relationship. Nonetheless, despite the clear association between bowel dilatation and adverse outcome, Garcia et al. [4] do not recommend elective preterm delivery as it may add further hazard to the inherent surgical morbidity inherently present and that prolonging delivery beyond 37 weeks of gestation does not serve any benefits.

3.5. Liver Herniation. Although bowel herniation is routinely observed in fetal gastroschisis, liver herniation is less common [20]. As a result, recent literature often categorizes infants into “complex” and “simple” gastroschisis but the presence of liver herniation is not specifically evaluated [20]. In a retrospective chart review, McClellan et al. [20] aimed to evaluate the prognosis of liver herniation in gastroschisis and found that it was significantly associated with a higher rate of mortality. The survival rates were 43% and 97% for gastroschisis with liver herniation and without, respectively [20]. The extent of liver herniation appeared to predictive of comorbidities, including pulmonary hypoplasia, and poor outcome. Of the 7 patients with herniated liver, 3 only had a small portion of the liver herniated and did not seem to be affected [20]. In contrast, the remaining 4 had a larger portion of the liver herniated, had a mortality rate of 100%, and were more likely to require large silos for closure [20]. Despite the apparent association between liver herniation and adverse neonatal outcome, there is limited research on this topic (1 study, n = 117); therefore in order to draw a firm conclusion in regard to clinical recommendations, further research must be conducted.
3.6. Bladder Herniation. Similar to liver herniation, bladder herniation is observed less frequently in gastroschisis patients, with an incidence varying from 4.3% to 14% [21]. Fetuses with gastroschisis have a greater risk of stillbirth during the third trimester and fetal distress which is likely partially related to cord compression due to the herniated bowel. In a retrospective cohort study, Mousty et al. [21] hypothesized that bladder evisceration could cause the cord to be more prone to compression thus increasing perinatal mortality and fetal distress. Mousty et al. [21] was the first study to evaluate the specific outcome (e.g., intrauterine fetal demise (IUD) and neonatal death) of infants with bladder herniation. Of the six infants, the indications for delivery included one IUD, three fetal distresses (i.e., abnormal fetal movement, ultrasound monitoring, and pyelectasis), and one planned C-section. These results appear to support a relationship between bladder herniation and adverse outcome. Therefore, in cases such as these, increased surveillance may be justified. However, future study is required as current investigations fail to report odds ratios or P values.

3.7. Delta Dilatation and Final Bowel Dilatation. In a retrospective chart review, Janoo et al. [6] defined delta dilatation as final bowel dilatation minus baseline bowel dilatation, which was taken from the first ultrasound readings. This review reported no differences in adverse neonatal outcomes with regard to bowel dilatation and bowel thickening, although there was a significant association between delta dilatation (at 4 mm) and final dilatation to time to feeding. However, given the limited research with small sample sizes on this topic (1 study, $n = 19$) these results must be interpreted with caution with respect to their direct clinical impact.

4. Prenatal Ultrasound Markers Likely Unrelated to Adverse Outcome

4.1. Abdominal Circumference (AC). AC measures are smaller in infants with gastroschisis in part because the intestines protrude through the abdominal wall defect [18]. Consequently, this then leads to a false positive appearance of IUGR which in turn leads to unnecessary interventions (i.e., elective preterm delivery) [18]. For example, Ajayi et al. [18] using a retrospective chart review examined AC less than the 5th percentile and its effect on several adverse outcomes including, mortality, primary closure, necrotizing enterocolitis, short gut syndrome, length of stay, days intubated, days until room air oxygen, days until full enteral feeding, and days on TPN. Neonatal outcomes in patients with small AC (<5th percentile) were similar to those with a normal AC. Similarly, Payne et al. [22] validated previous findings that AC less than 5th percentile had no predictive value for either gastrointestinal complications or the need for a silo. The concordant results of Ajayi et al. [18] and Payne et al. [22] may be attributed to similar designs (i.e., both retrospective chart reviews) or attention to confounding variables. Payne et al. [22] accounted for various maternal demographics and clinical characteristics including age, race, marital status, and cigarette use and examined their relationship with hospital length of stay. However, none of the relationships appeared statistically significant. Despite their similar study designs, Ajayi et al. [18] did not examine any maternal parameters. Overall, the concordance between the three studies reporting these outcomes suggests that abdominal circumference <5th percentile is of little concern to clinicians for infants with gastroschisis as there have been no significant relationships found between AC <5th percentile and adverse neonatal outcome of any kind.

4.2. Stomach Herniation and Dilatation. In a retrospective cohort study, Nicholas et al. [17] revealed a slightly higher incidence of adverse outcome in fetuses with stomach dilatation, but the data failed to reach statistical significance. Similarly, Kuleva et al. [11] compared the prevalence of stomach herniation and dilatation between the simple gastroschisis group and the complex gastroschisis group. In agreement with the previous findings, this retrospective case control study confirmed that there was no significant difference in prevalence between the two groups suggesting that stomach herniation and dilatation were not predictive markers. Lastly, using a retrospective chart review, Alfaraj et al. [23] reported comparable results with regard to stomach dilatation. Yet, gastric dilatation was not predictive of the presence of neonatal bowel atresia, necrosis, or perforation. There were also no statistically significant differences in the need for intestinal resection, age at full enteral feeding, length of hospital stay, presence of short bowel syndrome, or neonatal death. However, in contrast to the above studies, Ajayi et al. [18] revealed that meconium-stained amniotic fluid at delivery was more common in fetuses presenting with gastric dilatation (53%) than in those without (24%) ($P = 0.017$). Both Kuleva et al. [11] and Alfaraj et al. [23] report few, if any, maternal characteristics, demographics, or lifestyle factors. On the contrary, Nicholas et al. [17] evaluation several maternal and lifestyle factors and assessed their association with adverse outcome but results yielded no significance relationships. Overall, a significant association between stomach herniation or dilatation and adverse neonatal outcome remains to be conclusively demonstrated.

4.3. Extra-Abdominal Bowel Dilatation (EABD). Dilatation of the herniated portion of the fetal bowel may be more reflective of impaired peristalsis rather than true obstruction [1]. This hypothesis appeared to be consistent with the findings of the four studies evaluated [1, 11, 12, 24]. Extra-abdominal bowel dilatation (Figures 3 and 4) was common in many of the studies included in this review despite no association between EABD of any threshold and adverse outcome [1, 11, 12, 24]. For instance, in a retrospective chart review, Contro et al. [12] frequently observed EABD >6 mm but failed to find an association with adverse outcomes. Similarly, both Kuleva et al. [11] and Goetzinger et al. [1] used EABD >6 mm as a threshold and noted that it was not predictive of complex gastroschisis or bowel atresia, respectively. With respect to study design, Kuleva et al. [11] and Goetzinger et al. [1] were retrospective case-control and retrospective cohort studies, respectively. Lastly, using a retrospective chart
### Table 2: Table of excluded studies.

<table>
<thead>
<tr>
<th>Study excluded</th>
<th>Reason for exclusion</th>
</tr>
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</table>
Focus: GA, BW, route, intent of delivery, timing of delivery |
Focus: effect of time to surgery on gastroschisis outcome |
Focus: bowel appearance after birth |
Focus: timing of delivery |
Focus: intestinal transplants |
| C.L. Snyder, "Outcome analysis for gastroschisis," *Journal of Pediatric Surgery*, vol. 34, no. 8, pp. 1253–1256, 1999. | Date of publication too old (wanted to stay relevant with research and practice) |
Focus: multidisciplinary prenatal care and mode of delivery |
Focus: SNAP-II score |
Focus: comparison of diagnosis using 3D ultrasound between 20th and 21st centuries |
Focus: timing of delivery |
Focus: complex versus simple gastroschisis |
Focus: classifying vanishing gastroschisis |
Focus: diagnosis and surgical management |
Focus: EFW calculations |
Focus: challenges and outcomes of management of abdominal wall defects |
Focus: diagnosis, treatment, risk factors, neurodevelopmental outcomes, incidence |
Table 2: Continued.

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<th>Study excluded</th>
<th>Reason for exclusion</th>
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4.4 Future Directions. There is much discrepancy in the literature regarding significant predictors of adverse outcome in fetal gastroschisis. All of the studies included in this review were retrospective in nature (i.e., chart reviews, cohort, or case-control studies). Moving forward, in order to help eliminate bias and discordant findings, prospective studies examining antenatal sonographic markers and their potential associations with adverse neonatal outcomes should be conducted. Although it is difficult to get a large number of patients with fetal gastroschisis given the low prevalence of the condition it is essential to compile a larger patient database to eliminate incongruity, maximize power, and produce valid and reliable results. Furthermore, establishing a consistent definition of adverse outcome (e.g., complex gastroschisis, death, prolonged NICU length of stay, and multiple surgical interventions) with specific attention given to the most sensitive thresholds for bowel dilatation and bowel wall thickness is encouraged. In the current review all published studies used inconsistent definitions of bowel dilatation and bowel wall thickness; therefore the discrepant...
results are expected. It was noted by Garcia et al. [4] that their data confirmed previous reports of a significant and positive correlation between bowel diameter and gestational age. This emphasizes the importance of adjusting the definition of bowel dilatation with varying gestational age, a covariate which should be accounted for in future investigations to improve accuracy.

5. Conclusion

Fetal gastroschisis is associated with several morbidities that may lead to secondary adverse outcomes including prolonged time to start oral feeding, time on ventilator, long-term use of TPN, multiple surgical interventions, and neonatal complications including sepsis, necrotizing enterocolitis, and short bowel syndrome [4, 5]. Despite this, there is still much discrepancy in the literature regarding which ultrasound predictors are most sensitive and clinically relevant to the prediction of adverse neonatal outcomes. Future prospective studies with adequate power and appropriate samples sizes that employ standardized definitions of adverse outcome will help generate reliable and valid data that can be used to inform patient care and ultimately improve maternal-fetal health.

Appendix

See Table 2.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References


