Prenatal Risk Factors and Outcomes in Gastroschisis: A Meta-Analysis

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BACKGROUND AND OBJECTIVE: Gastroschisis is a congenital anomaly with increasing incidence, easy prenatal diagnosis and extremely variable postnatal outcomes. Our objective was to systematically review the evidence regarding the association between prenatal ultrasound signs (intraabdominal bowel dilatation [IABD], extraabdominal bowel dilatation, gastric dilatation [GD], bowel wall thickness, polyhydramnios, and small for gestational age) and perinatal outcomes in gastroschisis (bowel atresia, intra uterine death, neonatal death, time to full enteral feeding, length of total parenteral nutrition and length of in hospital stay).

METHODS: Medline, Embase, and Cochrane databases were searched electronically. Studies exploring the association between antenatal ultrasound signs and outcomes in gastroschisis were considered suitable for inclusion. Two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. All meta-analyses were computed using individual data random-effect logistic regression, with single study as the cluster unit.

RESULTS: Twenty-six studies, including 2023 fetuses, were included. We found significant positive associations between IABD and bowel atresia (odds ratio [OR]: 5.48, 95% confidence interval [CI] 3.1–9.8), polyhydramnios and bowel atresia (OR: 3.76, 95% CI 1.7–8.3), and GD and neonatal death (OR: 5.58, 95% CI 1.3–24.1). No other ultrasound sign was significantly related to any other outcome.

CONCLUSIONS: IABD, polyhydramnios, and GD can be used to an extent to identify a subgroup of neonates with a prenatal diagnosis of gastroschisis at higher risk to develop postnatal complications. Data are still inconclusive on the predictive ability of several signs combined, and large prospective studies are needed to improve the quality of prenatal counseling and the neonatal care for this condition.

Drs D’Antonio and Giuliani designed and conceptualized the study, extracted the data, performed the statistical analysis, wrote the manuscript, and reviewed and revised the manuscript; Dr Virgone designed and conceptualized the study, extracted the data, performed the statistical analysis, wrote the manuscript, and reviewed and revised the manuscript; Drs Rizzo, Khalil, Cohen-Overbeeck, Baud, Kuleva, and Salomon designed the study, contributed to data extraction, and reviewed and revised the manuscript; Drs Flacco and Manzoli designed the study, performed statistical analysis, and reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Gastroschisis is an abdominal wall defect located on the right side of the umbilicus that allows herniation of the abdominal content and its direct exposure to the amniotic fluid for the majority of the pregnancy. The incidence of gastroschisis has risen worldwide in recent decades to reach 2 to 5 per 10,000 live births. The postnatal outcome is favorable in cases of simple gastroschisis (continuous intestine) with a survival rate >95% and low morbidity. In contrast, complex gastroschisis (intestinal atresia, necrosis, or perforation) is associated with worse survival rate (70%–80%), longer hospital stay, and higher long-term morbidity.

The highly variable return to functional bowel (due to chronic intestinal inflammation) and the occurrence of bowel atresia (BA) requiring intestinal surgery in ~10%–20% of cases) are the main factors affecting length of hospital stay (LOS) as well as total parenteral nutrition (TPN) dependence and associated neonatal complications (ie, recurrent sepsis, TPN cholestasis, adhesive bowel obstruction).

Different surgical techniques (primary vs staged closure) to repair this abdominal wall defect did not show significant differences in outcomes. In developed countries, prenatal diagnosis allows a 90% detection rate of gastroschisis within the second trimester of pregnancy. A regular ultrasound monitoring of the fetus with gastroschisis aims to define size and quality of the herniated intestine (bowel dilatation or thickening), amount of amniotic fluid, and fetal growth. Prenatal definition of simple and complex gastroschisis is important to establish accurate prenatal counseling and to plan delivery site and postnatal medical and surgical treatments. Recently, several ultrasound signs, such as bowel dilatation, polyhydramnios, and bowel wall thickness (BWT), have been reported to be associated with the occurrence of unfavorable outcomes and, in particular, with BA.

However, these studies were often based on small sample sizes, and the results did not reach good evidence examining single data sets in isolation. The aim of this study was to define which prenatal ultrasound markers were associated with postnatal outcome in gastroschisis. A meta-analysis was conducted to pool any relative risk estimates from the existing literature on the association between various ultrasound signs and the occurrence of atresia, intrauterine death (IUD), and neonatal death (NND); LOS, time to full enteral feeding (TFEF), and length of TPN (LTPN) in an attempt to determine if there was an association and, if so, its magnitude.

**METHODS**

**Protocol, Eligibility Criteria, Information Sources and Search**

This review was performed according to an a priori designed protocol and recommended for systematic reviews and meta-analysis. Medline, Embase, the Cochrane Library including the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and the Cochrane Central Register of Controlled Trials were searched electronically in June 2014 using combinations of the relevant medical subject heading terms, key words, and word variants for “gastroschisis” and “outcome” (Supplement 1). The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed (Supplementary Fig 2, Supplement 2). The study was registered with the PROSPERO database (registration number: CRD42014007640).

**Study Selection, Data Collection, and Data Items**

Studies were assessed according to the following criteria: population, outcome, gestational age at examination, and ultrasound signs explored. Two authors (FD, CV) reviewed all abstracts independently. Agreement about potential relevance was reached by consensus, and full-text copies of those articles were obtained. Two reviewers (FD, CV) independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached. If >1 study was published for the same cohort with identical end points, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies (Supplement 3).

**Summary Measures, Synthesis of the Results, and Risk of Bias**

The ultrasound signs analyzed in this review were as follows:

- Intraabdominal bowel dilatation (IABD)
- Extraabdominal bowel dilatation (EABD)
- Gastric dilatation (GD)
- BWT
- Polyhydramnios
- Small for gestational age (SGA)

The outcomes analyzed in this systematic review were as follows:

- BA
- IUD
- NND
- LOS
- TFEF
- LTPN

IABD was defined as the dilatation of the bowel inside the abdomen irrespective of the presence of EABD. EABD was
defined as the occurrence of the dilatation of the extruded part of the bowel only. This choice was based on the assumption that EABD is almost invariably present in fetuses with gastroschisis, most likely representing the consequence of bowel exposure to the amniotic fluid, whereas IABD is only occasionally described in this condition. GD was defined as the enlargement of the stomach, and BWT was the measurement of the wall of the bowel inside or outside the defect. SGA was defined as an estimated fetal weight \( \leq 5\text{th} \) or 10th percentile according to the cutoff adopted. In view of the multitude of cutoffs reported for all these ultrasound measurements, a subanalysis according to the threshold chosen to define an ultrasound sign as abnormal was carried out when possible. BA was defined as a congenital obstruction of the bowel lumen. IUD was defined as fetal loss in the second and third trimester of pregnancy, and NND as the occurrence of a death in the neonatal period, up to 28 days of life. LOS was defined as the time from birth to discharge home. TFEF was defined as the time necessary to achieve full enteral nutrition and LTPN as the time of full dependency on parenteral nutrition.

Only studies reporting prenatal ultrasound data of fetuses with gastroschisis were considered suitable for the inclusion in the current systematic review; postnatal studies or studies from which cases diagnosed prenatally could not be extracted were excluded. Autopsy-based studies were excluded on the basis that fetuses undergoing termination of pregnancy are more likely to show associated major structural and chromosomal anomalies. Studies not reporting the site of the dilatation (intra or extra-abdominal) were not considered eligible for the inclusion.

Studies published before 2000 were not included in the current systematic review because advances in prenatal imaging techniques has led to a huge improvements in the diagnosis and definition of prenatal structural anomalies. Furthermore, a recent systematic review exploring the association between EABD and several adverse perinatal outcomes included studies published before 2000.17

Case reports, conference abstracts, and case series with \(< 3\) cases, irrespective of whether the anomalies were isolated, were also excluded to avoid publication bias.

**Statistical Analysis**

Overall, we evaluated separately the association between 6 potential predictors (IABD, EABD, GD, polyhydramnios, SGA) and 6 adverse clinical outcomes (IUD, NND, BA, TFEF, LTPN, LOS). A sufficient number of studies with comparable outcomes were available for only 3 outcomes (IUD, NND, and BA), and a total of \(6 \times 3 = 18\) separate meta-analyses were thus carried out. For the other outcomes (LOS, LTPN, and TFEF), heterogeneity in the data did not allow to perform a meta-analysis.

The units of the meta-analysis were single comparisons of subjects with abnormal versus normal ultrasound signs in predicting each of the selected clinical outcomes during the scheduled follow-up. Accordingly, when a study reported separate relative risks for different patient characteristics (ie, levels of dilation), all subgroups were grouped, and a single estimate of risk was calculated for the study. Unfortunately, the scarce number of studies did not permit meaningful stratified meta-analyses to explore the test performance in subgroups of patients who may be less or more susceptible to bias. For the purpose of this analysis, when multiple cutoffs were reported, that showing the highest degree of association, as reported by the authors, was selected to calculate the ORs.

We included observational cohort studies in which

(a) many comparisons reported 0 events in 1 group,

(b) several comparisons reported 0 events in both groups, and

(c) exposed and unexposed group sizes were frequently severely unbalanced.

Many of the most commonly used meta-analytical methods, including those using risk difference (which could be used to handle total zero-event studies), can produce biased estimates when events are rare.10,19 When many studies are also substantially imbalanced, the best performing methods are the Mantel-Haenszel odds ratio (OR) without zero-cell continuity corrections, logistic regression, and an exact method.20,21 Mantel-Haenszel ORs cannot be computed in studies reporting 0 events in both groups, the exclusion of which may, however, cause a relevant loss of information and the potential inflation of the magnitude of the pooled exposure effect.18 To keep all studies into the analyses, we thus performed all meta-analyses using individual data random-effect logistic regression, with single study as the cluster unit. The pooled data sets with individual data were reconstructed using published 2 tables. When 1 of the overall pooled arms showed no events, we used exact logistic regression including individual studies as dummy variables. The assessment of the potential publication bias was performed with Egger’s regression asymmetry test.22

All analyses were performed using Stata version 13.0 (Stata Corp, College Station, TX).

**RESULTS**

A total of 869 articles were identified, 73 were assessed with respect to their eligibility for inclusion (Supplementary Table 8). Twenty-six studies were included in the
systematic review (Fig 1). These 26 studies included 2023 fetuses with a prenatal diagnosis of gastroschisis.

The general characteristics of the studies included in the systematic review are reported in Table 1. Quality assessment of the included studies was performed using Newcastle-Ottawa Scale for cohort studies. Almost all the included studies showed an overall good rate with regard to the selection and comparability of the study groups and to the ascertainment outcome of interest (Table 2).16 The major weaknesses of these studies were represented by their retrospective design, with the lack of a blind assessment of antenatal imaging in relation to the outcome explored, different thresholds adopted to defined an ultrasound sign as abnormal, and lack of a standardized outcome measure.

The definitions of the ultrasound signs used in each study are shown in Table 3. Several cutoffs were used among the studies to define a scan as abnormal; furthermore, most of the included studies did not assess the reproducibility, interobserver, and intraobserver variability of a given sign. Finally, for most of the ultrasound signs explored, an objective explanation in terms on how (ie, imaging plane, ultrasound machine setting, type of scan) and when a given sign was assessed was missing (Table 3).

The assessment of the potential publication bias was problematic because of the scarce number of studies and sparse events. The formal tests for funnel plot asymmetry cannot be used when the total number of publications included for each outcome is <10 because its power is too low to distinguish chance from real asymmetry.20 Furthermore, in 2 of the 3 comparisons including 10 studies, the number of events was too scarce to allow formal testing (n < 15 overall). We were thus able to

![Flow chart of studies included in the meta-analysis.](image-url)
to assess publication bias in a meta-

analysis only (IABD as a predictor of

BA): we displayed the ORs of

individual studies versus the

logarithm of their SE (–0.144287,

95% confidence interval [CI] =

–1.290532 to 1.001958, P = .779)
(Supplemental Figure 2).

IABD

Nine studies (673 fetuses) explored

the association between IABD and the

occurrence of BA.

Fetuses with ultrasound evidence of

IABD, irrespective of the presence of

EABD, had a signifi-
cantly higher risk of

BA diagnosed at surgery (OR: 5.48, 95%

CI 3.1 – 9.8), whereas the risk of

IUD or

NND was not signi-

fi-
cantly higher than

fetuses without IABD (Table 4).

Three studies24,34,41 explored the

association between IABD and the

overall postnatal LOS. These studies

used different thresholds of

dilatation to de-

fi-
nite the bowel as

abnormal; in the largest study,24

fetuses with an IABD

14 mm had

as

i

gi-

fi-
cant prolonged LOS

compared with those with less

dilated bowel (80.5 days,

interquartile range [IQR], 34.5

– 136.5

vs 47.5 days, IQR 31.0

– 78.0,

P ; .02). Likewise, Nick,41 using GA-
corrected cutoff for bowel dilatation,

reported a median LOS of 84 days in

fetuses with dilatation compared

with those without,

whereas Huh34 could not

fi-

nd any

association between IABD and length

of hospitalization (Table 5).

Two studies24,34 explored the

association between IABD and the TFEF.

Both did not report any signifi-
cantly increased risk in fetuses showing IABD

regarding this outcome (Table 6).

Finally, the presence of IABD was not

found to be significantly associated

with the occurrence of BA.

EABD

Ten studies (659 fetuses) explored

the association between EABD and

the occurrence of bowel atresia.

TABLE 1 General Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>GA at Scan</th>
<th>Fetuses (n)</th>
<th>Prenatal Ultrasound Signs Explored</th>
<th>Outcome(s) Explored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overcasha</td>
<td>2014</td>
<td>United States</td>
<td>Retrospective</td>
<td>1 wk before delivery</td>
<td>191</td>
<td>SGA</td>
<td>BA, NND</td>
</tr>
<tr>
<td>Godzinger</td>
<td>2014</td>
<td>United States</td>
<td>Retrospective</td>
<td>33.7 ± 26 wk</td>
<td>94</td>
<td>IABD, EABD, BWT</td>
<td>BA, NND, LOS, LTPN, TFEF</td>
</tr>
<tr>
<td>Janoo</td>
<td>2013</td>
<td>United States</td>
<td>Retrospective</td>
<td>2–3 wk from delivery</td>
<td>25</td>
<td>SGA, polyhydramnios</td>
<td>IUD, NND</td>
</tr>
<tr>
<td>Durfee</td>
<td>2013</td>
<td>United States</td>
<td>Retrospective</td>
<td>7.6 d (0–8) before delivery</td>
<td>84</td>
<td>EABD, BWT, SGA</td>
<td>IUD</td>
</tr>
<tr>
<td>Earni</td>
<td>2012</td>
<td>Canada</td>
<td>Retrospective</td>
<td>Third trimester</td>
<td>83</td>
<td>IABD, EABD, GD, SGA, polyhydramnios</td>
<td>BA</td>
</tr>
<tr>
<td>Ghanzoli</td>
<td>2012</td>
<td>United Kingdom</td>
<td>Retrospective</td>
<td>From 30 wk</td>
<td>130</td>
<td>IABD, EABD, GD, polyhydramnios</td>
<td>BA</td>
</tr>
<tr>
<td>Overton</td>
<td>2012</td>
<td>United Kingdom</td>
<td>Retrospective</td>
<td>Second-third trimester</td>
<td>217</td>
<td>Polyhydramnios, SGA</td>
<td>IUD, NND</td>
</tr>
<tr>
<td>Kuleva</td>
<td>2011</td>
<td>France</td>
<td>Retrospective</td>
<td>Third trimester</td>
<td>105</td>
<td>IABD, EABD, GD, SGA, BWT</td>
<td>BA, IUD, NND</td>
</tr>
<tr>
<td>Ajayi</td>
<td>2011</td>
<td>United States</td>
<td>Retrospective</td>
<td>Second-third trimester</td>
<td>74</td>
<td>SGA, polyhydramnios</td>
<td>IUD, NND</td>
</tr>
<tr>
<td>Alfaroa</td>
<td>2011</td>
<td>Canada</td>
<td>Retrospective</td>
<td>Within 2 wk of delivery</td>
<td>98</td>
<td>IABD, GD, polyhydramnios</td>
<td>BA, IUD, NND, LOS, TFEF, LTPN</td>
</tr>
<tr>
<td>Mears</td>
<td>2010</td>
<td>United Kingdom</td>
<td>Retrospective</td>
<td>Second-third trimester</td>
<td>47</td>
<td>IABD, EABD</td>
<td>BA, NND, LTPN</td>
</tr>
<tr>
<td>Contro</td>
<td>2010</td>
<td>United Kingdom</td>
<td>Retrospective</td>
<td>From 32 wk</td>
<td>48</td>
<td>IABD, EABD, polyhydramnios</td>
<td>BA, IUD, NND</td>
</tr>
<tr>
<td>Garciaa</td>
<td>2010</td>
<td>Brazil</td>
<td>Retrospective</td>
<td>35.6 ± 1.6 wk</td>
<td>94</td>
<td>EABD</td>
<td>BA, IUD, NND, LOS, TFEF</td>
</tr>
<tr>
<td>Huh</td>
<td>2010</td>
<td>United States</td>
<td>Retrospective</td>
<td>Second-third trimester</td>
<td>43</td>
<td>IABD</td>
<td>BA, IUD, NND, LOS, TFEF</td>
</tr>
<tr>
<td>Hidaka</td>
<td>2009</td>
<td>Japan</td>
<td>Retrospective</td>
<td>Second-third trimester</td>
<td>11</td>
<td>Polyhydramnios</td>
<td>IUD, NND</td>
</tr>
<tr>
<td>Payne</td>
<td>2009</td>
<td>United States</td>
<td>Retrospective</td>
<td>Within 4 wk of delivery</td>
<td>150</td>
<td>Polyhydramnios</td>
<td>LOS</td>
</tr>
<tr>
<td>Towers</td>
<td>2008</td>
<td>United States</td>
<td>Retrospective</td>
<td>Not stated</td>
<td>75</td>
<td>Polyhydramnios</td>
<td>IUD</td>
</tr>
<tr>
<td>Henig</td>
<td>2008</td>
<td>Germany</td>
<td>Retrospective</td>
<td>Not stated</td>
<td>14</td>
<td>EABD, BWT</td>
<td>BA, BA</td>
</tr>
<tr>
<td>Cohen-Overbeck</td>
<td>2008</td>
<td>The Netherlands</td>
<td>Retrospective</td>
<td>Second-third trimester</td>
<td>24</td>
<td>IABD, EABD, SGA, polyhydramnios</td>
<td>BA, IUD, NND</td>
</tr>
<tr>
<td>Santiago-Munzra</td>
<td>2007</td>
<td>United States</td>
<td>Retrospective</td>
<td>Second-third trimester</td>
<td>58</td>
<td>SGA, GD</td>
<td>IUD</td>
</tr>
<tr>
<td>Brantberg</td>
<td>2006</td>
<td>Norway</td>
<td>Prospective</td>
<td>From 34–36 wk</td>
<td>60</td>
<td>IABD</td>
<td>BA, IUD, NND</td>
</tr>
<tr>
<td>Nick</td>
<td>2006</td>
<td>United States</td>
<td>Retrospective</td>
<td>Second-third trimester</td>
<td>58</td>
<td>IABD, SGA</td>
<td>BA, IUD, LOS, NND</td>
</tr>
<tr>
<td>Puliglandaa</td>
<td>2004</td>
<td>Canada</td>
<td>Retrospective</td>
<td>Second-third trimester</td>
<td>96</td>
<td>SGA</td>
<td>BA</td>
</tr>
<tr>
<td>Aina-Mumuney</td>
<td>2004</td>
<td>United States</td>
<td>Retrospective</td>
<td>28–36 wk</td>
<td>34</td>
<td>GD</td>
<td>BA, IUD, NND, LOS, TFEF</td>
</tr>
<tr>
<td>Strauss</td>
<td>2003</td>
<td>United States</td>
<td>Retrospective</td>
<td>Not stated</td>
<td>60</td>
<td>EABD, SGA</td>
<td>BA, IUD, NND</td>
</tr>
<tr>
<td>Japaraj</td>
<td>2003</td>
<td>Australia</td>
<td>Retrospective</td>
<td>Within 2–3 wk of delivery</td>
<td>45</td>
<td>EABD, BWT, polyhydramnios, SGA</td>
<td>IUD, NND, LOS</td>
</tr>
</tbody>
</table>

* Additional information provided by the authors.
Fetuses showing evidence of EABD were not at increased risk of having BA. Likewise, the risk of IUD and NND in those fetuses was not significantly higher than that of the control population (Table 4).

Two studies33,45 analyzed the association between EABD and LOS. In the study by Garcia et al,34 the authors found that fetuses with ultrasound evidence of EABD >25 mm had a significantly longer LOS (42.4 ± 19.7 days) compared with those without (33.3 ± 22.3 days, P = .04), whereas Japaraj, using a different threshold of dilatation (17 mm), did not find any association between EABD and LOS (Table 5).

Only 1 study34 explored the association between EABD and TFEF and found that fetuses with EABD >25 mm had significantly longer times to reach the full enteral feeding (25.7 ± 12.8 vs 18.2 ± 9.9 days, P = .02) compared with those without EABD (Table 6).

Finally, the only study31 exploring the association between EABD and LTPN could not find any significant association between this ultrasound sign and the observed outcome (Table 7).

### GD

Five studies (449 fetuses) explored the association between GD and outcome. Fetuses with GD diagnosed in those fetuses was not significantly higher than that of the control population (Table 4).

A study can be awarded a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for comparability. See Supplement 2.

### Table 2 Quality Assessment of the Included Studies According to Newcastle-Ottawa Scale

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overcash23</td>
<td>2014</td>
<td>★★ ★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Goetzinger24</td>
<td>2013</td>
<td>★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Janoo25</td>
<td>2013</td>
<td>★★★★</td>
<td>★★★★</td>
<td>★★★★</td>
</tr>
<tr>
<td>Durfee26</td>
<td>2013</td>
<td>★★★★</td>
<td>★★★★</td>
<td>★★★★</td>
</tr>
<tr>
<td>Emii77</td>
<td>2012</td>
<td>★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Ghionzoli8</td>
<td>2012</td>
<td>★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Overton28</td>
<td>2012</td>
<td>★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Kuleva3</td>
<td>2011</td>
<td>★★★★</td>
<td>★★★★</td>
<td>★★★★</td>
</tr>
<tr>
<td>Ajayi29</td>
<td>2011</td>
<td>★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Alfaraj30</td>
<td>2011</td>
<td>★★★★</td>
<td>★★★</td>
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</tr>
<tr>
<td>Mears31</td>
<td>2010</td>
<td>★★★★</td>
<td>★★★</td>
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</tr>
<tr>
<td>Contro32</td>
<td>2010</td>
<td>★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Garcia33</td>
<td>2010</td>
<td>★★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Huh34</td>
<td>2010</td>
<td>★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Hidaka35</td>
<td>2009</td>
<td>★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Payne10</td>
<td>2009</td>
<td>★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Towers36</td>
<td>2008</td>
<td>★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Heing79</td>
<td>2008</td>
<td>★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Cohen-Overbeek38</td>
<td>2008</td>
<td>★★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Santiago-Munoz29</td>
<td>2007</td>
<td>★★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Brantberg40</td>
<td>2006</td>
<td>★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Nick41</td>
<td>2006</td>
<td>★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Puligandla42</td>
<td>2004</td>
<td>★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Aina-Mumuney43</td>
<td>2011</td>
<td>★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Strauss44</td>
<td>2003</td>
<td>★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Japaraj45</td>
<td>2003</td>
<td>★★★★★</td>
<td>★★★</td>
<td>★★★</td>
</tr>
</tbody>
</table>

A study can be awarded a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for comparability. See Supplement 2.

### Table 3 Description of Ultrasound Signs Used Among the Studies Included

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>IABD</th>
<th>EABD</th>
<th>GD</th>
<th>BWT</th>
<th>SGA (Percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overcash23</td>
<td>2014</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Goetzinger24</td>
<td>2013</td>
<td>&gt;6, &gt;10, &gt;14, &gt;18 mm</td>
<td>&gt;6, &gt;10, &gt;14, &gt;18 mm</td>
<td>—</td>
<td>&gt;3 mm</td>
<td>—</td>
</tr>
<tr>
<td>Janoo25</td>
<td>2013</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Durfee26</td>
<td>2013</td>
<td>—</td>
<td>&gt;8 mm</td>
<td>—</td>
<td>&gt;1 mm</td>
<td>—</td>
</tr>
<tr>
<td>Emii77</td>
<td>2012</td>
<td>—</td>
<td>Not stated</td>
<td>—</td>
<td>Not stated</td>
<td>—</td>
</tr>
<tr>
<td>Ghionzoli8</td>
<td>2012</td>
<td>&gt;18 mm</td>
<td>&gt;18 mm</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Overton28</td>
<td>2012</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kuleva3</td>
<td>2011</td>
<td>&gt;6 mm</td>
<td>&gt;6 mm</td>
<td>&gt;2 SD</td>
<td>&gt;3 mm</td>
<td>&lt;10th</td>
</tr>
<tr>
<td>Ajayi29</td>
<td>2011</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alfaraj30</td>
<td>2011</td>
<td>—</td>
<td>—</td>
<td>&gt;2 SD</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mears31</td>
<td>2010</td>
<td>&gt;10 mm</td>
<td>&gt;10 mm</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Contro32</td>
<td>2010</td>
<td>&gt;6 mm</td>
<td>&gt;6 mm</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Garcia33</td>
<td>2010</td>
<td>&gt;15, &gt;20, &gt;25, &gt;30 mm</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>Huh34</td>
<td>2010</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hidaka35</td>
<td>2009</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Payne10</td>
<td>2009</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Towers36</td>
<td>2008</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Heing79</td>
<td>2008</td>
<td>—</td>
<td>&gt;15, &gt;20, &gt;25 mm</td>
<td>—</td>
<td>&gt;3 mm</td>
<td>&lt;10th</td>
</tr>
<tr>
<td>Cohen-Overbeek38</td>
<td>2008</td>
<td>—</td>
<td>&gt;10 mm</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Santiago-Munoz29</td>
<td>2007</td>
<td>—</td>
<td>GA dependent</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Brantberg40</td>
<td>2006</td>
<td>Not stated</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nick41</td>
<td>2006</td>
<td>GA dependent</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>&lt;10th</td>
</tr>
<tr>
<td>Puligandla42</td>
<td>2004</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>&lt;5th</td>
</tr>
<tr>
<td>Aina-Mumuney43</td>
<td>2004</td>
<td>—</td>
<td>GA dependent</td>
<td>—</td>
<td>—</td>
<td>Not stated</td>
</tr>
<tr>
<td>Strauss44</td>
<td>2003</td>
<td>—</td>
<td>29–42 mm</td>
<td>—</td>
<td>—</td>
<td>&lt;10th</td>
</tr>
<tr>
<td>Japaraj45</td>
<td>2003</td>
<td>—</td>
<td>&gt;17 mm</td>
<td>—</td>
<td>&gt;3 mm</td>
<td>&lt;10th</td>
</tr>
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</table>
### Table 4: Results of the Meta-Analyses Evaluating the Association Between Selected Ultrasound Signs and Various Clinical Outcomes

<table>
<thead>
<tr>
<th>Ultrasound Sign</th>
<th>A. BA</th>
<th>B. IUD</th>
<th>C. NND</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies, n (Total)</td>
<td>Raw Data</td>
<td>Pooled OR</td>
</tr>
<tr>
<td>IABD</td>
<td>9 (673)</td>
<td>44/205 vs 30/170</td>
<td>5.48 (1.9–15.7)</td>
</tr>
<tr>
<td>EABD</td>
<td>10 (659)</td>
<td>29/226 vs 40/433</td>
<td>1.54 (0.8–2.9)</td>
</tr>
<tr>
<td>GD</td>
<td>5 (449)</td>
<td>1/95 vs 4/195</td>
<td>1.23 (0.6–2.6)</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>5 (30)</td>
<td>1/50 vs 3/150</td>
<td>0.76 (0.1–4.8)</td>
</tr>
<tr>
<td>BWT</td>
<td>3 (213)</td>
<td>5/34 vs 17/179</td>
<td>1.94 (0.6–6.2)</td>
</tr>
<tr>
<td>SGA</td>
<td>6 (485)</td>
<td>1/14 vs 3/40</td>
<td>8, 24, 37</td>
</tr>
</tbody>
</table>

* Number of events / Total of subjects in the exposed group (ie, bowel thickness) versus Number of events / Total of subjects in the unexposed group (ie, normal bowel). The total sample of the meta-analyses does not exactly match the total sample derived from the sum of individual studies as reported in Table 1 because for some outcomes/signs, the number of subjects included in each study slightly varied. All raw datasets are available on request from the authors.

b Indicates the signs associated with an increased risk of a specific adverse outcome.
the thresholds used to define an ultrasound sign as abnormal did not allow any meaningful subanalysis according to the cutoff used. Gestational age at examination is another particular issue with most of the included studies not reporting the time at scan. In this scenario, it is plausible that the relationship between a given ultrasound sign and an outcome may change according to the gestational age at scan.

**Comparison With Other Systematic Reviews**

A previous systematic review\(^\text{17}\) explored the prognostic value of EABD in 273 fetuses with isolated gastroschisis. The authors analyzed 27 years (1980–2007) of published literature on the topic without finding any significant correlation between bowel dilatation and risk of adverse perinatal outcome. They also underlined the inconsistent definition of bowel dilatation used by different authors and the lack of randomized control trials. In our systematic review, we analyzed a larger population with EABD (659 cases) and found a longer LOS (42.4 vs 33.3 days) compared with those without dilatation only considering an EABD cutoff >25 mm. More significant was the association between IABD >14 mm and LOS (80 vs 47 days) compared with fetuses without intestinal dilatation. This was explained by the higher risk of BA associated with IABD and therefore increased LOS.

A second systematic review\(^\text{46}\) compared the postnatal outcome in newborns with simple and complex gastroschisis (atresia, necrosis, perforation, or volvulus). The authors showed a significantly higher mortality rate in complex compared with simple gastroschisis (16.7% vs 2.2%, respectively). Moreover, infants with complex gastroschisis showed worse outcome in terms of later ability to feed orally, longer time to reach full feeds, longer time on parenteral nutrition, and longer length of hospital stay.\(^\text{46}\) Because of high data heterogeneity, we were not able to perform a meta-analysis for the following outcomes: LOS, LTPN, and TFEF. Looking at selected papers (Table 5 and 6) and assuming that IABD was a prenatal sign of complex gastroschisis, we showed that in the 3 largest series, there was a significant association between IABD/EABD and longer LOS.\(^\text{24,33,41}\)

In a recent systematic review, our group explored the role of prenatal ultrasound in detecting non-duodenal small bowel atresia in otherwise normal fetuses.\(^\text{47}\) We found that ultrasound had a poor accuracy in detecting small bowel atresia either using bowel dilatation or polyhydramnios. In gastroschisis, we could not define the accuracy of prenatal ultrasound in detecting BA but we could calculate a four times increased risk when IABD was present.

**Implication for Clinical Practice**

BA in fetuses with gastroschisis is likely to be the result of an ischemic necrosis from a constriction/obstruction at the level of the umbilical ring or a volvulus of the herniated bowel producing a vascular compromise. Our results showed that both IABD and polyhydramnios were associated with the presence of BA.

---

**TABLE 5 Results of the Systematic Review Evaluating the Association Between Selected Ultrasound Signs and LOS**

<table>
<thead>
<tr>
<th>Ultrasound Sign</th>
<th>Definition</th>
<th>Exposed Group</th>
<th>Unexposed Group</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>IABD</td>
<td>Nick(^\text{41}) (2009)(^\text{a})</td>
<td>GA dependent</td>
<td>10 84.0</td>
<td>48 26.5</td>
</tr>
<tr>
<td></td>
<td>Huh(^\text{34}) (2010)(^\text{a})</td>
<td>Not stated</td>
<td>16 40.9 ± 27.8</td>
<td>27 34.4 ± 20.3</td>
</tr>
<tr>
<td></td>
<td>Goetzinger(^\text{24}) (2014)(^\text{b})</td>
<td>≥14 mm</td>
<td>28 80.5 (34.5–138.5)</td>
<td>86 47.5 (31.0–78.0)</td>
</tr>
<tr>
<td>EABD</td>
<td>Japara(^\text{45}) (2003)(^\text{a})</td>
<td>≥17 mm</td>
<td>19 46.7</td>
<td>26 58</td>
</tr>
<tr>
<td></td>
<td>Garcia(^\text{33}) (2010)(^\text{a})</td>
<td>≥25 mm</td>
<td>16 42.4 ± 19.7</td>
<td>78 33.5 ± 22.3</td>
</tr>
<tr>
<td>GD</td>
<td>Aina-Mumuney(^\text{43}) (2003)(^\text{b})</td>
<td>GA dependent</td>
<td>13 75 ± 57</td>
<td>21 45 ± 30</td>
</tr>
<tr>
<td></td>
<td>Alfaraj(^\text{30}) (2011)(^\text{a})</td>
<td>&gt;2 SD</td>
<td>32 46.1 ± 29.5</td>
<td>65 59.0 ± 46.3</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>Payne(^\text{10}) (2009)(^\text{b})</td>
<td>—</td>
<td>10 41 (28–77)</td>
<td>31 (26–38) 131</td>
</tr>
<tr>
<td></td>
<td>Alfaraj(^\text{30}) (2011)</td>
<td>14 62.28 ± 49.97</td>
<td>80 53.64 ± 40.74</td>
<td>.481</td>
</tr>
<tr>
<td>BWT</td>
<td>Goetzinger(^\text{24}) (2014)(^\text{b})</td>
<td>≥3 mm</td>
<td>6 100.5 (82.0–196.0)</td>
<td>88 48.5 (31.0–81.5)</td>
</tr>
</tbody>
</table>

\(^{a}\) Values expressed as median, median and range, or IQR or 95% CI.

\(^{b}\) Values reported as mean or mean (± SD).

\(^{c}\) *P* < .05 is significant.

---

**TABLE 6 Results of the Systematic Review Evaluating the Association Between Selected Ultrasound Signs and TFEF**

<table>
<thead>
<tr>
<th>Ultrasound Sign</th>
<th>Definition</th>
<th>Exposed Group</th>
<th>Unexposed Group</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>IABD</td>
<td>Huh(^\text{34}) (2010)(^\text{a})</td>
<td>Not stated</td>
<td>16 29.6 ± 17.7</td>
<td>27 29.8 ± 18.3</td>
</tr>
<tr>
<td></td>
<td>Goetzinger(^\text{24}) (2014)(^\text{b})</td>
<td>≥14 mm</td>
<td>28 36.0 (25.0–52.0)</td>
<td>66 38.5 (21.5–65.5)</td>
</tr>
<tr>
<td>EABD</td>
<td>Garcia(^\text{33}) (2010)(^\text{a})</td>
<td>≥25 mm</td>
<td>16 25.7 ± 12.8</td>
<td>78 18.2 ± 9.9</td>
</tr>
<tr>
<td>GD</td>
<td>Aina-Mumuney(^\text{45}) (2003)(^\text{b})</td>
<td>GA dependent</td>
<td>13 71 ± 58</td>
<td>21 38 ± 29</td>
</tr>
<tr>
<td></td>
<td>Alfaraj(^\text{30}) (2011)(^\text{a})</td>
<td>&gt;2 SD</td>
<td>32 33.1 ± 22.7</td>
<td>65 45.3 ± 35.1</td>
</tr>
<tr>
<td>BWT</td>
<td>Goetzinger(^\text{24}) (2014)(^\text{b})</td>
<td>≥3 mm</td>
<td>6 16.5 (11.0–22.0)</td>
<td>88 17.0 (12.0–21.0)</td>
</tr>
</tbody>
</table>

\(^{a}\) Values reported as mean or mean (± SD).

\(^{b}\) Values expressed as median, median and range or IQR or 95% CI.

\(^{c}\) *P* < .05 is significant.
This can be explained by an obstruction and blockage at the level of the small bowel with accumulation of amniotic fluid (polyhydramnios) and proximal bowel dilatation (IABD). However, EABD was not found to be associated with BA, IUD, or NND. EABD is a common finding during the prenatal ultrasound of fetuses with gastroschisis; it is usually the result of the prolonged exposure of the extruded bowel to the amniotic fluid and may not necessarily imply the presence of bowel complications.

Although advances in the neonatal care have led to a dramatic reduction in mortality, infants with gastroschisis are still at high risk of neonatal and long-term morbidity. It has been observed that most short- and long-term complications occur in cases in which an intestinal atresia is present. Furthermore, newborns with gastroschisis and associated BA were found to be more TPN dependent, at higher risk of chronic liver damage (eg, cholestasis), and have severe infectious complications. Published series showed that only 60% of the time was possible to confirm an atresia at birth or during the first surgical procedure (primary closure or silo placement).

Even if a BA is identified at birth, the surgeon is often facing the dilemma whether performing an early or a delayed repair of the interrupted intestine. The main surgical concerns in this situation are about the degree of bowel inflammation, edema, necrosis, and the increased abdominal pressure after the abdominal wall closure that can all increase the risk of surgical complications. For this reason, being able to predict the presence of BA in newborns with gastroschisis could significantly help the surgeon to plan the repair, either with an anastomosis or with a diverting ileostomy at the time of the abdominal wall closure.

Parental counseling should take into account the presence of IABD and polyhydramnios and their association with BA. These signs are suspicious of BA, and the possibility of postnatal and postsurgical complications should be disclosed with parents during the prenatal period.

GD was associated with the occurrence of NND in the current meta-analysis. GD may indicate the presence of a proximal intestinal obstruction (midgut volvulus or atresia), which has been reported to be associated with a higher risk of mortality. However, it was not possible to rule out other confounders, such as prematurity, the size of the defect, or postnatal medical complications.

### Implications for Research

In view of the wide heterogeneity in study design, thresholds adopted to define an ultrasound marker as abnormal, gestational age at assessment, and outcome definition, large prospective studies are needed to clarify the role of antenatal ultrasound in stratifying the perinatal risk in fetuses with gastroschisis. Ideally, these studies should take into account objectively defined ultrasound signs and assess their reproducibility and association with a given outcome at a given gestational age at examination. The association between an ultrasound sign and a given outcome may be due to other cofactors. In this scenario, regression models should be used to find those signs independently associated with a given outcome.

Furthermore, predicative models using different ultrasound signs, alone or in combination, should be constructed by including only those signs showing independent and significant association with a given outcome and the diagnostic performance of the different signs should be explored by taking into account all the possible thresholds. The number of ultrasound signs needed to label a scan as suggestive for a given outcome represents another particular problem; it might be hypothesized that reduction in the number of sonographic criteria may increase the sensitivity but is likely to reduce the specificity of the test. Conversely, an increase in the number of criteria needed to label a case as positive would reduce sensitivity but would improve specificity. Finally, each ultrasound sign should be evaluated in relation to the optimal cutoff needed to more accurately predict a given outcome. In this scenario, large prospective studies are needed to standardize the different ultrasound measurements and to provide gestational age dependent cutoffs for each ultrasound sign.

### Conclusions

Antenatal ultrasound can be used at some extent to identify a subgroup of neonates with a prenatal diagnosis of...
gastroschisis at higher risk to develop postnatal complications. IABD and polyhydramnios are associated with an increased risk of BA, and GD is associated with NND. Large prospective studies looking at the association of various ultrasound signs with antenatal and postnatal outcomes are needed to clarify the role of antenatal ultrasound in predicting an adverse outcome and to improve parental counseling for this anomaly.

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ABBREVIATIONS

BA: bowel atresia
BWT: bowel wall thickness
CI: confidence interval
EABD: extraabdominal bowel dilatation
GD: gastric dilatation
IABD: intraabdominal bowel dilatation
IQR: interquartile range
IUD: intrauterine fetal death
LOS: length of hospital stay
LTPN: time on total parenteral nutrition
NND: neonatal death
OR: odds ratio
SGA: small for gestational age
TFEF: time to full enteral feeding
TPN: total parenteral nutrition

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Prenatal Risk Factors and Outcomes in Gastroschisis: A Meta-Analysis
Francesco D’Antonio, Calogero Virgone, Giuseppe Rizzo, Asma Khalil, David Baud, Titia E. Cohen-Overbeek, Marina Kuleva, Laurent J. Salomon, Maria Elena Flacco, Lamberto Manzoli and Stefano Giuliani

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