

ARTICLE



Prenatal ultrasound markers for prediction of complex gastroschisis—single-center retrospective cohort study

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OBJECTIVE: To evaluate prenatal ultrasound markers for distinguishing simple gastroschisis (sGS) from complex gastroschisis (cGS) and identifying fetuses at risk of complications.

STUDY DESIGN: A retrospective cohort study analyzed 61 fetuses with isolated gastroschisis at a tertiary center from 2011 to 2021, utilizing serial ultrasounds from 14 to 35 weeks' gestation. A general linear model, quantile regression, and logistic regression assessed ultrasound markers, fetal weeks, and gastroschisis risk, yielding predictive models.

RESULTS: *IABL dilatation* showed the highest PPV but low NPV. *Non-free floating bowel loops (NFFBL)* indicated the best PPV to NPV ratio. Combinations of markers yielded the highest predictive value for cGS. *EABL collapsed* and *non-free floating bowel loops* were significant, consistent risk factors.

CONCLUSIONS: Prenatal ultrasounds can predict cGS risk, particularly using *IABL dilatation* and *NFFBL* as markers. Accurate assessment requires considering gestational age, qualitative symptoms, emphasizing experienced perinatologists' role and monitoring, particularly after 30 weeks of gestation.

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INTRODUCTION

Gastroschisis (GS) is a congenital abdominal wall defect located in most cases to the right of the insertion of the umbilical cord, in which the intestine is located outside the abdominal cavity [1]. Survival of newborns with GS is high, but morbidity remains significant. Based on the absence or presence an additional intestinal complications (atresia, perforation, necrosis, volvulus), two forms of defect were distinguished—simple (sGS) and complex GS (cGS) [2]. Complex GS compared to simple GS is associated with significantly increased neonatal morbidity and mortality, longer hospitalization and longer duration of parenteral nutrition, days of mechanical ventilation, and postoperative complications [2–4]. We have no control over the incidence of cGS and intestinal complications associated with this defect, but there is room to reduce fetal/neonatal mortality and morbidity through proper fetal monitoring and appropriate perinatal management. Prenatal diagnosis and monitoring of the defect allows already before birth to delineate a group of newborns at high risk of severe complications, so research has focused on using ultrasound signs that could be potential signs of cCG. Particular attention to disease dynamics, adverse intestinal ultrasound symptoms suggestive of cGS, or closing GS may identify those fetuses that may benefit from early delivery [5].

Several studies have investigated the associations between ultrasound (US) markers and perinatal outcomes or gastrointestinal complications in fetuses with cGS. [2, 4–10] Few studies have investigated the associations between US markers and cGS [5, 8, 11–16].

The results of these studies are sometimes contradictory due to analyses based on small groups of mainly retrospective nature, the lack of a uniform assessment protocol, evaluation in different time intervals, which makes it difficult to compare data. Therefore, there is a need for further in-depth analyses of ultrasound markers and their relationship to cGS, including a combined assessment of several US signs, to increase the usefulness of them in predicting cCG.

The aim of our study is to assess the usefulness of ultrasound intestinal markers that may be valuable in differentiating between sGS and cGS, and consequently in identifying fetuses at risk in utero and postnatal complications.

The clinical purpose of this study was to identify ultrasound signs that can predict complex GS which might help obstetricians and pediatric surgeons in counseling parents with fetal diagnosis of GS regarding perinatal and postnatal management.

MATERIALS AND METHODS

Study design

This retrospective cohort study included fetuses with prenatally diagnosed GS. This report is written according to the STROBE Statement for cohort study [17].

Setting

Patients were diagnosed and monitored at the Department of Obstetrics and Gynecology between 2011 and 2021 and treated at the Department of Pediatric and Adolescent Surgery of the Institute of Mother and Child in

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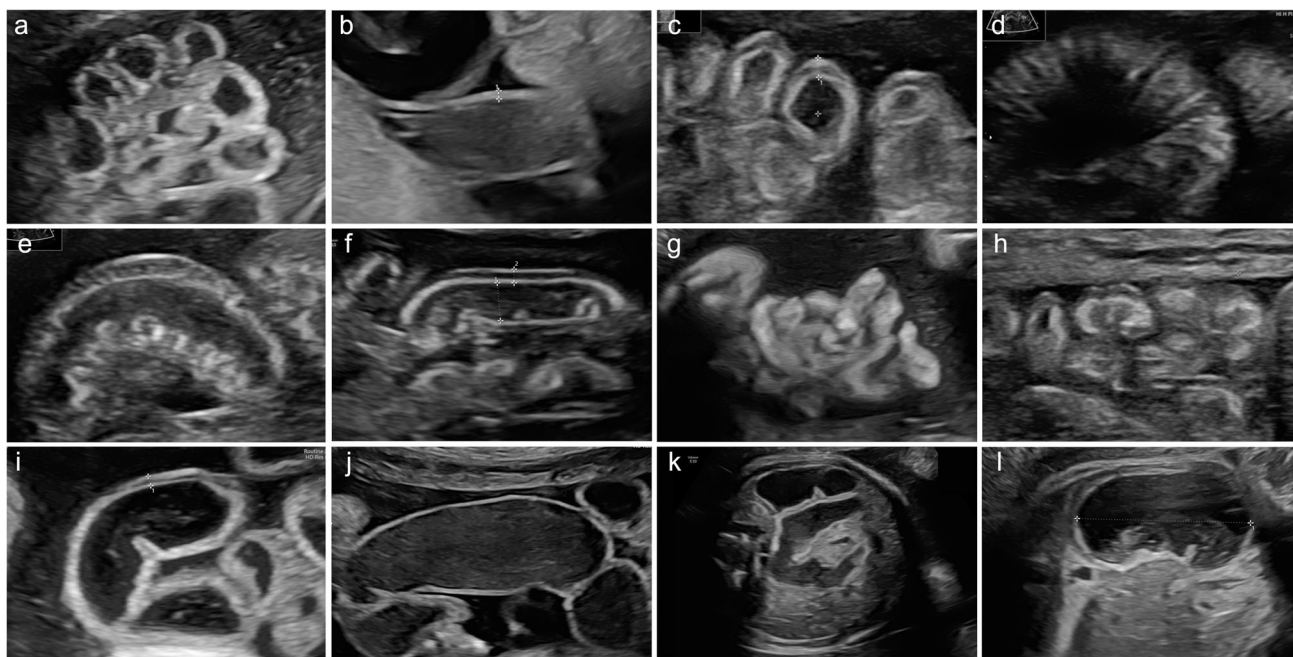


Fig. 1 Small bowel, large bowel, and stomach qualitative assessment. **a** Extra-abdominal small bowel loops in uncomplicated gastroschisis. Free coiling and free-floating small bowel loops, with normal echogenicity of intestine wall, without edema and dilatation. Fetus at 34.4 weeks. **b** Extra-abdominal large bowel loops in uncomplicated gastroschisis. Fetus at 33.5 weeks. **c** Small bowel wall edema—thickening wall, including echogenic bowel, the appearance of three echos—layers of the small intestinal wall—mucosa, muscle, and serosa. Fetus at 34.5 weeks, small bowel wall thickness—2.9 mm. **d** Corrugating wall—symptom appearing together with edema, probably associated with edema of the circular layer of the small bowel wall muscle—logitudinal view of the loop - tangential section. **e** Perpendicular section of the intestinal wall with edema (3.7 mm) and white dots in small bowel wall—thickened circular muscles. Fetus at 33.4 weeks. **f** Non free-floating bowel loops—straightened intestinal loops, majority seen in long axis which suggests straightening of the bowel rather than free coiling of the loops. Fetus at 33.3 weeks—extra abdominal small bowel diameter 6.8 mm. **g, h** Extra-abdominal small bowel loops collapsed (EABL collapsed)- absence/lack of intestinal lumen of extra-abdominal small bowel loops adequate for gestational age without (g) and with wall edema (h). Fetus at 32.0 weeks (g). Fetus at 33.6 weeks (h). **i, j** EABL dilatation - extra abdominal small bowel diameter greater than 10 mm (i), extra abdominal large bowel diameter greater than 18 mm (j). Fetus at 33.4 weeks—extra abdominal small bowel diameter—11 mm (i). Fetus at 33.5 weeks—extra abdominal large bowel diameter—24 mm (j). **k** IABL dilatation—extra abdominal large bowel diameter—12.9 mm. Fetus at 32.0 weeks. **l** Gastric dilatation—the longest diameter in the longitudinal plane (56 mm), greater than 2 standard deviations. Fetus at 33.4 weeks.

Warsaw (Poland). All newborns were delivered via planned preterm cesarean section after receiving corticosteroid therapy to prevent infant respiratory distress syndrome and divided into two groups, simple and complex gastroschisis, based on the paper of Molik [2].

Participants

61 fetuses were included in the study. The first ultrasound examination was performed at 14.2 weeks of pregnancy, the last at 34.6 weeks of pregnancy. On average, there were 6.3 ultrasound examinations per fetus (range 1–12 examinations).

Procedures, variables, and measurement

During examination, fetal biometry, amniotic fluid index, and doppler measurements were evaluated.

Extra-abdominal bowel loops (EABL), intra-abdominal bowel loops (IABL), stomach, and abdominal wall defects were assessed.

Efforts were made to distinguish and separately evaluate the condition of the small and large intestine. Prenatal ultrasound markers were examined during every US exam. Parameters were evaluated by qualitative and quantitative methods (for a detailed description- see Supplement).

Qualitative assessment

The 61 fetuses in which the presence of one or more of the following symptoms was assessed were qualitatively evaluated: small bowel wall edema (Fig. 1c), corrugated wall (Fig. 1d, e), non free-floating bowel loops (NFFBL) (Fig. 1f), extra-abdominal bowel loops collapsed (EABL collapsed, EABLc) (Fig. 1g, h), extra-abdominal small and large bowel loops dilatation (EABL dilatation, EABLd) (Fig. 1i, j), intra-abdominal bowel loops dilatation (IABL dilatation, IABLd) (Fig. 1k), gastric dilatation (GD) (Fig. 1l) [18]. (for a detailed description- see Supplement).

Quantitative assessment

In fetuses with fetal GS monitored at our center, we measured the four quantitative parameters separately for the small and large intestine due to the fact that normal values in healthy fetuses differ:

EABL small bowel diameter, EABL large bowel diameter, EABL small bowel wall thickness, EABL large bowel wall thickness (Fig. 2a–d) (for a detailed description- see Supplement).

Data sources

Medical records of pregnancy, ultrasound images, images of the intestinal status of the newborns, and records of the treatment of the newborns were used. We retrospectively analyzed ultrasound scans and compared the changes occurring in the bowel pattern depending on the week of gestation in fetuses with GS.

Bias

The diameter and wall thickness of the small and large bowel were not measured in the three fetuses in whom we observed the absence of an intestinal lumen in all US examinations. We obtained good-quality measurements of the small intestine in 50 fetuses and measurements of the large intestine in 49 fetuses.

Statistical analysis

The study assessed the distribution normality of quantitative variables using histogram and Q-Q plot interpretation, while Pearson's Chi2 test analyzed qualitative variables, presenting cases and percentages with *p* values. The homogeneity of the groups was examined using the Levene test. A general linear model evaluated the relationship between ultrasound symptoms and fetal development weeks, using a second-order polynomial model for the non-linear time course. Quantile regression identified 10th

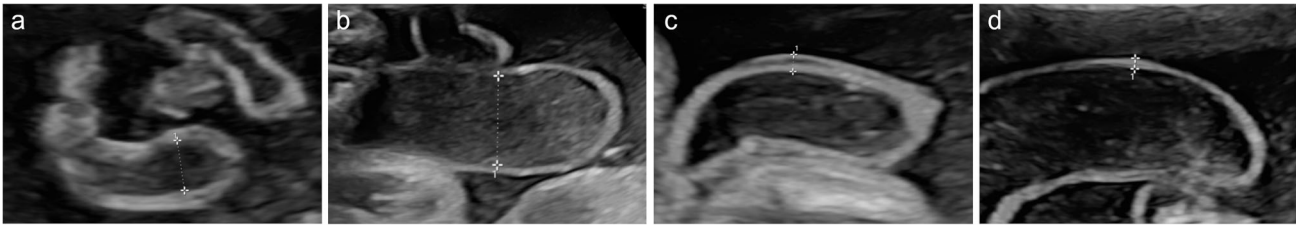


Fig. 2 Small and large bowel quantitative assessment. **a** *EABL* small bowel diameter (5.3 mm) in uncomplicated gastroschisis. Fetus at 32.2 weeks. **b** *EABL* large bowel diameter (16.6 mm) in uncomplicated gastroschisis. Fetus at 33.4 weeks. **c** *EABL* small bowel wall thickness (1.9 mm) in uncomplicated gastroschisis. Fetus at 33.6 weeks. **d** *EABL* large bowel wall thickness (1.5 mm) in uncomplicated gastroschisis. Fetus at 33.6 weeks. The same fetus as in Fig. 2c.

and 90th percentile cut-off values, creating a dichotomous variable for each parameter to mark cases outside these percentiles. Logistic regression determined the association between variables and complex gastroschisis risk, initially through univariate models (presented as odds ratios with confidence intervals and p values), then multivariate prediction models. The analysis was performed in R language within the RStudio environment, including sensitivity, specificity, and predictive values for the models.

Ethical consideration

In accordance with Polish law, there is no requirement to obtain ethical approval from a bioethics committee for conducting retrospective studies.

RESULTS

The characteristics of the group are shown in Table 1. There were no significant differences in this regard between the sGS and cGS groups.

Qualitative assessment of US signs

Qualitative ultrasound signs were evaluated in 61 fetuses. The presence of at least 1 ultrasound sign was described in 12 (92.3%) fetuses in the cGS group and in 12 (25%) fetuses in the sGS group. The type of symptoms described, divided into sGS and cGS groups, and statistical significance are shown in Table 1. In the cGS group, only 1 fetus showed no ultrasound sign. Except for the symptom of *EABL collapsed* in three fetuses and *IABLd* in two fetuses, the remaining symptoms occurred after 30 weeks of gestation, demonstrating the need for intensive fetal monitoring in the third trimester of pregnancy (Supplementary Table 1).

Small bowel wall assessment

Thickening/edema of the small bowel wall was described in 6 of fetuses in the cGS group and 10 fetuses with this sign were classified as sGS. We adopted 2.5 mm as the cut-off threshold to define edema, because when the thickness of the intestinal wall exceeded this value, the echo of the small bowel wall started to become very clearly visible in the form of three lines, where the widest (middle) layer was the swollen intestinal wall musculature (Fig. 1c, e, f, h). That symptom was not observed in the large bowel wall. In 7 fetuses, wall edema was accompanied by *corrugated wall*. This symptom was seen in 2 fetuses with cGS and in 5 with sGS. There were no statistically significant differences in that two US symptoms between the groups.

NFFBL

The symptom was described in 7 fetuses in the cGS group and in 3 fetuses in the sGS group, and there was a significant difference in incidence between sGS and cGS group ($p < 0.001$). In 5 fetuses with cGS and one fetus with sGS, the sign was associated with *EABLd*.

EABLc

This symptom was observed in 7 fetuses, significantly more often in the cGS group ($p = 0.003$). Four of them were diagnosed

prenatally and confirmed postnatally with closing gastroschisis and in all of them combined symptoms were observed: *EABL collapsed*, *IABL dilatation* and *gastric dilatation*. One fetus was in sGS group (type A according to Perrone) and three fetuses were in cGS group (types B and C according to Perrone) [19]. In two fetuses with closing GS, absence of the intestinal lumen occurred already in the second trimester of pregnancy, and in these fetuses the consequence was the occurrence of SBS. In three fetuses in which changes in bowel lumen (decreasing intestinal diameter) were observed and the *EABL collapsed* sign was described in third trimester, a decision was made to preterm delivery before significant closure of the wall defect occurred to prevent the consequences of closing GS.

EABLd

EABLd (small or/and large intestine) was described in 9 fetuses - in 3 fetuses with sGS and 6 with cGS. The occurrence of this sign was significantly more frequent in cGS group ($p = 0.002$). In 6 fetuses the dilatation was described in the small bowel and in 8 fetuses the dilatation involved the large bowel. In 5 fetuses the dilatation involved small and large bowel occurred together, and 4 of them were in the cGS group. In 5 fetuses with cGS and *small bowel EABLd*, the sign of *NFFBL* was visible.

IABLd

Dilatation of intra-abdominal loops of intestine was observed in 18 fetuses of which 8 (16.7%) were in the sGS group and 10 (76.9%) in the cGS group ($p < 0.001$). *IABL* diameter ranged from 8 to 21 mm. *IABL* diameter >18 mm was observed in 3 fetuses with cGS, and *EABL collapsed* was seen in these fetuses at the same time.

GD

This sign occurred in 16 fetuses and, as with *IABLd*, showed a significant difference in prevalence between sGS and cGS ($p < 0.001$). In 15 fetuses *GD* and *IABLd* occurred together. Dilatation of the intra-abdominal bowel loops and enlargement of the stomach are signs of gastrointestinal obstruction, and at least one sign was seen in 11 out of 13 fetuses with cGS. *GD* and/or *IABL dilatation* occurred in 10 out of 11 fetuses diagnosed with small and/or large bowel atresia.

Quantitative assessment of US signs

We obtained serial measurements of the small intestine in 50 and the large intestine in 49 fetuses. This group included 11 fetuses with cGS and 39 with sGS. In one fetus, the large bowel could not be visualized and measured, and it was a fetus with cGS. In the 3 fetuses undergoing quantitative analysis only 1 ultrasound examination was performed due to the advanced age of the pregnancy (35 weeks) at the time the patients were referred to our center.

Distribution of serial measurements of all quantitative variables with model-predicted 10th, 50th, 90th percentile curves, calculated based on linear mixed modeling, for simple gastroschisis and complex gastroschisis groups are shown in Fig. 3.

Table 1. Characteristics of study groups and ultrasound findings in two types of gastroschisis.

Variable	Total	Simple GS n = 48	%/SD	Complex GS n = 13	%/SD	p
Age	25.1	25.35	5.1	24.08	5.2	0.372
Delivery time (weeks)						
32.0–32.6	7	4	8.3	3	23.1	0.136
33.0–33.6	11	7	14.6	4	30.8	
34.0–34.6	30	25	52.1	5	38.5	
35.0–35.6	13	12	25.0	1	7.7	
Neonatal birth weight	2102	2131	350	1998	349	0.238
Any ultrasound sign	24	12	25.0	12	92.3	<0.001
<i>Small bowel wall edema</i>	16	10	20.8	6	46.2	0.137
<i>Corrugated wall</i>	7	5	10.4	2	15.4	0.993
<i>Non-free floating bowel loops</i>	10	3	6.3	7	53.8	<0.001
<i>EABL collapsed</i>	7	2	4.2	5	38.5	0.003
<i>EABL dilatation</i>	9	3	6.3	6	46.2	0.002
<i>EABL small bowel diameter > 10 mm</i>	6	1	2.1	5	38.5	<0.001
<i>EABL large bowel diameter > 18 mm</i>	8	3	6.3	5	38.5	0.009
<i>IABL dilatation</i>	18	8	16.7	10	76.9	<0.001
<i>Gastric dilatation</i>	16	7	14.6	9	69.2	<0.001
Closing GS	4	1	2.1	3	23.1	0.007

EABL - extra-abdominal bowel loops, IABL - intra-abdominal bowel loops, GS - gastroschisis.

The highest coefficient of determination was observed for the *EABL large bowel diameter* (0.52) and the *EABL small bowel wall thickness* (0.42). The *EABL small bowel diameter* and *EABL large bowel wall thickness* had a low coefficient of determination. A normal distribution of the residuals and a mean value of the residuals close to zero were obtained for each model (Supplementary Table 2).

Data presenting the number of fetuses that were outside the 10th or 90th percentile range in each symptom at any time during the examination are presented in Supplementary Table 3. It was observed that the incidence did not differ significantly between groups.

In the univariate logistic regression, significant associations with complex gastroschisis were found for *EABL collapsed* (OR = 9.38, $p = 0.007$), *IABL dilatation* (OR = 16.67, $p < 0.001$), *gastric dilatation* (OR = 13.18, $p < 0.001$), and *NFFBL* (OR = 17.50, $p < 0.001$). *EABL small* (OR = 3.75, $p = 0.049$) and *large bowel diameter* (OR = 3.52, $p = 0.053$) showed marginal significance. However, *EABL small* (OR = 0.48, $p = 0.275$) and *large bowel wall thickness* (OR = 0.86, $p = 0.806$) had no significant relationship with gastroschisis type (Table 2).

In the first multivariate logistic regression analysis, the study identified *EABL collapsed* (OR = 95.87, $p = 0.004$) and *non-free floating bowel loops* (OR = 75.59, $p = 0.009$) as significant risk factors for complex gastroschisis (cGS), while other variables like *IABL dilatation* and *gastric dilatation* didn't show significance. The model had a specificity of 87.5% and sensitivity of 92.3%. The second analysis, focusing only on significant variables from the first, reaffirmed the importance of *IABL dilatation* (OR = 70.00, $p = 0.001$) and *NFFBL* (OR = 98.00, $p < 0.001$) in predicting cGS, with consistent sensitivity and specificity. In the third analysis, which combined qualitative and quantitative symptoms, *EABL collapsed*, *NFFBL* and *EABL large bowel wall thickness* were significant, demonstrating the importance of both variable types in predicting cGS with a specificity of 95.8% and sensitivity of 92.3%. The fourth analysis, concentrating on variables significant in the third model, found *EABL collapsed* (OR = 62.72, $p = 0.001$) and *NFFBL* (OR = 84.57, $p < 0.001$) as robust risk factors, though the model's specificity decreased to 87.5% while maintaining the same sensitivity level (Table 2).

DISCUSSION

Many authors draw attention to the limitations in the clinical use of ultrasound signs to predict prognosis in gastroschisis and analyze if that markers should have an influence on prenatal management to decrease the incidence of adverse perinatal outcomes [5, 13, 20].

Final neonatal outcomes are influenced by other factors, not only intestinal complications in cGS, so we did not analyze the relationship of ultrasound signs with neonatal outcomes, but only the direct relationship of the occurrence of these markers with the complex form of the defect, and aimed to establish a correlation between prenatal ultrasound findings of fetuses diagnosed and monitored before birth and the postnatal diagnosis of sGS and cGS.

Sonographic markers—qualitative assessment of signs

Analyzing the presence of *small bowel wall edema*, we found no significant difference in incidence between sGS and cGS. Similar conclusions were published by other authors [8, 21].

Adverse changes in the intestinal wall (edema, wall thickening, increased wall echogenicity) are not related to atresia, perforation, necrosis or volvulus, but are rather a result of inflammatory changes, covering the intestinal wall with fiber exposed to amniotic fluid. [9, 10, 22–25] Therefore, this sign was visible in both sGS and cGS fetuses and may be a useful marker for identifying a group of fetuses with adverse intestinal lesions (inflammatory process) in both groups of the defect.

The *corrugated wall* sign also showed no significant association with the cGS, but it was a marker observed in fetuses in which small bowel wall edema has been described, regardless of the defect type. It is probably associated with a clearly visible swollen layer of the small bowel's circular musculature and progressive adverse inflammatory changes of the bowel. We did not observe this symptom in the wall of the large intestine, just as no edema of the the large intestine wall was observed in any fetus. This may be due to a different structure of the colon wall. To the best of our knowledge, this paper is the first to describe the *corrugated wall* of a small bowel as an ultrasound sign, seen in fetuses with GS. Further observations are needed to assess the significance of this marker.

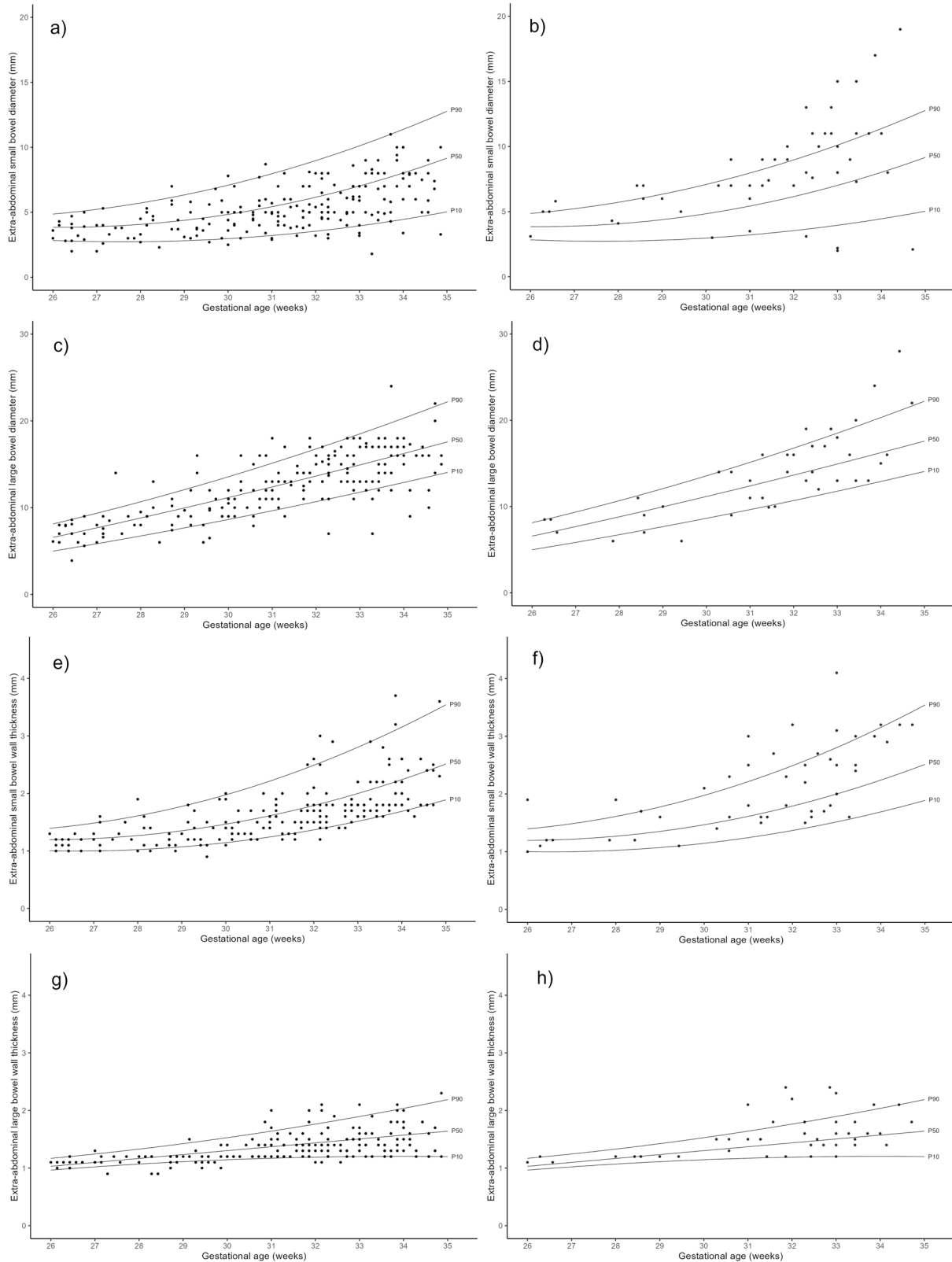


Fig. 3 Distribution of serial measurements of extra-abdominal bowel loops parameters according to gestational age. The extra-abdominal small bowel diameter in fetuses in sGS (a) and cGS (b) group, extra-abdominal large bowel diameter in fetuses in sGS (c) and cGS (d) group, extra-abdominal small bowel wall thickness in fetuses in sGS (e) and cGS (f) group, extra-abdominal large bowel wall thickness in fetuses in sGS (g), and cGS (h) group. Model-predicted 10th, 50th, 90th percentile curves, calculated based on linear mixed modeling, are shown for sGS (a, c, e, g) and cGS (b, d, f, h) groups.

Table 2. Results of the univariate model and multivariable models for prediction of complex gastroschisis.

Variable	OR	2.50%	97.50%	p	specificity	sensitivity	PPV	NPV
UNIVARIATE MODEL								
<i>Non-free floating bowel loops</i>	17.50	3.84	101.0	<0.001	93.75%	53.85%	88.24%	70.00%
<i>EABL collapsed</i>	9.38	1.93	53.8	0.007	93.75%	38.46%	84.91%	62.50%
<i>EABL dilatation</i>	12.857	2.77	73.4	0.002	93.75%	46.15%	86.54%	66.67%
<i>EABL small bowel diameter^a</i>	3.75	1.06	15.5	0.049	62.50%	69.23%	88.24%	33.33%
<i>EABL large bowel diameter^a</i>	3.52	1.01	13.4	0.053	47.92%	69.23%	47.92%	69.23%
<i>EABL small bowel wall thickness^a</i>	0.48	0.12	1.7	0.275	68.75%	61.54%	86.84%	34.78%
<i>EABL large bowel wall thickness^a</i>	0.86	0.24	2.9	0.806	50.00%	53.85%	80.00%	22.58%
<i>IABL dilatation</i>	16.67	4.11	88.2	<0.001	83.33%	76.92%	93.02%	55.56%
<i>Gastric dilatation</i>	13.18	3.38	61.1	<0.001	85.42%	69.81%	86.53%	66.67%
MULTIVARIATE MODEL I								
(Intercept)	0.02	0.00	0.10	<0.001	87.5%	92.3%	97.67%	66.67%
<i>Non-free floating bowel loops</i>	75.59	4.45	3961.76	0.009				
<i>EABL collapsed</i>	95.87	6.00	4473.20	0.004				
<i>EABL dilatation</i>	6.31	0.55	95.57	0.153				
<i>IABL dilatation</i>	0.29	0.01	5.70	0.442				
<i>Gastric dilatation</i>	2.25	0.16	41.67	0.541				
MULTIVARIATE MODEL II								
(Intercept)	0.02	0.00	0.11	<0.001	87.5%	92.3%	98%	67%
<i>Non-free floating bowel loops</i>	98.00	12.41	2206.49	<0.000				
<i>EABL collapsed</i>	70.00	8.21	1614.67	0.001				
MULTIVARIATE MODEL III								
(Intercept)	0.01	0.00	0.11	0.003	95.8%	92.3%	96%	100%
<i>Non-free floating bowel loops</i>	396.22	8.42	79915.04	0.010				
<i>EABL collapsed</i>	60.63	2.68	3749.84	0.018				
<i>EABL small bowel diameter^a</i>	7.62	0.45	309.45	0.185				
<i>EABL large bowel diameter^a</i>	2.26	0.13	39.19	0.560				
<i>EABL large bowel wall thickness^a</i>	0.01	0.01	0.25	0.036				
<i>IABL dilatation</i>	12.24	0.04	14478.01	0.415				
<i>Gastric dilatation</i>	0.98	0.01	56.55	0.991				
MULTIVARIATE MODEL IV								
(Intercept)	0.02	0.00	0.10	<0.001	87.5%	92.3%	98%	67%
<i>Non-free floating bowel loops</i>	84.57	10.31	1941.85	0.000				
<i>EABL collapsed</i>	62.72	7.16	1462.46	0.001				
<i>EABL small bowel diameter^a</i>	1.74	0.26	11.29	0.553				

EABL - extra-abdominal bowel loops, *IABL* - intra-abdominal bowel loops.

^aOutside the range of 10–90 percentiles.

A characteristic feature of the bowel US image in uncomplicated GS is the free arrangement and floating of the bowel loops in the amniotic fluid—then, most of the loops are visible in cross-section because of the loose positioning and coiling. If the loops begin to be segmentally visible in the long axis, this indicates their straightening, stiffness, caused by reduction in the flexibility of the wall to change its shape and free positioning (edema, inflammation, fiber covering).

The occurrence of this sign in our analysis was significantly related to cGS. The 17-fold increase in the likelihood of cGS resulting from this symptom was shown in our study.

Underlying this prenatal sign may be intestinal dysmotorism [22]. Bowel dysfunction in gastroschisis is more multifactorial than the duration of bowel exposure to amniotic fluid or overt evidence of bowel inflammation [24–27]. There are several other causes that may underlie of impaired intestinal motility and affect the peristalsis of the intestine and lead to the occurrence of fragments

of the bowel with limited mobility and thickening of the intestinal wall [28–31]. In our analysis, the occurrence of *non-free floating bowel loops* was not always associated with the dilatation of the bowel loops. In half of the fetuses, the *NFFBL* sign was accompanied by *EABL dilatation* and all of them were in the cGS group. In 9 out of 10 of fetuses, *NFFBL* occurred together with *small bowel wall edema* or/and *EABL dilatation*.

The authors emphasize the importance of changes in appearance of the bowel during pregnancy [11, 21]. This process is gradual in an uncomplicated type of defect. Too rapid dilatation of *EABL*, lack/ absence of lumen, decreasing of previously visible intestinal lumen, and concomitant occurrence of *IABLD* are alarming symptoms.

The absence of *extra-abdominal bowel lumen* or the decreasing lumen of the bowel seen in earlier US examination is more serious symptom than *EABLD* and may be a sign of complex (or particular closing) gastroschisis [13]. This entity represented an in-utero

narrowing of the abdominal defect wall that strangulates the *EABL* typically resulting in atresias at the abdominal entry and exit points [3].

We know that the clinical consequences of dilatation of the large intestine may be less severe than those of dilatation of the small intestine (colonic atresia rarely occurs in gastroschisis), so when monitoring fetuses with GS, we focus more on the changes seen in the small intestine imaging [32, 33].

The authors describe a triad of symptoms indicating the possibility of premature wall defect closing: *EABL collapsed*, *IABL dilatation*, and *small abdominal wall defect* [12, 34]. Carnaghan reported that combined *IABD/EABD* or *IABD/collapsed extra-abdominal bowel*, particularly before 30 weeks was suggestive of complex gastroschisis [35]. Attention should be paid to the fact that closing GS can occur in both forms of the defect [19].

Our analysis included two fetuses in which the lumen of the intestine was not visible in any of the ultrasound examinations performed and 5 fetuses in which the intestinal lumen began to decrease during observation. In the group with *EABL collapsed* sign 4/7 fetuses had a severe form of the defect - closing GS. The absence or decreasing of the previously visible small bowel lumen was a significant predictor of cGS occurrence.

To be able to assess whether the bowel image is indicative of an uncomplicated defect, it is necessary to know the naturally occurring changes in the bowel appearance, to have experience in interpreting the US images, and to serial and precise evaluate the changes that occur.

In the literature, there are different cut-off thresholds for the diagnosis of *EABD* and the obtained measurements are not always adjusted for gestational age, which makes it difficult to compare the data. First, because intestinal norms in healthy fetuses are different for the small intestine and the large intestine, it seems obvious that the cut-off thresholds at which we recognize *EABD* should be different. Secondly, these values in healthy fetuses change during pregnancy, therefore gestational age should also be considered in the bowel assessment in fetuses with GS.

If the range of cut-off points adopted in the analyses for *EABD* ranges from 6–25 mm, then different results should be expected [8, 13, 35–41]. Some studies have analyzed *EABD* in relation to the trimesters of pregnancy, others to the intervals of several weeks, or the appearance of the symptom before and after the 30th week of pregnancy [12, 13, 21, 37, 39]. There are studies available in which there is no distinction between *IABD* or *EABD*—and are considered as the *BD-NOS* (*bowel dilatation—non otherwise specified*), or the same cut-off points for *EABD* and *IABD* were adopted [8, 35, 37–40, 42]. When bowel dilatation was collectively evaluated, without specification of location (*EABD* and *IABD*), no association with cCG was found [42–45]. The intestine in the abdominal cavity is in different conditions – it is “packed”, while the extra-abdominal loops of the intestine floats freely in the amniotic fluid, which, in our opinion, affects the value of lumen measuring. Lap et al. drew attention to various values of measurements in sGS depending on the location of the intestine (*IABD/EABD*), that even in the group of fetuses with simple gastroschisis, the *intra-abdominal bowel diameter* was similar to the colon diameter in normal fetuses, but the *extra-abdominal bowel diameter* was generally larger [5].

Thus, the usefulness of this marker in the diagnosis of cGS and the severity of the defect depends on the determination of the cut-off point, separately for the small intestine and the large intestine, distinction between *IABD* and *EABD* and depending on gestational age.

Only a small series of studies have shown a positive association between *EABD* and cGS, but majority of studies have shown no correlation [8, 15, 38, 46, 47]. In the Sun meta-analysis, the risk of complex gastroschisis was higher in fetuses with *EABD* (OR = 2.27; 95%CI 1.40–3.66; $p < 0.001$) compared with *non-EABD* fetuses. But the analysis of the second and third trimesters showed that only

EABD detected in the second trimester was significantly associated with a higher probability of cGS (OR = 2.3; 95%CI 0.6–8.8; $p = 0.006$), while the Ferreria’s meta-analysis based on seven included studies indicated that *EABD* is a predictor of cGS (RR 1.55, 95% CI 1.01–2.39; $p = 0.000$) [7, 43]. In our study, assuming a 10 mm cut-off point for the small intestine and 18 mm for the large intestine, we found *EABD* in 9 (14.75%) fetuses in the entire study group, in 6.3% of fetuses with sGS and in 46.2% fetuses with cGS. Despite the fact that we showed a different frequency of occurrence of *EABD* in a simple and complex form, the obtained values did not reach statistical significance. The same cut-off values, without distinction between small and large bowel, were used in the Nitzsche’s study. They found that *EABD* values below and above 18 mm had sensitivities of 45.5% and 72.7%, respectively. However, these values were not suitable for predicting complex gastroschisis in the studied group. Specifically, an *EABD* value of ≥ 18 mm could predict cGS in only 45.5% of fetuses, while it predicted sGS in 27.3% of fetuses [48].

Some researchers have pointed out that *EABD* affects most GS fetuses and therefore has low specificity [8, 46, 49]. *Extra-abdominal bowel dilatation* is considered by some to be a normal occurrence in gastroschisis [40, 50]. The hypothesis that dilation of the herniated portion of fetal bowel may be more reflective of impaired peristalsis rather than true obstruction [36]. Therefore, the observed values greater than in healthy fetuses may not be a bowel dilatation, but a normal appearance of the intestine located in a different environment. However, some cut-off point must be adopted and the prediction of this marker will depend on this point.

Therefore, in the evaluation of *EABL*, fixed cut-off thresholds that do not respect gestational age and small bowel and colon diameters in healthy fetuses are not applicable if we expect a high predictive value in the evaluation of this marker. *EABL* could be measured and expressed as the ratio of observed over expected measurement for gestational age, according to reference data established in normal fetuses, or it would be necessary to establish values in uncomplicated GS on a large group of fetuses and compare the results obtained with these data.

In the literature, there are different cut-off thresholds for *IABD* diagnosis: between 6 and 20.5 mm, which makes it difficult to compare the results of many studies similarly to the *EABD* analysis [8, 12, 13, 16, 35–38, 48, 51–53].

Adopting the correct cut-off point also seems to affect the conclusions of the obtained measurements. The conclusions of most studies are consistent – *IABD* is a strong cGS marker [8, 12, 13, 15, 36, 50].

In our analysis, the diagnosis of *IABL dilatation* was also significantly more common in fetuses with cGS. As the cut-off point, we assumed the upper norm of the diameter of the small intestine in healthy fetuses. *IABL* measurements can be referred to the intestinal norms present in literature, because they are located in the natural environment—in the abdominal cavity and on this basis can be assessed the presence of *IABL dilatation*. *IABD* is the result of accumulation of fluid in the bowel lumen proximal to the site of obstruction, resulting in the sonographic appearance of bowel dilatation. 80% of atresia involves the small intestine, so we assumed that *IABL dilatation* is a symptom of small bowel lumen widening [5, 8, 32, 33, 36, 54]. Significant dilatation of *IABL* > 18 mm occurred in 3 fetuses, only in the cGS group, and was accompanied by this *EABL collapsed* sign.

Ferreira et al. in meta-analysis based on seven included studies reported the occurrence of *IABD* in 46.84% of fetuses with cGS and 15.30% of fetuses with sGS. This meta-analysis indicated that *IABD* is a predictor of complex GS (RR 3.01, 95% CI 2.22–4.08; $p = 0.310$) [7]. In our analysis, we observed a similar frequency in the sGS group, but in the group with cGS, this symptom was visible in almost 77% of fetuses.

As indicated above, the vast majority of studies report that *IABD* is a predictor of cGS, however, the prognostic values of this marker

are varied: sensitivity: 27.3–75%; specificity: 86–100%. Similarly PPV: 22–100 and NPV 81–92 [5, 8, 13, 16, 35, 39, 42, 48]. In some studies, OR or RR were also analyzed.

In the Lap study, it was found that when $IABD \geq 97.7$ th percentile occurred at least three times during fetal monitoring, it became a strong predictor of cGS (OR = 4.39; 95% CI, 1.46–13.21; $p = 0.009$). Although the specificity of this symptom was high (86.4%), its sensitivity was relatively low (40.9%). Therefore, although the marker has shown potential to differentiate between sGS and cGS, its clinical use may be limited [5]. Among the numerous studies analyzing the usefulness of $IABD$ in the prediction of cGS, there are also those that have not shown a relationship [14, 38].

The Sun's meta-analysis showed an association between GD and cGS (OR = 1.88; 95%CI 1.22–2.92) [43]. Mazzoni, on the other hand, did not notice *gastric dilatation* in his analysis either in the sGS group or in the cGS group [39]. In our study, the occurrence of this sign differed significantly between the sGS and cGS groups. The presence of this symptom increased the risk of cGS by 13 times.

Sonographic markers—quantitative assessment of signs

It is difficult to compare the data that we obtained with the literature data, because we made $EABL$ measurements separately for the small and the large intestine, referring them to the weeks of pregnancy and analyzing by type of defect. Lap et al. presented *extra-abdominal bowel diameter* and *intra-abdominal bowel diameter* measurements including sGS and cGS relating the obtained values for weeks of gestation and the values of colon measurements in healthy fetuses, without separating the large and small bowel [5, 55].

To assess the usefulness of measuring intestinal wall thickness, we did not use the 3 mm cut-off threshold published by other authors [8, 16, 36], because wall thickness depends on gestational age and one value cannot be assumed for the entire gestation period [11]. In addition, we observed different measurement values after distinguishing between the small intestine and the large intestine, which is related to the different structure of the wall. The need to distinguish between the small and large intestine has already been pointed out by other authors [14, 56]. Although these conclusions concerned the measurement of intestinal diameter, we believe that the same should be done in the assessment of wall thickness.

Most of the papers evaluating BWT (*bowel wall thickness*) concerned correlation with neonatal outcomes [8, 11, 21, 57–59]. Few studies analyze the relationship between BWT and cGS [15, 16]. Dewberry et al. reported a significantly higher percentage of fetuses in the cGS with finding of bowel wall thickening on prenatal ultrasound at GA at 21, 28, and 32 weeks [16]. However, in the Andrade study, BWT was not a differentiating sign between sGS and cGS [15].

In our study, 27.3% of fetuses with cGS and 20.0% of fetuses with sGS had small bowel wall thickness above the 90th percentile. However, when assessing the thickness of the colon wall, 50.0% and 20.5%, respectively.

The criteria for intestinal dilation vary between studies, making comparison difficult, and data are not always adjusted for gestational age. Correctly distinguishing between small and large bowel loops, the use of norms separately for small and large intestine, and defined bowel dilatation may improve the prediction of cGS and complicated sGS.

When analyzing the $EABL$ small bowel diameter, we showed values above the 90th percentile in 15.4% of fetuses with sGS and 54.5% of fetuses with cGS, while for the $EABL$ large bowel diameter, 25.6% and 60.0%, respectively. Interestingly, one fetus was diagnosed with both: $EABLD$ involving the large bowel and $EABL$ collapsed within the small bowel.

Without distinguishing which part of the bowel the measurements refer to, it is difficult to diagnose of bowel dilatation. When

evaluating small bowel measurements in our analysis and Martilotti's cut-off points ($EABD > 13$ mm for the second trimester and >25 mm for the third trimester) in any fetus small bowel measurements did not exceed these thresholds during the entire observation. However, when analyzing the measurements of the large intestine in one fetus in the second trimester of pregnancy and one in the third trimester of pregnancy, the measurement of the large bowel exceeded these thresholds [13].

To the best of our knowledge, this is the first work to quantitatively analyze these symptoms (including division into the small and the large intestine), and does not use cut-off points, in addition independent of gestational age.

In our study, the highest predictive value as a single symptom was obtained by *non-free floating bowel loops* with OR = 17.50 [95% CI 3.84–101.0] (specificity = 93.75; PPV at 88.24%), the significance of this parameter in the prediction of cGS is clear. In literature there are also studies whose results suggest a lack of appropriate ultrasound markers for the prediction of cGS [14, 60]. Mazzoni's assessment of dilatation, thickening, and hyperechogenicity of bowel loops didn't show statistical significance in differentiating between simple and complex gastroschisis [39].

Nitzsche's analysis combining $IABD$ and $EABD$ markers, with varied cut-off values, demonstrated fluctuating sensitivity, specificity, PPV, and NPV [48]. Carnaghan et al., focused on the gestational age of symptom occurrence, found varied PPV values for cGS [35]. Andrade's analysis of combined markers ($IABD$, $EABD$, *polyhydramnios*) only considered the number of symptoms, yielding OR values but lacking sensitivity, specificity, PPV, and NPV for comparison [15]. Ferreira's meta-analysis reported a 50% occurrence rate of these symptoms in cGS cases, without allowing for direct comparison [7]. Our study's results, showing higher specificity and sensitivity, differ from Fisher's findings, which included variables like polyhydramnios and external bowel changes [21].

Our models display higher accuracy in identifying cGS cases, with significant impact from $EABL$ collapsed and *non-free floating bowel loops* across models. Our third model, incorporating both qualitative and quantitative variables along with gestational age, provides a more comprehensive analysis.

This model in our study showed excellent predictive ability for cGS with the highest specificity (95.8%) and strong sensitivity (92.3%). The second model, while less precise, is simpler, using only two variables—*non-free floating bowel loops* and $EABL$ collapsed—which may make it more practical for clinical use. The choice between these models should balance predictive accuracy and usability in specific research or clinical contexts.

Clinical implication

Our results emphasize the importance of closely monitoring ultrasound symptoms and drawing conclusions preferably based on a combination of several markers. The occurrence of adverse ultrasound symptoms, their proper interpretation, and the planned preterm delivery, which is a compromise between the maturity of the fetus and the best condition of the intestine, creates a chance for optimal treatment in a given situation.

Due to the variety, variability, and dynamics of changes in the ultrasound images of the defect, it is difficult to determine a simple scheme of management and treatment that could be widely used. Close prenatal surveillance of fetuses with gastroschisis in reference centers, by experienced specialists is necessary due to the high risk of adverse perinatal and neonatal outcomes, including intrauterine fetal death during the third trimester. In the vast majority of fetuses, qualitative symptoms occurred after 30 weeks, which draws attention to the need for close monitoring during this period and it is important information for potential use of the fetal surgery.

Strength and limitations

The main limitation of the work is its retrospective nature. A single-center study can be seen as a limitation or a strength. The

strength is the material from one tertiary center, in which fetal monitoring was performed in an establish protocol throughout the entire study period. In addition, ultrasound examinations were performed by the same team throughout the study (90% of them were performed by the first author of the manuscript - RJ), which may increase the subjectivity of the assessment and results but increases the chances of a uniform assessment. The weakness may be the bias/subjectivity of the center, as other centers may use different protocols. The disadvantage of many studies on GS is the small size of the group (rare defect). Additionally, a single-center study may lack generalizability to wider populations due to the unique characteristics and practices of the specific center. This can limit the applicability of the findings to other settings where different demographic or clinical conditions prevail.

Other strengths include the fact that we described a new marker visible during the development of small bowel wall edema, as well as taking measurements separately for the extra-abdominal small and the large intestine. Quantitative assessment of markers was performed taking into account gestational age. Our study used multivariate regression to assess the usefulness of symptom sets in identifying fetuses with complex GS.

The challenge for further research is the number of ultrasound symptoms used in predictive models. According to the results of our modeling, it can be hypothesized that a reduction in the number of ultrasound criteria may increase sensitivity but is likely to reduce the specificity of the test. Conversely, increasing the number of criteria needed to mark a case as positive would reduce sensitivity but improve specificity. Finally, each ultrasound sign based on the measurement should be evaluated in relation to the optimal cut-off point in order to properly interpret the obtained result. In this scenario, large prospective studies are needed to standardize different ultrasound measurements depending on gestational age and cut-off points for each marker.

CONCLUSIONS

Ultrasound can predict fetuses with a higher risk of cGS. The highest PPV value as a single marker was demonstrated by *IABL dilatation*, but it had a low NPV value. The best PPV to NPV ratio obtained the *NFFBL* sign. Our data prove that combinations of several markers give the highest predictive value of the occurrence of cGS. Many iterations of multivariate logistic regression analyses were used in the study. Key findings highlight that *EABL collapsed* and *NFFBL* are consistent, statistically significant qualitative risk factors across models.

In studies evaluating both the range of bowel diameter in GS and the cut-off point for bowel dilatation, it seems necessary to refer obtained values to the location of the intestine (*IABL* vs *EABL*), to the part of the intestine evaluated (small vs large), to gestational age, and to refer the obtained *EABL* diameters to the measurements in uncomplicated GS. The described US signs show predictive value, but they must be evaluated in a reference center by experienced perinatologists to be observed and properly interpreted.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author [RJ] upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization, RJ; methodology, RJ, BM, AN, TM, and ES; software, RJ; validation, TM, and ES; formal analysis, RJ, DM, and BM; investigation, RJ; data curation, RJ, BM, AN, and DM; writing—original draft preparation, RJ; writing—review and editing, DM, AN, BM, ES, and TM; supervision, TM, and ES; project administration, RJ All authors have read and agreed to the published version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

In accordance with Polish law, there is no requirement to obtain ethical approval from a bioethics committee for conducting retrospective studies.

ADDITIONAL INFORMATION

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