Oesophageal atresia: sonographic signs may prenatally predict surgical complexity

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ABSTRACT

Objective Oesophageal atresia (OA) is a major anomaly of varying severity. The complexity of surgical correction highly depends on the gap length of missing oesophagus and the presence of a distal fistula. The aim of this study was to identify antenatal sonographic findings associated with presence of a distal fistula and type of surgical repair

Methods Prenatal medical records of neonates postnatally diagnosed with OA were reviewed. Sonographic signs of OA (small/absent stomach, polyhydramnios, oesophageal pouch) and the trimester at sign detection were recorded and compared between (1) OA with and without a distal fistula and (2) early one-step versus delayed two-step anastomosis. Multivariate analysis was performed.

Results Overall, 80 cases of OA were included. Absence of a distal fistula was significantly associated with higher rates of small/absent stomach (100% vs 28.6%, P<0.0001), oesophageal pouch (100% vs 24.3%, P<0.0001) and severe polyhydramnios (66.7% vs 22.9%, P=0.006), compared with OA with a distal fistula.

Cases requiring a delayed two-step repair had higher rates of small/absent stomach (84.2% vs 16.7%, P>0.0001), severe polyhydramnios (47.4% vs 16.7%, P=0.008) and oesophageal pouch (73.7% vs 18.5%, P<0.0001), compared with those corrected in an early one-step anastomosis.

Multivariate logistic regression found small/absent stomach and pouch to be significantly and independently associated with a delayed two-step anastomosis.

Conclusion OA without a distal fistula is associated with higher rates of prenatal sonographic signs. Both small/absent stomach and a pouch are independently associated with a delayed two-step anastomosis. These findings may help improve antenatal parental counselling regarding the anticipated surgical repair.

What is already known on this topic?

- Oesophageal atresia without a distal fistula, types A and B, is characterised by a long oesophageal gap and therefore requires a two-step delayed anastomosis.
- Oesophageal atresia consisting of a distal fistula, types C and D, is characterised by a short gap and is therefore amenable to a one-step anastomosis.
- Distal fistulas are not directly detectable prenatally, therefore, it is not possible to determine antenatally the type of atresia and the surgical complexity.

What this study adds?

- Proposed is a semiotic approach using prenatal sonographic signs to predict the presence of a distal fistula and type of surgical repair anticipated
- Oesophageal atresia without a distal fistula and a two-step anastomosis are both associated with higher prenatal detection rates of small/absent stomach, severe polyhydramnios and pouch.
- Fetuses prenatally detected with a small/absent stomach or an oesophageal pouch are 7.8 and 4.5 times more likely to require a delayed two-step repair, respectively.

INTRODUCTION

Oesophageal atresia with or without tracheoesophageal fistula (OA/TOF) is a major anomaly requiring postnatal surgical repair.[1–4] It may present prenatally with polyhydramnios, small\absent stomach or both.[5–8] Roughly only a third of OA/TOF cases are diagnosed prenatally by detection of an oesophageal pouch.[9–12] The Gross classification divides OA/TOF into five major types (A–E) according to the presence of OA and the presence and location of fistulas connecting the oesophagus and trachea (figure 1).[13] Generally, OA types lacking a distal fistula (types A and B) have a longer oesophageal gap than types consisting of a distal fistula (types C and D).[14–16] Type E is not an OA per se, as it consists only of a fistula and does not require oesophageal anastomosis. The degree of surgical repair complexity depends on the gap length of missing oesophagus,[14 17–20] ranging from a single surgical anastomotic procedure to repeated surgical interventions.[20–23] Clearly, identifying sonographic findings associated with absence of a distal fistula and with postnatal surgical complexity could improve prenatal counselling.[20] To the best of our knowledge, this is the first study which addresses this issue.

The aim of this study was to identify antenatal sonographic findings associated with absence of a distal fistula and type of postnatal surgical repair.

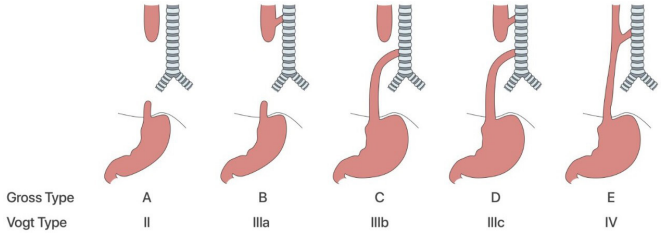

Figure 1 Diagram of oesophageal atresia types.

METHODS

The study was conducted at a single tertiary care centre between the years 2006 and 2020. Different subanalyses performed on a similar cohort of patients were published by our group in previous articles.[9 24] Included were cases that were diagnosed postnatally with OA, either during corrective surgery or at postmortem autopsy. Included cases underwent at least one anomaly scan during pregnancy. We excluded cases with an unknown OA type and patients not scanned during pregnancy.

The prenatal course was assessed for the rate and timing of appearance of the three principle sonographic findings of OA/TOF: (1) polyhydramnios (maximal vertical pocket (MVP) ≥8 cm or amniotic fluid index (AFI) ≥24 cm); (2) small/absent stomach (figure 2), both considered indirect suspicious signs; and (3) oesophageal pouch (figure 2), which was considered a diagnostic sign. The severity of polyhydramnios was recorded, with severe polyhydramnios defined as MVP ≥16 cm or AFI ≥35 cm.[25] An absent stomach was determined when the stomach bubble could not be discerned or distinguished from surrounding bowel loops. The stomach was considered small either subjectively, by the scanner, or objectively, using a fetal stomach size chart nomogram.[26]

Patients underwent at least one anomaly scan during pregnancy. A routine mid-trimester scan was performed between 19 and 25 weeks of gestation. Targeted third-trimester anomaly scans (>27 weeks) were performed in cases with suspected anomalies, polyhydramnios or abnormal growth.

Postnatally, the type of OA was determined during corrective surgery, among live births, and during postmortem examination among terminated cases. Corrective surgery was classified as early primary anastomosis, if performed during the first week of life in one stage, or delayed two-step anastomosis, if comprised a primary gastrostomy placement and a secondary definitive repair, at a later stage. The type of surgical procedure was decided by the performing surgeon, depending on the OA type and gap length of missing oesophagus.

We reviewed the medical records including ultrasound reports, images and video clips, genetic and laboratory workup, obstetric clinic visits, labour ward reports, neonatal intensive care unit reports and surgical reports.

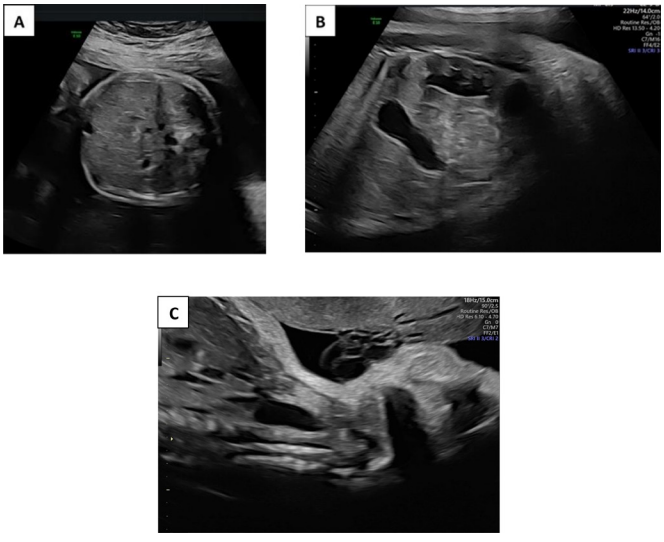

Figure 2 (A) A small stomach in type C oesophageal atresia. (B) A normal stomach in type C oesophageal atresia. (C) An oesophageal pouch.

Statistical analysis

Normality of the data was tested using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Data are presented as median and IQR. Comparison between unrelated variables was conducted with Student's t-test or Mann-Whitney U test, as appropriate. The χ^2 and Fisher's exact tests were used for comparison between categorical variables. Binary logistic regression analysis was used to determine which factors were significantly and independently associated with a delayed two-step repair. Significance was accepted at $p<0.05$. Statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (IBM SPSS V.23; IBM).

RESULTS

Overall, 83 cases with OA/TOF were detected at our centre during the study period. Excluded were two type E cases, as this subtype consists of an isolated TOF which does not develop sonographic signs and does not require anastomosis.[9] One type C case was excluded since it was not scanned during pregnancy. Thus, 80 cases were available for analysis. Of these, 19 cases underwent a routine mid-trimester anomaly scan, 7 cases underwent a targeted third-trimester scan and in 54 cases both types of scans were performed. At least one third-trimester growth scan was performed in all cases. The indications for a targeted third-trimester scan were polyhydramnios in 34.4% (21/61), small/absent stomach in 26.2% (16/61) and other conditions in 39.3% (24/61).

Characteristics of the study group are presented in online supplemental table 1s. Multiple pregnancies comprised a quarter (20/83) of the cohort. Over a third (32/83) of the cohort were affected by fetal growth restriction. Approximately 11% (5/45) had a genetic abnormality. Roughly 60% (50/83) presented multiple anomalies, the majority were part of a VACTERL (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies and limb abnormalities) association. The most common OA/TOF types were C (84.3%, 70/83) and A (10.8%, 9/83). Eight cases (9.8%) died in the neonatal period, six died prior to definitive surgery. The characteristics of the neonatal deaths are presented in online supplemental table 2s.

Sonographic findings associated with absence of a distal fistula

The sonographic findings and trimester at time of detection are presented in table 1.

There was a significantly higher prevalence of sonographic findings in the absent distal fistula compared with the distal fistula group: small/absent stomach (100% vs 28.6%, $p<0.0001$), absent stomach (80% vs 5.7%, $p<0.0001$), severe polyhydramnios (66.7% vs 22.9%, $p=0.02$) and oesophageal pouch (100% vs 24.3%, $p<0.0001$) (table 2). All absent distal fistula cases presented with a small/absent stomach, compared

Table 1 Sonographic findings and trimester of appearance according to the presence of distal fistula

Sonographic features	Absent distal fistula (n=10)	Distal fistula (n=70)*	P value
Small/absent stomach	100% (10/10)	28.6% (20/70)	<0.0001
Small stomach	20% (2/10)	22.9% (16/70)	1
Absent stomach	80% (8/10)	5.7% (4/70)	<0.0001
Second-trimester small/absent stomach	80% (8/10)	14.3% (10/70)	<0.0001
Third-trimester small/absent stomach†	100% (2/2)	16.7% (10/60)	0.035
Polyhydramnios‡	88.9% (8/9)	61.4% (43/70)	0.15
Severe polyhydramnios‡	66.7% (6/9)	22.9% (16/70)	0.006
Second-trimester polyhydramnios	10% (1/10)	8.6% (6/70)	0.88
Third-trimester polyhydramnios†	87.5% (7/8)	54.7% (35/64)	0.13
Pouch	100% (10/10)	24.3% (17/70)	<0.0001
Second-trimester pouch	30% (3/10)	1.4% (1/70)	0.005
Third-trimester pouch†	100% (7/7)	23.2% (16/69)	<0.0001
Presenting sign§			
Isolated polyhydramnios	0%	71.1% (32/45)	<0.0001
Small/absent stomach±polyhydramnios	100% (10/10)	28.9% (13/45)	
Absent sign	0% (0/10)	35.7% (25/70)	0.02

*Two type E cases and one type C case that was not scanned during pregnancy were omitted from analysis.
†Omitted from the third-trimester count were cases that developed the relevant sonographic sign during the second trimester.
‡One A type was omitted as the pregnancy was terminated at 26 weeks, before developing polyhydramnios.
§Fifty-five cases developed at least one sonographic sign.

with only 28.9% of cases in the distal fistula group. Within the distal fistula group, 35.7% of cases were devoid of sonographic signs while all of the absent distal fistula group developed at least one sonographic sign at some point (p=0.02).

A second-trimester small/absent stomach and oesophageal pouch were significantly more common in the absent distal fistula group (80% and 30% vs 14.3% and 1.4%, p<0.0001 and p=0.005, respectively). Similarly, in cases that were not previously detected with these signs, a third-trimester small/absent stomach and oesophageal pouch were significantly more common in the absent distal fistula group (100% vs 16.7% and 23.2%, p=0.035 and p<0.0001, respectively). There were non-significant differences in second-trimester and third-trimester polyhydramnios between the groups.

Type of surgical repair by presence of distal fistula

Most (84.6%) of the distal fistula group had a short gap and were amenable for an early primary anastomosis, while all of the absent distal fistula cases (100%) were planned for a two-step procedure to enable further growth of both ends of the oesophagus (online supplemental table 3s).

Sonographic findings associated with type of surgical repair

Seventy-three neonates survived to corrective surgery; 54 underwent early primary one-step anastomosis and 19 underwent a delayed two-step anastomosis.

The comparison of prenatal sonographic features and the trimester at which these findings were detected according to the type of surgical correction are presented in table 2.

Table 2 Comparison of sonographic findings according to type of surgical repair

Sonographic features	Early primary repair* (n=54)	Delayed two-step repair* (n=19)	P value
Small/absent stomach	16.7% (9/54)	84.2% (16/19)	<0.0001
Normal stomach	83.3% (45/54)	15.8% (3/19)	<0.0001
Absent stomach	1.9% (1/54)	42.1% (8/19)	<0.0001
Second-trimester small/absent stomach	5.6% (3/54)	57.9% (11/19)	<0.0001
Third-trimester small/absent stomach†	11.8% (6/51)	62.5% (5/8)	0.001
Polyhydramnios	59.3% (32/54)	78.9% (15/19)	1.0
Severe polyhydramnios	16.7% (9/54)	47.4% (9/19)	0.008
Second-trimester polyhydramnios	5.4% (3/54)	10.5% (2/19)	0.6
Third-trimester polyhydramnios†	51% (26/51)	76.5% (13/17)	0.07
Pouch	18.5% (10/54)	73.7% (14/19)	<0.0001
Second-trimester pouch	0%	10.5% (2/19)	0.06
Third-trimester pouch†	16.7% (9/54)	76.5% (13/17)	<0.0001
Presenting sign‡			
Isolated polyhydramnios	81.8% (27/33)	23.5% (4/17)	<0.0001
Small/absent stomach±polyhydramnios	18.2% (6/33)	76.5% (13/17)	
Absent sonographic signs‡	38.9% (21/54)	10.5% (2/19)	0.02

*Seventy-three cases included in the analysis; excluded were one termination of pregnancy, six neonatal deaths prior to surgery, two E types not requiring oesophageal anastomosis and one case that did not undergo prenatal scans.
†Omitted from the third-trimester count were cases that developed the relevant sonographic sign during the second trimester.
‡Fifty patients had sonographic findings, 23 did not have signs at any point during pregnancy.

Most cases requiring a delayed two-step procedure had a small/absent stomach compared with the early primary anastomosis group (84.2% vs 16.7%, p<0.0001). An absent stomach bubble was detected in 42.1% in the delayed two-step group compared with 1.9% in the early primary anastomosis group, respectively (p<0.0001). An oesophageal pouch was detected in 73.7% of the delayed repair group compared with 18.5% of the early repair group (p<0.0001). The first presenting sonographic finding was a small/absent stomach, with or without polyhydramnios in 76.5% of the delayed two-step group compared with 18.2% in the early primary repair group (p<0.0001). Within the early repair group, 38.9% did not develop sonographic signs at any point in pregnancy, compared with only 10.5% in the delayed two-step repair group (p=0.02). Severe polyhydramnios developed in 47.4% of the delayed two-step group compared with only 16.7% among the early repair group (p=0.008).

A small/absent stomach appearing in the second trimester was significantly more common in the delayed two-step group (57.9% vs 5.6%, p<0.0001). Similarly, in cases that were not previously detected with these signs, a small/absent stomach and an oesophageal pouch appearing in the third trimester were significantly more common in the delayed two-step group (62.5% and 76.5% vs 11.8% and 16.7%, p=0.001 and p<0.0001, respectively). There were non-significant differences in second-trimester and third-trimester polyhydramnios between the groups.

Binary logistic regression analysis was employed to determine which factors were independently and significantly associated with a delayed two-step repair while adjusting for a small/absent stomach, severe polyhydramnios and an oesophageal pouch. The final regression indicated that small/absent stomach and an oesophageal pouch were both found to be independently and significantly associated with a delayed two-step repair, with an OR of 7.8 (95% CI 1.7 to 35.6, p=0.008) and 4.5 (95% CI 1 to 20.7, p=0.049), respectively (online supplemental table 4s).

DISCUSSION

The principal finding of the study is that fetuses prenatally detected with a small/absent stomach or an oesophageal pouch are 7.8 and 4.5 times more likely to require a delayed two-step repair, respectively.

Although the postnatal and postoperative outcomes are not significantly different in prenatally detected compared with postnatally detected OA,[5 20 27] the antenatal diagnosis of this condition is of paramount importance for several reasons: (1) It provides an opportunity for parents to be prepared for the postnatal period and to be thoroughly consulted regarding the expected corrective surgery and postoperative course. (2) OA is associated with genetic abnormalities in 5%–10% of cases and multiple anomalies in 37%–60% of cases.[9 16 28–30] Therefore, its prenatal detection mandates a comprehensive diagnostic workup, including a meticulous anatomy scan and genetic investigation. This information is valuable for pregnancy management and decision-making.[14 15 22 31] (3) It prevents the inconvenience of postnatal transfer to a dedicated tertiary centre.

The effect of a distal fistula on sonographic manifestation

Previous studies comparing prenatally and postnatally diagnosed OA/TOF[6 15 20 27 32 33] found that pure OA (type A) was significantly more detected prenatally than type C. This difference is probably due to the ameliorating effect of the distal fistula on sonographic signs.

The fistula, which is connected to the trachea, introduces amniotic fluid into the stomach, thus attaining a normal-sized stomach and preventing polyhydramnios.[34] This phenomenon was observed in 35.7% of the distal fistula group in our study, which were completely devoid of sonographic signs, rendering them unsuspicious. In contrast, when a distal fistula is absent, amniotic fluid cannot reach the fetal stomach, reducing its clearance, leading to polyhydramnios and a small or even absent stomach,[9 32] as was observed in our cohort.

Elucidating the effect of a distal fistula on the rate and severity of prenatal sonographic signs can help clinicians to understand the variability of the prenatal manifestation of this major anomaly. Moreover, being aware that in a third of cases, indirect sonographic signs may be masked by the presence of a distal fistula might alleviate patients' confusion when OA is diagnosed postnatally despite normal scans.

Sonographic findings associated with type and complexity of surgical repair

The theoretical basis for a semiotic system that might predict the type of surgical procedure lies in the concept that a distal fistula usually confers a short gap[20] and it also ameliorates the sonographic manifestation, as previously elaborated. A short-gap OA enables an early one-step anastomosis in contrast to multiple surgical procedures required to correct long-gap OA.[14 18] The results of our study support the association between the presence of a distal fistula and the type of repair (online supplemental table 3s). All absent distal fistula cases in our study required multiple surgical procedures, while 84.6% of cases with a distal fistula had a short-gap OA that enabled a primary one-step anastomosis. This is in line with the current common practice of surgical repair of types A and B requiring at least two separate procedures[18]: (1) early gastrostomy placement, and (2) delayed anastomosis at 6 weeks of age, allowing oesophageal stub elongation with or without a Foker procedure.

Since direct demonstration of a distal fistula is not yet feasible prenatally,[35] indirect sonographic signs could serve as markers for its presence and can aid to predict the type of surgical repair. The current study indicates that a delayed two-step repair is significantly more associated with a small/absent stomach, an absent stomach, severe polyhydramnios and an oesophageal pouch. Early primary repair is more associated with absent sonographic findings. Binary logistic regression further suggested that both a small/absent stomach and an oesophageal pouch confer a higher risk for a delayed two-step repair, with an OR of 7.8 and 4.5, respectively.

To the best of our knowledge, this is the first study to correlate the type of surgical repair with prenatal sonographic signs and, thus, a comparison with existing literature is limited. While the current study investigated the association of sonographic signs and the type of repair, previous studies compared the type of repair between prenatally and postnatally detected OA/TOF.[4 15 20 27] In these studies, prenatal detection relied on the presence of polyhydramnios and/or a small/absent stomach, and occasionally on an oesophageal pouch. Kunisaki *et al* observed a higher prevalence of types A and B (both lacking a distal fistula) requiring a delayed oesophageal repair in the prenatally detected group.[15] A large study by Garabedian *et al* found that prenatally detected OA had a longer oesophageal gap, a higher rate of delayed two-step repair and a higher rate of postrepair complications.[20] The broad conclusion of these studies is that prenatally detected OA is more likely to be of types A and B requiring a more complex repair, compared with postnatally detected OA.

Strengths and weaknesses

To the best of our knowledge, this is the first study specifically designed to determine the association between antenatal sonographic findings and the complexity of corrective surgery. The clinical implications of this information may contribute significantly to the quality and precision of parental counselling.

Our study is limited by its retrospective nature. In a few cases of reported small/absent stomach, it was not clear whether this was a subjective perception or an objective measurement. To overcome this uncertainty, we retrospectively measured the stomach bubble on the abdominal circumference plane and compared it to a stomach size chart.[26] In most, but not all polyhydramnios cases, was an AFI reported, but rather commented normal/abnormal and the degree of severity. Another weakness of the study is the relatively small group of absent distal fistula. This is due to the rarity of the OA types A and B, which lack a distal fistula.

To conclude, the prenatal detection of a small/absent stomach, oesophageal pouch and severe polyhydramnios is associated with both an absent distal fistula and delayed two-step repair. Fetuses prenatally detected with a small/absent stomach or a pouch are 7.8 and 4.5 times more likely to require a delayed two-step repair, respectively.

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Table 1s Characteristics of pregnancies affected by Tracheoesophageal Fistula

Perinatal Characteristics		Study Group (N=83)	
Maternal Age		32 (28-35)	
IVF Pregnancy		20.5% (17/83)	
Multiple Pregnancy		24.1% (20/83)	
Male Gender		65% (54/83)	
Prenatal EA Detection**		32.9% (27/82)	
FGR		38.5% (32/83)	
Chromosomal Abnormality		11.1% (5/45)	2 Trisomy 18
			2 Pathogenic Copy Number Abnormality
			1 WES detected EFTUD2 mutation
Multiple Anomalies		60.2% (50/83)	
VACTERL Sequence		50.6% (42/83)	
Perinatal Outcome	Termination of Pregnancy	1.2% (1/83)	
	Livebirth	96.4% (80/83)	
	Neonatal Death	9.8% (8/82)	
TEF Type	A	10.8% (9/83)	
	B	1.2% (1/83)	
	C	84.3% (70/83)	
	D	1.2% (1/83)	
	E	2.4% (2/83)	

Data presented as Median (Interquartile Range) or Percentage (n/N)

** One case that did not undergo ultrasound scans during pregnancy was excluded

IVF- In Vitro Fertilization; EA- Esophageal Atresia; FGR- Fetal Growth Restriction; WES- Whole Exome Sequence; VACTERL-Vertebrae, Anal Atresia, Tracheoesophageal Fistula, Renal and Limb; TEF- Tracheoesophageal Fistula.

Table 2s Characteristics of Neonatal Death Cases

	Neonatal Deaths (N=8)
Gestational Age at Delivery (weeks)	34.3 (33.1-37.1)
Prematurity	75% (6/8)
Birthweight (grams)	1409 (1196-1978)
Small for Gestational Age	60% (5/8)
Multiple Anomalies	100% (8/8)
Esophageal Atresia Type C	100% (8/8)
Genetic Abnormalities	60% (3/5)
Age at Neonatal Death (days)	48 (27-60)
Reason of Death	Post-repair tracheal tear Cardiac Insufficiency Pulmonary Hypertension 2 Trisomy 18- Multisystem Insufficiency 2 Cardiac Arrest Multisystem Insufficiency

Data presented as Median (Interquartile Range) or Percent (n/N).

Type of Repair		TEF without Distal Fistula* (N=9)	TEF with Distal Fistula* (N=65)	P value
Type of Repair	Early Primary Repair	0% (0/9)	84.6% (55/65)	<0.0001
	Delayed Two Step Repair	100 % (9/9)	15.4% (10/65)	

Table 3s Type of Surgical Repair according to the presence of a distal fistula

*Excluded from calculation were 2 Type E cases, 6 Type C cases that expired prior to surgical repair and 1 Type A that was terminated.

Sonographic Sign	P value	OR	95% C.I.for OR	
			Lower	Upper
Small/absent Stomach	0.008	7.8	1.7	35.6
Pouch	0.049	4.5	1	20.7
Severe Polyhydramnios	0.98	0.39	.21	4.56

Table 4s Logistic Regression of Sonographic Signs Associated with a Delayed Two Step Repair.

OR- Odds Ratio; CI- Confidence Interval.