OBSTETRICS

The prenatal detection of distal tracheoesophageal fistulas in fetuses diagnosed with esophageal atresia

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BACKGROUND: Esophageal atresia is a major anomaly of varying severity. The complexity of surgical correction depends on the presence of a distal fistula.

OBJECTIVE: This study aimed to determine the feasibility and accuracy of prenatal ultrasound detection of the distal fistula in fetuses diagnosed with esophageal atresia.

STUDY DESIGN: This was an observational study conducted at a single tertiary care center between 2019 and 2021. Included were pregnant patients carrying a fetus prenatally diagnosed with esophageal atresia that was confirmed postnatally during corrective surgery or at postmortem autopsy. During the scan, the performing investigator determined the presence or absence of a distal fistula by scanning the location of the lower esophagus during fetal breathing. Cases in which the lower esophagus was observed distending with amniotic fluid during breathing were deemed "fistula present," and the remaining cases "fistula absent." Test feasibility and performance indices, including sensitivity, specificity, and positive and negative predictive value were calculated. The offline clips and images were reviewed by 2 investigators for the assessment of interoperator agreement using Cohen's Kappa formula.

RESULTS: Included were 16 fetuses with esophageal atresia scanned between 2019 and 2021. All fetuses were successfully scanned with sufficient resolution of the area of interest during at least 3 cycles of breathing. It took a median of 8.5 minutes to determine the presence or absence of a distal fistula. The feasibility of the test was 100% (16/16). The test's sensitivity, specificity, and positive and negative predictive values were 80% (95% confidence interval, 55—100), 100% (95% confidence interval, 60—100), 100% (95% confidence interval, 65—100), and 75% (95% confidence interval, 45—100), respectively. The Cohen's Kappa for interoperator agreement was calculated to be 1, $P<.001$, corresponding to a "perfect" level of agreement.

CONCLUSION: Distal fistulas in esophageal atresia can be demonstrated prenatally by targeted scanning using appropriate technique. The method provided is feasible, reproducible, and has excellent performance indices. This novel technique and observations may improve the prenatal diagnosis and counseling of esophageal atresia.

Key words: absent stomach, esophageal atresia, esophageal pouch, fetal esophagus, polyhydramnios, prenatal diagnosis, small stomach, tracheoesophageal fistula

Introduction

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is a major anomaly requiring postnatal surgical repair.[1–4] Using conventional ultrasound methods, approximately a third of EA cases are diagnosed prenatally by detection of an esophageal pouch.[5–8] A recent prospective study published by our group presented a novel technique aimed to significantly increase the detection rate of EA by using a method termed DEPA (Dynamic Esophageal Patency Assessment). This method relies on the direct visualization of fluid propagation through the esophagus during swallowing.[9] However, this method does not determine the presence or absence of a distal fistula (DF), an important factor affecting surgical complexity.[10] EA gross types A and B, lacking DF (Figure 1),[10] have a longer esophageal gap, require repeated surgical interventions, and bear a less favorable prognosis than EA types C and D with DF (Figure 1),[10] which are commonly repaired in a single surgical anastomotic procedure.[10–17] Therefore, prenatally determining the presence or absence of a DF may improve prenatal counseling.[18]

Currently, only indirect sonographic signs, such as a small or absent stomach, esophageal pouch, and polyhydramnios and its severity are used to predict the presence of a DF and the surgical complexity anticipated.[10]

This study addressed the direct demonstration of a DF in fetuses prenatally diagnosed with EA.

This study aimed to determine the feasibility and accuracy of DF determination by ultrasound in fetuses diagnosed with EA.

Materials and Methods

This was an observational study conducted at a single tertiary care center between 2019 and 2021.

Inclusion criteria were: (1) prenatal diagnosis of EA by pouch demonstration, (2) postnatal EA type confirmation either during corrective surgery or postmortem autopsy, and (3) targeted scan performed at our center. Cases of pregnancy termination in which postmortem autopsy was not performed were excluded.

The scans were performed by 2 investigators (E.K. and T.W.), and included the following components: (1) a complete anomaly scan, (2) the DEPA method for diagnosing EA,[9] and (3) the investigational method for determining

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AJOG at a Glance

Why was this study conducted?

This observational study aimed to evaluate the performance of a method aiming to prenatally determine the presence or absence of a distal tracheoesophageal fistula in esophageal atresia.

Key findings

The proposed method demonstrated a sensitivity of 80% and specificity of 100%, with high interobserver agreement. A detailed description of the method's technique is provided.

What does this add to what is known?

This study proposed a systematic method for prenatally demonstrating tracheesophageal fistulas, thus far considered undetectable on prenatal ultrasound.

the presence of a DF, as subsequently described.

The sonographic demonstration of a distal fistula

Examinations were performed transabdominally or transvaginally, depending on gestational age, using a Voluson E8 or E10 ultrasound machine (GE Healthcare, Milwaukee, WI) and either a RM6C or RAB4 abdominal probe (GE Healthcare) or a RIC6-12-D vaginal probe (GE Healthcare), as appropriate. Generally, a transvaginal approach was used up to 18 weeks of gestation and a transabdominal approach from ≥18 weeks.

The course of the fetal esophagus (Figure 2, A) and its partition into an upper and lower segment on ultrasound have been previously described.[9] The lower esophagus (Figure 2, B), located below the level of the aortic arch, is the esophageal segment connected to the DF in EA types C and D. Its upper end is located behind the lower trachea and right main bronchus. Thereon, it courses caudally and anteriorly in the fetal mediastinum to come in contact with the posterior wall of the heart before traversing the diaphragm. The appearance of the collapsed fetal esophagus on ultrasound is a longitudinal structure composed of stripes of varying echogenicity,[9,19–21] with a central echogenic line which marks the opposed walls of the esophageal lumen (Figure 3). Once the collapsed lower esophagus is identified, the scanner should wait for esophageal distention, which is evident when anechoic fluid fills the lumen of the esophagus. This occurs during fetal swallowing through an intact esophagus (Figure 4, Supplemental Video 1) or during fetal breathing, when fluid is introduced through the TEF to the lower esophagus (Figure 5, Supplemental Video 2). Both fetal swallowing and breathing increase in frequency with advancing gestation, facilitating the demonstration of a distended lower esophagus as pregnancy progresses.[22,23] To demonstrate the distal TEF itself, the distended lower esophagus is traced to the point of connection with the trachea, close to the level of the carina (Figure 6). This is best demonstrated in a supine fetal lie but can also be demonstrated in prone position, when needed.

Distal fistula determination

DF was deemed present when fluid passage distending the lower esophagus was observed during fetal breathing (Figure 5, Supplemental Video 2). DF was deemed absent when a fluid-distended lower esophagus was not observed during at least 3 cycles of fetal breathing (Figure 7).

A breathing cycle was considered to span from the first to the last breathing movements documented in an episodic bout of fetal breathing.

Among fetuses determined "DF absent," the appearance of the residual lower esophagus was studied. We distinguished between short or absent lower esophageal segment (Figure 7, A) and long lower esophageal segment (Figure 7, B).

It is important to differentiate between the determination of the presence of a DF by detecting fluid passage through the lower esophageal end, and the direct DF demonstration by following the distended lower esophageal end to demonstrate the point of its fistulous connection with the trachea.

Evaluating the performance of distal fistula determination

The type of EA and presence of a DF were definitively determined during corrective surgery or postmortem examination. The prenatal sonographic DF determination was then compared with the postnatal definitive DF determination. Test performance indices, including sensitivity, specificity, and positive and negative predictive values were calculated.

All scans were independently reviewed offline for interoperator agreement assessment. The investigators were blinded to patients' details and the definitive type of EA.

The study protocol was approved by the Institutional Ethical Committee (approval number 5345-18-SMC).

Statistical analysis

Data are presented as median and interquartile range (IQR) for continuous variables and percentage and numbers for categorical variables. Test performance measures (sensitivity, specificity, negative and positive predictive values) and corresponding confidence intervals (CIs) were calculated. The Pearson chi square test was used for comparison of categorical variables, and Cohen's Kappa formula for interobserver agreement. Level of agreement was defined according to the Kappa result, as previously described by Landis and Koch[24]: poor (0−0.2), fair (0.21−0.4), moderate (0.41−0.6), good (0.61−0.8), and near perfect (0.81−1). Significance was accepted at $P<.05$. Statistical analyses were conducted using the IBM SPSS Statistical software, version 25 (IBM Corp, Armonk, NY).

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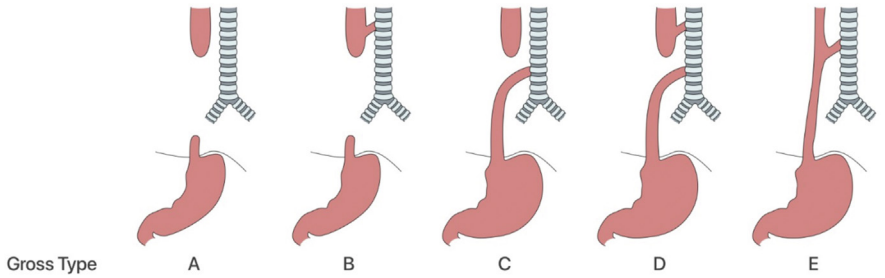
FIGURE 1
Gross classification of esophageal atresia types



Types A and B lack a distal fistula and are considered "long-gap." Types C and D consist of a distal fistula, having a "short gap." Type E is a pure tracheoesophageal fistula without esophageal atresia.

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Results

Included were 16 fetuses prenatally diagnosed with EA, scanned at a single tertiary center between 2019 and 2021, with scans available for review. Maternal demographics, scan information, and the type of EA are presented in Table 1. The median gestational age at time of scan was 28.5 weeks (IQR, 25.1−32.1), with the earliest having been performed at 17.5 weeks. It took a median of 8.5 minutes to determine the presence or absence of a DF. The most frequent referral indications for a targeted scan were polyhydramnios, a small or absent stomach, or a combination of both. Two cases were referred because of a suspected interrupted esophagus during the early anomaly scan, as described in a previous article.[19] In all cases the course of the lower esophagus was successfully demonstrated, and the presence of a DF was determined by one of the investigators.

Performance of prenatal sonographic distal fistula determination

Test performance measures were calculated on the basis of a contingency table (Table 2) comparing the DF determination result (present or absent) with the postnatal diagnosis (DF present or absent). The test's sensitivity, specificity, and positive and negative predictive values were 80% (95% CI, 55−100), 100% (95% CI, 60−100), 100% (95% CI, 65−100), and 75% (95% CI, 45−100), respectively.

Of the 8 prenatal "DF absent" cases, 3 demonstrated a persistently collapsed lower esophagus, coursing from the diaphragm to the aortic arch (Figure 7, B). This appearance was suspicious for a DF. However, because fluid was not seen passing through this structure at any point, these cases were determined "DF absent." The cases were scanned at 17, 21, and 23 weeks of gestation. At postmortem, 2 were found to be type C with DF, and 1 type A without DF.

Interoperator agreement

The interobserver agreement is displayed in Table 3. There was a perfect agreement (Kappa=1) between the index interpretation of operator 1 and the interpretation of operator 2.

The contribution of magnetic resonance imaging

Fetal body magnetic resonance imaging (MRI) was performed in 4 cases (Table 1). In 3 cases it was performed after the diagnosis of EA and determination of DF were made by ultrasound. In these cases, MRI was in agreement with the sonographic diagnosis. In one case it was performed before EA was diagnosed, and neither a pouch nor a DF were observed on MRI.

Comment

Principal findings

The novel observation of the study is that the distal fistula in esophageal atresia can be visualized prenatally using a highly feasible and reproducible method. This method requires focused scanning of the correct anatomic region, as described herein, supplemented by knowledge of the subtle appearance of the fetal esophagus, collapsed or distended. Considering that EA without DF mandates a more complex and delayed anastomotic repair than EA with DF,[10] the determination of the presence or absence of a DF may improve prenatal counseling and better prepare couples for the anticipated postnatal course and type of surgical repair.

Results in the context of what is known

A recent study published by our group suggested a semiotic approach, relying on indirect signs, to prenatally predict the presence of a DF and the type of surgical correction that would be required.[10] However, a systematic method for directly demonstrating the distal TEF and esophagus is a novel advancement in the field of prenatal diagnostics.

The performance of prenatal distal fistula demonstration

The feasibility of demonstrating the course of the lower esophagus was 100%. This observation is in agreement with previous studies showing that the demonstration of the lower fetal esophagus in healthy fetuses throughout pregnancy is highly feasible using a similar technique.[9,19−21,25] Unlike the upper segment of the fetal esophagus, the plane required to demonstrate the lower esophagus, from the level of the aortic arch and downward, is easier to acquire and is less obscured by acoustic

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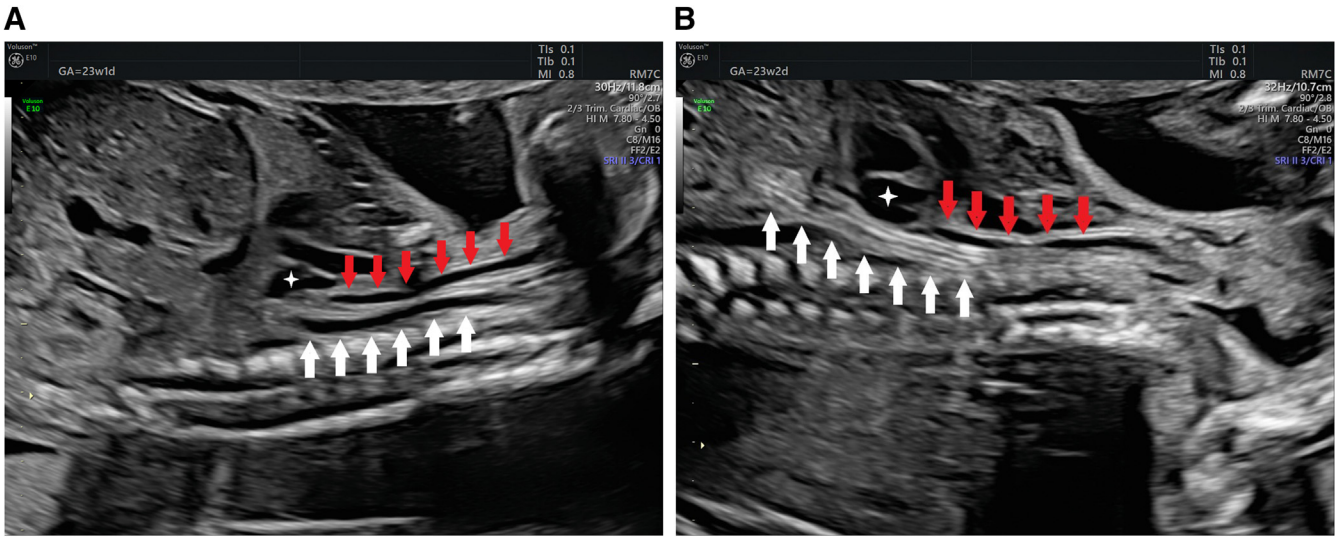
FIGURE 2
The course and appearance of the fetal esophagus



The course and appearance of **A,** the whole esophagus (*white arrows*) in a normal fetus, distended with fluid, coursing from the neck to the diaphragm, behind the prominent trachea (*red arrows*) and left cardiac atria (*white star*). **B,** The lower esophagus (*white arrows*) in a normal fetus, running posterior to the trachea and right main bronchus (*red arrows*), coursing anteriorly to come in contact with the posterior cardiac wall (*white star*), just before traversing the diaphragm.

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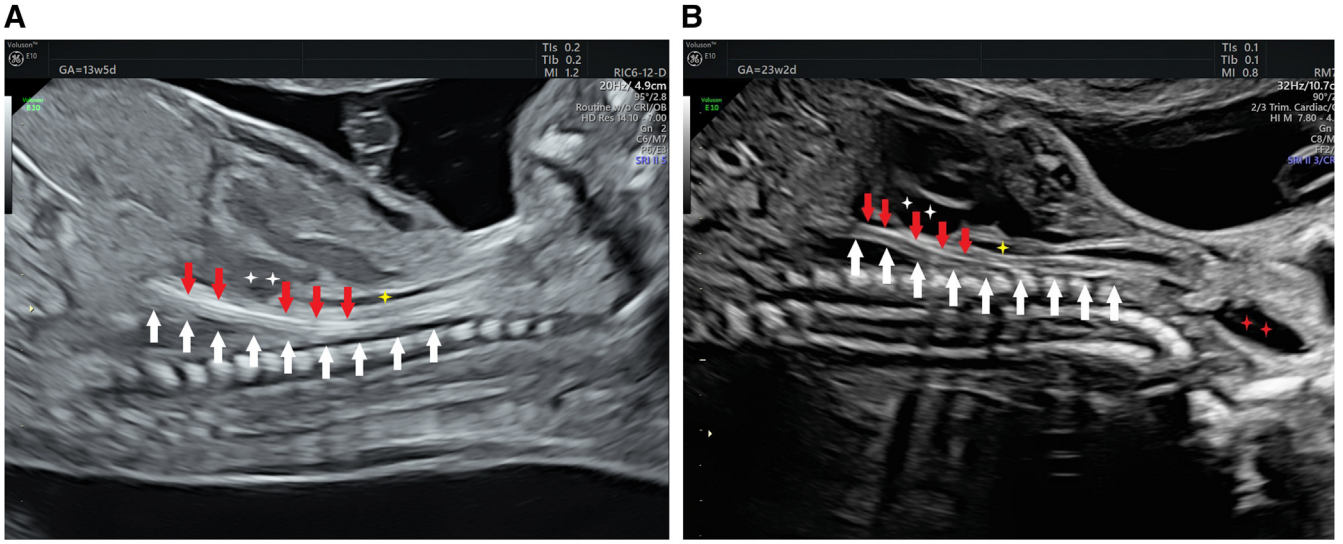
FIGURE 3
The appearance of the collapsed esophagus



The sonographic appearance of the fetal esophagus is a longitudinal structure (*white arrows*) composed of stripes of varying echogenicity with a central echogenic line (*red arrows*) representing the opposed collapsed walls of the esophageal lumen. The esophagus courses behind the prominent fluid-filled trachea (*yellow star*) and down behind the wall of the left atrium (*double star*), toward the diaphragm **A,** at 13 weeks and **B,** at 23 weeks. In this image, (*red stars*) mark the fluid-filled pharynx. In the latter half of pregnancy, the stripes of the fetal esophagus become subtle and more difficult to discern. The identification of the collapsed fetal esophagus is important when performing a focused scan of the esophagus.

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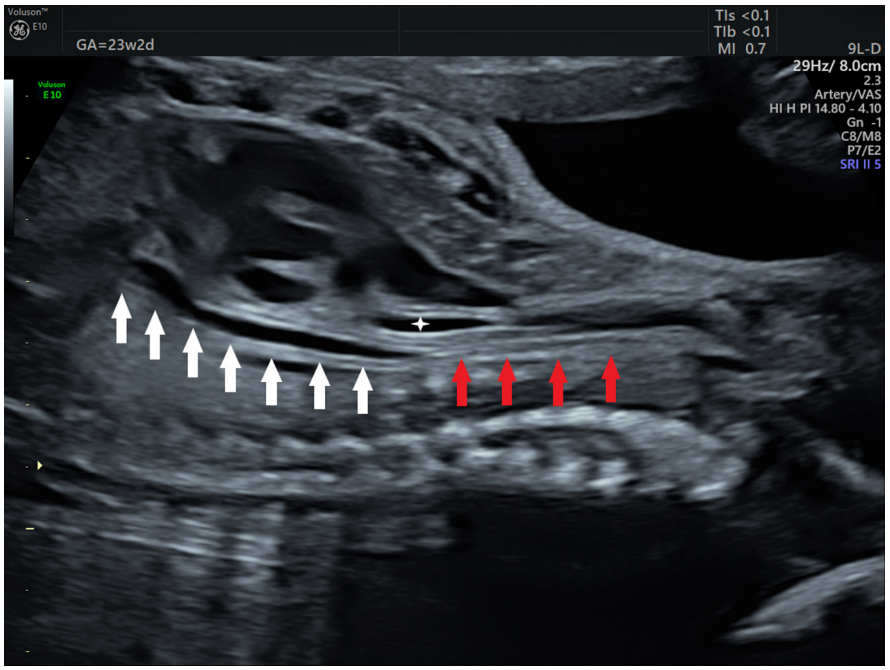
FIGURE 4
Lower esophageal distention



A, Lower esophageal distention; anechoic fluid fills the lumen of the esophagus (*white arrows*) during fetal swallowing through an intact esophagus. The collapsed upper esophagus (*red arrows*), after completion of a peristaltic wave, is demonstrated behind the trachea (*star*). **B,** Distention of both the upper and lower esophagus in a normal fetus (*white arrows*).

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shadows. Moreover, the fetal heart, filled with hypoechogenic fluid, provides an acoustic window for the lower esophagus, coursing behind it and enhancing the visualization of its echogenic stripes.

Interobserver agreement

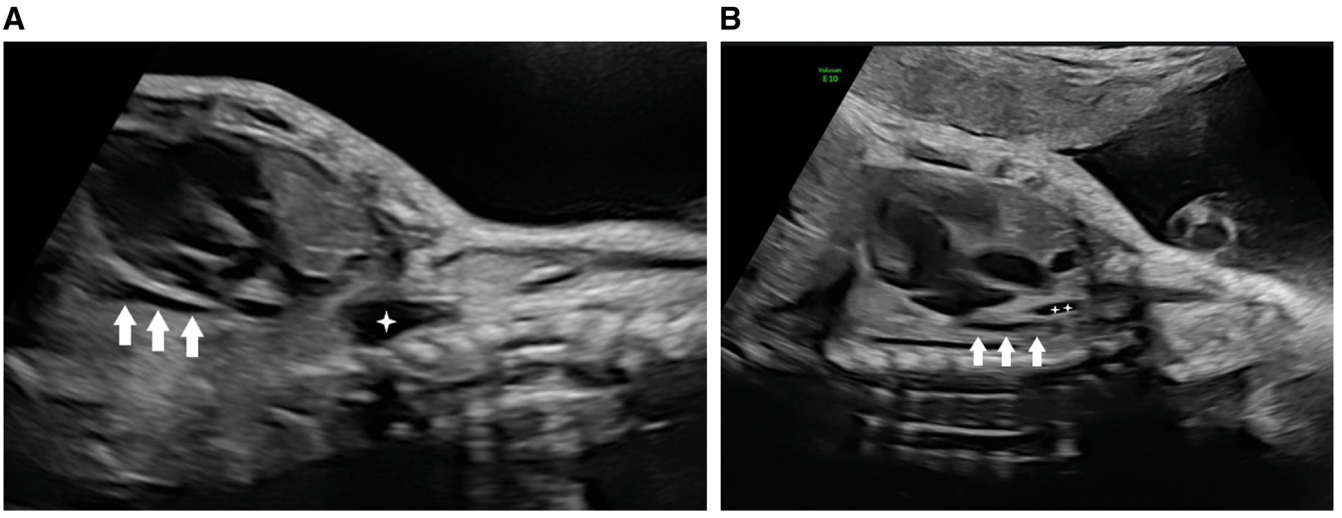
The interobserver agreement of DF determination scored "perfect," emphasizing that the interpretation of the sonographic appearance is straightforward once defined criteria are met.

The significance of a persistently collapsed lower esophagus

There were 3 inconclusive cases demonstrating a noninterrupted normally appearing lower esophagus stretching from the level of the aortic arch and down to the diaphragm. However, distention of this segment was not observed during repeated cycles of fetal breathing (Figure 7, B). These cases were diagnosed with EA at 17, 21, and 23 weeks of gestation. Two had an absent stomach bubble, and the third case had a small stomach bubble. Of these, 2 had a DF (type C) and the third lacked a DF (type A) on postmortem autopsy.

This observation suggests 2 theoretical implications. First, it might be that

FIGURE 5
Distal fistula present in esophageal atresia



A, Fluid passing through the lower esophageal segment (*white arrows*). An esophageal pouch (*star*) appears anterior to the spine. **B,** Fluid passing through the lower esophageal segment (*white arrows*). The trachea (*double star*) is demonstrated anterior to the esophagus.

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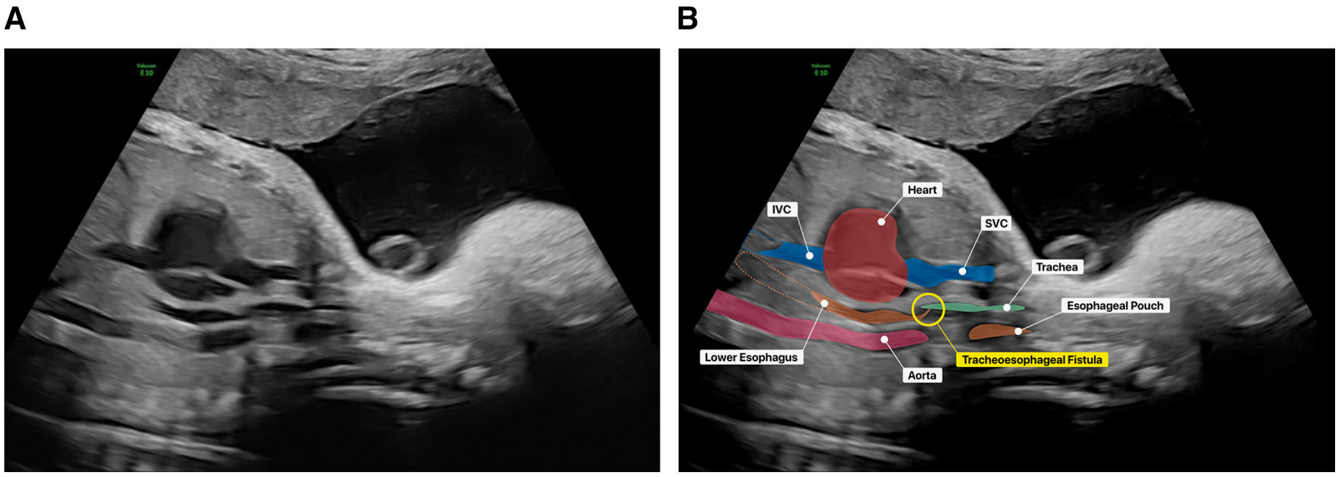
FIGURE 6
The demonstration of the distal fistula by prenatal ultrasound



Distal fistula between the trachea and lower esophageal segment in a fetus with esophageal atresia. An esophageal pouch appears between the spine and trachea. **A,** Plain ultrasound image. **B,** The same image with a schematic illustration of the different structures.

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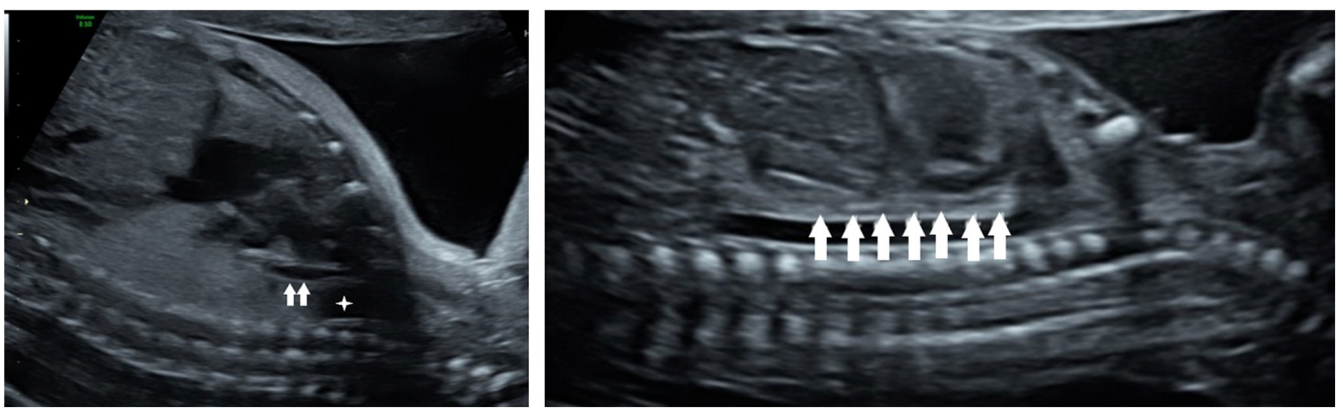
not all DFs pass fluid prenatally. This is supported by previous studies reporting EA type C cases with an absent stomach bubble on ultrasound throughout pregnancy, suggesting a nonpatent or extremely narrow DF.[5,26–29] Because these cases resulted in a termination of pregnancy at 23 weeks of gestation, it is unknown whether the fistula would have become patent and filled the stomach at a later stage in pregnancy. Second, the lower esophageal segment in gross types A and B, which is not connected to the trachea, might reach close to the level of the carina in early pregnancy. However, as the fetus grows in the absence of any traction on its lower blind esophageal end, the lower esophageal segment might not continue to elongate, resulting in a relatively short residual segment, as commonly seen at term.[1,10,11,14,17,30] These examples emphasize that the demonstration of a collapsed lower esophagus,

FIGURE 7
Distal fistula absent in esophageal atresia type A



A, A distended lower esophagus was not seen at all during at least 3 cycles of fetal breathing in an appropriate plane. An esophageal pouch (*star*) is demonstrated behind the trachea (*white arrows*) in the upper chest. **B,** A persistently collapsed long-segment distal esophageal stub (*white arrows*) demonstrated in an additional case.

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regardless of its length, is insufficient to determine the presence of a DF, especially in early stages of pregnancy. Only cases with clear fluid passage through the lower esophagus can be confidently confirmed to have a DF.

The significance of the sonographic appearance of the stomach

The appearance of the fetal stomach is an indirect indication of the presence of a DF.[10,18,31,32] A normal-sized stomach is likely to have a concomitant DF, filling it with amniotic fluid during fetal breathing. However, cases with a small or absent fetal stomach may or may not have a DF. This previously reported observation,[10] supported by the current study (Table 1), implies that DF determination is expected to be beneficial, especially in cases presenting a small or absent stomach.

The contribution of magnetic resonance imaging to esophageal atresia and without tracheoesophageal fistula detection

By implementing the previously described DEPA technique, the use of MRI for diagnosing EA drastically declined at our center because DEPA demonstrated better performance.[9,26,32–36] In the 4 cases in which MRI was performed in our cohort, there was no added value to that of the sonographic evaluation. Moreover, MRI did not detect EA or TEF in one of the cases. This was subsequently detected by ultrasound.

Clinical implications

EA types with or without DF confer different prognoses and postnatal outcomes.[11,13–15,17,37,38] Therefore, prenatally determining the presence or absence of a DF may improve parental counseling by offering more precise prognostication to support couples' decision-making.

Research implications

Future studies with more cases could further elucidate the clinical significance of a persistently collapsed lower esophageal end, whether this phenomenon is constant throughout pregnancy, and whether there is a prognostic difference between a prenatally patent and nonpatent DF.

TABLE 1
Study group characteristics

Background characteristics	N=16
Multiple pregnancies, %	12.5% (2/16)
Indication for scan	
Polyhydramnios	37.5% (6/16)
Small or absent stomach	37.5% (6/16)
Polyhydramnios and small or absent stomach	12.5% (2/16)
Interrupted esophagus suspected on early anomaly scan	12.5% (2/16)
Patient body mass index, kg/m^2	28.3 (26.5–30.25)
Gestational age at exam, wk	28.5 (25.1–32.1)
Range	17.5–35.3
Time taken to determine fistula presence (min)	8.5 (5–12)
Range (min)	1–23
Successful MRI distal fistula determination[a]	75% (3/4)
Type of esophageal atresia	
A	37.5% (6/16)
C	62.5% (10/16)
Cases with small or absent stomach on target scan by type	
A	100% (6/6)
C	70% (7/10)

Data are presented as percentage (number) or median (interquartile range).

MRI, magnetic resonance imaging.

[a] In the 3 correctly determined cases, MRI was performed after the diagnosis was established on ultrasound. The fourth case was missed on MRI.

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Strengths and limitations

The strength of this study is the novelty of prenatal DF demonstration. In addition, we provided a sonographic method that effectively determines the presence of DFs in EA. The feasibility and accuracy of this method is further supported by test performance analysis, as detailed. Furthermore, this study offers theoretical insights regarding the significance of a persistently collapsed lower esophagus, implying that not all DFs are patent and that the residual lower esophageal end in types A and B may occasionally be relatively long in early pregnancy. These insights may contribute to our understanding of the evolution of EA throughout pregnancy.

The limitations of the study should also be acknowledged. Because of the rarity of this condition, our study is limited by a relatively small sample size, decreasing its statistical power. In addition, the fact that some parents opted for termination of pregnancy precluded long-term sonographic follow-up during pregnancy.

Conclusions

DFs in EA can be demonstrated prenatally. Prenatal DF determination may

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TABLE 2
Distal fistula determination contingency table

Distal fistula determination performance

Cases with postnatal or postmortem distal fistula assessment (N=16)	Postnatal distal fistula present (n=10)	Postnatal distal fistula absent (n=6)	Total
Prenatal distal fistula determination			
DF present	80% (8/10)	0% (0/6)	8
DF absent	20% (2/10)	100% (6/6)	8
	10	6	16

Performance index	Percentage (%)	95% confidence interval (%)
Sensitivity	80	55–100
Specificity	100	60–100
Positive predictive value	100	65–100
Negative predictive value	75	45–100

Pearson chi square, $P=.002$.

DF, distal fistula.

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enhance our ability to anticipate the postnatal outcome and complexity of surgical repair. The method provided is feasible, reproducible, has excellent test performance indices, and may improve the prenatal diagnosis and counseling of EA. ■

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TABLE 3
Interobserver agreement

Fistula determination Interobserver agreement

	Operator 1 result		
	Fistula present	Fistula absent	Total
Operator 2 result			
Fistula present	100% (8/8)	0% (0/4)	8
Fistula absent	0% (0/4)	100% (8/8)	8
	8	8	16

Kappa=1, $P<.0001$.

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