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REVIEW ARTICLE

Prognosis in Congenital Diaphragmatic Hernia Diagnosed During Fetal Life

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Abstract Congenital diaphragmatic hernia (CDH) is a malformation that continues to cause significant morbidity and mortality and can be difficult to clinically manage. Determination of prognosis can greatly add to the decision-making process in prenatally recognized CDH, predominantly by the recognition of specific ultrasound findings. Ultrasound findings that are important include hernia type, laterality, lung size, position of the fetal liver and stomach, and the presence or absence of other anomalies. In general, prognosis is best in cases where CDH is an isolated anomaly, the liver and stomach remain within the abdominal cavity, and the lung size corresponds to a lung area to head circumference ratio of $\geq$1. Position of the stomach also corresponds with prognosis, is easier to reliably determine with ultrasound, and can indirectly predict the position of the liver. The following is a review of the literature and experience in the care of fetuses with CDH at the University of California, San Francisco, a large tertiary referral center, in using these ultrasound findings to predict prognosis.

Keywords CDH · Congenital diaphragmatic hernia · Ultrasound · Prognosis

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Introduction

Mortality rates in congenital diaphragmatic hernia (CDH) have decreased over time but remain as high as 10%–30% [1, 2]. CDH is a complex multifactorial disease process making prediction of individual prognoses challenging. However, multiple sonographic findings have been shown to be associated with survival and when combined, prenatal ultrasound is a powerful tool to guide critical decision-making. These findings include hernia type, whether the hernia is associated with other anomalies (nonisolated), laterality, lung hypoplasia, and position of the fetal stomach and liver (Fig. 1).

Postnatal clinical factors that affect prognosis and survival include persistent pulmonary hypertension, gestational age at diagnosis and delivery, birth weight, need for extracorporeal membrane oxygenation (ECMO), and inborn status [3]. Morbidity is most related to respiratory failure. ECMO can lead to possible ischemic/hemorrhagic neurological complications, but prenatal sonographic signs can predict need for ECMO. Persistent pulmonary hypertension (PHTN) is another serious postnatal complication leading to right ventricular failure; however, clear antenatal predictors are currently lacking [4].

Prenatal therapies for CDH include tracheal balloon occlusion in fetuses that meet certain surgical criteria, and potential medical therapy including maternal corticosteroids or medication to prevent pulmonary hypertension [5]. Postnatal treatment for CDH usually involves surgical correction within days to weeks after birth. Timing of postnatal surgery may also be affected by other comorbidities or anomalies [6]. Lastly, in cases with poor prognosis, discontinuation of the pregnancy may also be a consideration.

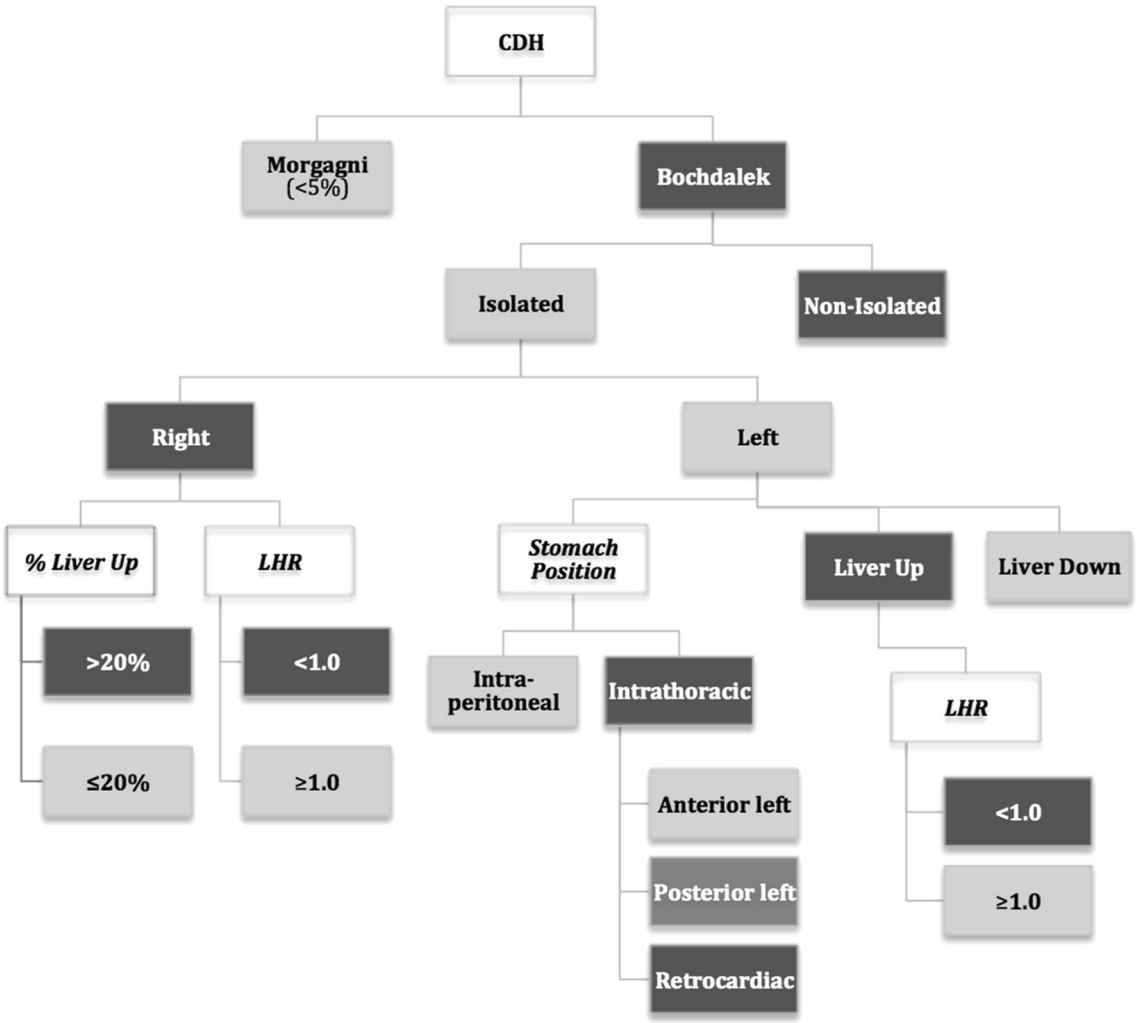

Fig. 1 Prognosis in fetal CDH. Characteristics of CDH determined by sonographic signs shown can help predict prognosis. The *light colored boxes* are associated with better prognosis and the *darker boxes* are associated with a poorer prognosis

Hernia Type

The embryologic development of the diaphragm although not completely understood, occurs by convergence of muscular and fascial layers during the 4th–12th weeks of gestation. Gaps separating the muscular components where only pleura and peritoneum are present are locations of inherent weakness where herniation of the abdominal contents may occur. The Bochdalek hernia is the most common, and occurs in the Bochdalek space, along the posterior diaphragm due to incomplete fusion of the pars lumbaris and pars costalis [7]. A triangular gap in the right parasternal space between the pars sternalis and pars costalis also exists and can result in a Morgagni hernia, however, this hernia type is much less common and are generally has a delayed presentation (postnatal to adulthood) [8]. Eventration, which is not a true hernia, occurs from muscular hypoplasia allowing for bulging of the intra-abdominal contents into the thoracic cavity [7]. Although the thoracic and abdominal cavities remain separate, the amount of protrusion can sometimes be profound and is an important mimic of CDH. Bochdalek hernias represent 95%–97% of CDH and therefore only will be considered for the remainder of the discussion [9, 10].

Isolated Versus Nonisolated CDH

Isolated CDH is the term used to describe when a CDH is the only anatomic anomaly present. Morbidity in isolated CDH is related to abnormalities that are secondarily, but directly related to the hernia. These include lung hypoplasia (the most important), bowel malrotation, cardiac shift, and/or patent ductus arteriosus. Nonisolated CDH is the presence of one or more additional anomalies unrelated to the CDH and occurs commonly (20%–73%; Fig. 2) [11, 12]. Anomalies can involve any organ system, with or without the presence of a genetic syndrome. More than 50 genetic syndromes associated with CDH have been

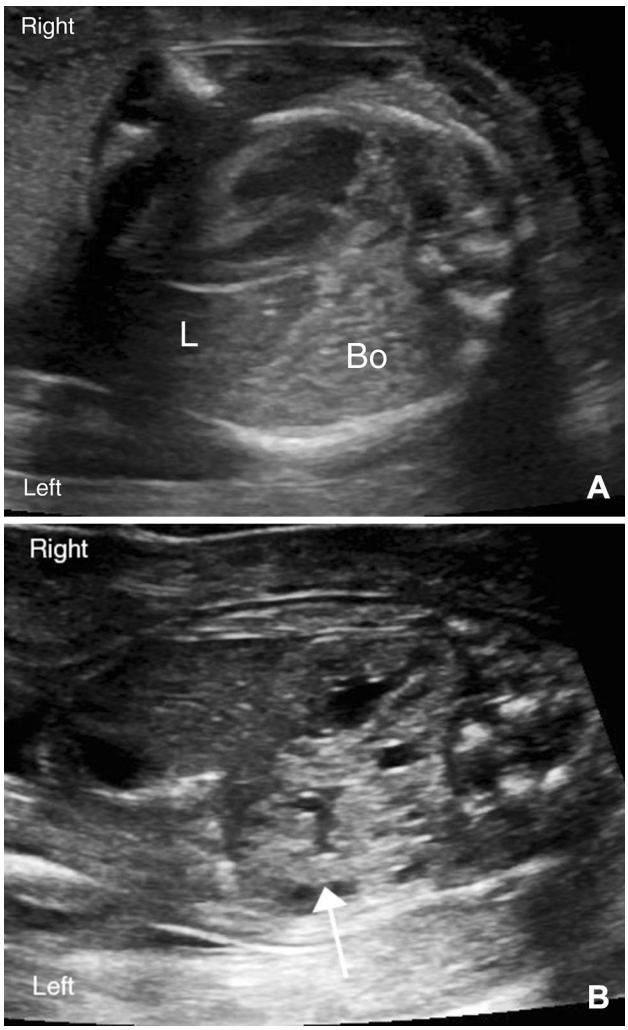

Fig. 2 Left CDH with additional anomalies **a** transverse view of liver (L) and bowel (Bo) up and **b** coronal view shows hyperechoic downside left kidney with cystic dysplasia (*arrow*) and normal upside right kidney. Additional cardiac anomaly of tetralogy of Fallot (not shown). Constellation of findings were concerning for Fryns syndrome

identified the most notable are Fryns and Donnai–Barrow syndrome where CDH is a cardinal feature. The survival for nonisolated CDH is significantly lower than for isolated CDH (66.7 vs. 80.6% in one series when a major anomaly was considered) [12].

Cardiac abnormalities are the most common additional anomaly [13] and range from hemodynamically insignificant to significant defects occurring in up to 10.6% [14]. Six-month mortality increases more than 100-fold in the presence of a major cardiac defect [12]. Survival falls to as low as 5% with a single ventricle anatomy [14]. Alternatively, the presence of a genetic syndrome increases morbidity and/or mortality rate to 54% at 6 months [12]. In contrast, the presence of minor cardiac or other structural abnormalities has been shown to have similar outcomes as isolated CDH and their significance may need to be considered on more of a case-by-case basis [13]. In cases where ultrasound findings are equivocal, fetal MRI should be considered [15].

CDH Laterality

Left-sided hernias are most common (4:1 compared with right), and even more rarely bilateral hernias can occur (2%) [16]. The rate of prenatal detection is lower for right versus left due to decreased conspicuity of herniated liver within the right chest (40.5 vs. 73.5%) [17].

Outcomes in left versus right CDH have been reported with mixed conclusions, showing either no difference [18], better [19], or poorer outcome in right CDH [20]. A confounding factor is whether or not the liver is herniated into the thoracic cavity, which worsens prognosis and is almost invariably present in right-sided CDH (Fig. 3) [21]. Therefore, the overall prognosis for right-sided CDH can be presumed similar to left CDH with liver in the thoracic cavity.

Some research has suggested differences in the occurrence of specific anomalies between left and right CDH [22]. Several specific cardiac anomalies maybe be more common in left CDH [23] as well as facial and skeletal abnormalities where others have suggested an overall higher incidence of cardiac disease in right versus left CDH [14]. Factors that affect the prognosis for right CDH are similar to left CDH (discussed below) and include improved survival with lung area-to-head circumference ratio (LHR) $\geq$1.0 [24] and smaller volumes of herniated liver within the chest.

Prognosis for Left CDH

Left CDH is the most common form of CDH. Specific findings that have the greatest impact on prognosis and survival are herniation of the liver, stomach position, and LHR. Fetuses with isolated left-sided CDH with liver herniation, stomach position in the right hemithorax (retrocardiac), and/or LHR of <1.0 have the poorest prognosis.

Liver Up Versus Down

Liver herniation into the chest occurs in 57% [25] of all CDH and 51.5% of left CDH [16]. Liver within the chest results in a threefold increase in need for ECMO [4], increases the likelihood of persistent PHTN [26], and decreases survival (46 vs. 74%) [13, 25]. The greater the volume of herniated liver is, the worse the prognosis and is a stronger predictor than the presence of liver herniation alone [27]. When >20% of liver herniation is noted, there is an association with increased mortality and need for ECMO [27]. Herniation of 5% or less has been described as

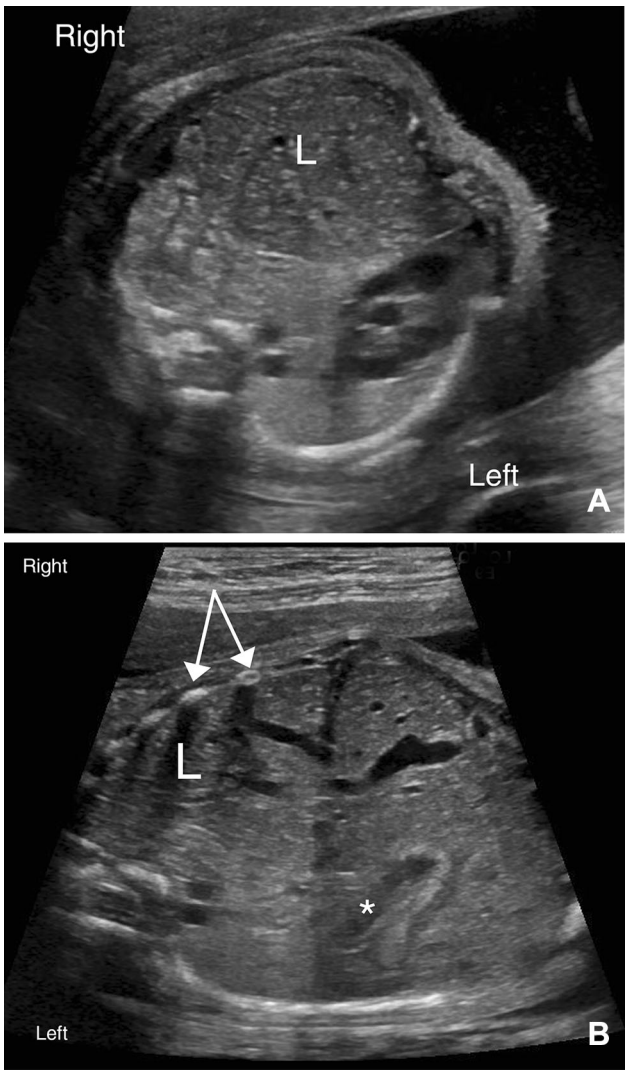

Fig. 3 Right CDH **a** transverse and **b** longitudinal views with leftward cardiac deviation and liver (L) seen above defect in the right thorax. Stomach (*) and ribs (*arrows*)

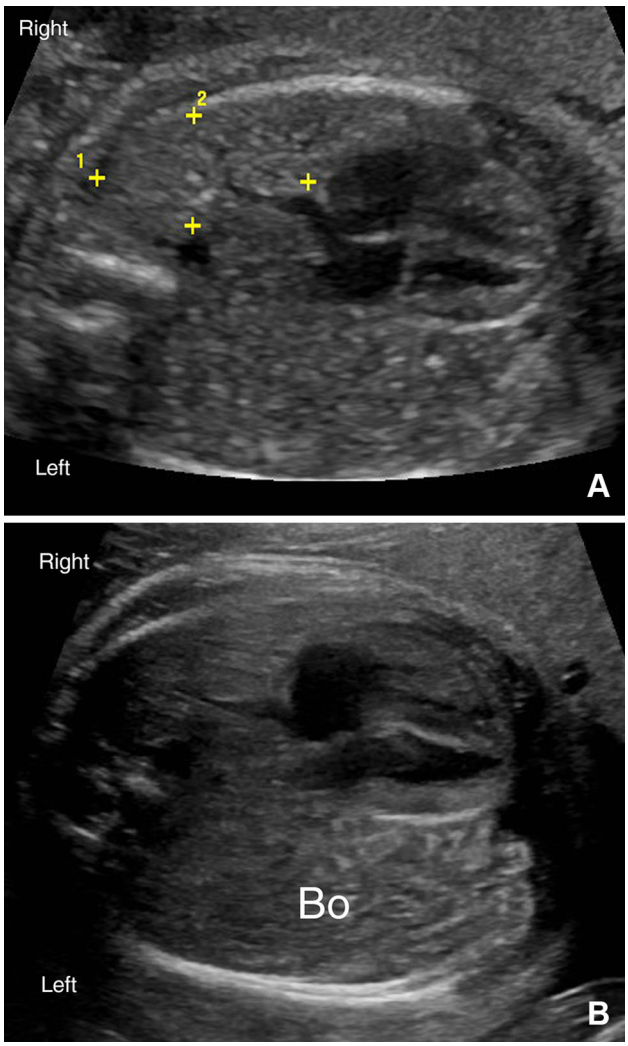

Fig. 4 Left liver down CDH containing bowel only **a** LHR measurement bound by calipers at the level of the four-chamber heart view and **b** transverse view with rightward cardiac deviation and decompressed bowel (Bo) loops in the left thorax

trivial and not even classified as "liver-up" [16]. Those with liver herniation, isolated CDH, and LHR <1.0, may be candidates for fetoscopic tracheal balloon occlusion [32] [28]. In cases where liver position is difficult to determine, MRI should be considered [15]. Additionally, stomach position may assist in prediction of liver herniation as discussed below.

Assessment of Lung Size

Ability to predict severity of lung hypoplasia is a strong prognostic indicator for CDH and can be assessed using LHR (lung area to head circumference ratio), o/e LHR (observed to expected lung area to head circumference ratio), or total lung volume.

LHR compares a ratio of the lung size contralateral to the side of the hernia with the fetal head circumference (as an indicator of fetal age) and is an independent predictor of postnatal survival (Fig. 4a). It can help to guide decision-making regarding treatment including possible fetal surgery in both left and right CDH. An LHR of <1.0 predicts a 1.7-fold increased need for ECMO [4]. LHR ≥1.0 has an odds ratio of 5 for survival [29]. Studies comparing LHR with outcomes are most often calculated at a gestational age of 24–26 weeks, however, LHR also predicts survival at gestational ages up to 37 weeks although the LHR at a later gestational age predictive of survival is slightly higher (≥1.06 vs. 1.0). LHR at a gestational age of less then 24 weeks is less reliable [30]. Increase in LHR overtime throughout gestation also indicates a favorable prognosis. Additionally, fetuses without herniation of the liver tend to have a favorable prognosis, even if LHR is low.

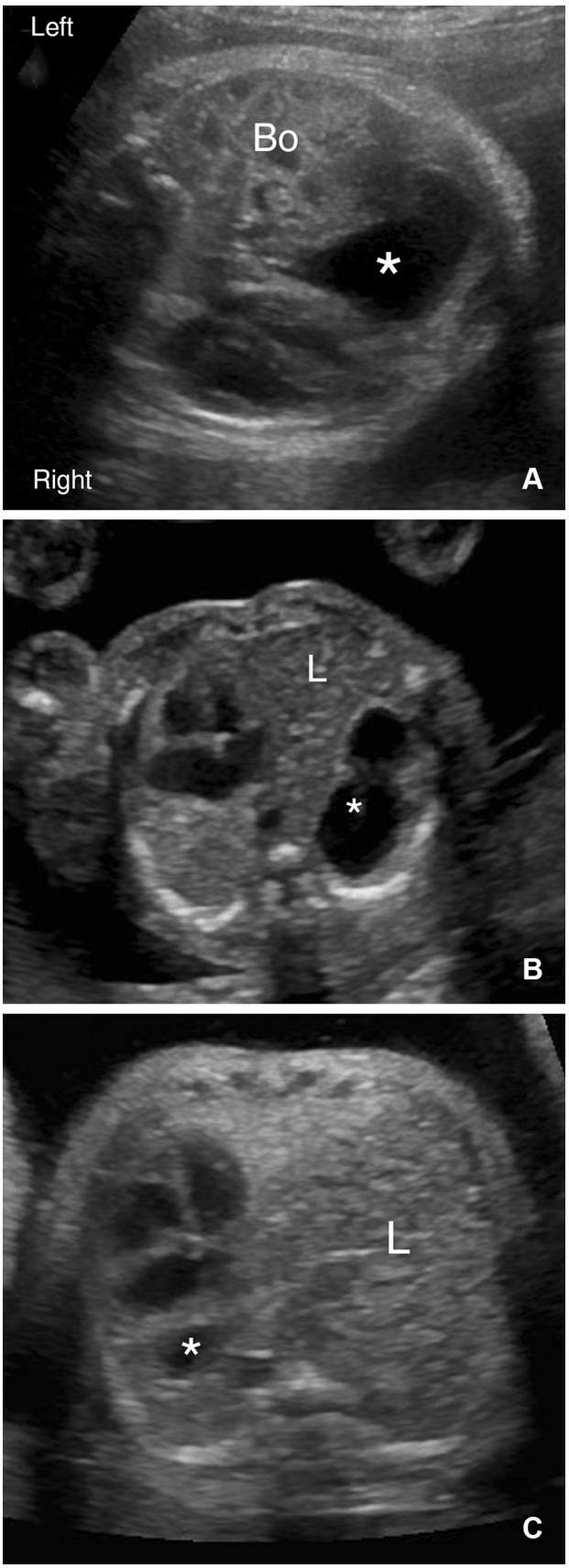

Fig. 5 Three cases of left CDH with liver and stomach up ▶ **a** transverse image demonstrating the stomach (*) within the anterior and bowel (Bo) within the posterior left chest, **b** transverse view of liver (L) and stomach (*) in the midposterior left chest and **c** different case with stomach (*) posterior to the heart

The observed expected LHR (o/e LHR) is a measurement that expresses the amount of lung measured in a fetus with CDH as a fraction of the expected amount of lung present at the corresponding gestational age. Because fetal lung grows at a much higher rate than the fetal head circumference throughout gestation, LHR is expected to increase throughout pregnancy, even if the relative amount of lung hypoplasia is similar. The o/e LHR is independent of gestational age (therefore does not change over time) and takes into account this variability. A large study by Jani et al. demonstrated that o/e LHR is significantly lower in fetuses with CDH averaging 39% (range 7–79%) versus 100% in normal fetuses [31].

MRI can be used to calculate relative lung volume, by measuring the observed to expected total fetal lung volume for gestational age. This measurement has high inter-observer agreement and positively correlates with LHR [32]. Volumetric imaging has the advantage of more accurately estimating the size of the three-dimensional structure, rather than the 2D measurement used for LHR. This is currently a useful adjunct in patients where ultrasound evaluation is limited and/or findings are equivocal or near cutoff values and additional information would guide decision-making. This may also have an increasing role in the assessment and determination of CDH prognosis in the future.

Stomach Position

Measuring the LHR has been criticized for having significant inter-observer variation. Stomach position may be an easier observation for those without experience in evaluating CDH prognosis.

Position of the fetal stomach in isolated left CDH independently predicts morbidity and mortality including risk of death [33] and need for ECMO and/or prolonged mechanical ventilation and is a highly reproducible sign to identify. Intra-abdominal stomach location is associated with the best outcome (up to 100% survival), with decreased survival in those with an intra-thoracic stomach location (Fig. 4b). Mortality for stomach position within the anterior left chest is 6% compared with mid to posterior left chest of 32%, and is highest in the retrocardiac position of 61% [34] (Fig. 5).

Stomach position has also been shown to indirectly determine liver position, which is more difficult to determine sonographically, and an important indicator of

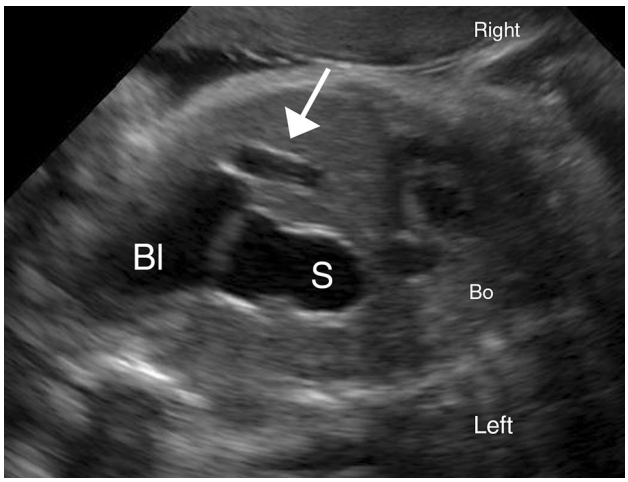

Fig. 6 Left CDH with bowel (Bo) only within the chest; longitudinal view shows the stomach (S) down in the abdomen and the gallbladder in contact (*arrow*) with the urinary bladder (Bl)

prognosis [35]. Determination of stomach position is highly reproducible and demonstrates a low inter-observer variability, with similar predictability in outcomes as liver position and LHR [34].

Recognition of bowel only CDH (intra-abdominal location of the stomach) can be difficult due to the similar appearance of collapsed bowel loops to normal lung. Left-to-right mediastinal shift is often the only suggestive intrathoracic finding present with a bowel-only left CDH. Distinguishing bowel loops is improved using a high frequency transducer, but this is not always part of the standard sonographic evaluation and requires some index of suspicion of an abnormality (Fig. 4). An additional clue to the diagnosis of bowel only CDH is an abnormally low position of the fetal stomach and/or gallbladder, seen in contact with the wall of the fetal urinary bladder (Fig. 6). This occurs as a result of displacement of the bowel loops that are normally interposed between these organs into the thoracic cavity. In difficult cases, a definitive means of confirming a CDH is to observe paradoxical movement of the diaphragm with real-time sonography [36]. When these sign(s) are observed, careful search for a CDH, if not already recognized is recommended [37].

Scoring Systems for Prognosis

Scoring systems have been developed to combine multiple of the sonographic factors above to determine prognosis. The composite prognostic index, for example, combines 10 different parameters relating to genetics (2), cardiac (3), hernia (2), and lung (3) to predict prognosis. A combined score of 8 or greater is associated with a significantly higher survival than a score of less than 8 (89 vs. 38%) [38].

Conclusion

CDH is a complex disorder affected by multiple factors. Ultrasound is useful in identifying features that are strongly predictive of survival and can guide clinical decision-making and treatment, especially during the time period prior to fetal viability. These observations aid determining delivery planning and postnatal care for infants with CDH.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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