The intrapartum strategy for thoracoscopic repair of congenital diaphragmatic hernia(CDH): five cases report and literature review

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The intrapartum strategy for thoracoscopic repair of congenital diaphragmatic hernia(CDH): five cases report and literature review

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Abstract

Purpose: To introduce a new method of minimally invasive repair of Congenital diaphragmatic hernia intrapartum(CDH). **Methods:** We present five CDH cases diagnosed prenatally. Each patient was evaluated by a multidisciplinary team and received thoracoscopic defect repair on placental support. The neonates were transferred to NICU for further treatment, and all cases were under follow-up.

Results: The patients enrolled were mild to moderate, with thoracic herniation of the liver occurring in one case. All five cases were repaired on placenta support. Maternal morbidity was reported in one case for acute pulmonary embolism (case 2), but no recorded case of maternal mortality. Postoperative neonatal death occurred in two cases (case 2,3), the remaining three neonates are under follow-up with a good prognosis. **Conclusion:** The intrapartum thoracoscopic repair is feasible and safe for selected CDH cases.

1 Introduction

Congenital diaphragmatic hernia(CDH)is a congenital anomaly in which fetal abdominal organs herniate into the thoracic cavity during embryonic development. The resulting fetal lung hypoplasia and pulmonary hypertension are the main factors contributing to the poor prognosis of the child. The incidence of CDH in newborns is approximately 2.5/10,000[1], and it is more common in male fetuses. The etiology of CDH is still unclear, 50%-70% of CDH are isolated defects, while the remaining may be associated with structural malformations, chromosomal abnormalities, or monogenic disorders[2, 3]. With the improvement of nursing and surgery, the overall survival rate of CDH is more than 70%, but the mortality in severe patients remains more than 50%. Intrapartum surgery is a surgical intervention that proceeded during delivery. It avoids serious complications such as premature, compared with prenatal therapy and can remove the pathogenic factors early[4]. The present study retrospectively analyzed 5 cases of intrapartum CDH repair and reviewed the treatment of CDH.

2 Materials and methods

2.1 Patients

We present five cases of CDH in Women's Hospital, Zhejiang University School of Medicine from May 2020 to March 2022. All the cases were diagnosed as isolated left CDH by ultrasound or MRI, and the amniocentesis or non-invasive prenatal testing (NIPT) did not indicate any abnormality. The diagnosed gestational age, lung head ratio (LHR), observed/expected LHR (O/E LHR), and liver position were recorded. O/E LHR was calculated according to https://totaltrial.eu with the longest axis method. Maternal characteristics and prenatal assessment are listed in Table 1.

2.2 Mehthods

The surgery was implemented by a multidisciplinary team. The patients underwent fetal CDH repair with placental support when cesarean section under

Table 1 Maternal characteristics and prenatal evaluation

Case	1	2	3	4	5
Age(year)	31	34	24	26	36
BMI	35.30	23.03	29.27	23.44	26.04
G/P	4/0	2/0	1/0	2/0	3/1
Obstetric complications	Hypertensive disorder	/	/	/	/
Delivery mode	CS	CS	CS	CS	CS
Diagnosed GA (week)	26	22	23	36	27
Right lung(cm)	5.7∗1.6	3.3∗1.0	2.4∗1.4	2.7∗2.2	3.4∗2.1
AFI (cm)	29.4	10.2	16.1	7.8	13.4
LHR	2.75	1.07	1.1	1.8	2.13
O/E LHR (%)	86.6	32.6	49.2	37.3	67.1
Liver in chest	No	No	Yes	No	Yes
Delivery GA(week)	37+6	37+3	37+2	39+5	38+2

BMI: Body Mass Index; AFI: Amniotic fluid index; CS: cesarean section; GA: gestational age; LHR: lung head ratio; O/E LHR: observed/expected LHR

general intravenous anesthesia combined with epidural anesthesia and sevoflurane inhalation anesthesia. Blood pressure and central venous pressure (CVP) were monitored by radial artery puncture and deep vein catheterization before the operation. Lidocaine/ropivacaine was used for epidural anesthesia; when the anesthesia plan was established, used midazolam 0.1 mg/kg, vecuronium 0.15 mg/kg, sufentanil 0.5ug/kg, and propofol 80mg for rapid induction. Subsequently, mechanical ventilation was implemented, and sevoflurane was inhaled. A continuous ultrasound was performed to verify the fetal position and the placental margin. The hysterotomy was made away from the placenta in the lower uterine segment. After delivered the fetus, adjunctive myometrial tocolytics, like ritodrine and nitroglycerine, were inhaled to suppress contraction, the uterine cavity was filled with a simple homemade balloon, and warm saline was circulated to maintain the volume of the uterine cavity for ex utero intrapartum treatment (EXIT). Fetal heart rate and blood oxygen saturation were monitored by probes on limbs and kept oxygen saturation above 40%. The pulsation of the umbilical cord was observed with the naked eye.

Fetal anesthesia can be achieved through the maternal placenta and assistance with intravenous or intramuscular injection. Four cases were operated on placental support via thoracoscopic way. Due to the large defect, Case 3 was finally transferred to transabdominal repair and placed a patch intraoperatively. The neonates were held in the right recumbent position, an incision for the observation port was made in the fourth intercostal space at the midaxillary line, while two utility incisions were placed: 1cm beside the anterior axillary line in the seventh intercostal space, and the sixth intercostal space at the posterior axillary line. Returned the herniated contents to the abdominal cavity and closed the hernia defects with non-absorbable sutures. At last, increase airway pressure to test lung expansion, and place rubber drainage. All newborns were transferred to the NICU for respiratory support.

After the hernia defect was repaired, the umbilical cord was severed. The official contraction inhibitor was stopped immediately, and oxytocin was added to activate contraction. We generally used uterine gauze to prevent postpartum hemorrhage.

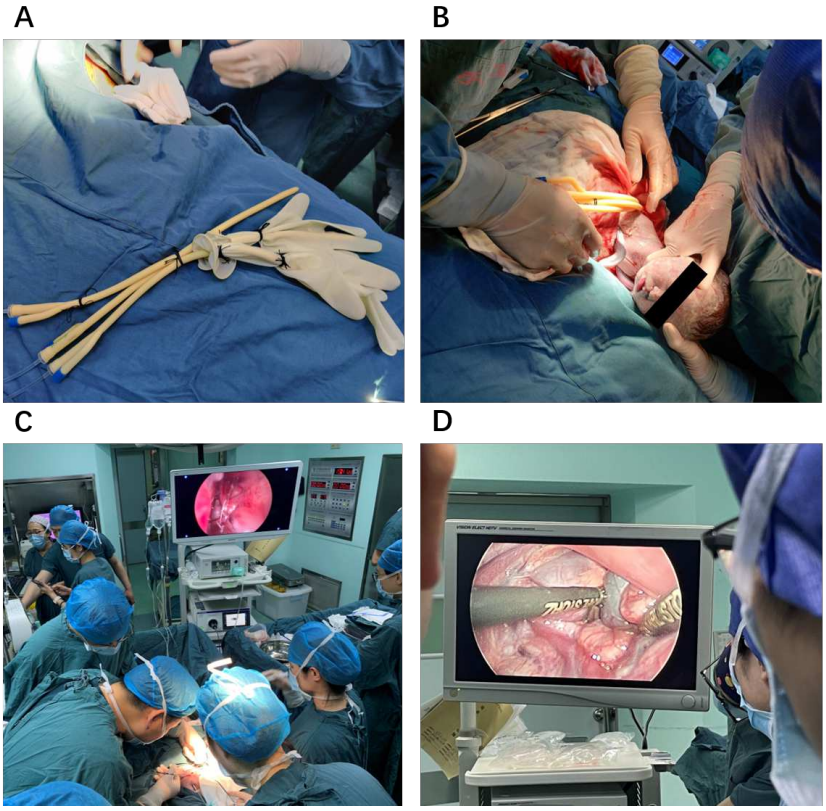

Fig. 1 EXIT to thoracoscopic repair of CDH.(A)The simple homemade balloon;(B) Intrauterine infusion when delivery;(C)the multidisciplinary team;(D)returned the herniated contents to the abdominal cavity

3 Results

Maternal morbidity was reported in one case for acute pulmonary embolism (case 2), but there were no recorded cases of maternal mortality. Postoperative neonatal death occurred in two cases (case 2,3) who received extracorporeal membrane oxygenation (ECMO); the remaining three patients are under follow-up with a good prognosis. The surgical procedure and outcome are shown in Table 2.

Table 2 The surgical procedure and outcome

	Case	1	2	3	4	5
Mother	Operation time(min)	180	155	140	150	200
	Bleeding(ml)	500	300	500	400	600
	Hospital stays (days)	3	8	4	3	5
	Maternal complications	Hypertension	Acute pulmonary embolism	/	/	/
Neonate	Fetal surgery approach	Thoracoscopic	Thoracoscopic	Thoracoscopic, Transabdominal	Thoracoscopic	Thoracoscopic
	Repair time(min)	80	60	75	70	90
	Bleeding(ml)	1	1	2	1	1
	Gender	F	F	F	F	M
	Birth weight(g)	3460	2800	2400	2490	3050
	Apgar score 1-5min	3/4	4/4	2/2	4/4	4/5
	ECMO	No	Yes	Yes	No	No
	Recurrence	No	No	No	No	No
	Outcome	Alive	Death	Death	Alive	Alive

4 Literature Review

We used PubMed, Web of Science, and Cochrane Library to search engines for articles containing terms such as ((intrapartum operation) OR (intrapartum surgery) OR (intrapartum treatment)) AND ((congenital diaphragmatic hernia) OR (CDH)) AND ((fetal) OR (prenatal) OR (antenatal) OR (fetus)) in recent ten years. The literature search has six published articles on CDH with intrapartum treatment. The characteristics of the cases are summarized in Table 3. The series of reviews comprised 49 fetuses with different degrees of CDH prenatal. The most common indication for EXIT in CDH is to open the airway, and its safety and feasibility were indicated in 1 article[5]when 3 patients removed the balloon on placental support and died of severe pulmonary hypertension[6, 7]. Another application of EXIT in CDH was EXIT-to-ECMO. But Shieh et al. showed that EXIT-to-ECMO did not increase the survival rate of children in severe CDH[8], while Stoffan et al. drew the same conclusion[9]. It was supposed that the patients in the EXIT-to-ECMO group might be more severe. Our research is consistent with the above studies. We considered EXIT to be a convenient and effective approach for CDH treatment. Still, the severity of the disease is an essential factor affecting the prognosis.

5 Discussion

The improvement in prenatal diagnosis makes it possible to diagnose CDH in early GA, with a mean of 22−24 weeks[11]. Even if the early diagnosis and timely intervention significantly improve the lethal postpartum outcome, the mortality remains high in severe CDH, leading to the evolution of the treatment.

5.1 Prenatal Evaluation

The prognosis of isolated CDH depends on classification and severity. According to the anatomist, CDH can be divided into posterior lateral (Bochdalek hernia), anterolateral (Morgagni hernia), and central hernias. Bochdalek hernias are the most common, accounting for 70%-75%, while central hernias are rare, accounting for only 2%-7%[12]. Several studies have shown that infants

with right-sided CDH have a lower survival rate than those with left-sided (50% vs. 75%)[13]. The severity of CDH depends on several factors, including liver herniation, lung head ratio (LHR), and total lung volume (TLV). The study has demonstrated that the survival rate in cases without liver herniation was 75%-80%, whereas only 20%-27% in liver herniation[14]. LHR, obtained by measuring the ratio of contralateral lung area to head circumference at the level of the four-chambered heart of the fetus, has a predictive value for complication rates and mortality[15, 16]. When LHR was below 0.6, the mortality rate was 100%, while a 60% mortality rate was reported when LHR was between 1.0 to 1.4[17]. O/E LHR was proposed to correct the increased LHR during gestation. For isolated CDH cases with O/E LHR less than 25%, 25%-45%, and over 45%, the survival rates were 18%, 66%, and 89%, respectively[18], suggesting increased O/E LHR is associated with higher survival rates. Diaphragmatic defect size and diagnosed GA can also be used to risk-stratify. Usually, diagnosed early cases are characterized by a more significant defect and a need for patch repair. Several researchers have concluded that a diagnosis before 25 GA is associated with higher mortality than a diagnosis after 25 GA[16, 19]. Bouchghoul et al. showed a significant relationship between GA at CDH diagnosis and morbidity and mortality, even after adjustment for factors of severity of CDH[20], suggesting that diagnosed GA is an independent predictor for isolated CDH.

5.2 Surgery Procedure

Treatment aims to reverse lung hypoplasia and repair anatomical defects. Though targeted pulmonary vasodilator therapies, including endothelin receptor antagonists, prostacyclin analogs, and phosphodiesterase type 5 inhibitors, may result in hemodynamic and functional improvement in children[21], operative repair of the diaphragmatic defect is indispensable for survival. According to the timing of the operation, it can be divided into prenatal, intrapartum, and postpartum procedures. The former two refer to fetal operations, including intrauterine repair, intrauterine balloon implantation, and intrapartum fetal operation.

5.2.1 Intrauterine Repair

The intrauterine repair was first proposed in the 1980s. Harrison et al. performed the opening repair of the diaphragm for six severe CDH fetuses, but only 2 cases were born alive[22]. In 1993, they enrolled 14 patients with isolated left CDH, 9 of whom completed the surgery, and four were finally born alive[23]. A subsequently randomized trial evaluated the postpartum outcome of opening intrauterine repair for CDH and found that opening intrauterine repair did not increase the potential benefits compared with the traditional postpartum repair. On the contrary, it increased the risk of premature delivery[14]. Therefore, the intrauterine open diaphragmatic hernia repair was eliminated.

5.2.2 Fetal Endoscopic Tracheal Occlusion (FETO)

The hypothesis that temporary tracheal obstruction prevents severe pulmonary hypoplasia is based on the clinical observation of congenital laryngeal/tracheal atresia[24]. When the first experiment was conducted on a lamb model, the researchers found that tracheal obstruction accelerates lung growth and improves postnatal oxygenation and ventilation[25]. The plug (typically titanium clip or foam plug) was performed by a laparotomy surgery initially, but it was gradually replaced by the invention of fetal endoscopic tracheal occlusion because it risked preterm delivery. In 1997, Vander Wall et al. reported a case of a 30 GA CDH fetus treated with FETO and found that FETO reduced maternal or fetal trauma compared with open hysterotomy[26]. In 2001, Harrison et al. proposed a detachable balloon and implemented it in 2 severe CDH cases, which reduces the technical difficulty and the risk of recurrent laryngeal nerve and trachea injury during operation[27]. Another randomized controlled trial compared the effects of FETO and standard postpartum care in severe CDH. The results showed no significant difference in the 90-day fetal survival rate or neonatal incidence rate between the intervention group and the control group (73 vs. 77%, P=1.00). Still, premature rupture of membranes and preterm birth were more common in the intervention group (30.8±2.0 weeks vs. 37.0±1.5 weeks, P ¡ 0.001). Since the survival rate of the control group was higher than the historical control group, The authors speculate it may be related to the improvement of perinatal care in the control group[28]. Deprest et al. treated severe CDH with percutaneous FETO and revealed that FETO was associated with improving the postnatal survival rate and reducing premature rupture of membranes[29]. The drawback of the current tracheal occlusion (TO) procedure is the need for a second invasive intervention to re-establish airway patency, causing potential neonatal injury during the process. To solve the shortcomings of traditional FETO, the University of Strasbourg has developed an alternative occlusion device, referred to as 'smart' tracheal occlusion (Smart-TO), which has a magnetic valve that opens under the influence of the magnetic field present around any magnetic resonance scanner. The results show that Smart-TO effectively saves lung hypoplasia caused by CDH and has no adverse effect on the tracheal wall[30], but it has not yet been applied to clinical practice.

The timing of FETO depends on the severity of CDH. A multicenter study evaluated the efficiency of FETO extremely severe CDH at early GA (22-24 GA). It concluded that the survival rate of infants in the early FETO group was significantly higher than the standard group (62.5% vs. 11.1%, P¡0.01), while the survival rate without FETO was 0%[31]. For severe CDH, FETO at 27-29 GA is better than expected care in terms of hospital survival rate, and this benefit lasts until six months after birth[32]. For moderate CDH, fetuses who received FETO at 30-32 GA had no significant advantage in terms of survival after discharge and the need for oxygen supplementation at six months, but FETO increased the risk of premature delivery, rupture of membranes, and preterm delivery[33].

5.2.3 Intrapartum Fetal Operation

Intrapartum fetal operation (IFO) refers to the surgical treatment of birth defects during and immediately after the delivery of the fetus, including 1) EXIT: a technique developed to establish cardiopulmonary support at delivery while maintaining placental bypass, further divided into EXIT to the airway, EXIT to ECMO, EXIT to resection, EXIT to separation. 2) Delivery room surgery: the operation performed immediately after delivery in the delivery room. 3) Operation on placental support (OOPS): fetal operation under placental circulation. For CDH treatment, IFO is applied to EXIT to the airway, EXIT to ECMO, and OOPS.

OOPS is performed simultaneously based on EXIT. Compared with EXIT and delivery room surgery, OOPS ensures placental circulation enabling the supply of nutrients and oxygen for the removal of obstruction of respiratory. Anesthetics pass through the maternal placental circulation, avoiding the risk of anesthesia for children. On the other hand, OOPS is regarded as an extremely early neonatal operation that may be helpful for the recovery of the newborn. In 1989, Norris reported the first OPPS case for fetal cervical mass[33]. With gradually expanding indications, it was widely used in fetal neck masses, congenital high airway obstruction syndrome (CHAOS), congenital cystic adenomatoid malformation, etc. The 5 cases in our research were directly repaired on placenta support, which avoids the risk of abnormal ventilation and internal environment disorder caused by the continued diaphragmatic hernia after a spontaneous breath or endotracheal intubation. At the same time, the sterile state after delivery reduces the risk of surgical infection. The lungs are not expanded during the operation, and there is little gas in the intestinal cavity, which is conducive to the recovery of abdominal organs such as the intestine, making the operation convenient.

5.2.4 CDH Repair

The optimal timing of surgical repair in CDH has been controversial over the years. For mild CDH, the correlation between repair time and survival rate is unclear[34, 35]. A prospective study involving 477 moderate CDH recommends performing a surgical repair within 48 hours in the moderate case[36], but another study did not encourage surgery within 24 hours in moderate CDH patients[35]. For patients requiring ECMO, the survival rates of early (within 72 hours) and delay (after 72 hours) were 73% and 50%, respectively, indicating early repair may reduce complications and improve survival rate in ECMO-supporting cases[34]. The existing literature did not draw a consensus about the standard timing of repair, but in general, it is safe and effective for mild cases to operate after stable, but for severe ones, early treatment would be better (regardless of whether ECMO is used).

CDH repair is performed in 2 categories: open and minimally-invasive surgery (MIS). Laparotomy is the most common and time-honored approach, usually via a subcostal incision, while thoracotomy is an alternative open approach[37].

Thoracoscopic repair of CDH has gained popularity recently for its cosmesis and less risk of adhesions but is technically challenging due to the small workspace, which could prolong the operative time and increase the post-operative complications. None of the approaches has shown absolute superiority, making it difficult to choose the optimal surgical method. Classical laparotomy has the advantage of serving a good view of the defect, and it allows inspection and correction of the abdominal organs. However, it inevitably leaves a scar, and postoperative adhesive obstruction risk is higher than MIS. Thoracotomy shares similar disadvantages with laparotomy, but visualization of the defect and inspection of the herniated organs might be difficult[38]. Proper patient selection is essential to achieve good outcomes for the thoracoscopic approach; several research has found that for patients of low-risks born with small-size defects, a thoracoscopic approach was associated with decreased hospital length of stay, mechanical ventilation days, and parenteral nutrition time[37, 39]. Thoracoscopic CDH repair did not increase the recurrence rate when excluding severe cases with large defects[38]. But a meta-analysis of the literature has highlighted that neonatal thoracoscopic CDH repair was associated with greater recurrence rates and operative times[40]. Another concern is the development of hypercapnia and acidosis during thoracoscopic CDH repair[41]. Pulmonary hypoplasia, pulmonary hypertension, and functional residual capacity may lead to the CO2 sensitivity increase in CDH patients, and diffusion of CO2 into the circulation with subsequent hypercapnia and acidosis can potentially result in ischemic brain damage[42]. Although the study did not find differences in enhanced pCO2 values after the MIS and open CDH repair[43], the operation time must be controlled strictly.

Intrapartum CDH repair is challenging technology. The surgical indications and preoperative evaluation are vital. The duration of placental circulation is about 11-93 min (the longest 150 min)[4], requiring the operation should be controlled strictly. Otherwise, the placenta will be abrupt. The patients enrolled in the current research were mild to moderate according to O/E LHR. Thoracic herniation of the liver occurred in case 3. The diagnosed GA is between 22 to 36 weeks. Since they missed the most optimal time for FETO when transferred to our institution, we implemented thoracoscopic repair at term, with an average time of 75min. Three neonates recovered well and did not have hypercapnia or acidosis. 2 neonates finally died of pulmonary dysplasia, including: Case 2, diagnosed at 22 GA, received ECMO for 10 days and died 5 months after surgery; Case 3, diagnosed at 23 GA with the large defect, received ECMO immediately after birth and died after weaning from ECMO. The low sample size related to the rarity of the disease make the overall neonatal mortality rate is relatively high, but all the death cases were diagnosed at an early gestational age and required ECMO support, which is consistent with the previous literature.

6 Conclusion

Up to now, the intrapartum strategy for thoracoscopic repair of CDH is still at an initial stage and only carried out in a few medical institutions. To grasp the surgical indications and make a proper patient selection is crucial to maximizing the advantages of surgery, which requires the operator to consider reducing the adverse prognosis of the fetus and how to reduce the damage to the mother. Our preliminary conclusion is that thoracoscopic repair of diaphragmatic hernia is technical feasible in cases with minor defects that do not need ECMO support. However, whether it can benefit severe patients with large defects still need multi-center research with a large sample size in future research.

What does this study add to the clinical work?

Thoracoscopic repair of diaphragmatic hernia on placenta support has combined the advantages of fetal surgery and delivery room surgery which removes pathogenic factors at the earliest stage and provides a novel idea for the surgical treatment of congenital diaphragmatic hernia.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Authors' contributions

LY, YS, JC authors have contributed equally to this work and share first authorship. QL and YC contributed to the project development. QL, YC, BZ, CL, ZT contributed to surgical management.MY, YJ and TD were responsible for data acquisition and analysis. LY wrote the first draft of the manuscript. LY, YS and JC wrote sections of the manuscript. QL and YC revised the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Ethics approval

All subjects gave their written informed consent to participate and the study protocol was approved by the hospital's research ethics committee(IRB-20200298-R).

References

[1] McGivern, M.R., Best, K.E., Rankin, J., Wellesley, D., Greenlees, R., Addor, M.C., Arriola, L., de Walle, H., Barisic, I., Beres, J., Bianchi, F., Calzolari, E., Doray, B., Draper, E.S., Garne, E., Gatt, M., Haeusler,

M., Khoshnood, B., Klungsoyr, K., Latos-Bielenska, A., O'Mahony, M., Braz, P., McDonnell, B., Mullaney, C., Nelen, V., Queisser-Luft, A., Randrianaivo, H., Rissmann, A., Rounding, C., Sipek, A., Thompson, R., Tucker, D., Wertelecki, W., Martos, C.: Epidemiology of congenital diaphragmatic hernia in europe: a register-based study. Arch Dis Child Fetal Neonatal Ed **100**(2), 137–44 (2015). https://doi.org/10.1136/archdischild-2014-306174

[2] Pober, B.R.: Overview of epidemiology, genetics, birth defects, and chromosome abnormalities associated with cdh. Am J Med Genet C Semin Med Genet **145c**(2), 158–71 (2007). https://doi.org/10.1002/ajmg.c.30126

[3] Lin, A.E., Pober, B.R., Adatia, I.: Congenital diaphragmatic hernia and associated cardiovascular malformations: type, frequency, and impact on management. Am J Med Genet C Semin Med Genet **145c**(2), 201–16 (2007). https://doi.org/10.1002/ajmg.c.30131

[4] Bence, C.M., Wagner, A.J.: Ex utero intrapartum treatment (exit) procedures. Semin Pediatr Surg **28**(4), 150820 (2019). https://doi.org/10.1053/j.sempedsurg.2019.07.003

[5] Ruano, R., Klinkner, D.B., Balakrishnan, K., Novoa, Y.N.V.A., Davies, N., Potter, D.D., Carey, W.A., Colby, C.E., Kolbe, A.B., Arendt, K.W., Segura, L., Sviggum, H.P., Lemens, M.A., Famuyide, A., Terzic, A.: Fetoscopic therapy for severe pulmonary hypoplasia in congenital diaphragmatic hernia: A first in prenatal regenerative medicine at mayo clinic. Mayo Clin Proc **93**(6), 693–700 (2018). https://doi.org/10.1016/j.mayocp.2018.02.026

[6] Belfort, M.A., Olutoye, O.O., Cass, D.L., Olutoye, O.A., Cassady, C.I., Mehollin-Ray, A.R., Shamshirsaz, A.A., Cruz, S.M., Lee, T.C., Mann, D.G., Espinoza, J., Welty, S.E., Fernandes, C.J., Ruano, R.: Feasibility and outcomes of fetoscopic tracheal occlusion for severe left diaphragmatic hernia. Obstet Gynecol **129**(1), 20–29 (2017). https://doi.org/10.1097/aog.0000000000001749

[7] Osborn, A.J., Baud, D., Macarthur, A.J., Propst, E.J., Forte, V., Blaser, S.M., Windrim, R., Seaward, G., Keunen, J., Shah, P., Ryan, G., Campisi, P.: Multidisciplinary perinatal management of the compromised airway on placental support: lessons learned. Prenat Diagn **33**(11), 1080–7 (2013). https://doi.org/10.1002/pd.4200

[8] Shieh, H.F., Wilson, J.M., Sheils, C.A., Smithers, C.J., Kharasch, V.S., Becker, R.E., Studley, M., Morash, D., Buchmiller, T.L.: Does the ex utero intrapartum treatment to extracorporeal membrane oxygenation procedure change morbidity outcomes for high-risk congenital diaphragmatic

hernia survivors? J Pediatr Surg **52**(1), 22–25 (2017). https://doi.org/10.1016/j.jpedsurg.2016.10.010

[9] Stoffan, A.P., Wilson, J.M., Jennings, R.W., Wilkins-Haug, L.E., Buchmiller, T.L.: Does the ex utero intrapartum treatment to extracorporeal membrane oxygenation procedure change outcomes for high-risk patients with congenital diaphragmatic hernia? Journal of Pediatric Surgery **47**(6), 1053–1057 (2012). https://doi.org/10.1016/j.jpedsurg.2012.03.004

[10] Zhao, Y., Wang, Y., Liu, C., Jiang, Y., Wei, Y., Meng, H., Jian, S., Zhu, X., Pei, L., Bai, X., Feng, F., Lv, Y., Zhou, X., Qi, Q., Li, J., Ma, L.: Ex utero intrapartum therapy in infants with congenital diaphragmatic hernia: a propensity score matching analysis. World J Pediatr Surg **5**(4), 000425 (2022). https://doi.org/10.1136/wjps-2022-000425

[11] Benachi, A., Cordier, A.G., Cannie, M., Jani, J.: Advances in prenatal diagnosis of congenital diaphragmatic hernia. Semin Fetal Neonatal Med **19**(6), 331–7 (2014). https://doi.org/10.1016/j.siny.2014.09.005

[12] Deprest, J., Brady, P., Nicolaides, K., Benachi, A., Berg, C., Vermeesch, J., Gardener, G., Gratacos, E.: Prenatal management of the fetus with isolated congenital diaphragmatic hernia in the era of the total trial. Semin Fetal Neonatal Med **19**(6), 338–48 (2014). https://doi.org/10.1016/j.siny.2014.09.006

[13] Fisher, J.C., Jefferson, R.A., Arkovitz, M.S., Stolar, C.J.: Redefining outcomes in right congenital diaphragmatic hernia. J Pediatr Surg **43**(2), 373–9 (2008). https://doi.org/10.1016/j.jpedsurg.2007.10.049

[14] Harrison, M.R., Adzick, N.S., Bullard, K.M., Farrell, J.A., Howell, L.J., Rosen, M.A., Sola, A., Goldberg, J.D., Filly, R.A.: Correction of congenital diaphragmatic hernia in utero vii: a prospective trial. J Pediatr Surg **32**(11), 1637–42 (1997). https://doi.org/10.1016/s0022-3468(97)90472-3

[15] Lipshutz, G.S., Albanese, C.T., Feldstein, V.A., Jennings, R.W., Housley, H.T., Beech, R., Farrell, J.A., Harrison, M.R.: Prospective analysis of lung-to-head ratio predicts survival for patients with prenatally diagnosed congenital diaphragmatic hernia. J Pediatr Surg **32**(11), 1634–6 (1997). https://doi.org/10.1016/s0022-3468(97)90471-1

[16] Metkus, A.P., Filly, R.A., Stringer, M.D., Harrison, M.R., Adzick, N.S.: Sonographic predictors of survival in fetal diaphragmatic hernia. J Pediatr Surg **31**(1), 148–511512 (1996). https://doi.org/10.1016/s0022-3468(96)90338-3

[17] Sydorak, R.M., Harrison, M.R.: Congenital diaphragmatic hernia: advances in prenatal therapy. World J Surg **27**(1), 68–76 (2003). https:

//doi.org/10.1007/s00268-002-6739-0

[18] Jani, J., Nicolaides, K.H., Keller, R.L., Benachi, A., Peralta, C.F., Favre, R., Moreno, O., Tibboel, D., Lipitz, S., Eggink, A., Vaast, P., Allegaert, K., Harrison, M., Deprest, J.: Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. Ultrasound Obstet Gynecol **30**(1), 67–71 (2007). https://doi.org/10.1002/uog.4052

[19] Thébaud, B., Azancot, A., de Lagausie, P., Vuillard, E., Ferkadji, L., Benali, K., Beaufils, F.: Congenital diaphragmatic hernia: antenatal prognostic factors. does cardiac ventricular disproportion in utero predict outcome and pulmonary hypoplasia? Intensive Care Med **23**(10), 10062–9 (1997)

[20] Bouchghoul, H., Senat, M.V., Storme, L., de Lagausie, P., Begue, L., Khen-Dunlop, N., Bouyer, J., Benachi, A.: Congenital diaphragmatic hernia: does gestational age at diagnosis matter when evaluating morbidity and mortality? Am J Obstet Gynecol **213**(4), 535–17 (2015). https://doi.org/10.1016/j.ajog.2015.06.012

[21] Avitabile, C.M., Vorhies, E.E., Ivy, D.D.: Drug treatment of pulmonary hypertension in children. Paediatr Drugs **22**(2), 123–147 (2020). https://doi.org/10.1007/s40272-019-00374-2

[22] Harrison, M.R., Langer, J.C., Adzick, N.S., Golbus, M.S., Filly, R.A., Anderson, R.L., Rosen, M.A., Callen, P.W., Goldstein, R.B., deLorimier, A.A.: Correction of congenital diaphragmatic hernia in utero, v. initial clinical experience. J Pediatr Surg **25**(1), 47–55567 (1990). https://doi.org/10.1016/s0022-3468(05)80163-0

[23] Harrison, M.R., Adzick, N.S., Flake, A.W., Jennings, R.W., Estes, J.M., MacGillivray, T.E., Chueh, J.T., Goldberg, J.D., Filly, R.A., Goldstein, R.B., et al.: Correction of congenital diaphragmatic hernia in utero: Vi. hard-earned lessons. J Pediatr Surg **28**(10), 1411–714178 (1993). https://doi.org/10.1016/s0022-3468(05)80338-0

[24] Wigglesworth, J.S., Desai, R., Hislop, A.A.: Fetal lung growth in congenital laryngeal atresia. Pediatr Pathol **7**(5-6), 515–25 (1987). https://doi.org/10.3109/15513818709161415

[25] Hedrick, M.H., Estes, J.M., Sullivan, K.M., Bealer, J.F., Kitterman, J.A., Flake, A.W., Adzick, N.S., Harrison, M.R.: Plug the lung until it grows (plug): a new method to treat congenital diaphragmatic hernia in utero. J Pediatr Surg **29**(5), 612–7 (1994). https://doi.org/10.1016/0022-3468(94)90724-2

[26] VanderWall, K.J., Skarsgard, E.D., Filly, R.A., Eckert, J., Harrison, M.R.: Fetendo-clip: a fetal endoscopic tracheal clip procedure in a human fetus. J Pediatr Surg **32**(7), 970–2 (1997). https://doi.org/10.1016/s0022-3468(97)90379-1

[27] Harrison, M.R., Albanese, C.T., Hawgood, S.B., Farmer, D.L., Farrell, J.A., Sandberg, P.L., Filly, R.A.: Fetoscopic temporary tracheal occlusion by means of detachable balloon for congenital diaphragmatic hernia. Am J Obstet Gynecol **185**(3), 730–3 (2001). https://doi.org/10.1067/mob.2001.117344

[28] Harrison, M.R., Keller, R.L., Hawgood, S.B., Kitterman, J.A., Sandberg, P.L., Farmer, D.L., Lee, H., Filly, R.A., Farrell, J.A., Albanese, C.T.: A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. N Engl J Med **349**(20), 1916–24 (2003). https://doi.org/10.1056/NEJMoa035005

[29] Deprest, J., Gratacos, E., Nicolaides, K.H., Group, F.T.: Fetoscopic tracheal occlusion (feto) for severe congenital diaphragmatic hernia: evolution of a technique and preliminary results. Ultrasound Obstet Gynecol **24**(2), 121–6 (2004). https://doi.org/10.1002/uog.1711

[30] Basurto, D., Sananès, N., Bleeser, T., Valenzuela, I., De Leon, N., Joyeux, L., Verbeken, E., Vergote, S., Van der Veeken, L., Russo, F.M., Deprest, J.: Safety and efficacy of smart tracheal occlusion device in diaphragmatic hernia lamb model. Ultrasound Obstet Gynecol **57**(1), 105–112 (2021). https://doi.org/10.1002/uog.23135

[31] Ruano, R., Peiro, J.L., da Silva, M.M., Campos, J.A., Carreras, E., Tannuri, U., Zugaib, M.: Early fetoscopic tracheal occlusion for extremely severe pulmonary hypoplasia in isolated congenital diaphragmatic hernia: preliminary results. Ultrasound Obstet Gynecol **42**(1), 70–6 (2013). https://doi.org/10.1002/uog.12414

[32] Deprest, J.A., Benachi, A., Gratacos, E., Nicolaides, K.H., Berg, C., Persico, N., Belfort, M., Gardener, G.J., Ville, Y., Johnson, A., Morini, F., Wielgoś, M., Van Calster, B., DeKoninck, P.L.J.: Randomized trial of fetal surgery for moderate left diaphragmatic hernia. N Engl J Med **385**(2), 119–129 (2021). https://doi.org/10.1056/NEJMoa2026983

[33] Norris, M.C., Joseph, J., Leighton, B.L.: Anesthesia for perinatal surgery. Am J Perinatol **6**(1), 39–40 (1989). https://doi.org/10.1055/s-2007-999541

[34] Fallon, S.C., Cass, D.L., Olutoye, O.O., Zamora, I.J., Lazar, D.A., Larimer, E.L., Welty, S.E., Moise, A.A., Demny, A.B., Lee, T.C.: Repair of

congenital diaphragmatic hernias on extracorporeal membrane oxygenation (ecmo): does early repair improve patient survival? J Pediatr Surg **48**(6), 1172–6 (2013). https://doi.org/10.1016/j.jpedsurg.2013.03.008

[35] Yamoto, M., Ohfuji, S., Urushihara, N., Terui, K., Nagata, K., Taguchi, T., Hayakawa, M., Amari, S., Masumoto, K., Okazaki, T., Inamura, N., Toyoshima, K., Uchida, K., Furukawa, T., Okawada, M., Yokoi, A., Kanamori, Y., Usui, N., Tazuke, Y., Saka, R., Okuyama, H.: Optimal timing of surgery in infants with prenatally diagnosed isolated left-sided congenital diaphragmatic hernia: a multicenter, cohort study in japan. Surg Today **51**(6), 880–890 (2021). https://doi.org/10.1007/s00595-020-02156-7

[36] Okuyama, H., Usui, N., Hayakawa, M., Taguchi, T.: Appropriate timing of surgery for neonates with congenital diaphragmatic hernia: early or delayed repair? Pediatr Surg Int **33**(2), 133–138 (2017). https://doi.org/10.1007/s00383-016-4003-1

[37] Putnam, L.R., Tsao, K., Lally, K.P., Blakely, M.L., Jancelewicz, T., Lally, P.A., Harting, M.T.: Minimally invasive vs open congenital diaphragmatic hernia repair: Is there a superior approach? J Am Coll Surg **224**(4), 416–422 (2017). https://doi.org/10.1016/j.jamcollsurg.2016.12.050

[38] Bawazir, O.A., Bawazir, A.: Congenital diaphragmatic hernia in neonates: Open versus thoracoscopic repair. Afr J Paediatr Surg **18**(1), 18–23 (2021). https://doi.org/10.4103/ajps.AJPS_76_20

[39] Criss, C.N., Coughlin, M.A., Matusko, N., Gadepalli, S.K.: Outcomes for thoracoscopic versus open repair of small to moderate congenital diaphragmatic hernias. J Pediatr Surg **53**(4), 635–639 (2018). https://doi.org/10.1016/j.jpedsurg.2017.09.010

[40] Lansdale, N., Alam, S., Losty, P.D., Jesudason, E.C.: Neonatal endosurgical congenital diaphragmatic hernia repair: a systematic review and meta-analysis. Ann Surg **252**(1), 20–6 (2010). https://doi.org/10.1097/SLA.0b013e3181dca0e8

[41] Bishay, M., Giacomello, L., Retrosi, G., Thyoka, M., Garriboli, M., Brierley, J., Harding, L., Scuplak, S., Cross, K.M., Curry, J.I., Kiely, E.M., De Coppi, P., Eaton, S., Pierro, A.: Hypercapnia and acidosis during open and thoracoscopic repair of congenital diaphragmatic hernia and esophageal atresia: results of a pilot randomized controlled trial. Ann Surg **258**(6), 895–900 (2013). https://doi.org/10.1097/SLA.0b013e31828fab55

[42] Doné, E., Gucciardo, L., Van Mieghem, T., Jani, J., Cannie, M., Van Schoubroeck, D., Devlieger, R., Catte, L.D., Klaritsch, P., Mayer,

S., Beck, V., Debeer, A., Gratacos, E., Nicolaides, K., Deprest, J.: Prenatal diagnosis, prediction of outcome and in utero therapy of isolated congenital diaphragmatic hernia. Prenat Diagn **28**(7), 581–91 (2008). https://doi.org/10.1002/pd.2033

[43] Szavay, P.O., Obermayr, F., Maas, C., Luenig, H., Blumenstock, G., Fuchs, J.: Perioperative outcome of patients with congenital diaphragmatic hernia undergoing open versus minimally invasive surgery. J Laparoendosc Adv Surg Tech A **22**(3), 285–9 (2012). https://doi.org/10.1089/lap.2011.0356

Table 3 The surgical procedure and outcome

Reference	Cases	Diagnosis GA (week)	Intervention GA (week)	Intervention method	Outcome	Comments
Zhao Y et al[10]	30	23.8–30.0	37.0–37.6	EXIT-to-Airway	24 survived	EXIT-to-Airway can be performed safely for selected CDH cases
Shieh et al[8]	8	NA	36.0–39.0	EXIT-to-ECMO	1 recurred	EXIT-to-ECMO confers neither significant survival nor long-term morbidity benefit
Belfort et al[6]	1	20.6	34.3	EXIT-to- Airway	death	Fetoscopic tracheal occlusion is associated with improved postnatal outcomes in severe CDH
Rodrigo et al[5]	1	22.0	32.3	EXIT-to- Airway	survived	Fetoscopic therapy and EXIT-to-Airway for CDH are feasible and safe
Alexander et al[7]	2	19.0-22.0	36.4-37.0	EXIT-to- Airway	death	Patients who require management on placental support still have high mortality
Stoffan et al[9]	7	NA	36.0-38.0	EXIT-to-ECMO	2 survived	No clear survival benefit with the EXIT-to-ECMO procedure was demonstrated in the high-risk CDH population