Fetoscopic Temporary Tracheal Occlusion for Congenital Diaphragmatic Hernia: Prelude to a Randomized, Controlled Trial

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Objective: As previously reported, high postnatal mortality seen in fetuses with congenital diaphragmatic hernia (CDH) with liver herniation and low lung-to-head ratio (LHR) appears to be improved in fetuses who undergo fetoscopic temporary tracheal occlusion (TO). To test whether further evolution of this technique produces results that justify a randomized controlled trial comparing prenatal intervention to postnatal care, the authors analyzed 11 additional cases and the cumulative experience with 19 cases.

Methods: The authors analyzed retrospectively the outcome of 11 new and 8 previously reported cases of fetoscopic temporary tracheal occlusion. Various factors were studied including maternal morbidity, antenatal outcome, physiologic lung response, and neonatal course.

Results: Temporary TO can be accomplished using 3 5-mm radially expanding uterine ports without hysterotomy. Obstetric morbidity included mild pulmonary edema in 6 cases, chorioamniotic separation and premature rupture of membranes in 12 patients, and preterm labor and delivery in all patients. Thirteen of 19 (68%) neonates survived for 90 days after delivery; one died in utero, and 5 died after birth. Late mortality included one death caused by sepsis and 2 by complications associated with tracheostomies. Morbidity from gastroesophageal reflux requiring Nissen fundoplication, tracheal injury requiring repair or tracheostomy, and recurrent hernias after diaphragmatic repair were characteristic in longterm survivors.

Conclusions: Fetoscopic temporary TO may improve outcome in poor-prognosis fetuses with CDH. However, complications related to tracheal dissection, premature delivery and late morbidity are significant. This experience has led to simpler techniques for fetoscopic tracheal occlusion and to an National Institutes of Health–sponsored randomized controlled trial comparing fetoscopic tracheal occlusion with optimal postnatal care.

INDEX WORDS: Congenital diaphragmatic hernia, fetal surgery, fetoscopy, tracheal occlusion, prenatal diagnosis, clinical trial.

PULMONARY HYPOPLASIA and pulmonary hypertension are devastating consequences of infants born with congenital diaphragmatic hernia (CDH). Despite aggressive postnatal care and advances in neonatal therapy, high-risk fetuses, those with liver herniation into the chest and with lung-to-head ratios (LHR) less than 1.4, continue to do poorly with little improvement in survival rate.[1] Years of work, initially in experimental animal models and later in humans, have attempted to improve the outcome of fetuses with CDH by intervening prenatally. Attempts at open hysterotomy and repair of the diaphragmatic defect did not improve outcomes in randomized control and retrospective studies.[2,3] More recent efforts have utilized an alternative strategy, occlusion of the trachea, to allow the lungs to grow. Tracheal occlusion, by preventing the normal egress of lung fluid, stimulates lung growth and reverses the pulmonary hypoplasia and hypertension that are the characteristic causes of morbidity and mortality in these neonates.[4-6] In utero temporary tracheal occlusion using endoscopic techniques (Fetendo) has a similar effect in both animal models.[7] and in human fetuses.[8]

We previously reported that in 8 fetuses with severe left CDH, prenatal intervention with the Fetendo clip procedure resulted in 75% survival rate compared with 38% for a matched cohort treated postnatally.[8,9] We now report our experience with 11 additional cases. Review of these cases suggests that endoscopic placement of external tracheal clips may improve outcome for fetuses with the most severe CDH and has led to an National Institutes of Health (NIH)-sponsored trial comparing Fetendo clip to optimal postnatal care including extracorporeal membrane oxygenation (ECMO), inhaled nitric oxide, and high-frequency ventilation.

MATERIALS AND METHODS

From January 1996 to April 1999, 19 fetuses underwent fetoscopic temporary tracheal occlusion (Fetendo clip) for congenital diaphragmatic hernia (CDH) at the University of California at San Francisco

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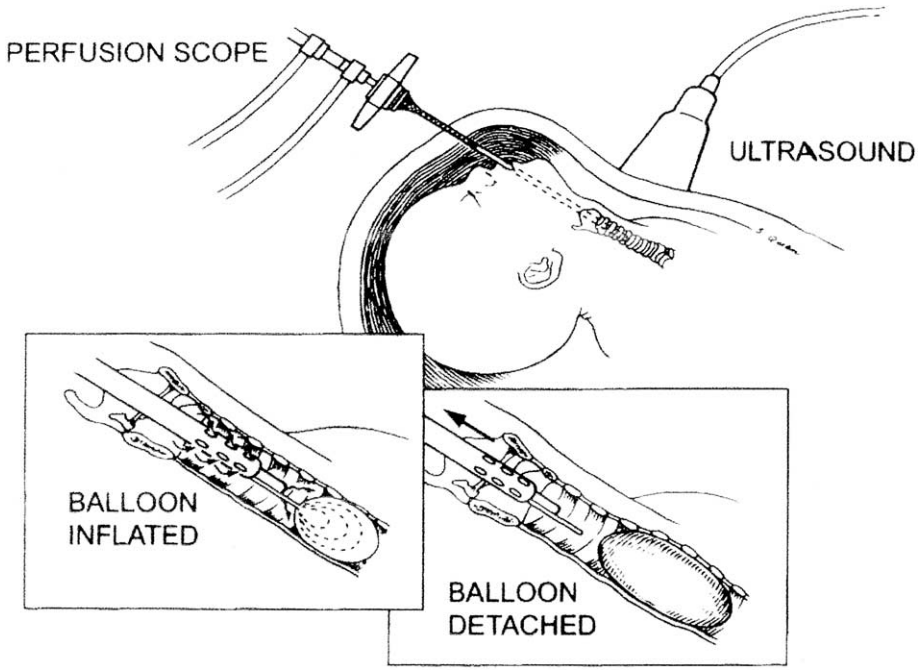

Fig 1. Method for occluding the trachea with clips. Under sonographic guidance, the fetus' neck is exposed and the head stabilized by placing a temporary transuterine chin suture. Using ultrasonography, a T-fastener and suture are placed in the fetal trachea to aid in locating the midline fetal neck. After anterior tracheal dissection, a tracheal "screw" can be placed in the anterior tracheal wall to facilitate safe posterolateral dissection, if necessary.

(UCSF) Fetal Treatment Center. We now update the previously reported experience with 8 left-sided CDHs[3] with an additional 8 left-sided and 3 right-sided CDH patients.

Fetuses eligible for prenatal intervention met criteria including (1) diagnosis of CDH made before 25 weeks' gestation, (2) a major portion of the liver herniated into the hemithorax, (3) lung-to-head ratio (LHR) less than 1.4 for left CDHs,[1] (4) normal karyotype and echocardiogram, and (5) no other anomalies detected by prenatal ultrasonography. Before fetal intervention, a multidisciplinary team including a pediatric surgeon, perinatologist, neonatologist, psychiatric social worker, and anesthesiologist rigorously counseled all candidate families. Each family was offered the following options: (1) standard postnatal care, (2) termination (if before 24 weeks' gestation), or (3) fetal temporary tracheal occlusion. During the period of this study, 45 families fulfilled all criteria. Of these, 19 families chose fetal intervention, 7 decided to terminate the pregnancy, and 19 opted for conventional postnatal care. All fetal temporary tracheal occlusion procedures were performed under an institutionally approved IRB protocol.

For those who chose to undergo fetal intervention, a fetoscopic approach (the Fetendo clip procedure) was attempted first, and, only if unsuccessful, an open hysterotomy would be performed. Although the original procedure has been described in detail,[3,9,10] briefly, the Fetendo clip procedure entails a maternal laparotomy with exposure of the uterus. Using ultrasonic guidance, the fetus is fixed in neck extension position with a chin stitch, and the trachea is isolated with a T-bar (Fig 1). In addition to general anesthesia via maternoplacental circulation, the fetus is relaxed with an intramuscular Pancuronium and Fentanyl injection. Fetoscopic instruments then are used to dissect the trachea, identify the recurrent laryngeal nerves, and apply 2 titanium transtracheal occluding clips. A specially designed perfusion pump that provides warmed irrigation and suction, maintaining the fetus in a homeostatic environment, facilitates visualization. Once the clips have been applied, the T-bar and chin stitch are removed, and the port sites are closed via instillation of a fibrin glue sealant followed by a single figure of 8 medium-sized absorbable suture.

Mothers were administered betamethasone before fetal intervention to mature the fetal lungs in case of emergent early postoperative delivery. In more recent cases, betamethasone was given to the mother at the time of planned intervention to improve fetal lung tissue compliance.[11,12] Whereas pre- and intraoperative tocolytic management remained the same (indomethacin, halogenated anesthetic agents, and small doses of nitroglycerin when necessary for acute intraoperative uterine relaxation), postoperative tocolysis has evolved and has been standardized through use of a clinical pathway (Table 1). Because β-adrenergic agonists reduce the production of fetal lung fluid experimentally,[13,14] they are now used sparingly. Magnesium sulfate, which is begun near the completion of the case, is weaned within 1 to 2 days, and an oral calcium channel blocker (Nifedipine) is used for maintenance tocolysis until delivery. The decision to discharge patients was made when there was no evidence of membrane rupture or separation, and preterm labor could be controlled with orally administered tocolytics.

After discharge, all mothers with fetal intervention stayed at a nearby Ronald McDonald House on bedrest precautions and underwent biweekly examination including fetal ultrasonography. All fetuses with the Fetendo clip were delivered using the EXIT (ex utero intrapartum treatment) procedure as described previously.[3,15] The fetus, while still on placental support, is delivered partially. The fetal neck is exposed and the clips removed with rigid bronchoscopic visualization. Lung fluid is aspirated, and surfactant is given immediately after endotracheal intubation. After establishment of an effective airway and good chest excursion, the infant is delivered and the umbilical cord clamped. Postnatal management of infants included high-frequency ventilation, ECMO for salvage therapy, and nitric oxide in cases of severe pulmonary hypertension. Repair of the diaphragmatic hernia was performed electively when the baby was stable, from 2 to 8 days after birth. Postnatal care in all infants included admission to the Intensive Care Nursery with maximal ventilatory support including high-frequency ventilation and ECMO.

All liveborn infants were evaluated in terms of gestational age (GA) at prenatal diagnosis, LHR, gestational age at the Fetendo clip procedure, interval between the clip and EXIT procedures, and birth weight. Survival was defined as alive at 90 days of age. Long-term survivors were all infants surviving beyond this time. Student's *t* test was applied to analyze the difference between the means in survivors and nonsurvivors; probabilities less than .05 were considered significant. Fol-

Table 1. Clinical Pathway for Mothers Undergoing Fetal Intervention

	Day 1 (DOS)	Day 2 (POD 1)	Day 3 (POD 2)	Day 4 (POD 3)	Day 5 (POD 4)	Day 6 (POD 5)
Activity	Lateral position, HOB elevated, bed rest	Lateral position, HOB, elevated, bed, rest	Bed exercises, dangling	OOB with assistance	Shower	Ambulate
Diet/nutrition	NPO, 3,000 mL fluid restriction	Clears, 3,000 mL fluid restriction	ADAT, 3,000 ML fluid restriction	Regular diet		
Pain management	Epidural	Epidural	D/C Epidural PO Vicodin	PO Vicodin		
Antibiotics	Cefotetan, 2 g BID	Cefotetan, 2 g BID	D/C Cefotetan			
Treatments	Teds/SCDs, Foley, abdominal shave	Foley, Teds/SCDs	D/C Foley, D/C SCDs	D/C Teds		
Tocolysis	Indocin, 50 mg PR; $MgSO_4$, 4-6 g/h in OR; 2-4 g after operation	Indocin, 50 mg PR q6 h; $MgSO_4$ stopped if stable; Nifedipine 10-20 mg PO q6 h	Indocin, 25 mg PO q6 h, Nifedipine 5-40 mg PO q6 h	D/C Indocin, Nifedipine, 5-40 mg PO q6 h	Nifedipine, 5-40 mg PO q6 h or Terbutaline if oral Nifedipine not effective	Nifedipine, 5-40 mg PO q6 h
Monitoring		Echo, Sono, AFI, FHR, CBC q6 h, urine dip	Sono, AFI, FHR, CBC, urine dip	Sono, AFI, FHR, labs pm	Sono, AFI, FHR	Sono, AFI, FHR

Abbreviations: DOS, day of surgery; POD, postoperative day; HOB, head of bead; OOB, out of bed; NPO, nothing by mouth; ADAT, advance diet as tolerated; D/C, discontinue; PO, by mouth; Teds, stockings; SCDs, sequential compression devices; Echo, echocardiogram; Sono, ultrasonography; AFI, amniotic fluid index; FHR, fetal heart rate; CBC, blood count; pm, as needed; OR, operating room.

low-up and general information was obtained through Fetal Treatment Center and hospital records and through patient visits to the Pediatric Surgical clinic.

RESULTS

Operation

Although open hysterotomy was available as a back-up procedure if fetoscopic placement could not be accomplished for technical reasons (fetal position, visualization, bleeding), the last 16 cases (all new cases and the last 5 cases of the previous series) were accomplished without hysterotomy. Eleven of the 19 cases had the more favorable posterior placenta, whereas 8 had less-favorable anterior or fundal locations. Average operating time was 221 minutes ± 69 minutes. The first 8 cases averaged 259 minutes ± 70 minutes, and the most recent 11 cases, 193 minutes ± 56 minutes. Average blood loss was 221 mL ± 127 mL with none of the mothers requiring a transfusion. Perfusion pump volumes were fairly consistent at 26 L ± 10 L. Whereas the first 5 procedures required 4 or 5 5- or 10-mm balloon tip trocars, more recent operations have only required 3 5-mm radially expanding trocars (InnerDyne, Inc, Salt Lake City, UT) because there has been a reduction in the size of the irrigating endoscope and instruments. We now use a 4.5-mm irrigating hysteroscope (Karl Storz Endoscopy-America, Inc; Culver City, CA).

Obstetrical Outcome

All patients required bedrest, periodic monitoring, and tocolysis from the time of the procedure (27.4 ± 1.6 weeks) to delivery by EXIT procedure. Maternal length of stay averaged 10 days ± 7.7 days after fetal surgery. Six patients had mild, noncardiogenic pulmonary edema visible on chest radiographs on the first postoperative day, which required supplemental nasal oxygen and resolved within 2 days without sequelae. Twelve of 19 patients eventually had sonographic evidence of chorioamniotic membrane separation, most often after several weeks (2.3 ± 1.5 weeks postoperatively). Twelve patients had premature rupture of membranes (PROM) usually prompting preterm labor and delivery (Table 2). Lung growth was assessed subjectively by serial ultrasonography and was found to occur in the majority of patients within 7 to 10 days.

The timing of delivery by the EXIT procedure was in response to varied fetomaternal conditions. Three patients had uterine contractions unresponsive to tocolysis; 5 had vaginal bleeding suggesting a placental abruption, 3 had low-grade fever suggesting chorioamnionitis, and 4 had evidence of fetal distress associated with PROM or membrane separation. In addition, there was one patient with intrauterine fetal demise, one with a clot near the umbilical cord, and 2

Table 2. Maternal Outcome in 19 Patients With Prenatal Tracheal Occlusion Using the Fetendo Clip Procedure

Age (yr)	Parity	LHR	GA at Diagnosis (wk)	GA at Surgery (wk)	GA at Delivery (wk)	LOS (d)	CAS	PE	PROM	Delivery Indication
24	G1, P0	1.4	23	29.6	32.6	11	No	No	Yes	Fetal distress
34	G6, P3	1.07	16	29.7	31.4	15	No	Yes	Yes	CA
28	G3, P1	1.12	21	30.4	33.4	9	Yes	Yes	No	Unresponsive
30	G3, P0	1.2	19	28	34.6	9	Yes	Yes	Yes	CAS
32	G11, P1	0.68	20	29	34.7	6	Yes	Yes	No	Fetal distress
30	G3, P2	0.69	19	27.3	30.7	6	Yes	No	Yes	Fetal distress
21	G2, P1	0.72	18	27.7	29.1	5	Yes	No	Yes	Vaginal bleed
32	G4, P0	1	19	27.3	32	12	No	No	Yes	Unresponsive
37	G2, P1	0.95	22.7	28.7	32	6	No	No	Yes	Vaginal bleed
32	G3, P2	0.6	23.9	27.7	31.1	8	Yes	No	Yes	Vaginal bleed
21	G2, P1	1.1	20	26	29.9	8	Yes	No	Yes	CA
35	G3, P0	0.8	15.9	25.3	25.7	7	No	No	No	IUFD
20	G2, P1	0.65	18.7	26.4	27.3	11	No	No	Yes	Unresponsive
19	G2, P0	0.7	21.4	25.6	30.1	7	Yes	No	No	Umbilical cord clot
25	G1, P0	0.93	23.9	27.1	32.1	40	Yes	No	Yes	CA
22	G2, P0	1	21	26.1	32.6	10	Yes	Yes	No	CAS
38	G2, P2	0.6	16.9	25	29.4	7	Yes	No	No	Fetal distress
37	G2, P1	0.65	16.7	26.3	31.4	7	Yes	Yes	No	Vaginal bleed
36	G4, P2	0.93	16.6	26.4	31.7	7	No	No	Yes	Vaginal bleed

Abbreviations: GA, gestational age; LOS, length of stay; CAS, chorioamniotic membrane separation; PE, pulmonary edema; PROM, premature rupture of membranes; CA, chorioamnionitis; unresponsive, unresponsive to tocolytics; IUFD, intrauterine fetal demise.

patients with worsening membrane separation or shredding, all of which prompted delivery.

Fetal Outcome and Factors Affecting Survival

Thirteen of 19 (left sided, 16; right sided, 3) fetuses (68%) survived 90 days after delivery. One fetus died in utero on the second postclip day after prolonged postoperative bradycardia with no determinable cause at autopsy. The other 18 infants were all liveborn, and 13 survived to 90 days of life (72% survival of liveborns, Table 3). Stratified by LHR, the 12 patients with LHR less than 1.0 had a survival rate of 63%, with only one infant requiring ECMO support. The 7 patients with LHR greater than 1.0 had a survival rate of 86% also with only one requiring ECMO support. Statistically, there was no difference between the 13 survivors and 6

Table 3. Ninety-Day Outcome of 18 Liveborn Neonates Who Underwent Prenatal Tracheal Occlusion for Congenital Diaphragmatic Hernia

Fetal Diagnosis	LHR	GA at Delivery (wk)	Days of tracheal occlusion	Birth Weight (g)	LOS (d)	Day of CDH Repair	Outcome	Comment
L CDH	1.4	32.6	21	1,350	3	None	Dead	Multiple pterygium syndrome
L CDH	1.07	31.4	12	1,620	99	7	Alive	
L CDH	1.12	33.4	21	3,000	65	1	Alive	
L CDH	1.2	34.6	46	2,500	96	5 (ECMO)	Alive	
L CDH	0.68	34.7	40	2,250	3	None	Dead	No biologic response
L CDH	0.69	30.7	24	1,600	96	1	Alive	
L CDH	0.72	29.1	10	1,390	73	8	Alive	
L CDH	1	32	33	1,290	63	4	Alive	
L CDH	0.95	32	23	2,000	139	7	Alive	
L CDH	0.6	31.1	24	1,100	2	None	Dead	No biologic response
L CDH	1.1	29.9	27	1,200	96	8	Alive	
L CDH	0.65	27.3	6	750	82	4	Dead	Sepsis (pneumonia)
R CDH	0.7	30.1	32	1,860	3	3	Dead	Pulmonary hemorrhage during CDH repair
L CDH	0.93	32.1	35	2,120	56	4	Alive	
L CDH	1	32.6	45	2,000	49	3	Alive	
L CDH	0.6	29.4	31	1,200	171	4	Alive	
R CDH	0.65	31.4	36	2,400	105	9	Alive	
R CDH	0.93	31.7	37	2,000	61	7	Alive	

Abbreviations: L, left; R, right; CDH, congenital diaphragmatic hernia; GA, gestational age; LOS, length of stay.

nonsurvivors in maternal age (survivors v nonsurvivors, 30.1 ± 6.3 *v* 27.0 ± 6.9 years), gestational age at prenatal diagnosis (survivors v nonsurvivors, 19.2 ± 2.4 *v* 20.5 ± 2.9 weeks' gestation), LHR (survivors *v* nonsurvivors, 0.92 ± 0.19 *v* 0.81 ± 0.30), gestational age at Fetendo clip (survivors *v* nonsurvivors, 27.4 ± 1.5 *v* 27.3 ± 1.8 weeks' gestation), interval between the fetal and EXIT procedures or tracheal clip days (survivors *v* nonsurvivors, 29.2 ± 11.2 *v* 21.0 ± 14.4 days), birth weight (survivors *v* nonsurvivors, 1,870 ± 553 *v* 1,345 ± 606 g), and gender.

Neonatal Outcome

Five liveborn infants did not survive the neonatal period. One infant with a normal karyotype was diagnosed as having multiple pterygium syndrome immediately after birth. Although there was good lung growth and function (FIO_2 of 21% at 24 hours of age), support was withdrawn because of the previously unrecognized lethal anomaly. Two fetuses showed no response to tracheal occlusion and died shortly after delivery. One infant was found at autopsy to have left pulmonary agenesis. The other had no lung expansion before birth, developed severe fetal distress with cardiac arrest during the EXIT procedure, and died on day of life 3 despite ECMO support. One infant suffered a pulmonary hemorrhage during CDH repair on day of life 3. The last infant died at 78 days of life from sepsis caused by obstructed ischemic bowel. Average number of hospitalization days for liveborn infants was 66 days ± 49 days and 90 days ± 35 days for long-term survivors.

Fifteen of 18 liveborn infants were stabilized after delivery and underwent diaphragmatic repair using a Gore-Tex (W.L. Gore, Flagstaff, AZ) patch at the age of 4.9 ± 2.5 days. One survivor had the CDH repair while on ECMO support. Other nonlethal anomalies in survivors that required treatment included a small ventricular septal defect (1), patent ductus arteriosus (1), and an atrial septal defect (1). Additional anomalies including a left extrapulmonary sequestration, an ileal web, and a Meckel's diverticulum were found and resected at the time of CDH repair. Although evidence of lung growth in utero was subtle and slow to appear, postnatal imaging and subjective operative appearance showed that the lungs were markedly larger than other CDH babies without fetal intervention.

In the group of 13 long-term survivors, there have been 3 major types of morbidity: tracheal injuries, gastroesophageal reflux, and recurrent diaphragmatic herniation. Five of 18 liveborn infants had tracheal injuries that required treatment at the time of the EXIT procedure (closure of lacerations). In the group of long-term survivors, 7 of 13 infants have had some form of tracheal problem. The 2 most significant have been bilateral recurrent laryngeal nerve injury and tracheomalacia. These were found at bronchoscopy when extubation of these infants was not possible. Four infants have had bilateral nerve injury leading to vocal cord paresis. Each had stridor shortly after extubation and required a tracheostomy for airway protection. Two have subsequently died from accidents caused by tracheostomy dislodgement at home (Table 4). Two infants have had tracheomalacia with collapse of the airway on inspiration, necessitating stenting in both and a Cotton procedure in one with resection of a stenotic portion of trachea. Significant gastroesophageal reflux has necessitated a Nissen fundoplication in 7 patients; small bowel obstruction and necrotizing enterocolitis with sepsis developed in one other patient. Six patients thus far have had symptomatic separation of the Gore-Tex patch. In 3, the Gore-Tex patch was replaced with a latissimus dorsi muscle flap reinnervated by anastomosing the ipsilateral phrenic nerve to the transected long thoracic nerve. The other 3 had a new Gore-Tex patch placed. Other complications have included pleural or lung infections in 2 patients and ipsilateral chylothoraces after CDH repair in 4 infants (2 requiring surgical closure, Table 4).

There was late mortality related to the postnatal treatment of severe CDH. Of the 13 infants that survived 90 days, 3 have since died. As previously stated, 2 of these died at home at 11 and 15 months of age, apparently secondary to tracheostomy accidents. The other late death at 9 months was from sepsis associated with a case of meningitis. As of June 2001, the average follow-up for long-term survivors is 41 months (range, 26 to 63 months). Ten infants currently are alive and well for a survival rate of 53%.

DISCUSSION

Two decades of extensive experimental investigation and agonizing and often frustrating clinical trials led to development of the prenatal strategy of temporary tracheal occlusion to enlarge the lungs of fetuses with the most severe form of CDH. Previous retrospective and prospective studies have found that without prenatal intervention, high-risk infants do poorly even with optimal postnatal care with mortality rates of 60% for LHRs less than 1.4 and nearly 100% for LHRs less than 1.0.[1,16] Our experience with 19 patients, all with LHRs less than 1.4 and most less than 1.0, suggests that the Fetendo clip procedure may improve survival rate when compared with fetuses treated after birth with standard care. Retrospective analysis of this uncontrolled series provides many insights into the technical problems and emphasizes the need for a prospective, randomized trial of this promising new therapy.

There has been a remarkable evolution in the technical aspects of in utero treatment of CDH: from hysterotomy

Table 4. Long-Term (>90 day) Outcome in 13 Infants Who Underwent Prenatal Tracheal Occlusion for Congenital Diaphragmatic Hernia

LHR	Days of Tracheal Occlusion	Nissen	Redo CDH	Chylo	Tracheal Injury	Comment	Outcome
1.07	12	No	Gore-Tex and lat dorsi flap	Yes	None		Alive at 63 mo
1.12	21	Yes	No	No	Yes	VC paresis, tracheostomy	Died 11 mon; tracheostomy dislodgement
1.2	46	Yes	Gore-Tex	No	Yes	VC paresis tracheostomy	Alive at 55 mo
0.69	24	No	No	No	Yes	Laceration repair at EXIT	Alive at 54 mo
0.72	10	Yes	No	No	No	Removal T-bar at second operation	Alive at 48 mo
1	33	Yes	No	No	No		Alive at 47 mo
0.95	23	Yes	No	Yes (ligation duct)	No		Died 9 mo, meningitis
1.1	27	No	No	No	Yes	VC paresis, tracheostomy	Died 15 mo, tracheostomy dislodgement
0.93	35	No	Gore-Tex	No	Yes	Laceration, repair at EXIT	Alive at 34 mo
1	45	Yes	Lat dorsi flap	Yes (ligation duct)	No		Alive at 30 mo
0.6	31	Yes	Gore-Tex	Yes	Yes	VC paresis, tracheostomy, malacia with multiple stents	Alive at 28 mo
0.65	36	No	Lat dorsi flap	No	Yes	malacia with multiple stents, Cotton procedure	Alive at 27 mo
0.93	37	No	No	No	No		Alive at 26 mo

Abbreviations: Chylo, chylothorax; CDH, congenital diaphragmatic hernia; lat Dorsi flap, latissimus dorsi flap; VC, vocal cord.

and complete repair (the "CDH two-step"),[17] to hysterotomy and internal tracheal occlusion, to hysterotomy and tracheal clip,[7,8,18] and finally to fetoscopic tracheal clip (Fetendo clip).[3] Given the technical difficulties of achieving fetoscopic tracheal dissection and placement of a clip, perhaps the most important and surprising conclusion from our early experience is that the Fetendo clip procedure can be reliably carried out without resorting to open hysterotomy in all fetuses regardless of placental location, fetal position, or gestational age. We have not had to open the uterus for fetal CDH in more than 4 years. There has been a striking evolution in technique from the use of four 10-mm ports to 3 5-mm ports, made possible by miniaturization of not only the ports but the irrigating scope, the continuous perfusion pump, and the methods of fetal positioning and fixation. Indeed, there has already been further evolution in techniques, because we now have developed techniques to place an endotracheal occluding device (balloon) through a single, small port.[19]

In a similar way, technical innovation will be required to overcome 2 persistent problems that were present in the majority of our patients: maternal morbidity related to fetal intervention and fetal tracheal complications related to the neck dissection and clip occlusion. Maternal morbidity was reflected in the high incidence of chorioamniotic membrane separation, premature rupture of membranes, early delivery, and pulmonary edema. Whereas the latter problem appears to be declining based on improvements in tocolysis, the former 3 are devastating complications that compromise the survival of the fetus and neonate. Our bias is that limiting the size of the hysterotomy through the use of Fetendo techniques and limiting the number of fetoscopic ports can reduce the incidence of these complications. The rationale behind this comes from several sources: (1) early work in monkeys showed the size of the hysterotomy was directly related to the amount of uterine activity[20]; (2) fetuses undergoing operative intervention suffer from pain and manifest a stress response[21-23]; (3) work in humans related that there was a reduction (not statistically significant) in preterm labor, tocolysis, length of

stay, and subjective maternal discomfort with the Fetendo approach.[3] This important problem is being approached in several ways: development of introduction devices to minimize membrane separation during puncture, refinement of radially expanding trocars, development of alternative methods of closing the membranes and the myometrium after removal of the trocar, and, most promising, introduction of alternative one-trocar methods of tracheal occlusion by Fetendo placement of an intratracheal balloon.

In our series, the problem of tracheal injury and recurrent laryngeal nerve damage from the fetal tracheal dissection was a significant one. Seven of 13 long-term survivors had some form of tracheal injury; 4 of them needed a permanent tracheostomy secondary to bilateral recurrent laryngeal nerve paralysis. Although we have been insistent on seeing both recurrent laryngeal nerves while the clip is being applied, this complication has not disappeared. Extensive manipulation to fully dissect the trachea has been necessary because work in both rats, sheep, and humans has shown that complete occlusion of the trachea is required to achieve lung expansion.[5,18,24] Despite our efforts, visualization in Fetendo cases may be suboptimal, because in most of these cases, both nerves appeared to be identified and preserved. Cases of tracheal stenosis and tracheomalacia after tracheal clipping also have been troublesome. Two of the 3 longest length-of-hospital stays in long-term survivors were in infants with this complication. whereas improvements in visualization, instrumentation, and skill may partly reduce these complications, it appears that the tracheal clip approach may be fraught with difficulty. These difficulties compelled us to develop endotracheal balloons that can be deployed through the larynx, thus, eliminating the need for tracheal dissection.[19,25] The Fetendo balloon technique has now replaced the Fetendo clip technique.

One major area of controversy has arisen regarding tracheal occlusion. This involves the optimal amount of time tracheal occlusion needs to be present to achieve maximal effect, a fact that is not known. Recent studies in fetal sheep and rats have shown that although long-term tracheal occlusion improves lung size, oxygenation, and ventilation, it leads to a reduction in surfactant protein production secondary to a redistribution of type I and type II lung cell populations, changes that may not benefit the fetus.[26,27] Whereas this protein deficiency may be partially normalized by exogenous surfactant, it may not be fully reversible.[28] Other work in sheep has shown that short-term tracheal occlusion (2 to 3-week duration) can result in significant functional improvement in lung function even in the absence of lung growth, and at the same time preserve the number of type I and II cells.[29-32] Although reversing tracheal occlusion in human fetuses has not been accomplished and would certainly be difficult after an external clip is placed, an internal tracheal balloon would be much easier to deflate and may facilitate this strategy in the future.

There also is much to be learned from our failures and complications. Unfortunately, we have no clear explanation for the postoperative in utero demise of one fetus or for the lack of physiologic response to tracheal occlusion in 2 other fetuses who died shortly after birth. The most likely explanation is failure of occlusion because we know that even a tiny leak will negate the physiologic response. Two other fetuses died with unrecognized associated anomalies, suggesting that increased vigilance for associated lethal anomalies is crucial to improving the outcome. We withdrew support from an infant with multiple pterygium syndrome, which was recognized only after birth. This rare syndrome can only be diagnosed if subtle findings of webbing across joints, neck edema, and mild facial anomalies are specifically sought. Left pulmonary agenesis in the other infant was not recognized until postmortem but may be distinguished by fetal magnetic resonance imaging (MRI), which is capable of visualizing the hypoplastic left lung[33] or by color Doppler sonography of the pulmonary vessels. However, the ability to detect very subtle anomalies by imaging studies (sonography, MRI, color Doppler.) is never perfect, and more sophisticated biochemical and genetic modalities will be necessary.

In terms of long-term outcome, the difficulty of treating the patient with CDH is self-evident. Despite prenatal intervention, only one of the neonates we followed had no complications. Most required interventions for gastroesophageal reflux disease, recurrent diaphragmatic hernia, tracheal injury, and chylothorax. However, given that many of these survivors were in the highest risk category with LHRs less than 1.0, a status that predicts nearly 100% mortality in historical controls, the simple fact that they are alive is significant.

This retrospective analysis of the promising new strategy of temporary tracheal occlusion suggests that the Fetendo clip technique, although capable of salvaging some fetuses with severe CDH, is technically difficult with significant complications and should be superceded by simpler techniques such as Fetendo balloon.

The most important conclusion from this retrospective analysis is that the strategy of temporary tracheal occlusion to enlarge the hypoplastic lung, whether accomplished by the Fetendo clip or the newer Fetendo balloon technique must be evaluated in a proper prospective, randomized trial. Despite the ethical, logistical, and financial difficulties of assigning or withholding an innovative surgical procedure for a life-threatening fetal condition, it is imperative to establish the place of this promising new therapy early in its development before it becomes established without being scientifically tested.

There are obviously very difficult impediments to performing a proper randomized trial of a potentially life-saving surgical therapy for a potentially fatal disease. The timing of any proposed trial is crucial because further positive experience with this new technique will surely lead to increasing clinical application in response to desperate patients and referring physicians, as has been the case for virtually all "dramatic" new therapies (eg, ECMO). Because this procedure has been developed and applied at a single institution, we recognize an obligation to test its effectiveness before the technology becomes accepted and disseminated. Since this report was first submitted, we have initiated an NIH-sponsored, prospective, randomized controlled trial comparing Fetendo clip/balloon to optimal postnatal repair and have agreed that eligible patients will not be offered the procedure outside the trial.[19] Women carrying fetuses with a left-sided diaphragmatic hernia with the liver herniated, an LHR less than 1.4, and no other detectable fetal anomalies are assigned randomly to endoscopic fetal occlusion or optimal postnatal care including ECMO support, inhaled nitric oxide, and high-frequency ventilation. Outcome variables include neonatal mortality as well as long-term morbidity and cost. Enrollment has been surprisingly good, and the results will be reported when available.

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