

ORIGINAL ARTICLE

A Randomized Trial of Fetal Endoscopic Tracheal Occlusion for Severe Fetal Congenital Diaphragmatic Hernia

Michael R. Harrison, M.D., Roberta L. Keller, M.D., Samuel B. Hawgood, M.D., Joseph A. Kitterman, M.D., Per L. Sandberg, M.D., Diana L. Farmer, M.D., Hanmin Lee, M.D., Roy A. Filly, M.D., Jody A. Farrell, M.S.N., P.N.P., and Craig T. Albanese, M.D.

ABSTRACT

BACKGROUND

Experimental and clinical data suggest that fetal endoscopic tracheal occlusion to induce lung growth may improve the outcome of severe congenital diaphragmatic hernia. We performed a randomized, controlled trial comparing fetal tracheal occlusion with standard postnatal care.

METHODS

Women carrying fetuses that were between 22 and 27 weeks of gestation and that had severe, left-sided congenital diaphragmatic hernia (liver herniation and a lung-to-head ratio below 1.4), with no other detectable anomalies, were randomly assigned to fetal endoscopic tracheal occlusion or standard care. The primary outcome was survival at the age of 90 days; the secondary outcomes were measures of maternal and neonatal morbidity.

RESULTS

Of 28 women who met the entry criteria, 24 agreed to randomization. Enrollment was stopped after 24 patients had been enrolled because of the unexpectedly high survival rate with standard care and the conclusion of the data safety monitoring board that further recruitment would not result in significant differences between the groups. Eight of 11 fetuses (73 percent) in the tracheal-occlusion group and 10 of 13 (77 percent) in the group that received standard care survived to 90 days of age ($P=1.00$). The severity of the congenital diaphragmatic hernia at randomization, as measured by the lung-to-head ratio, was inversely related to survival in both groups. Premature rupture of the membranes and preterm delivery were more common in the group receiving the intervention than in the group receiving standard care (mean [\pm SD] gestational age at delivery, 30.8 \pm 2.0 weeks vs. 37.0 \pm 1.5 weeks; $P<0.001$). The rates of neonatal morbidity did not differ between the groups.

CONCLUSIONS

Tracheal occlusion did not improve survival or morbidity rates in this cohort of fetuses with congenital diaphragmatic hernia.

From the Fetal Treatment Center (M.R.H., S.B.H., J.A.K., P.L.S., D.L.F., H.L., R.A.F., J.A.F., C.T.A.), the Departments of Surgery (M.R.H., D.L.F., H.L., J.A.F., C.T.A.), Pediatrics (M.R.H., R.L.K., S.B.H., J.A.K., D.L.F., H.L., C.T.A.), Obstetrics, Gynecology and Reproductive Sciences (M.R.H., P.L.S., D.L.F., H.L., R.A.F., C.T.A.), and Radiology (R.A.F.), and the Cardiovascular Research Institute (R.L.K., J.A.K.), University of California, San Francisco, San Francisco. Address reprint requests to Dr. Harrison at the University of California, San Francisco, Fetal Treatment Center, 513 Parnassus Ave., HSW-1601, San Francisco, CA 94143-0570, or at fetus@surgery.ucsf.edu.

N Engl J Med 2003;349:1916-24.

Copyright © 2003 Massachusetts Medical Society.

CONGENITAL DIAPHRAGMATIC HERNIA can now be accurately diagnosed by mid-gestation, and the outcome in individual cases can be predicted on the basis of sonographic measurement of the lung-to-head ratio and the presence or absence of liver herniation into the thorax.¹⁻⁴ Mortality is low for full-term fetuses without liver herniation and a favorable lung-to-head ratio (above 1.4) at tertiary centers.⁴ However, fetuses with liver herniation and a low lung-to-head ratio have high rates of mortality and morbidity, despite recent advances in intensive neonatal care, including extracorporeal membrane oxygenation, nitric oxide inhalation, high-frequency ventilation, and delayed operative repair of the diaphragmatic hernia.⁵⁻¹¹

The fundamental problem in babies born with a congenital diaphragmatic hernia is pulmonary hypoplasia. A number of strategies have been used in an attempt to improve the growth of hypoplastic lungs before they are needed for gas exchange at birth. Anatomical repair of the hernia through open hysterotomy proved feasible, but it did not decrease mortality and was abandoned.¹²⁻¹⁹ Fetal tracheal occlusion was developed as an alternative strategy to promote fetal lung growth by preventing normal egress of lung fluid. Occlusion of the fetal trachea was shown to stimulate fetal lung growth in a variety of animal models.²⁰⁻²⁷ Techniques to achieve reversible fetal tracheal occlusion were explored in animal models^{28,29} and then applied clinically, evolving from the use of external metal clips placed on the trachea by means of open hysterotomy or fetoscopic neck dissection³⁰⁻³³ to internal tracheal occlusion with a detachable silicone balloon placed with the use of fetal bronchoscopy through a single 5-mm uterine port.³⁴

Our initial experience suggested that fetal endoscopic tracheal occlusion improved survival in human fetuses with severe congenital diaphragmatic hernia.^{33,34} To evaluate this novel therapy, we conducted a randomized, controlled trial from April 1999 through July 2001 in which we compared tracheal occlusion with standard care; all women referred after April 1999 who were carrying fetuses with severe left-sided congenital diaphragmatic hernia and who met the inclusion criteria were invited to participate.

METHODS

REFERRAL AND EVALUATION

Women carrying fetuses with left-sided congenital diaphragmatic hernia and a normal karyotype un-

derwent evaluation at the University of California, San Francisco, when the fetuses were 22 to 27 weeks of gestational age, including ultrasonography, calculation of the lung-to-head ratio, echocardiography, obstetrical consultation, and psychosocial assessment.

The eligibility criteria were the presence of left-sided congenital diaphragmatic hernia, a normal fetal echocardiogram, no ultrasonographic evidence of other anomalies, a normal karyotype, liver herniation into the left hemithorax, a lung-to-head ratio below 1.4 as measured between 22 and 28 weeks of gestation, a fetal age between 22 and 28 weeks of gestation, a singleton pregnancy, no preterm labor, and no medical contraindication to general anesthesia or psychosocial contraindication to participation by the mother. Families who met the eligibility criteria were extensively counseled, and those who wished to participate provided written, informed consent for both randomization and treatment. No fetal intervention was offered outside the trial. The committee on human research of the University of California, San Francisco, approved the trial protocol.

BLOCK RANDOMIZATION

Because lung-to-head ratio is the most accurate predictor of survival for fetuses with isolated left congenital diaphragmatic hernia and a herniated liver,^{1,3} randomization was performed with the use of permuted blocks stratified according to the lung-to-head ratio. Three strata of lung-to-head ratios were used: 0.78 or less, 0.79 to 1.06, and 1.07 to 1.39.

FETAL ENDOSCOPIC TRACHEAL OCCLUSION AND PRENATAL CARE

The technique of fetal endoscopic tracheal occlusion has been described previously.²⁹ Betamethasone was given to the mother preoperatively to improve fetal lung compliance.³⁵ With the mother and fetus under general anesthesia and using a low transverse maternal laparotomy, we passed a 4-mm perfusion hysteroscope through a 5-mm trocar and guided it through the fetal vocal cords with the aid of both fetoscopic and cross-sectional ultrasonographic visualization. A detachable silicone balloon (Target Therapeutics) was placed in the fetal trachea midway between the carina and the vocal cords. The balloon was inflated with isosmotic contrast material so that it filled the fetal trachea (diameter, 0.5 mm) for a length of at least 2 cm. Experimental studies have shown that this maneuver effectively occludes the fetal trachea.^{34,36} The first two patients in this

study underwent a three-port fetal endoscopic tracheal clip procedure,³⁰ which was then replaced by the balloon-occlusion technique; the data safety monitoring board approved the change.

The women in the intervention group were treated with a preoperative indomethacin suppository (50 mg), intraoperative halogenated anesthetic agents with small doses of nitroglycerin as needed, postoperative magnesium sulfate and indomethacin (for a maximum of two days), and an oral calcium-channel blocker (nifedipine) until delivery. Beta-adrenergic agonists, which reduce the production of fetal lung fluids in animals,^{37,38} were used sparingly. The mothers were discharged to the nearby Ronald McDonald House of San Francisco, where they rested in bed and underwent ultrasonography and nonstress testing every other week until delivery.

All fetuses with tracheal occlusion were delivered by the EXIT (ex utero intrapartum therapy) procedure, as previously described.³⁹ Briefly, the fetal head was delivered and bronchoscopy was performed through a low transverse cesarean hysterotomy. The balloon occluding the trachea was deflated and removed, the airway was suctioned, an endotracheal tube was inserted, an exogenous surfactant (Exosurf Neonatal, Glaxo Wellcome) was administered at a dose of 3 ml per kilogram of body weight, and assisted ventilation was begun before the umbilical cord was divided.

The women assigned to standard care were treated expectantly, with a planned return to the University of California, San Francisco, at 36 weeks of gestation. Antenatal steroids were administered if there was preterm labor (one case) or if the lung profile indicated immaturity (seven cases). If spontaneous labor did not occur, labor was induced. Delivery was vaginal unless cesarean section was indicated.

NEONATAL RESUSCITATION AND RESPIRATORY CARE

All infants in both groups underwent intubation immediately at birth and received pancuronium and sedatives as soon as vascular access was obtained (within five minutes in all cases). Conventional mechanical ventilation was performed to maintain the partial pressure of arterial carbon dioxide in the range of 45 to 60 mm Hg (permissive hypercapnia) and right-hand (preductal) oxygen saturation above 90 percent. Higher values for the partial pressure of arterial carbon dioxide and lower oxygen-saturation values were tolerated in the first hours of life. If ven-

tilation and oxygenation were inadequate, high-frequency oscillatory ventilation, inhaled nitric oxide, and extracorporeal membrane oxygenation were used as needed. The diaphragmatic hernia was repaired when the infant's respiratory status had stabilized. The infants remained paralyzed and sedated from birth until 24 hours after operative repair. Once they had been weaned from ventilatory support, the infants continued to receive supplemental oxygen until the oxygen saturation was maintained at a level above 95 percent while they were breathing ambient air.

OUTCOME ANALYSIS

The primary outcome was survival to the age of 90 days. Additional outcomes were short-term measures of neonatal pulmonary morbidity, including the need for extracorporeal membrane oxygenation and the duration of neonatal ventilatory support and administration of supplemental oxygen; gastrointestinal morbidity; neurologic morbidity; survival to discharge from the hospital; the duration of hospitalization; and maternal physical and psychological morbidity. Assessments of other measures of long-term morbidity (including the need for supplemental oxygen, rates of recurrent infection and repeated hospitalization, and neurodevelopmental outcomes) are ongoing and are not included here.

On the basis of a logistic-regression model derived from our historical data (57 cases of left-sided congenital diaphragmatic hernia, a lung-to-head ratio under 1.4, and liver herniation), a survival rate of 37 percent was predicted in the group receiving standard care. We calculated that a sample size of 40 subjects would provide the study with 80 percent power to detect an increase in the survival rate to 77 percent in the group undergoing fetal tracheal occlusion, at an alpha level of 0.05, with allowance for an interim review of the data.

We analyzed the data with the use of Student's *t*-test, the Mann-Whitney rank-sum test, the chi-square test, Fisher's exact test, logistic regression, and survival analysis (based on Cox proportional-hazards models). The results are reported as means \pm SD and hazard ratios with 95 percent confidence intervals. A *P* value of less than 0.05 was considered to indicate statistical significance. The study was monitored by a data safety monitoring board appointed by the National Institutes of Health (NIH) (see the Appendix).

RESULTS

EARLY TERMINATION OF THE TRIAL

Enrollment was terminated early, in August 2001, after 24 patients had been randomly assigned to treatment groups, on the recommendation of the data safety monitoring board. This recommendation was based on a conditional probability calculation that predicted a failure to detect a difference in survival to 90 days of age with the planned enrollment; this interim analysis was performed when data on 18 subjects were available for review of the primary outcome 27 months after enrollment had begun.

CHARACTERISTICS OF THE STUDY SUBJECTS

A total of 157 women were referred by telephone, and 57 of them came to San Francisco for evaluation. Twenty-nine did not meet the criteria for enrollment (because of associated anomalies in 11, a diaphragmatic hernia that did not meet the criteria for severity in 12, and psychosocial factors in 6). Twenty-four of the 28 eligible women agreed to randomization.

The majority of the enrolled women had fetuses that were in the middle stratum of lung-to-head ratio (0.79 to 1.06). Eleven women were initially randomly assigned to receive standard care (mean lung-to-head ratio, 0.96 ± 0.20), and 13 were randomly assigned to undergo fetal tracheal occlusion (mean lung-to-head ratio, 0.97 ± 0.14). Two of the women randomly assigned to undergo fetal tracheal occlusion opted to have standard care, so that 13 women received standard care (lung-to-head, ratio 0.96 ± 0.20), and 11 underwent fetal tracheal occlusion (lung-to-head ratio, 0.97 ± 0.14). The base-line characteristics of the two groups according to the actual treatment received are shown in Table 1. The lung-to-head ratio did not differ significantly between the groups, whether the data were analyzed on an intention-to-treat basis ($P=0.82$) or according to the actual treatment ($P=0.52$), nor were there significant differences in any other base-line characteristics, whether they were compared on the basis of the assigned treatment or the actual treatment. The duration of tracheal occlusion was 36.2 ± 14.7 days, with a range of 16 to 64 days.

PREGNANCY OUTCOMES AND COMPLICATIONS

As expected, there was substantial short-term maternal morbidity after the fetal intervention. All women in the tracheal-occlusion group required to-

colysis for uterine contractions. Three women had mild pulmonary edema and required supplemental oxygen for less than 48 hours. Uterine puncture resulted in ultrasonographically detectable chorioamniotic separation in 7 of 11 women (64 percent), and all 11 women who underwent fetal tracheal occlusion had preterm premature rupture of the membranes, as compared with 3 of 13 women (23 percent) who received standard care ($P<0.001$) (Table 2). In the tracheal-occlusion group, preterm premature rupture of the membranes did not lead to immediate delivery; the mean time from preterm premature rupture of the membranes to delivery was 9.5 ± 8.5 days.

All infants in the tracheal-occlusion group were delivered prematurely (by the planned ex utero intrapartum therapy procedure), as compared with 4 of 13 (31 percent) in the standard-care group ($P<0.001$). In the latter four cases, spontaneous premature labor developed, and the infants were delivered before the women could return to the University of California, San Francisco. Thus, the gestational age at delivery and the birth weight were significantly lower in the tracheal-occlusion group than in the standard-care group ($P<0.001$ for both comparisons) (Table 2). All women in both groups who desired subsequent pregnancies were able to conceive and carry to term healthy children (five women in the tracheal-occlusion group and four in the standard-care group).

NEONATAL OUTCOMES

There was no significant difference in survival among infants between the standard-care group

Table 1. Base-Line Characteristics According to the Actual Treatment.*

Characteristic	Standard Care (N=13)	Tracheal Occlusion (N=11)
Maternal age — yr		
Mean	28.5±5.7	29.5±5.6
Range	19–39	21–40
Fetal sex — no. of males (%)	9 (69)	8 (73)
Fetal gestational age at randomization — wk		
Mean	25.4±1.3	24.5±1.6
Range	23.1–27.4	22.3–27.0
Lung-to-head ratio†	0.96±0.20	0.97±0.14

* Plus-minus values are means ±SD.

† The lung-to-head ratio is the length times the width of the right lung at the level of the cardiac atria, divided by the head circumference, with all measurements in millimeters.

Table 2. Pregnancy Outcomes and Complications According to the Actual Treatment.*

Outcome or Complication	Standard Care (N=13)	Tracheal Occlusion (N=11)	P Value
Maternal death — no. (%)	0	0	
Maternal blood transfusion — no. (%)	0	0	
Maternal infection (wound) — no. (%)	0	1 (9)	
Preterm labor — no. (%)	4 (31)	8 (73)	0.10
PROM — no. (%)	3 (23)	11 (100)	<0.001
Time from tracheal occlusion to PROM — days			
Mean		24.8±14.8	
Range		5–52	
Time from PROM to delivery — days			
Mean	<1	9.5±8.5	
Range		0–28	
Placental abruption — no. (%)	1 (8)	3 (27)	0.30
Mode of delivery — no. (%)			
Planned EXIT		11 (100)	
Induced vaginal delivery	12 (92)	0	
Cesarean delivery	1 (8)	0	
Gestational age at delivery — wk			<0.001
Mean	37.0±1.5	30.8±2.0	
Range	34.0–39.0	28.0–34.0	
Birth weight — kg	3.03±0.48	1.49±0.36	<0.001

* Plus-minus values are means ±SD. PROM denotes premature rupture of the membranes, and EXIT ex utero intrapartum therapy.

Table 3. Ninety-Day Survival According to Assigned and Actual Treatment and According to the Lung-to-Head Ratio.

Group	Lung-to-Head Ratio			Total
	≤0.78	0.79–1.06	1.07–1.39	
	number/total number(percent)			
Assigned treatment				
Standard care	0/0	6/9 (67)	2/2 (100)	8/11 (73)
Tracheal occlusion	0/1	7/9 (78)	3/3 (100)	10/13 (77)
Actual treatment				
Standard care	0/0	8/11 (73)	2/2 (100)	10/13 (77)
Tracheal occlusion	0/1	5/7 (71)	3/3 (100)	8/11 (73)
Total	0/1	13/18 (72)	5/5 (100)*	18/24 (75)

* P=0.04 for a trend of increased survival with a higher lung-to-head ratio (non-parametric test for trend).

and the tracheal-occlusion group, whether the data were analyzed according to the actual treatment (10 of 13 infants, or 77 percent, survived, vs. 8 of 11, or 73 percent; P=1.00) or the assigned treatment (8 of 11, or 73 percent, vs. 10 of 13, or 77 percent; P=1.00)

(Table 3 and Fig. 1). The overall rate of survival at 90 days was 75 percent.

Of the three infants in the standard-care group who died, two died before repair of their congenital diaphragmatic hernia (one from respiratory insufficiency at 4 days of age, and the other after withdrawal from life support at 1 day of age because of previously undiagnosed Fryn's syndrome), and the third died at 30 days of age from pulmonary hypertension. In the tracheal-occlusion group, all infants survived to repair of their congenital diaphragmatic hernia. Two infants died shortly after repair (one from respiratory insufficiency at 9 days, and the other from sepsis at 14 days); the third died at 71 days from pulmonary hypertension. One baby in each group died at more than 90 days of age, both from chronic pulmonary hypertension.

There was a nonsignificant inverse relation between gestational age at delivery and mortality. The gestational age at delivery was 34.9±3.4 weeks among survivors and 32.0±3.4 weeks among non-survivors (P=0.09). Analysis of pooled data from the two treatment groups revealed a direct association between the stratum of lung-to-head ratio and 90-day survival (Table 3).

To establish a more precise cutoff value for the lung-to-head ratio in order to predict survival, we stratified all the infants into two groups according to whether the lung-to-head ratio was low or high. We used receiver-operating-characteristic curves with cutoff values for the lung-to-head ratio of 0.85, 0.90, 0.95, and 1.0; a cutoff value of 0.90 resulted in the greatest area under the curve (0.78).

We used survival analysis with a censoring date of November 1, 2002 (3.5 years after initiation of the study), to identify the factors potentially affecting survival in this cohort. The treatment group was not a significant predictor of survival; the hazard ratio for death associated with tracheal occlusion, as compared with standard care, was 1.20 (95 percent confidence interval, 0.29 to 4.67). However, the lung-to-head ratio was a strong predictor of survival. The hazard ratio for death associated with a lung-to-head ratio greater than 0.90, as compared with a ratio less than or equal to 0.90, was 0.13 (95 percent confidence interval, 0.03 to 0.64).

RESPIRATORY, GASTROINTESTINAL, AND NEUROLOGIC OUTCOMES

The rates of respiratory and gastrointestinal complications among survivors at discharge (at a mean of 60.9±23.5 days) are shown in Table 4. There were

no significant differences between survivors in the tracheal-occlusion group and those in the standard-care group, despite the differences in gestational age at delivery. All infants required intensive respiratory support; one infant in the standard-care group received five days of extracorporeal membrane oxygenation before the repair was performed. There was no significant difference in age at the time of repair of congenital diaphragmatic hernia, the need for a prosthetic patch at repair of congenital diaphragmatic hernia, age at extubation, age at discharge, or the proportions of infants in the two treatment groups requiring supplemental oxygen. There was substantial gastrointestinal morbidity in both groups, with little difference between the groups.

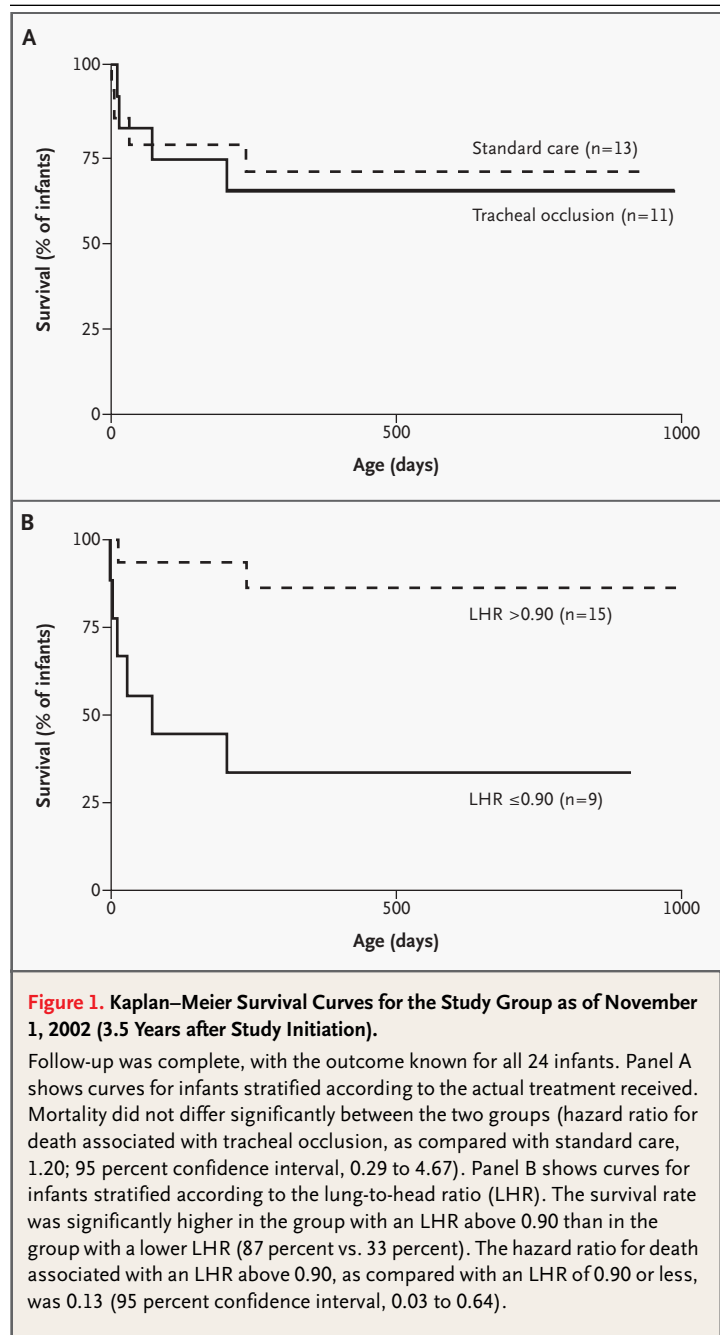
Seven infants (five receiving standard care and two undergoing tracheal occlusion) underwent computed tomographic imaging of the brain before discharge from the hospital; no abnormalities were seen. Ten infants underwent magnetic resonance imaging of the brain before discharge (four in the standard-care group and six in the tracheal-occlusion group); five infants had evidence of mild-to-moderate white-matter injury (three in the standard-care group and two in the tracheal-occlusion group). There were no detectable neurologic deficits on examination among survivors in either group at discharge.

DISCUSSION

In this randomized, controlled study, a strategy to enhance lung growth before birth by occluding the fetal trachea proved no better than planned delivery and high-level neonatal care at a tertiary care center in improving the outcome for fetuses with severe congenital diaphragmatic hernia. The rate of survival among infants randomly assigned to treatment with fetal endoscopic tracheal occlusion (73 percent) met our expectations (predicted value, 77 percent) and was higher than the rate among historic controls (37 percent), but it proved no better than that among concurrent randomized controls.

The unexpectedly high survival rate in the group that received standard care (planned delivery and intensive postnatal care at a tertiary care center) led the data safety and monitoring board to conclude that even with further enrollment, the 90-day survival rates in the two groups would prove to be indistinguishable.

The higher-than-expected survival in the stan-



dard-care group may be due to the “trial effect.” The study design required that infants in both treatment groups be delivered, resuscitated, and intensively treated in a unit experienced in caring for critically ill newborns with pulmonary hyperplasia. Because “standard care” in this study was really optimal care (available at tertiary centers), conclusions about the general applicability of the trial results must be guarded.

Table 4. Respiratory and Gastrointestinal Outcomes According to the Treatment Group.*

Outcome	Standard Care	Tracheal Occlusion	P Value
Age at CDH repair — days	6.7±2.2	5.7±2.3	0.27
Prosthetic patch CDH repair — no./total no. (%)	10/11 (91)	11/11 (100)	1.00
Age at successful extubation — days	35.3±20.5	38.8±15.5	0.33
Age at hospital discharge — days	62.1±28.7	59.6±17.9	0.85
Supplemental oxygen at discharge — no./total no. (%)	4/9 (44)	4/8 (50)	1.00
Age at full enteral feeding — days	27.2±10.5	31.9±11.9	0.33
Fundoplication — no./total no. (%)	8/11 (73)	7/11 (64)	1.00
Gastrostomy tube — no./total no. (%)	3/10 (30)	1/9 (11)	0.58
Tube feeding at discharge — no./total no. (%)	5/9 (55)	4/8 (50)	1.00
Antireflux medications at discharge — no./total no. (%)	8/9 (89)	7/8 (88)	1.00
Weight gain at discharge — g	680±490	570±540	0.36

* Denominators vary because some infants did not survive to discharge. Plus-minus values are means ±SD. CDH denotes congenital diaphragmatic hernia.

Attempts to improve the outcome of severe congenital diaphragmatic hernia with treatments provided either before or after birth have proved to be double-edged swords. Intensive care after birth has improved survival but has increased long-term sequelae in survivors, and it is expensive.^{8,14-18} Intervention before birth may increase lung size, but prematurity caused by the intervention itself can be detrimental. In our small study, babies with severe congenital diaphragmatic hernia who underwent tracheal occlusion before birth were born at an average of 31 weeks of gestational age, as a consequence of the intervention. The finding that their rates of survival and respiratory outcomes (including the duration of oxygen supplementation) were similar to those among infants who did not undergo tracheal occlusion, who were born at an average of 37 weeks, suggests that any potential pulmonary benefits of tracheal occlusion were counterbalanced by adverse effects of earlier delivery on pulmonary function.

The results of our study underscore the importance of randomized trials in evaluating promising new therapies. This is the second NIH-sponsored trial of a new prenatal intervention for severe fetal congenital diaphragmatic hernia. The first trial showed that complete surgical repair of the anatom-

ical defect (which required hysterotomy), although feasible, was no better than postnatal repair in improving survival and was ineffective when the liver as well as the bowel was herniated.²⁶ That trial led to the abandonment of open complete repair at our institution and subsequently at centers around the world. Information derived from that trial led to the development of measures of the severity of pulmonary hypoplasia, including liver herniation and lung-to-head ratio. The failure of complete repair in that trial led to the development of an alternative physiological strategy to enlarge the hypoplastic fetal lung through temporary tracheal occlusion³¹ and to the development of less invasive fetal endoscopic techniques that did not require hysterotomy to achieve temporary, reversible tracheal occlusion.

Our ability to accurately diagnose and assess the severity of congenital diaphragmatic hernia before birth has improved dramatically. Fetuses with congenital diaphragmatic hernia and associated anomalies do poorly, whereas fetuses with isolated congenital diaphragmatic hernia, no liver herniation, and a lung-to-head ratio above 1.4 have an excellent prognosis (100 percent survival in our experience). In this study, which involved delivery at a tertiary care center, fetuses with a lung-to-head ratio between 0.9 and 1.4 had more than an 80 percent chance of survival. The small number of fetuses in both treatment groups with lung-to-head ratios of 0.9 or less had a poor prognosis.

It is possible that approaches to tracheal occlusion other than that used here might be beneficial. Although the duration of occlusion in this study (36.2±14.7 days) was similar to that used in animal models,³⁵⁻³⁹ the optimal timing and duration of occlusion in humans are not known. Short-term occlusion later in gestation and earlier occlusion (with possible reversal in utero) have been studied in animal models²⁵⁻²⁷ and applied in humans by ourselves and others. On the basis of the results of this trial, the Eurofoetus group is developing a randomized trial of fetoscopic endoluminal tracheal occlusion for fetuses with liver herniation and a lung-to-head ratio of less than 0.9 (Deprest J; personal communication). It is also possible that the risk of premature rupture of the membranes, leading to preterm labor and delivery, might be reduced by using smaller (2-mm) fetoscopes percutaneously and new techniques to seal the membranes, although these approaches require study.

The current findings demonstrate that fetal tra-

cheal occlusion at 23 to 27 weeks of gestation to treat congenital diaphragmatic hernia is feasible with the use of minimally invasive fetoscopic techniques, but the results, in terms of fetal mortality and morbidity rates, are no better than those with postnatal care at a tertiary center. Fetuses with lung-to-head ratios of less than 0.9 have a low rate of survival and remain the focus for the development of new treatment strategies, either before or after birth.

Supported by a grant (R01 HL62433) from the National Institute of Child Health and Human Development, National Institutes of Health (to Dr. Albanese), by the Nicholson Fund, and by Glaser Pediatric Research Network.

We are indebted to the nurses, physicians, and support staff of the University of California, San Francisco, who provided superb care to the families in our study; to Dr. Christopher Dowd of Neuro-radiology for balloon technology; to Dr. David Glidden for statistical support; to Stephanie Berman, M.S.W., for psychosocial evaluation; to Robin Bisgaard, R.N., for trial coordination and management; and to the staff of Ronald McDonald House of San Francisco.

APPENDIX

Data Safety Monitoring Board members included B.L. Short, M.D., R. O'Brien, Ph.D., H. Nielsen, M.D., L. Singer, M.D., and J. Frader, M.D.

REFERENCES

- Harrison MR, Adzick NS, Estes JM, Howell LJ. A prospective study of the outcome for fetuses with diaphragmatic hernia. *JAMA* 1994;271:382-4.
- Metkus AP, Filly RA, Stringer MD, Harrison MR, Adzick NS. Sonographic predictors of survival in fetal diaphragmatic hernia. *J Pediatr Surg* 1996;31:148-52.
- Keller RL, Glidden DV, Paek BW, et al. The lung-to-head ratio and fetoscopic temporary tracheal occlusion: prediction of survival in severe left congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol* 2003;21:244-9.
- Albanese CT, Lopoo J, Goldstein RB, et al. Fetal liver position and perinatal outcome for congenital diaphragmatic hernia. *Prenat Diagn* 1998;18:1138-42.
- Stege G, Fenton A, Jaffray B. Nihilism in the 1990s: the true mortality of congenital diaphragmatic hernia. *Pediatrics* 2003;112:532-5.
- The Congenital Diaphragmatic Hernia Study Group. Does extracorporeal membrane oxygenation improve survival in neonates with congenital diaphragmatic hernia? *J Pediatr Surg* 1999;34:720-4.
- Cacciari A, Ruggeri G, Mordenti M, et al. High-frequency oscillatory ventilation versus conventional mechanical ventilation in congenital diaphragmatic hernia. *Eur J Pediatr Surg* 2001;11:3-7.
- Desfrere L, Jarreau PH, Dommergues M, et al. Impact of delayed repair and elective high-frequency oscillatory ventilation on survival of antenatally diagnosed congenital diaphragmatic hernia: first application of these strategies in the more "severe" subgroup of antenatally diagnosed newborns. *Intensive Care Med* 2000;26:934-41.
- Muratore CS, Kharasch V, Lund DP, et al. Pulmonary morbidity in 100 survivors of congenital diaphragmatic hernia monitored in a multidisciplinary clinic. *J Pediatr Surg* 2001;36:133-40.
- Muratore CS, Utter S, Jaksic T, Lund DP, Wilson JM. Nutritional morbidity in survivors of congenital diaphragmatic hernia. *J Pediatr Surg* 2001;36:1171-6.
- Boloker J, Bateman DA, Wung JT, Stolar CJ. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. *J Pediatr Surg* 2002;37:357-66.
- Harrison MR, Jester JA, Ross NA. Correction of congenital diaphragmatic hernia in utero. I. The model: intrathoracic balloon produces fatal pulmonary hypoplasia. *Surgery* 1980;88:174-82.
- Harrison MR, Bressack MA, Churg AM, de Lorimier AA. Correction of congenital diaphragmatic hernia in utero. II. Simulated correction permits fetal lung growth with survival at birth. *Surgery* 1980;88:260-8.
- Harrison MR, Ross NA, de Lorimier AA. Correction of congenital diaphragmatic hernia in utero. III. Development of a successful surgical technique using abdominoplasty to avoid compromise of umbilical blood flow. *J Pediatr Surg* 1981;16:934-42.
- Adzick NS, Outwater KM, Harrison MR, et al. Correction of congenital diaphragmatic hernia in utero. IV. An early gestational fetal lamb model for pulmonary vascular morphometric analysis. *J Pediatr Surg* 1985;20:673-80.
- Harrison MR, Adzick NS, Longaker MT, et al. Successful repair in utero of a fetal diaphragmatic hernia after removal of herniated viscera from the left thorax. *N Engl J Med* 1990;322:1582-4.
- Harrison MR, Langer JC, Adzick NS, et al. Correction of congenital diaphragmatic hernia in utero. V. Initial clinical experience. *J Pediatr Surg* 1990;25:47-55.
- Harrison MR, Adzick NS, Flake AW, et al. Correction of congenital diaphragmatic hernia in utero. VI. Hard-earned lessons. *J Pediatr Surg* 1993;28:1411-7.
- Harrison MR, Adzick NS, Bullard KM, et al. Correction of congenital diaphragmatic hernia in utero. VII. A prospective trial. *J Pediatr Surg* 1997;32:1637-42.
- Alcorn D, Adamson TM, Lambert TF, Maloney JE, Ritchie BC, Robinson PM. Morphological effects of chronic tracheal ligation and drainage in the fetal lamb lung. *J Anat* 1977;123:649-60.
- Nardo L, Hooper SB, Harding R. Lung hypoplasia can be reversed by short-term obstruction of the trachea in fetal sheep. *Pediatr Res* 1995;38:690-6.
- Wilson JM, DiFiore JW, Peters CA. Experimental fetal tracheal ligation prevents the pulmonary hypoplasia associated with fetal nephrectomy: possible application for congenital diaphragmatic hernia. *J Pediatr Surg* 1993;28:1433-9.
- DiFiore JW, Fauza DO, Slavin R, Peters CA, Fackler JC, Wilson JM. Experimental fetal tracheal ligation reverses the structural and physiological effects of pulmonary hypoplasia in congenital diaphragmatic hernia. *J Pediatr Surg* 1994;29:248-56.
- Hedrick MH, Estes JM, Sullivan KM, et al. Plug the lung until it grows (PLUG): a new method to treat congenital diaphragmatic hernia in utero. *J Pediatr Surg* 1994;29:612-7.
- Wild YK, Piasecki GJ, De Paep ME, Luks FI. Short-term tracheal occlusion in fetal lambs with diaphragmatic hernia improves lung function, even in the absence of lung growth. *J Pediatr Surg* 2000;35:775-9.
- Luks FI, Wild YK, Piasecki GJ, De Paep ME. Short-term tracheal occlusion corrects pulmonary vascular anomalies in the fetal lamb with diaphragmatic hernia. *Surgery* 2000;128:266-72.
- Flageole H, Evrard VA, Piedboeuf B, Laberge JM, Lerut TE, Deprest JA. The plug-unplug sequence: an important step to achieve type II pneumocyte maturation in the fetal lamb model. *J Pediatr Surg* 1998;33:299-303.
- Albanese CT, Jennings RW, Filly RA, et al. Endoscopic fetal tracheal occlusion: evolution of techniques. *Pediatr Endosurg Innovative Tech* 1998;2:47-53.
- VanderWall KJ, Bruch SW, Meuli M, et al. Fetal endoscopic ("Fetendo") tracheal clip. *J Pediatr Surg* 1996;31:1101-3.
- VanderWall KJ, Skarsgard ED, Filly RA, Eckert J, Harrison MR. Fetendo-clip: a fetal endoscopic tracheal clip procedure in a human fetus. *J Pediatr Surg* 1997;32:970-2.
- Harrison MR, Mychaliska GB, Albanese CT, et al. Correction of congenital diaphragmatic hernia in utero. IX. Fetuses with poor prognosis (liver herniation and low lung-to-head ratio) can be saved by fetoscopic tem-

- porary tracheal occlusion. *J Pediatr Surg* 1998;33:1017-22.
32. Flake AW, Crombleholme TM, Johnson MP, Howell LJ, Adzick NS. Treatment of severe congenital diaphragmatic hernia by fetal tracheal occlusion: clinical experience with fifteen cases. *Am J Obstet Gynecol* 2000;183:1059-66.
33. Harrison MR, Sydorak RM, Farrell JA, Kitterman JA, Filly RA, Albanese CT. Fetoscopic temporary tracheal occlusion for congenital diaphragmatic hernia: prelude to a randomized, controlled trial. *J Pediatr Surg* 2003;38:1012-20.
34. Harrison MR, Albanese CT, Hawgood SB, et al. Fetoscopic temporary tracheal occlusion by means of detachable balloon for congenital diaphragmatic hernia. *Am J Obstet Gynecol* 2001;185:730-3.
35. Boland RE, Nardo L, Hooper SB. Cortisol pretreatment enhances the lung growth response to tracheal obstruction in fetal sheep. *Am J Physiol* 1997;273:L1126-L1131.
36. Chiba T, Albanese CT, Farmer DL, et al. Balloon tracheal occlusion for congenital diaphragmatic hernia: experimental studies. *J Pediatr Surg* 2000;35:1566-70.
37. Walters DV, Olver RE. The role of catecholamines in lung liquid absorption at birth. *Pediatr Res* 1978;12:239-42.
38. Lawson EE, Brown ER, Torday JS, Madansky DL, Taeusch HW Jr. The effect of epinephrine on tracheal fluid flow and surfactant efflux in fetal sheep. *Am Rev Respir Dis* 1978;118:1023-6.
39. Mychaliska GB, Bealer JF, Graf JL, Rosen MA, Adzick NS, Harrison MR. Operating on placental support: the ex utero intrapartum treatment procedure. *J Pediatr Surg* 1997;32:227-30.

Copyright © 2003 Massachusetts Medical Society.

ELECTRONIC ACCESS TO THE JOURNAL'S CUMULATIVE INDEX

At the Journal's site on the World Wide Web (www.nejm.org), you can search an index of all articles published since January 1975 (abstracts 1975–1992, full text 1993–present). You can search by author, key word, title, type of article, and date. The results will include the citations for the articles plus links to the abstracts of articles published since 1993. For nonsubscribers, time-limited access to single articles and 24-hour site access can also be ordered for a fee through the Internet (www.nejm.org).