TITLE: RANDOMIZED TRIAL OF FETOSCOPIC ENDOLUMINAL TRACHEAL OCCLUSION (FETO) VERSUS EXPECTANT MANAGEMENT DURING PREGNANCY IN FETUSES WITH LEFTSIDED AND ISOLATED CONGENITAL DIAPHRAGMATIC HERNIA AND MODERATE PULMONARY HYPOPLASIA

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TOTAL TRIAL

RANDOMIZED TRIAL OF FETOSCOPIC ENDOLUMINAL TRACHEAL OCCLUSION (FETO) VERSUS EXPECTANT MANAGEMENT DURING PREGNANCY IN FETUSES WITH LEFT-SIDED AND ISOLATED CONGENITAL DIAPHRAGMATIC HERNIA AND MODERATE PULMONARY HYPOPLASIA

Principal Investigator:
Michael A Belfort, MD, PhD, MBBCH, FACOG, FRCOG, FRCSC
Texas Children's Hospital Pavilion for Women
Baylor College of Medicine
6651 Main Street
Houston, TX 77030

Sub-investigators:

Oluyinka Olutoye, MB, ChB, PhD
Olutoyin A. Olutoye, MB, ChB
Jimmy Espinoza, MD
Christopher Cassady, MD
Timothy Lee, MD
Magdalena Sanz Cortes, MD, PhD
Alireza Abdollah Shamshirsaz, MD
Sundeep Keswani, MD
Wesley Lee, MD

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Baylor H-39398

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1.0 PURPOSE

This trial will test whether temporary fetoscopic tracheal occlusion rather than expectant management during pregnancy, followed by standardized postnatal management, increases survival at discharge and decreases oxygen need at 6 months in case of survival till discharge.

The target group are fetuses with isolated moderate CDH hence predicted rates of survival rate of 60% or lower and predicted rates of bronchopulmonary dysplasia of 33% or higher.

The rationale is that FETO triggers lung growth and maturation to such an extent that the chances of neonatal survival are significantly increased as compared to standard postnatal care in the same severity group. Further, we hypothesize that improved lung development lessens the need for ventilatory assistance, hence decreases pulmonary morbidity and therefore might improve quality of life of survivors.

A precondition for such an assumption is that both FETO and postnatal treatment are undertaken in specialist centers with extensive experience in the management of affected fetuses. We impose adherence to the consensus guidelines drafted after a meeting of several leading European centers (Mannheim, 2006) and updated after the completion of the VICI trial (demonstrating no added value of primary high frequency oscillatory ventilation). [1, 2.]

1.1 Primary Objectives

To determine if FETO added to standardized postnatal management increases survival at discharge and decreases oxygen need at 6 months in survivors, as compared to what is observed after standard postnatal management alone.

1.2 Secondary Objectives

To determine whether FETO improves additional morbidity indicators. The subjects will be followed up for long-term neurodevelopmental and pulmonary functional outcomes, if the necessary funding can be secured.

2.0 BACKGROUND AND RATIONALE

Congenital Diaphragmatic Hernia (CDH) is associated with major chromosomal and other abnormalities in about 30% of cases and in this group the mortality rate is higher than 85%. In the case of isolated CDH there is a high risk of perinatal death and morbidity mainly because of pulmonary hypoplasia and pulmonary hypertension. These complications can be predicted prenatally by the ultrasonographic measurement of the lung area to head circumference ratio (LHR). In the case of fetuses with severe CDH (defined by a ratio of the observed to the expected normal mean for gestation (O/E) LHR of less than about 25% and intrathoracic herniation of the fetal liver) the predicted survival rate with the traditional expectant antenatal management and postnatal ventilatory support for stabilization followed by surgery is less than 30% [3]. In addition, in the survivors there is a high rate of morbidity with evidence of bronchopulmonary dysplasia in more than 70% of cases, which also relates to prenatally measured LHR.[4]

In the last seven years the members of the applying consortium have pioneered, developed and applied in more than 150 cases of severe CDH an intrauterine therapeutic approach, which consists of percutaneous fetoscopic endoluminal tracheal occlusion (FETO) typically performed at 26-29 weeks of gestation, with removal of the balloon at about 34 weeks [5]. This has been shown to be safe for the mother and to improve the estimated survival from less than 30% (most centres obtain <15%) to about 55%. In addition, the improved survival with FETO was associated with apparent reduction in morbidity with the rate of bronchopulmonary dysplasia decreasing from the estimated rate of more than 70% to less than 40% in the same severity group[6]. Also this consortium has shown that results of FETO are predicted by LHR measurement prior to the procedure, so that better results can be expected in fetuses with larger lung size[7]. As of 2009, the FETO consortium has performed over 200 of these procedures, with steady results, i.e. a 50% survival rate after FETO. FETO is also associated with a consistent risk for PPROM (15% within 3 weeks) and an earlier gestational age at delivery (mean: 35.3 weeks) [8]. Also the fetal lung response is more vigorous when occlusion is made earlier, rather than later in pregnancy [9].

In fetuses with moderate CDH (=O/E LHR 25-34.9%, irrespective of the liver position as well as O/E LHR 35-44.9% with intrathoracic herniation of the liver) managed expectantly the estimated rate of postnatal survival is 60% or lower and the rate of broncho-pulmonary dysplasia in survivors is 33% or higher. It is not known whether percutaneous fetoscopic tracheal occlusion in this group would improve survival and reduce morbidity.

2.1 Report of Prior Investigations

Fetuses with CDH presenting with liver herniation and a lung area-to-head circumference ratio (LHR) of less than 1.0 have a high chance for neonatal death due to pulmonary hypoplasia. Fetal tracheal occlusion (TO) prevent egress of lung liquid, and this has been shown to trigger lung growth. Initially animal experiments showed that a minimally invasive technique for Fetoscopic Endoluminal Tracheal Occlusion (FETO) with a detachable balloon was possible and effective in reducing lung hypoplasia from CDH.[2]

In 2001, Deprest et al[10] demonstrated the feasibility of FETO by percutaneous access, using a fetoscope, in fetuses with severe CDH. In a retrospective multicenter review, the same group obtained LHR measurements and noted the position of the liver in 134 babies with isolated left-sided CDH between 26 and 28 weeks gestation.[10, 11] The overall survival of the live born babies was 47% (58/123). The LHR and position of the liver both had a direct correlation with subsequent survival.[12.13] A combination of both variables best predicted neonatal outcome: the presence of the liver in the chest and a LHR < 1.0 predicted a survival of 9%. When the LHR was < 0.6, there were no survivors irrespective of liver position. Deprest's group successfully performed endotracheal placement of the FETO balloon in 20 cases at a median gestational age of 26 weeks. The mean duration of the operation was 22 (range 5-54) minutes. In 11 (55%) of these patients, there was postoperative preterm (i.e.,<37 weeks) rupture of the membranes (PPROM). The membranes ruptured before 32 weeks in 35% of cases, with a decreasing trend as experience increased. Ultrasound scans after FETO demonstrated an increase in the echogenicity of the lungs within 48 hours and improvement in the LHR from a median 0.7 (range 0.4-0.9) before FETO to 1.8 (range 1.1- 2.9) within 2 weeks after surgery. The median gestation at delivery was 33.2 (range 27-38) weeks, and in 14 (70%) this occurred after 32 weeks.[10]

Postpartum surgical repair of the diaphragmatic hernia was achieved in 13 babies, and in all but 1 the defect was extensive and required the insertion of a patch. Survival to discharge was 50%. At the time of publication in 2005 the 10 long-term surviving babies were aged 7 to 26 (median 19) months without known neurologic morbidity. Eight babies died in the neonatal period due to complications of the underlying disease. Two non-survivors died from other causes but with appropriately developed lungs. Improved survival coincided with increasing experience, in turn related to a reduced incidence of postoperative PPROM, later delivery, and a change in the policy on the timing of removal of the balloon from intrapartum to the prenatal period. Survival in eligible contemporary controls was 1/12 (8%). They concluded that the presence of liver herniation and a low lung-to-head ratio (LHR <1.0) is a good predictor of poor prognosis at different tertiary centers around the world, and that severe CDH may be successfully treated with FETO, which is minimally invasive and may improve postnatal survival.[4, 14]

Another group working in Spain has assessed the postnatal outcomes of a group of babies treated with the FETO procedure. They studied twelve babies who were born at 34 weeks after having been treated with FETO in the early third trimester and concluded that CDH patients with a poor prognosis undergoing FETO had postnatal outcomes similar to non- prenatally studied cases and CDH cases that did not have FETO but who had a good prognosis predicted by a LHR > 1.0.3 Harrison, et al (2003) conducted the only randomized controlled trial done in the USA. Although the results failed to show benefit from prenatal therapy, there were a number of problems with this study design and statistical analysis. This study lacked power to document the potential advantage of prenatal therapy in severe cases because the data were stratified and the individual data groups were too small to accurately assess small benefits. In addition, the fetal obstruction surgery included a number of different procedures such as tracheal clipping with open fetal surgery (through a uterine incision) and an exteriorized fetus, balloon procedures done via a maternal laparotomy, and fetoscope placement through an exposed uterus, all of which were all done under general anesthesia.[15]

This is very different to the current European approach,[16] which is minimally invasive and all done through a fetoscope under regional or local anesthesia. The plug-unplug sequence has been refined and the benefits of FETO on pulmonary vascular function are now appreciated to a much greater extent.[17, 18] Maternal risks have been minimized and PPROM rate and need for tocolytics therapy have been lessened. This fact has been well appreciated by the Fetal Surgery community in the USA. The same group that published the USA RCT experience applied for, and was granted, an IDE to perform a research trial on the FETO procedure using the same methodology as practiced by the European groups.[19] We follow these guidelines and use more stringent criteria and procedures as already approved by the FDA for the University of California – San Francisco IDE granted to Dr. Lee and currently used in Europe.[20]

In fetuses with ***moderate*** CDH (=O/E LHR 25-34.9%, *irrespective* of the liver position as well as O/E LHR 35-44.9% *with* intrathoracic herniation of the liver) managed expectantly the estimated rate of postnatal survival is 60% or lower and the rate of broncho-pulmonary dysplasia in survivors is 33% or higher. It is not known whether percutaneous fetoscopic tracheal occlusion in this group would improve survival and reduce morbidity. Although the FETO procedure has shown promise as an intervention for severe and extremely severe CDH, moderate CDH has not been studied adequately in the United States. This study will help extend current trials of FETO to include the population of the United States.

2.2 Current Rationale for Prenatal Treatment of Moderate CDH

The rationale is that FETO triggers lung growth and maturation to such an extent that the chances of neonatal survival are significantly increased as compared to standard postnatal care in the same severity group. Further, we hypothesize that improved lung development lessens the need for ventilatory assistance, hence decreases pulmonary morbidity and therefore might improve quality of life of survivors. A precondition for such an assumption is that both FETO and postnatal treatment are undertaken in specialist centers with extensive experience in the management of affected fetuses. We impose adherence to the consensus guidelines drafted after a meeting of several leading European centers (Mannheim, 2006) which is attached as a separate document, and was updated after the completion of the VICI trial (demonstrating no added value of primary high frequency oscillatory ventilation).

2.3 Justification for the Investigation

The hypothesis is that prenatal intervention will improve morbidity (increase survival rate until discharge) and decrease the number of survivors requiring oxygen at six months of age in patients with isolated, moderate CDH.

3.0 INVESTIGATIONAL DEVICE INFORMATION

The device is a detachable latex balloon (called the "GoldBal"), delivered with a 1mm diameter catheter (called the "BALTACCIPBPE 100" Microcatheter). The current manufacturer is Balt Extrusion located in Montmorency, France. The balloon was originally designed to treat Carotid-Cavernous Fistulas via a less-invasive catheter procedure under fluoroscopic guidance and it was called Goldvalve. The Goldvalve Balloon has been approved for this indication and marketed in Europe for over 15 years. Nfocus Neuromedical acquired the device and submitted it for US FDA clearance via the Class II (510(k)) application. This device did not receive approval for the vascular indication as Nfocus Neuromedical was bought by Acta Vascular Systems, Inc. and they did not want to pursue approval.

3.1 Intended Use of the Device

The deflated Goldbal Balloon, mounted on the catheter tip, is introduced into the trachea of the affected fetus through intrauterine endoscopy and endotracheal intubation of the fetus. Once positioned, the balloon is inflated with saline, delivered through the catheter, and detached from the catheter tip. The inflated balloon is compliant enough to prevent deformation of the fetal trachea, yet provides adequate and complete obstruction. While the present study will utilize this device for an indication not anticipated during the design or previous testing of the GoldBal Balloon, the sizes and soft, compliant nature of the balloon have proven useful for fetal tracheal occlusion in the hands of other investigators.

4.0 STUDY DESIGN

This is a multi-center, non-blinded randomized controlled trial in fetuses with isolated moderate CDH, i.e. moderate lung hypoplasia (as determined by prenatal assessment of lung development). It essentially compares fetal therapy added to conventional postnatal care, versus expectant prenatal management during pregnancy followed by conventional postnatal care.

There are currently 11 participating centers, of which seven see moderate only cases, one sees severe only cases, and three see both severe and moderate cases. Dr. H. Sago in Tokyo, Japan is preparing to join the study. As sites are added to the study, they are updated in the main study's website, http://www.totaltrial.eu and at www.ClinicalTrials.gov (NCT00763737).

Lead Investigator	Institution(s)	Case Type	Country
Dr. Jan Deprest	University Hospitals Leuven	Severe and Moderate	Belgium
Dr. Michael Belfort	Baylor College of Medicine Texas Children's Hospital	Moderate	United States of America
Dr. Eduard Gratacos	Hospital Clínic, University of Barcelona	Moderate	Spain
Dr. Alexandra Benachi	Hôpital Antoine Béclère	Severe and Moderate	France
Dr. Yves Ville	Hôpital Necker – Enfants Malades	Severe and Moderate	France
Dr. Kypros Nicolaides	King's College Hospital	Moderate	United Kingdom
Dr. Christoph Berg	University Hospital of Bonn	Moderate	Germany
Dr. Glenn Gardener	Mater Mother's Hospital	Moderate	Australia
Dr. Nicola Persico	Ospedale Maggiore Policlinico	Moderate	Italy
Dr. Pietro Bagolan	Ospedale Pediatrico Bambino Gesù	Moderate	Italy
Dr. Greg Ryan	Mount Sinai Hospital	Severe	Canada

Subjects will be randomized into two groups ("FETO" and "expectant") after assessment in a FETO center. In the event that the potential participant is unable to travel to our Fetal Center, we will accept appropriate images within three weeks of the date of randomization. As long as the quality of the images are appropriate enough to make the necessary measurements, they can be accepted by the Fetal Center staff for decision-making purposes. If a screening ultrasound or MRI (standard of care diagnostic exams) takes place outside of TCH, it will also be read by TCH physicians responsible for the trial. If possible, the participants should be assessed at TCH. In the FETO group the balloon will be introduced between 30 weeks plus 0 day and 31 weeks plus 6 days and whenever clinically feasible, removed at 34 weeks plus 0 d to 34 weeks plus 6 days. Following completion of an inclusion/exclusion criteria checklist on the internet (www.eurocdh.org) and obtaining informed consent, the subject will be randomized over the internet with equal likelihood to either arm of the study. Randomization lists will be computer generated consisting of an initial block of 80 patients which were used as an internal pilot, since there were no data on the outcomes of percutaneous FETO in moderate hypoplasia. This group was analyzed for efficacy (as foreseen in initial protocol) and an adjusted sample size was calculated. It showed that in total 98 patients were required to demonstrate an increase in survival from 40 to 60%. Using a sequential design with an overall one-sided alpha of 2.5% and power of 80%, five interim analyses for efficacy are planned after 40, 60, 70, 80, and 90% of the sample size at the final analysis (59, 69, 79, 89 and 98 patients in each arm respectively).

GROUPS:

I. Standardized postnatal care (expectant group): mothers will be expectantly managed during

pregnancies and babies will receive standardized postnatal care at a tertiary center used to manage babies with CDH. The recommendation is that they adhere to consensus guidelines published on the study website at www.eurocdh.org.

II. Prenatal intervention (FETO group): patients will undergo fetoscopic tracheal occlusion and ideally prenatal reversal of the occlusion followed by standardized postnatal care as in group I. In this study FETO is to be done between 30 weeks plus 0 day and 31 weeks plus 6 days and removal of the balloon at 34 weeks plus 0 day to 34 weeks plus 6 days.

This study trial is a pragmatical or efficacy trial: ideally mothers will deliver after removal of the balloon at those tertiary centers, typically offering postnatal care for the patient involved. In group II (FETO-group), mothers will, in between placement and removal of the balloon, thus carrying a fetus with obstructed airways, ideally remain under the care of our local fetal treatment center (further referred to as FETO center). As many as possible precautions are taken to avoid problems with balloon removal in case of earlier than expected delivery.

- Balloons are to be electively removed prior to 35 weeks. FETO centers will provide 24/24 hours and 7/7 days services for management of fetuses with obstructed airways, either in utero or during labor and delivery.

- Patients in the study and randomized to FETO, are required to stay within 30 minutes of the FETO center while the fetus' airway is blocked by the balloon. After reversal of the occlusion, the patient will be referred to the tertiary care center where delivery and postnatal care will be undertaken.

- Preterm Labor:

In the event of progressive and unremitting preterm labor in a patient who has a FETO balloon in situ, the balloon will be removed emergently using the same procedure described above, time permitting. If this is not possible the baby will be delivered by cesarean section using the EXIT (ex utero intrapartum therapy) procedure. In this procedure, only the fetal head will be delivered initially through a cesarean section incision while the mother is under general anesthesia. Once the head is delivered, a neonatologist or pediatric surgeon will perform bronchoscopy and the balloon occluding the trachea will be deflated and removed. The airway will be suctioned, an endotracheal tube inserted, and exogenous surfactant (Exosurf Neonatal, Glaxo Wellcome) will be administered at a dose of 3 ml/kg body weight, and assisted ventilation will be started before the umbilical cord is divided. Once the baby is ventilated the body of the child will be delivered and the umbilical cord will be cut. This procedure allows the baby to be oxygenated while the balloon is removed and the endotracheal tube is placed. In the event that the baby delivers precipitously without the EXIT procedure being possible, a pediatric surgeon will be in the operating room to puncture the balloon and remove it as soon as possible after the delivery. Patients will be counseled as to the importance of returning for care if there is any possibility of progressive preterm labor and delivery so the necessary preparations can be made.

III. Postnatal:

Neonates will be assessed at discharge, 6 months, 1 year, and 2 years after delivery with regard to their need for supplemental oxygen.

Postnatal Death: Permission should be requested for full postmortem examination in all cases of fetal or postnatal death. If this is not granted then permission for an MRI or CT examination and histological examination of open lung biopsies should be requested. If none of the above is possible the cause of death will be determined on the basis of clinical findings.

5.0 PATIENT ELIGIBILITY

5.1 Patient Recruitment and Enrollment

This study involves the enrollment of pregnant women, and so precautions will be taken to protect this vulnerable population. Potential subjects will be approached by the PI or coinvestigator and informed about the study. Interested individuals will be counseled extensively. Interpreters will be used as necessary.

Patients with a fetus that has been diagnosed with a CDH that meets the eligibility criteria for moderate left sided and isolated CDH will be offered the FETO procedure at Texas Children's Hospital (TCH). The PI and co-investigator fetal surgeon will be the primary contacts at TCH and the team who will make the initial assessment of whether the patient is a candidate or not.
We will enroll eligible subjects in the United States for this study diagnosed prenatally with moderate left sided and isolated CDH. Subjects will be randomized to either receive the FETO procedure or standard of care. Outcome data will be compared between the two groups.

Patients may be referred to our center from their primary physician anywhere in the country. We will be contacted by the referring physicians to determine whether the patient is a suitable candidate. If this is determined to be the case (after discussion with the referring physician) the patient will be contacted and the proposed surgery and our study will be discussed.

Once the patient has had sufficient opportunity to read and understand the consent form, the PI and/or the study staff will answer any and all questions to the satisfaction of the potential subject.

The study staff will obtain informed consent of both, the pregnant mother and the father of the baby (unless the father is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest), and after all of the parent's questions have been answered to the their satisfaction.

Written consent will be signed by each participant as well as an appropriate witness if necessary. At all stages, it will be emphasized that enrollment is strictly voluntary and that a refusal to participate will in no way influence the willingness or ability of her providers to care for her. Cognitively impaired patients will not be enrolled.

This study begins with enrollment of a pregnant mother and includes later follow up on the newborn to two years of life. Thus, this study involves the enrollment of children. Parents will be counseled about the follow-up checks that will be done on their child to assess neuromotor and mental development and will consent to the enrollment of their children.

After signing the informed consent document, the participant will complete release of information forms (one for her and one for the child) which will allow study staff to gather data from their medical records. The participant (mother) may be contacted by phone, email, and/or mail by the

study staff to sign a medical record release every year if necessary to allow this to occur. She may also be contacted by study staff regarding any changes to the study while she is a participant.

In the event that the potential participant is unable to travel to our Fetal Center, she and the father of the baby will be counseled over the phone by our multidisciplinary team, which may also include the family meeting, prior to signing the informed consent. This conversation will include the purpose of the trial ,the aspects of the trial that are experimental, the inclusion/exclusion criteria, the random assignment to each treatment, the subjects responsibilities, the alternative procedures or courses of treatment that may be available, the anticipated expenses. It will also provide the subject the opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial will be answered before informed consent is obtained. The consent form will be mailed or securely emailed to them.

The subject will undergo a detailed ultrasound assessment performed by a maternal fetal medicine specialist, who is trained to perform the assessment. If, after ultrasound and physical examination, the subject still meets all of the criteria, she will be randomized to either receive standard care or undergo the FETO intervention. Subjects who meet the eligibility criteria will be extensively counseled for each arm.

Neonatal treatments for CDH (such as hernia repair) are not part of the study. Parents will be asked to consent on behalf of their child (for neonatal follow-up) before the child is born.

5.2 Inclusion Criteria

FETUSES:

1. Left-sided diaphragmatic hernia

2. Fetuses presenting at the latest at 31 weeks plus 5 days (intervention at the latest on 31 weeks plus 6 days).

3. Severity: Predicted moderate pulmonary hypoplasia[10]. The degree of hypoplasia will be determined by the ultrasonographic measurement of the observed to expected lung area to head circumference ratio (O/E LHR) in a FETO center at entry to the study, at the latest the day before occlusion, but ideally between 26 and 31 weeks for practical reasons. (The O/E LHR is a measure that is gestational age independent.)

The following criteria for moderate pulmonary hypoplasia will be used: • O/E LHR 25-34.9% (included) irrespective of the liver position, or • O/E LHR 35-44.9% (included) with intrathoracic herniation of the liver.

In this group there is a predicted risk for postnatal death of 40% or higher and the risk of broncho-pulmonary dysplasia in case of survival is 33% or higher.

4. Chromosomally normal fetus.

5. Fetus with no major anomalies that would impact the clinical course or outcomes.

MOTHER SUBJECTS:

1. Patients aged 18 years or more, who are able to consent.

2. Singleton pregnancy.

3. Gestation at randomization prior to 31 weeks plus 5 days or so that occlusion is done at the latest on 31 weeks plus 6 days.

4. Estimated to have moderate pulmonary hypoplasia, defined prenatally as:

- O/E LHR 25-34.9% (included; irrespective of the position of the liver) • O/E LHR 35-44.9% (included) with intrathoracic liver herniation as determined by ultrasound or MRI.

- The O/E LHR will be determined by the FETO centers as follows:

- Measurement of the contralateral lung area preferentially by the tracing method at the 4-chamber view of the heart; if by other method adjusted normative ranges must be used.

- Measurement of the head circumference at the standard biparietal view of the head.

- The observed lung area: calculation of the LHR as the ratio of the measurements of the lung area to head circumference.

- The expected lung area is the lung area of a normal gestational age match, as determined by the head circumference of the index case in a normogram established for the same measurement method (tracing method in this case). A calculator for this will be available on the website of the study.

- Calculation of the observed over expected lung area.

5. Acceptance of randomization and the consequences for the further management during pregnancy and thereafter, this includes the required observation following FETO surgery, which lasts approximately 4 weeks after balloon is in place, until balloon is removed.

6. The patients must undertake the responsibility for either remaining close to, or at the TCH FETO center, or being able to travel swiftly and within acceptable time interval (within 30 minutes) to the TCH FETO center until the balloon is removed. Intended postnatal treatment center must subscribe to suggested guidelines for “standardized postnatal treatment.”

7. Provide written consent to participate.

5.3 Exclusion Criteria

1. Maternal contraindication to fetoscopic surgery or severe medical condition in pregnancy that make fetal intervention risky.

2. Technical limitations precluding fetoscopic surgery, such as severe maternal obesity, uterine fibroids or potentially others, not anticipated at the time of writing this protocol.

3. Preterm labor, cervix length of ≤ 15 mm at randomization or uterine anomaly strongly predisposing to preterm labor, placenta previa.

4. Patient age less than 18 years.

5. Psychosocial ineligibility, precluding consent.

6. Diaphragmatic hernia: right-sided or bilateral, major anomalies, isolated left-sided outside the O/E LHR limits for the inclusion criteria.

7. Patient refusing randomization, to comply with required 4-week observation after balloon placement, or to comply with return to FETO center during the time period the airways are occluded or for elective removal of the balloon.

8. Patient allergic to latex.

6.0 TREATMENT PLAN

6.1 Study Schedule – Prior to Delivery for Group I (standard of care) and Group II (FETO procedure)

Study Procedure	Up until 31w +6d (before any intervention) **GROUP I & II**	Plug Procedure 30w- 31w+6d **GROUP II**	Postsurgical **GROUP II**	Monitoring between PLUG and UNPLUG **GROUP II**	UNPLUG 34w- 34w+6d **GROUP II**	Monitoring after UNPLUG **GROUP II**	Delivery[5,6] **GROUP I & II**	Postnatal **GROUP I & II**
Eligibility	X							
CDH counseling	X							
Maternal History	X							
Maternal Physical exam, vital signs	X	X	X	X	X		X	X
Measurement of cervix length	X							
Family Meeting	X							
Informed Consent	X							
Randomization	X							
Patient Education	X							
Patient randomized to FETO procedure Clearance by Anesthesia and Obstetrical staff	X				X			
Surgery		X			X			
Hospitalization		X	X		X		X	
Ultrasound	X_2	X_2	X_2	X_2	X_2	X_2		
Comprehensive Ultrasound	X_4			X_4		X_4		
MRI	X							
Fetal surveillance by biophysical profiles and Doppler studies			$X_{1,3}$	$X_{1,3}$		$X_{1,3}$		

[1]*Fetal surveillance will be performed weekly post balloon placement.*

[2]*Serial measurements of sonographic lung volume and LHR will begin within 24-48 hours following surgery and continue weekly by targeted ultrasound evaluation.*

[3]*Amniotic fluid level and membrane status will also be monitored at weekly intervals.*

[4]*Comprehensive ultrasonography for fetal growth will be performed every 1-2 weeks.*

[5]*After removal of the balloon, patients will have the choice of delivering at Texas Children's Hospital Pavilion for Women with the CDH managed and repaired at TCH, or returning to their obstetrician for delivery with subsequent repair of the CDH by the pediatric surgeons at their referring facility.*

[6]*Delivery will be ideally scheduled at term*

6.2 Study Schedule – Neonate

Age of Neonate	6 weeks	Age at Discharged	6 months	1 year	2 years
Assessing with regards to need for supplemental O^2		X	X	X	X
Developmental Testing [2]		X		X	X
Pulmonary function and volume testing[1]	X	X		X	

[1]Pulmonary function and volume testing before and after CDH repair, at discharge and one year of age if the necessary funding can be secured

[2]Developmental testing will start at 3 months old

In case of fetal or neonatal death:

Permission should be requested for full postmortem examination in all cases of fetal or postnatal death. If this is not granted then permission for an MRI or CT examination and histological examination of open lung biopsies should be requested. If none of the above is possible the cause of death will be determined on the basis of clinical findings.

6.3 Procedure

EXPECTANT MANAGEMENT GROUP PROCEDURES:

Participants in this arm will not undergo any operation during their pregnancy. The management of patients will be at the discretion of the treating physicians and may be decided by clinical needs, which may include (but not limited to) ultrasound scans and/or magnetic resonance imaging. Study staff will also monitor signs of increased fluid around the baby that might need to be drained in order to avoid premature delivery

FETO GROUP PROCEDURES:

Participants in this arm will undergo the FETO procedure as follows:

6.4.1 Preoperative

Prior to surgery the mother will be given an antibiotic (such as Cefazolin 2 g IV x1, Clindamycin 900 mg IV, Azithromycin 500 mg IV, and/or Metronidazole 500 mg IV) and if indicated will be treated with indomethacin (50mg orally), nifedipine (10 mg orally), Magnesium Sulfate, Terbutaline, and pain killers (such as Acetaminophen (500 mg - 1 g orally) and Acetaminophen/Hydrocodone).

6.4.2 Anesthesia

The procedure will be performed under spinal anesthesia (2% Chloroprocaine 11mg/kg/dose for a maximum of 800mg, Ropivacaine 2.5mg/kg/dose for a maximum of 300 mg) or local anesthesia (0.25% Marcaine) with intravenous sedation (Fentanyl or Remifentanil). Regional anesthesia choices will be made by the attending anesthesiologist according to standard of care.

The fetus will receive an intramuscular injection of narcotic, anticholinergic (Fentanyl 15 mcg/kg and Atropine 20 mcg/kg) and a muscle relaxant (Vecuronium 0.1mg/kg) into her buttocks or any extremity using a 22G needle that passes through the maternal abdominal and uterine walls in order to provide muscle relaxation, sedation, and analgesia to the fetus.

Depending on the amniotic fluid volume in the uterus an amnioinfusion using a maximum of 1L normal saline given by manual injection may or may not be employed to optimize access to the fetal nose and mouth.

6.4.3 Balloon Placement

Using standard technique, a 9-12 Fr Teflon cannula will be inserted into the amniotic cavity using either a pyramidal trocar or the needle and guidewire Seldinger technique and a Storz endoscope or Storz fetoscope will be passed through the cannula into the amniotic fluid.

The scope will be guided into the fetal larynx either through a nostril and then via the nasal passage or through the fetal mouth, and then through the fetal vocal cords with the aid of both direct vision through the scope and cross-sectional ultra-sonographic visualization.

A detachable latex balloon will be placed in the fetal trachea midway between the carina and the vocal cords.

In the event of difficult access to the fetal larynx we will make reasonable attempts to visualize the correct area for deployment of the balloon as long as this, in the judgment of the surgeon, is safe for both mother and baby. If there is difficulty in accessing the fetal mouth or nose, repositioning of the baby or fetoscope/endoscope may be required.

If there is difficulty in seeing the vocal cords, despite having adequate access to the larynx, reasonable attempts to reposition the scope within the larynx will be made without exposing mother or baby to excessive risk. A maximum of 4 attempts will be made based on a risk benefit analysis and medical judgement. Ultimately, this is a difficult situation to quantify and the feasibility of the procedure will fall into the realm of the judgment and experience of the surgeon. For this multicenter study, however, failure to access the fetal trachea to achieve tracheal occlusion has so far been less than 4%; this was solved by a second attempt. If the trachea cannot be accessed due to fetal position, the procedure may need to be rescheduled.

The balloon can dislodge spontaneously either by deflation or increasing tracheal diameter. Reinsertion of a balloon will be considered if this complication occurs within 10 days of the initial insertion. This has so far been very uncommon (4%).

The balloon will be inflated with isosmotic contrast material so that it fills the fetal trachea (approximate diameter, 2.2 mm) for a length of at least 2 cm. Studies have shown that this maneuver effectively occludes the fetal trachea. In the case of an anterior placenta, every effort will be made to avoid placing the sheath and fetoscope/endoscope through the placenta. The region of insertion will be visualized with ultrasound prior to insertion to ensure that the placental integrity remains intact. Using a combination of amnioinfusion, fetal manipulation (external version), and careful placement of the fetoscope/endoscope, avoidance of an anterior placenta can be achieved in almost all cases.

In the event that it is impossible to place the fetoscope/endoscope without intentionally perforating the placenta, the procedure will be abandoned and attempted at a later time when conditions have changed such that the placenta will not be damaged (fetal position change). This procedure will not be done transplacentally.

6.4.4 Postoperative Care

Tocolysis: Postoperative tocolysis will be given as needed with either nifedipine (10 mg every 4 hours orally- for a maximum of two days), indomethacin (25 mg every 6 hours orally), Magnesium Sulfate and/or Terbutaline.

If necessary, tocolytic drugs will be administered until 34 weeks.

The mothers will be discharged once stable. Mothers may be contacted weekly by phone for follow up.

Patients will be on modified bed rest for the first 2 weeks post discharge, but subsequently allowed to graduate to moderate activity if the uterus is quiescent.

All discharged patients will stay within 30 minutes of TCH to permit standardized postoperative management and emergent retrieval of the balloon in the event of preterm labor or premature rupture of membranes prior to the scheduled removal.

Fetal Monitoring: Fetal surveillance will be performed weekly post balloon placement.

Serial measurements of sonographic lung volume and LHR will begin within 24-48 hours following surgery and continue weekly by targeted ultrasound evaluation.

Amniotic fluid level and membrane status will also be monitored at weekly intervals. Comprehensive ultrasonography for fetal growth will be performed every 1-2 weeks.

6.5 Balloon Removal

Balloon retrieval will be planned at between 34+0/7 and 34+6/7 weeks; at the discretion of the FETO center.

In the event of a patient relocating after having the balloon placed, despite having committed to remain in the area during consent process, she will be asked to return for the removal. Every effort to make arrangements for her to be managed by the nearest center capable of an EXIT procedure

or balloon retrieval (San Francisco or Philadelphia) will be made.

The optimal method for balloon retrieval (fetoscopic versus ultrasound guided percutaneous) will be decided case by case by the FETO team based on fetal position and fetal lung response.

Betamethasone (12 mg IM, 2 doses given 24 hours apart) will be given to the mother preoperatively to improve fetal lung compliance prior to removal if indicated.

Anesthesia, sedation, and tocolysis for the balloon retrieval will be as described above for the balloon placement.

Endoscopic balloon removal:

- As with placement of the balloon, fetoscopic/endoscopic retrieval will use a 9-12 Fr Teflon cannula loaded with a pyramidal trocar that is inserted into the amniotic cavity.
- A Storz endoscope or Storz fetoscope will be passed through the cannula into the amniotic fluid and maneuvered into the fetal larynx as noted above.
- The balloon will be visualized, punctured, grasped, and removed.
- The fetoscope/endoscope and cannula will be then removed.

Ultrasound guided balloon removal:

- Using a 22G needle and continuous ultrasound guidance the balloon will be punctured.
- The deflated balloon will be flushed from the trachea by the egress of pulmonary

secretions distal to the occlusion. Recovery post balloon removal:

- The mother will then recover in the usual way and be discharged once stable.
- After removal of the balloon, patients will have the choice of delivering at Texas Children's Hospital Pavilion for Women with the CDH managed and repaired at TCH, or returning to their obstetrician for delivery with subsequent repair of the CDH by the pediatric surgeons at their referring facility.
- Given the severity of the CDH, the baby will need to be delivered in a facility that has the capability of immediate pediatric surgery services.

Balloon retrieval reattempts:
In the event of a failed attempt to remove a balloon, depending on the reason for the failure, the patient will remain in-house and a re-attempt may be contemplated. If the reason for failure to even attempt an endoscopic removal (i.e. no placement of instruments in the amniotic cavity) is inability to position the fetus in such a way that access to the mouth is possible, a further attempt may be performed the next day or whenever the fetus is in an ideal position in the next 3 days. If fetal positioning remains impossible an ultrasound directed needle puncture of the balloon will be

attempted. In the event that the balloon has not been removed or punctured within the time period mandated by the protocol (< 35 weeks) despite reasonable attempts, further attempts will be undertaken at the discretion of the PI to remove or puncture the balloon up until the time of delivery. The patient will remain in-house until such time as the balloon is removed or punctured. In the event that the balloon is still in place at the time of labor or scheduled delivery a planned non-emergent EXIT procedure will be performed.

6.6 Delivery

Delivery will be ideally scheduled at term and the baby will be handed off to the pediatric surgery team for further management after delivery.

6.6.1 Scheduled Delivery

Delivery will be elective because of the need to have pediatric subspecialists at the delivery and this will be managed according to obstetric principles. A 24 hours a day, 7 days a week, on-call team consisting of one of the fetal interventionists and a pediatric surgeon will be available in the event of an unscheduled delivery or need for balloon retrieval. If the balloon cannot be removed by an in-utero procedure prior to delivery, the on-call team will be present at delivery and will coordinate a plan with on- call neonatology for immediate balloon removal at the time of the baby's birth. A neonatal intensive care team is always available at TCH given that the NICU is staffed 24 hours/day by a neonatologist. Delivery will be vaginal unless cesarean section is indicated.

6.6.2 Unscheduled Delivery for PPROM or Preterm Labor

Should preterm premature rupture of membranes (PPROM) occur prior to 34 weeks, standardized practice would entail administration of latency prolongation antibiotics and consideration for delivery at 34 completed weeks of gestation. In the event that the membranes rupture prior to retrieval or puncture of the balloon the patient will be admitted to TCH for monitoring of her status. If she is not contracting prolongation of the pregnancy will be attempted according to standard of care. If the balloon can be punctured using a sonographically guided needle this will be done at the appropriate time. If it is not possible to do this, and retrieval of the balloon is not feasible using the usual fetoscopic technique, the baby will be delivered by EXIT procedure at 34 weeks or at the time that she goes into labor. Final decisions on management of PPROM will be at the discretion of the attending physician, and the decision on delivery would be based on standard, accepted maternal and fetal indications.

6.7 Postnatal

Neonates will be assessed at discharge, 6 months, 1 year, and 2 years after delivery with regard to their need for supplemental oxygen.

6.7.1 Postnatal Death

Permission should be requested for full postmortem examination in all cases of fetal or postnatal death. If this is not granted then permission for an MRI or CT examination and histological

examination of open lung biopsies should be requested. If none of the above is possible the cause of death will be determined on the basis of clinical findings.

7.0 RISKS

Potential maternal and fetal risks associated with the FETO procedure are outlined below.

7.1 Mother

- Wound infection: Because this is an invasive procedure, there is always the risk of infection at the puncture site, or other wound infection.
- Chorioamnionitis: Because an instrument is passed from the outside into the cavity of the uterus there is always the risk that there could be infection in the amniotic fluid.
- Amniotic fluid leak: Puncturing the uterus and membranes could cause amniotic fluid to leak out and decrease the overall fluid level.
- Pseudomembranous colitis: Certain antibiotics given throughout the procedure may result in a slight risk of developing pseudomembranous colitis.
- Side effects of tocolytic agents: Tocolytic agents will be given to decrease any uterine contractions and the risk for going into preterm labor. The type of tocolytic agent given will determine the number and type of side effects that could occur including low blood pressure, headache, flushing, dizziness, weakness, depressed deep tendon reflexes, other cardiovascular risks, and pulmonary edema.
- Placental abruption: Because an instrument will be placed through the abdominal wall into the uterus, there is a risk of placental abruption.
- Side effects of general and epidural anesthesia: these will be explained in greater detail by the anesthesiologist.
- Bleeding: Because an instrument will be placed through the abdominal wall and into the uterus there is always a risk of significant bleeding from any of the structures that the instrument is placed through.
- Open surgery: If the procedure caused significant bleeding or damage to internal organs, the uterus, or abdominal wall then open surgery might be required to stop bleeding or to repair an injury.
- Cesarean section: There may be a need to deliver the baby immediately if the baby does not tolerate the balloon procedure and develops bradycardia or cardiac decompensation not amenable to in-utero resuscitation.
- Hysterectomy: If there is bleeding or some injury to the uterus that cannot be controlled, the uterus may have to be removed.
- Brain Damage: Injury or an anesthetic reaction may cause brain damage. The risk of this is very low.
- Death: The procedure or the anesthesia could cause death. The risk of this is very low and to date, no woman, to our knowledge, has died from fetoscopic CDH surgery.
- Damage to other organs in the abdomen: If there is a need for open surgery, cesarean section or other procedures, there could be damage to other organs such as the bowel or bladder.

- Failure of balloon positioning: The failure rate of entering the uterus or trachea, or positioning the balloon is currently estimated to be 2%. In most cases this can be anticipated, by assessing the fetal position and the degree of amniotic fluid volume. It might be wise to delay the procedure in such cases.

7.2 Fetus and Neonate

- Placental perforation: Because placental perforation can lead to significant bleeding of the mother there is a risk to the fetus. When a mother loses a lot of blood she could die or could have such low blood pressure that the baby may not get enough oxygen and may develop brain damage or die.
- Placental abruption: Membrane separation – anytime an instrument is passed through the uterine wall there is a small risk that it could cause bleeding between the membranes and the uterine wall. Most commonly a small abruption will not result in a need for delivery, but if there is a significant separation, there may be a need to perform a cesarean section and deliver the baby. There may also be a need for a blood transfusion for the mother.
- Bradycardia and cardiac decompensation: The fetus may not tolerate the FETO procedure and may develop bradycardia and cardiac decompensation not amendable to in-utero resuscitation so a cesarean surgery may be required.
- Intrauterine bleeding: Whenever an instrument passes through the uterine wall, there is an increased risk for bleeding which may result in the need to perform a cesarean section and deliver the baby.
- Chorioamnionitis: Because an instrument is passed from the outside into the cavity of the uterus there is always the risk that there could be infection in the amniotic fluid.
- Prematurity/preterm premature rupture of membranes/preterm labor: A 2009 study[22] showed a risk of Preterm Premature Rupture of Membranes ranging from 11% to 35% depending on duration of the FETO procedure. Although the risk of preterm birth and preterm rupture of membranes are increased with this procedure, experience to-date suggests that the chance of the baby's survival in cases of severe or extremely severe CDH (as defined by inclusion criteria of this study) is significantly increased with a successful tracheal occlusion procedure.
- Bronchial perforation – in the event that the balloon migrates into the bronchus during inflation there is a risk that the bronchus can be perforated or ruptured and the balloon extruded into the pleural space. This has happened once in our experience and the bronchus healed without complication.
- Bronchial abrasion – the endoscope or instruments placed through the scope (needle or grasper) could cause abrasions or perforation of the bronchus.
- Pleural effusion – irrigating the airways to keep them open could cause a pleural effusion if there is a bronchial rupture or communication between the bronchus and the pleural cavity.
- Vocal cord paresis/paralysis: Placing the balloon through the trachea creates the risk of damage to the developing vocal cords.
- Tracheomalacia (the collapse of the breathing tube) tracheomegaly (abnormally enlarged trachea): There is a risk of deformation of the fetal trachea and a theoretical risk of rupture of the fetal trachea from the balloon. There is also a risk of weakness to the cartilage of the airway that may create a floppy and/or unstable airway.
- Fetal hydrops: There is a theoretical risk that the baby could become hydropic from significant lung expansion. If this does occur, the balloon will be removed.[i]

- Chorioamniotic separation: Occasionally there may be leakage between the amnion and the chorion, which would allow amniotic fluid between the two which can increase the risk of leakage of fluid vaginally. Usually this will resolve spontaneously without complication but occasionally this may result in premature rupture of membranes.
- Failure of the balloon to work: There is a chance that the balloon could migrate from the place in which it was placed and be ejected from the windpipe.
- Migration of the balloon: It is possible that the balloon could move further into the baby's lungs than where it was placed. If this happens it will not work and will have to be removed after the baby is born.
- Inability to remove the balloon before delivery or after birth: There is a risk the baby could be delivered without there being time or opportunity for the balloon to be removed before delivery. There is the risk that there may be a delay in removing or an inability to remove the balloon that could results in long term brain damage or death of the baby. In a 2009 study[22], the incidence of death due to complications of balloon removal was 5%. All of the failures where when the retrieval was attempted in a non-FETO center. We, and investigators cited, believe this risk can be reduced by elective balloon removal at or before 34 weeks gestation, anticipation of the need to puncture the balloon externally, and having the patient reside near the hospital throughout the duration of the tracheal occlusion.
- Brain Damage: The procedure could cause injury to the brain.
- Death: There is always the risk that the procedure could cause injury to the baby and cause him or her to die.

7.3 Steps to Minimize Risks

Fetal risks:

The fetal procedures will be performed by specialists in fetal medicine with extensive experience in fetoscopy as well as FETO.

This is not an open study and eventual extension of the study consortium will be made dependent on a decision of the steering committee.

Maternal risks:

- Maternal infectious complications: prophylactic administration of intravenous antibiotics.
- Complications and side effects of epidural analgesia (if applied): the procedure will be carried out or under the direct supervision of an expert in this procedure.
- Preterm labor induced by the intervention: prophylactic administration of tocolytics.
- Maternal uterine / placental bleeding: ultrasound guidance of trocar insertion.

The FETO procedure and neonatal management of the patients will be undertaken in major university hospitals with multidisciplinary teams of experts familiar with both pre- and postnatal management of CDH and FETO.

7.4 Risk Balance Summary

Severe CDH (O/E LHR of less than 25%) is associated with high rates of mortality (more than 70%) and morbidity. In such cases FETO has been introduced as an alternative to the options of termination of pregnancy and expectant management. There is evidence from experience of more than 150 cases treated by FETO that the survival rate is improved. There is also evidence that this increased survival is not at the expense of an increased short term morbidity. In contrast survivors seem to have less morbidity than can be expected based on severity (O/E LHR).

The rationale for the proposed study is that in cases of moderate CDH, FETO in the third trimester would reduce morbidity and may increase survival.

On the basis of our current experience with FETO there is no apparent serious risk for the mother. The main risk for the fetus is iatrogenic prematurity which in this study is minimized by performing the procedure in the third trimester.

A randomized clinical trial is the only way to answer this question. If the results are favorable, we will offer a new therapeutic modality to future patients. If not favorable, we will have prevented untimely spread of this new operation that would have claimed benefits without scientific basis.

By

8.0 BENEFITS

The hypothesis is that prenatal intervention will improve morbidity, lung development and growth or survival in patients with isolated, moderate CDH. We do not know at this stage of the trial whether in fetuses with moderate diaphragmatic hernia FETO is beneficial or not. The results of this study will help us to manage moderate diaphragmatic hernia better in the future.

Although the FETO procedure has shown promise as an intervention for severe and extremely severe CDH, moderate CDH has not been studied adequately in the United States. This study will help extend current trials of FETO to include the population of the United States.

Even though the FETO procedure creates risks, the chance of the baby's survival is still probably much better with a successful FETO procedure. We believe the benefits will outweigh the risks. Risk to benefit ratio is favorable.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Precision

Primary endpoint has been changed to survival at discharge. Initially, it was estimated that 55% of patients in control arm would be alive at discharge. Given that we have decided that an absolute increase in survival rate of 20% in FETO arm would be an improvement, clearly clinically relevant and realistic, we'd then assume a survival rate of 75% in FETO arm to determine sample size. An absolute increase of 15% would still be acceptable. Although it is of importance in this trial to

avoid continuation when there is evidence of effectiveness of FETO, it'd be undesired to underestimate the required sample size because of an overestimated survival rate in control arm. Therefore, we decided to use data from administrative review to estimate sample size. This resembles the internal pilot study method by Friede and Kieser.[23] Using the overall average survival rate over the two groups (blinded data), which was 50.1%, we'd therefore use 40% vs 60% survival rate in control vs FETO arm. Based on blinded procedure, the size of the 'internal pilot', and the fact that an overall response rate of 50% maximizes required sample size [24] there is no need to adjust type I and II error rates.

We use a group sequential design with overall one-sided alpha of 2.5% and a power of 80%. Formal interim analyses are scheduled for efficacy only, although the DMC retains the right to stop the trial for clear futility. We adopted the O'Brien-Fleming method[25] to derive critical boundaries to stop the trial for efficacy. Five interim analyses are planned, after 40, 60, 70, 80, and 90% of sample size at final analysis. Using the abovementioned parameters and z-test for the difference in proportions, critical boundaries are obtained using PROC SEQDESIGN in SAS v9.3 (SAS Institute, Cary, USA).

Analysis	**N per arm**	**Efficacy boundary**	
		Difference in survival rates	p-value
Interim 1	40	0.365	0.0005
Interim 2	59	0.243	0.0036
Interim 3	69	0.209	0.0064
Interim 4	79	0.182	0.0099
Interim 5	89	0.162	0.0140
Final	98	0.146	0.0186

When deriving a sample size plan including formal boundaries to stop for futility, the overall sample size hardly changed. As a result, we left stopping for futility at the discretion of the Data Safety Monitoring Committee (DSMC).

The main secondary endpoint is survival without oxygen dependency at 6 months. A hierarchical testing procedure is suggested, where a formal hypothesis test for this endpoint will be undertaken only when statistical significance for the primary endpoint has been declared. Given the assumption of 40% vs 60% survival at discharge, we define 35% vs 55% as a related relevant difference between the groups. Then, 96 patients per group are needed to obtain 80% power at an upper one-sided alpha of 2.5%. Given that the above group-sequential method allows early stopping for efficacy, this number of patients may not be reached. Therefore, the DSMC retains the right to continue including patients in the FETO arm after an interim bound for efficacy has been reached in order to secure power at a chosen level. Given the O'Brien- Fleming boundaries described above, we computed for each interim analysis the number of patients required in the FETO arm to achieve 70, 75, or 80% power. The number of patients in the control arm is fixed at

the number that is included at the interim analyses where the efficacy boundary was reached. For example when the trial reached the efficacy boundary for the primary endpoint at the third interim analysis, there are 69 patients in each arm. Then, to achieve 80% power for the main secondary endpoint, 89 additional patients are needed in the FETO arm. In total, there would then be 69 patients in the control arm and 158 patients in the FETO arm. When the trial would be stopped at the first interim analysis, numbers show that it is not feasible to continue with the FETO arm in order to obtain an acceptable power level. In case no additional patients are needed, there is at least 80% power for the main secondary endpoint is desired. 16 more patients are needed in FETO arm.

Analysis where stopped for efficacy	**N per arm**	**Additional patients needed in FETO arm**		
		80% power	75% power	70% power
Interim 1	40	>1000	>1000	601
Interim 2	59	195	94	48
Interim 3	69	89	43	16
Interim 4	79	44	13	0
Interim 5	89	16	0	0
Final	98	0	0	0

9.2 Proposed Analysis

Achieved significance rule:

The initially anticipated increase in survival at discharge was 20%, yet at the moment of design of the trial no data on outcomes on percutaneous FETO with a balloon for moderate hypoplasia were known.

There is no stratification prior to or post randomization.

Null Hypothesis: The null hypothesis to be tested is that there is no difference in survival and in number of survivors requiring supplemental oxygen at the age of 6 months between fetuses managed expectantly during pregnancy versus those undergoing antenatal therapy.

Stopping rule:

The trial will be discontinued if there is a significant difference for the primary outcome measure (survival at discharge) at the foreseen time points of analysis. The DSMC, however, may consider continuation of the study in an adapted design to determine whether significance can be achieved for the co-primary variable (oxygen need at 6 months of life).

The DSMC is a group of physician and ethicist experts from Baylor College of Medicine who are

not otherwise involved with the study. The DSMC will assess, on an ongoing basis, the study conduct and monitor the safety of current and future patients as well as the validity and scientific integrity of the trial. The DSMC will meet to review data and will recommend continuation, modifications to the study design or discontinuation of the study. The DSMC will advise the Principal Investigator (PI) and study staff of any issues after the meetings.

Primary Analysis:

The primary analysis will compare the proportion of subjects who are surviving till discharge and the survivors requiring no oxygen at 6 months of age. The primary analysis will be based on the intent-to-treat principle.

Secondary Analyses:

A secondary analysis will compare the proportion of subjects that survived until discharge from the hospital in the two treatment groups, and those free of oxygen need at 6 months of age with an as-treated ("per protocol") analysis.

Data will also be analyzed depending on the case load at each postnatal treatment center, i.e. treatment centers with a case load above, respectively under 6/year.

Whenever possible, analysis of outcomes of non-randomized subjects will be made to provide the most complete synthesis of the data. We will keep data from any non-randomized patient that receives a FETO balloon on a compassionate basis and we will analyze the data in a separate analysis.

Methods of analysis

We will analyze the primary and co-primary endpoints with the z-test for unpaired proportions (equal to the Pearson chi-square test) using a one-sided alpha of 2.5%. To control for multiplicity, we will use a hierarchical approach. If the trial is stopped for efficacy for the primary endpoint (survival at discharge) at one of the interim analyses based on the z-test, we will evaluate the co-primary endpoint (survival without oxygen dependency at 6 months) with the same test. As explained in the sample size section, the DSMC first decides whether more patients in the FETO arm have to be recruited in order to reach the required sample size. If it is not feasible to reach the required sample size, we will not perform the z-test for the co-primary endpoint.
For the primary and co-primary endpoints, we will compute the difference in proportions between the study arms as well as the relative risk, both with a standard two-sided 95% CI. These results are at least as important as the determination of statistical significance based on the z-test.
For the secondary endpoints, we will not perform statistical testing. For categorical endpoints, we will compute relative risks and differences in proportion with their respective 95% confidence intervals. For continuous endpoints, we will compute 95% confidence intervals on the difference in medians using the percentile bootstrap method. We will analyze time-to-event outcomes (days to discharge from neonatal intensive care unit, days until end of ventilatory support, days until release from ECMO support, days until full enteral feeding) with a 95% confidence interval for the median cumulative incidence of the event, with death used as a competing event [26]

Sources of error:

- The power of the study will be adversely affected by patient's non-compliance with the randomly assigned regimen.

- The number of centers recruiting for postnatal treatment cannot be anticipated at this time. This will by definition be uncontrollable, and it may influence the outcome in either group. This is an accepted source of error by the investigators because it is a clinical reality (this is an effectiveness or pragmatic trial). The organizers do not have funding, neither the power nor logistics for having all postnatal management at one location. Guidelines for standardization of postnatal treatment are therefore being issued (Appendix I), which will reduce the impact of this source of error. An important source of error may also be case load at each of these participating centers. For that reason a post hoc analysis will be made according to the case load during the study period.

- Subjects randomized to postnatal care who seek fetal intervention elsewhere, may reduce study power. The consortium of FETO centers will not perform FETO in patients eligible for the present study, outside the herein described RCT. This seems ethical as FETO-treatment for this particular severity group so far has not been offered by the FETO consortium, and to their knowledge neither elsewhere.

- The extent to which non-FETO centers will carry out FETO in patients that are eligible for the herein proposed RCT cannot be estimated. Maximum efforts will be done to reduce the number of such centers. One method is to include those centers based on the criteria outline below. During the course of this study, other prenatal treatment centers have expressed their interest to join this study. If they are not or less experienced, this may be a source of error. The steering committee has met on this issue and has defined empirically criteria for eligibility for study participation, following which they may apply locally for ethics committee approval and ultimately they may participate to the present study under the same conditions as herein.

- Preterm pre-labor rupture of the membranes and as a consequence preterm labor prior to in utero reversal of the occlusion, with as a consequence "incomplete" prenatal therapy as well as problems directly due to the inability or difficulties to remove the balloon, may result in lower than expected survival chances. When this happens, it will cause delivery at one of the FETO centers, therefore leading to a higher than expected number of babies delivered at these institutions. However this is inherent to the prenatal therapy and not avoidable. A separate secondary analysis may be done as to judge on the biological effect of the complete course of prenatal therapy (balloon insertion and balloon removal followed by birth in the un-occluded state), but again, results will be reported on an intention to treat - basis.

- In the fetal treatment arm there is the potential of patients not complying during the period the airways are plugged, presenting in an emergency at their local center, or for whatever reason not returning to the FETO center for balloon removal. This may adversely affect the outcome in the treatment group, lead to a higher than expected death rate in that arm. It could only be

discounted by post hoc exclusion. This will however not be done, as it is considered as an inherent risk of prenatal therapy. Such an effect may however be documented in a secondary analysis as described above.

- Prenatal medical imaging techniques may fail to recognize a concomitant congenital anomaly that is therefore only diagnosed after birth. Since serious associated anomalies are an independent predictor of outcome, and their numbers should be low, patients may not be equally distributed in both treatment arms. These patients will be excluded post hoc from analysis. It will include patients with serious genetic anomalies (not known at the time of FETO), undiagnosed structural cardiac or other structural anomalies that directly compromise neonatal outcome. Analysis of cases to be excluded will be overseen by the Data Monitoring and Safety Committee (also referred to as Oversight Committee).

- Adjustments for error sources: The aforementioned error sources will be dealt with, in part, by following all subjects eligible for the primary outcome regardless of whether the subject consents to randomization or refuses to comply with the assigned randomization. Since the magnitude of these effects cannot be known in advance, the Steering Committee will be charged with examining randomization refusal rates and refusal of randomized treatment. They may suggest to modify the sample size, the study design, or terminate the study for inadequate accrual/power/data quality/safety issues in consultation with the Oversight Committee, who has the final word about this.

- Missing data for the primary endpoints are very unlikely. In addition, the DSMC will review data entry and quality at every interim analysis such that we will detect eventual issues quickly such that we can act appropriately to ensure complete data. Inspection of data quality at the first two interim analyses confirms that missing values are very rare. If there is a missing value for the primary endpoint of survival at discharge, we will exclude the case from the study. If there is a missing value for the co-primary endpoint of survival without oxygen dependency at 6 months, we will not use the case for the analysis of the co-primary endpoint.

- If there is a missing value or for any secondary endpoint, we will exclude the case for the analysis of that specific endpoint. If we observe more than 10% missing values for a secondary endpoint, we will not analyze this endpoint. There is no need for statistical imputation of missing data.

Outcome measures

Primary outcome measures:

•Survival until discharge

•Supplemental oxygen at 6 months of age.

Secondary postnatal outcome measures:

•Grade of oxygen dependency (grade 0-III; definition as above)

•Occurrence of severe pulmonary hypertension (yes / no; based on evidence on cardiac ultrasound

of predominant unidirectional right to left shunt) in the neonatal period [27]

•Need for ECMO support for centers offering it (yes / no) [28]

•Defect size as per classification by the CDH study group

•Number of days in neonatal intensive care unit (days); (if death occurs; day of death)

•Number of days of ventilatory support (days) ;

•Presence of periventricular leucomalacia at ≤2 months postnatally (yes / no)

•Presence of neonatal sepsis (yes/no)

•Presence of intraventricular hemorrhage (grade 0-III)

•Presence of retinopathy of prematurity (grade III or higher)

•Number of days till full enteral feeding (days)

•Presence of gastro-esophageal reflux (above one third of the esophagus on clinically indicated radiologic study)

•Day of surgery (days)

•Use of a patch (yes/no)

Secondary prenatal outcome measure:

•Lung volume as serially measured by 2D-ultrasound and/or fetal MRI (o/e LHR, o/e total lung volume)

•Liver position; in case of liver herniation, the liver-to-thorax volume.

Secondary longer term outcome variables:

•Pulmonary function and volume testing before and after repair, at discharge, and at one year of age

•Neurodevelopmental milestones at discharge, 12 months and 2 years (AGES and STAGES, validated English and Spanish questionnaires). Use of this questionnaire does not depend on additional funding.

•Death at 2 years (due to either primary illness or other causes)

9.3 SAFETY EVENTS/Reporting

The Investigator is responsible for the detection, documentation and follow-up of all safety events

meeting the criteria and definitions outlined below in subjects enrolled on this protocol. For purposes of this protocol subjects can be mother, fetus, and/or infant/child up to 2 years of age.

9.3.2 Definition of Safety Event

A safety event is any untoward medical occurrence, unintended disease or injury or any untoward clinical sign (including a clinically significant abnormal laboratory finding) in subjects whether or not related to the investigational devices or to the procedures involved (including any procedure in the clinical study protocol).

9.4 Not Device or Procedure Related – Adverse Event (AE)

Safety events which are not related to the investigational device or the procedure to place the balloon are referred to as Adverse Events (AEs).

9.5 Device or Procedure Related – Adverse Device Effect (ADE)

An Adverse Device Effect (ADE) is a safety event related to the use of an investigational medical device. This includes any safety event resulting from insufficiencies or inadequacies in the Instructions for use, the deployment, placement, operation, or any malfunction of the investigational medical device(s). This includes any event that is a result of a use error or intentional misuse.

9.6 Definitions of Serious Safety Events

A safety event is serious if the event:

- Led to a death.
- Led to a serious deterioration in health that either:
- Resulted in a life-threatening illness or injury, or
- Resulted in an injury or permanent impairment of a body structure or a body function, or
- Required in-subject hospitalization or prolongation of existing hospitalization, or
- Resulted in medical or surgical intervention to prevent life threatening illness.
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

This includes deficiencies that might have led to a serious adverse event if:

- Suitable action had not been taken or
- Intervention had not been made or

A planned hospitalization for a pre-existing condition, or a procedure required or described as a possibility by the protocol as part of procedures performed in regular clinical care, without a serious deterioration in health, is not considered to be a serious safety event. Events that occur after birth that are related to the underlying condition (CDH) and which are unrelated to this protocol (such as a complication with ECMO or other forms of neonatal treatment for CDH) will not be considered to be a serious safety event of the balloon placement.

9.7 Not Device or Procedure Related – Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is a safety event that has resulted from a serious safety event as assessed by the investigator and is not device or procedure related.

9.8 Device or Procedure Related – Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect (SADE) is a device or procedure related safety event that has resulted from a serious safety event and is an event by its nature, incidence, severity or outcome that has been previously identified in the Risks section (Section 7.0) of this protocol.

9.9 Unanticipated – Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the Investigational device(s), if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the clinical study protocol, Report of Prior Investigations, or application (including a supplementary plan or application), or any other unanticipated serious problem associated with an investigational product that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

9.10 Safety Event Assessments

All safety events will be monitored in conjunction with the study assessment schedule and will be reported to the IRB and FDA on an annual basis in the IDE Progress Report.

Unanticipated events will be collected, assessed and reported according to SOP P-15-XX-Documentation and Reporting of Serious Adverse Events and Unanticipated Problems.

The Sponsor (IDE holder) will be responsible for reporting all reportable unanticipated events to the appropriate regulatory agencies (e.g., IRB, FDA) as per each agency's individual reporting requirements and within that agency's required time frame.

9.11 Assessment of Causality

The Investigator will assess the relationship between each safety event and both the device and the procedure using the definitions listed below. Note that a safety event may be related to the device or the procedure or both. The Investigator should assess causality of each safety event to the device independent from the procedure and to the procedure independent from the device.

9.12 Investigational Product

- Definitely Related: The safety event has a strong temporal relationship to the device. The safety event is most likely explained by device. The safety event is consistent with a known response to the device. Another etiology is unlikely or significantly less likely.
- Probably Related: The safety event has a strong temporal relationship to the device. The safety event is more likely explained by the device than by another cause.
- Possibly Related: The safety event has a reasonable temporal relationship to the device.

The safety event could have been due to another equally likely cause.

- Not Related: The subject did not receive the device OR the safety event has no temporal relationship to the device OR the safety event has a much more likely alternate etiology OR the safety event is due to an underlying or concurrent illness or effect of another drug.

9.13 Procedure

- Definitely Related: The safety event has a strong temporal relationship to the procedure. The safety event is most likely explained by the procedure.
- The safety event is consistent with a known response to the procedure. Another etiology is unlikely or significantly less likely.
- Probably Related: The safety event has a strong temporal relationship to the procedure. The safety event is more likely explained by the procedure than by another cause.
- Possibly Related: The safety event has a reasonable temporal relationship to the procedure. The safety event could have been due to another equally likely cause.
- Not Related: The subject did not have the procedure OR the safety event has no temporal relationship to the procedure OR the safety event has a much more likely alternate etiology OR the safety event is due to an underlying or concurrent illness or effect of another drug.

Even in situations in which minimal information is available for the initial safety event, it is important that the Investigator always make an assessment of causality for every event. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his or her opinion of causality in light of follow-up information and amend the report accordingly.

All safety events must be followed until they are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up.

9.14 Serious Safety Events, Reporting Requirements

Once the Investigator determines that a safety event meets the definition of serious (SAE or SADE), the Sponsor-Investigator will provide an assessment within 5 days of becoming aware of the event.

9.15 Unanticipated Safety Event Reporting Requirements

If the Investigator determines that a safety event meets the definition of unanticipated (UADE), the Investigator or their designee must notify the IRB and FDA within 10 days of becoming aware of the event.

An evaluation of a UADE will be immediately conducted and results of the evaluations will be reported to FDA and all reviewing IRBs in accordance with the applicable national and local regulations.

9.16 Follow-up of Safety Events

SAE/SADE/UADEs will be followed until the event resolves, the condition stabilizes, the event is

otherwise explained, the subject is lost to follow-up or death occurs.

New or updated information will be recorded on a follow up Serious Adverse Event Report.

10.0 INFORMED CONSENT and RISKS

All subjects must sign an informed consent document consistent with local institutional and Federal guidelines stating that they are aware of the investigational nature of this protocol and of the possible risks of treatment. Further, subjects must be informed that no efficacy of this therapy is guaranteed, and that unforeseen risks may occur. Full confidentiality of patients and patient records will be provided according to institutional guidelines. The subjects or their families will not receive any payment for participation in this study. No charge will be made for the FETO procedure being performed as part of this study.

10.1 Changes to the protocol and/or informed consent form

Changes to the research covered by this protocol must be implemented by a formal protocol amendment. Protocol amendments must not be implemented without prior IRB and FDA approval. When the change(s) involve only logistic or administrative aspects of the study, the IRB only needs to be notified. During the course of the study, in situations where a departure from the protocol is unavoidable, the Investigator will contact the FDA for approval. Except in emergency situations, this contact should be made before implementing any departure from the protocol.

10.2 Withdrawal of informed consent

Withdrawal of consent from a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation in the study. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

11.0 TRIAL MONITORING PROCEDURES

11.1 Institutional Monitoring

The study will be monitored by the Fetal Therapy Board at Texas Children's Hospital. The Fetal Therapy Board is an institutional board established to examine ethical and clinical aspects of this type of procedures. The Board provides written concurrence after cases are reviewed to proceed with these activities. None of the members of the Fetal Therapy Board are professionally involved in the cases under consideration. The Board membership is comprised of physicians who have the education, training and expertise needed to monitor this protocol and data as well as a medical ethicist.

11.2 Written Monitoring Procedures

Case report forms are utilized to record study related data, including any procedural complications such as failed balloon placement or failed balloon retrieval, as well as surgical or anesthesia complications. Summary statistics of these data will be reviewed by the Fetal Therapy Board on an annual basis.

Maternal and neonatal outcomes will be recorded. Neonatal outcomes will include survival of the fetus, 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; and the duration of hospitalization. Assessments of other measures of long-term morbidity, including the need for supplemental oxygen, rates of recurrent infection, the need for repeated hospitalization, as well as neurodevelopmental outcomes, will be performed.

Maternal morbidity will also be assessed in terms of incidence of preterm delivery (spontaneous or indicated), cesarean section rate, length of hospitalization after the FETO procedure, length of hospitalization after balloon removal, post procedure vaginal bleeding, incidence of placental abruption, incidence of post-procedure rupture of membranes, incidence of oligohydramnios, and incidence of chorioamnionitis.

The Fetal Therapy Monitoring Board will monitor this study to ensure that the investigation is in accordance with the principles of Good Clinical Practice and that the investigators follow the protocol without any major deviations. The Fetal Therapy Monitoring Board will follow the progress of the trial including patient recruitment, data collection, management, and patient/infant outcomes.

The Fetal Therapy Monitoring Board will also review the annual and final IDE progress reports prior to submission to the FDA.

11.3 Monitoring, Audits and Inspections

The Investigator will assure that local study staff cooperate with monitoring and audits. The Investigator agrees to allow auditing of all essential clinical study documents and inspection by the FDA or other appropriate regulatory authorities. Auditing visits will be scheduled with the appropriate staff at mutually agreeable times as applicable.

12.0 REPORTING REQUIREMENTS

12.1 Registration

The research coordinator registers all subjects in the CDH-TOTAL enrollment log. The following forms/actions are completed:

- Eligibility Checklist
- Informed Consent
- Case Report Form (CRF)

As part of the randomization process, patient data are entered in the centralized electronic database at www.eurocdh.org.

12.2 Each Case

There will be a report generated on each case within 2 days of each procedure and within 90 days of delivery setting forth the circumstances and outcomes of mother and baby. If there are no serious adverse events, this information will be reported at the time of the annual IDE report.

12.3 Access to Original Records

Regulatory authorities expect that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard-copy and electronic records.

12.4 Records Retention

Health Insurance Portability and Accountability Act of 1996 - The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subjects' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45CFR Parts160 and164 (the Health Insurance Portability and Accountability Act of 1996 privacy regulation). The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act.

12.5 Data Security

Access to the data will be strictly controlled.

12.6 Storage

Investigational devices must be received by a designated person at the study locations, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access to. Upon receipt, all Investigational Devices should be stored in a locked and secured location.

The investigator or designated staff must maintain an accurate record of the shipment and use of the research system in an accountability ledger. Monitoring of the study accountability will be performed periodically and at the completion of the trial.

Medical records of research study participants are securely stored according to federal and legal requirements.

13.0 REGULATORY REQUIREMENTS

13.1 Ethical conduct of the study and regulatory review

The Investigator agrees to adhere to the instructions and procedures described in the protocol and to conduct the study in accordance with the Code of Federal Regulations (21 CFR Parts 11, 50, 54, 56, 312, 314, and 320), which originate from the ethical principles laid down in the current revision of the Declaration of Helsinki, GCP, and policies and procedures as outlined by the ethical requirements for IRB review and informed consent forms.

A copy of the protocol, proposed informed consent form and other written subject information, must be submitted to the IRB for written approval before recruitment of subjects into the study and shipment of investigational devices can begin.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Subjects who may have already been consented with the older consent form and for whom an amended consent form is relevant must be re-consented using the approved, amended forms. The investigator is to notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from the device manufacturer (if applicable), in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB approval /renewal throughout the duration of the study.

13.2 Study Management

The Investigator will assure proper implementation and conduct of the study will be performed according to the currently approved study protocol.

13.3 Training of study site personnel

The Investigator will assure research activities, including those study-related duties delegated, will be performed by appropriately qualified individuals. The Investigator will assure that study staff will demonstrate due diligence in recruiting and screening study patients.

13.4 Financial Disclosure

Participating Investigators will provide a signed Financial Disclosure Form and Investigator Agreement.

13.5 Confidentiality

All information provided by and all data and information generated as part of the study (other than a subject's medical records) will be kept confidential by the Investigator and other site staff. This information and data will not be used by the Investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to the following:

1) Information that becomes publicly available through no fault of the Investigator or site staff;
2) Information that must be disclosed in confidence to an IRB solely for the evaluation of the study results;
3) Information that must be disclosed in order to provide appropriate medical care to a study subject; or
4) Study results that may be published.

Appendix A: Medications Used in this Protocol

Mother:

Balloon placement and removal:

- Cefazolin 2 gm IV x1
- Clindamycin 900 mg IV
- Azithromycin 500 mg IV
- Indomethacin (50 mg orally)
- Nifedipine (10 mg orally)
- Chloroprocaine 2% (11mg/kg/dose to a maximum of 800 mg)
- Ropivacaine (2.5 mg/kg/dose to a maximum of 300 mg)
- Marcaine (0.25% local anesthesia) with intravenous sedation of either Fentanyl IV or Remifentanil IV sedation
- Betamethasone (12 mg IM, 2 doses given 24 hours apart) may be given to the mother preoperatively to improve fetal lung compliance prior to removal only.

Post-Surgery after balloon placement and removal:

- Postoperative tocolysis will be given as needed with either nifedipine (10 mg every 4 hours orally) or indomethacin (25 mg every 6 hours orally) for a maximum of two days

Neonate:

Balloon placement and removal:

- Fentanyl 15 mcg/kg narcotic, Atropine 20 mg/kg anticholinergic and Vecuronium 0.1 mg/kg Muscle relaxant given as one time intramuscular injection
- 1L isotonic solution

If Pre-term delivery:

- Exogenous surfactant (Exosurf Neonatal, Glaxo Wellcome) administered at a dose of 3 ml/kg of body weight

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