OBSTETRICS

Balloon removal after fetoscopic endoluminal tracheal occlusion for congenital diaphragmatic hernia

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BACKGROUND: Isolated congenital diaphragmatic hernia defect allows viscera to herniate into the chest, competing for space with the developing lungs. At birth, pulmonary hypoplasia leads to respiratory insufficiency and persistent pulmonary hypertension that is lethal in up to 30% of patients. Antenatal measurement of lung size and liver herniation can predict survival after birth. Prenatal intervention aims at stimulating lung development, clinically achieved by percutaneous fetal endoscopic tracheal occlusion under local anesthesia. This in utero treatment requires a second intervention to reestablish the airway, either before birth or at delivery.

OBJECTIVE: To describe our experience with in utero endotracheal balloon removal.

MATERIALS AND METHODS: This is a retrospective analysis of prospectively collected data on consecutive patients with congenital diaphragmatic hernia treated in utero by fetal endoscopic tracheal occlusion from 3 centers. Maternal and pregnancy-associated variables were retrieved. Balloon removal attempts were categorized as elective or emergency and by technique (in utero: ultrasound-guided puncture; fetoscopy; ex utero: on placental circulation or postnatal tracheoscopy).

RESULTS: We performed 351 balloon insertions during a 144-month period. In 9 cases removal was attempted outside fetal endoscopic tracheal occlusion centers, 3 of which were deemed impossible and led to neonatal death. We attempted 302 in-house balloon removals in 292 fetuses (217 elective [71.8%], 85 emergency [28.2%]) at 33.4 $\pm$ 0.1 weeks (range: 28.9−37.1), with a mean interval to delivery of 16.6 $\pm$ 0.8 days (0-85). Primary attempt was by fetoscopy in 196 (67.1%), by ultrasound-guided puncture in 62 (21.2%), by tracheoscopy on placental circulation in 30 (10.3%), and postnatal tracheoscopy in 4 cases (1.4%); a second attempt was required in 10 (3.4%) cases. Each center had different preferences for primary technique selection. In elective removals, we found no differences in the interval to delivery between fetoscopic and ultrasound-guided puncture removals. Difficulties during fetoscopic removal led to the development of a stylet to puncture the balloon, leading to shorter operating time and easier reestablishment of airways.

CONCLUSION: In these fetal treatment centers, the balloon could always be removed successfully. In 90% this was in utero, with the use of fetoscopy preferred over ultrasound-guided puncture. Ex utero removal was a fall-back procedure. In utero removal does not seem to precipitate immediate membrane rupture, labor, or delivery, although the design of the study did not allow for a formal conclusion. For fetoscopic removals, the introduction of a stylet facilitated retrieval. Successful removal may rely on a permanently prepared team with expertise in all possible techniques.

Key words: congenital diaphragmatic hernia, fetal therapy, fetoscopic endoluminal tracheal occlusion

In congenital diaphragmatic hernia (CDH), abdominal organs herniating through the defect interfere with lung development, eventually causing respiratory insufficiency and pulmonary hypertension in the neonate. The severity of lung hypoplasia can be measured prenatally by the observed/expected lung to head ratio and the presence of liver herniation.[1] In fetuses with poor prognosis,[1,2] fetal lung growth can be stimulated by fetal endoluminal tracheal occlusion (FETO) with a balloon.[3-7] Occlusion prevents egress of pulmonary fluid, which stretches the lung parenchymal cells, thereby promoting lung growth, maturation, and remodeling of pulmonary vasculature.[8] Compared with historical controls of similar severity, FETO apparently increases survival rate from 24% to 49% in left-sided CDH and from 17% to 42% in right-sided CDH with observed/expected lung to head ratio < 45%.[9,10] Currently 2 parallel randomized clinical trials are being performed to investigate whether FETO is truly effective in case of moderate and severe lung hypoplasia.[4]

Removal of the balloon is possible either in utero by ultrasound-guided puncture or fetoscopy. Prenatal removal is recommended based on experimental observations showing benefit of temporary tracheal occlusion[11,12] ("plug unplug" sequence). This is supported by observational studies demonstrating increased survival[3] and reduced morbidity rates.[13,14] One also can leave the occlusion until delivery,[7,15] which may theoretically lead to additional lung growth and avoid a second intervention. Conversely, it may lead to more emergency removals on placental circulation or even postnatally, which may be more challenging and even fail.[9] Herein, we describe our experience with balloon removal from the first case onwards. The problems and our suggested solutions may be useful for centers considering this procedure.

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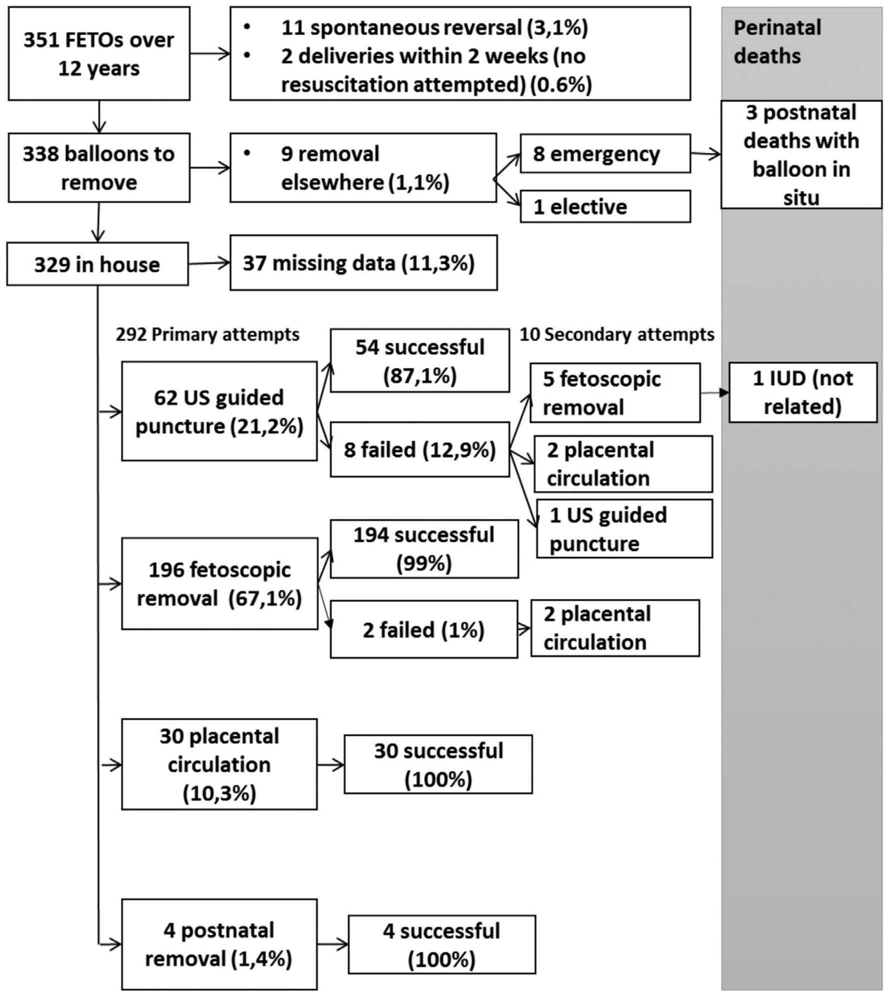
Materials and Methods

This is a 3-center analysis of prospectively collected data on consecutive fetuses with isolated CDH undergoing FETO at the University Hospitals of Leuven, Belgium; Hospital Clinic, Barcelona, Spain; and The Heart Hospital and Gestar Fetal Medicine and Surgery Center and Department of Obstetrics and Gynecology, São Paulo, Brazil. The first two teams pioneered the technique, and the lead surgeon in São Paulo was trained by them with the same technique and instruments.[3,16] The selection criteria, technique, and instruments for FETO and balloon removal can be found in Supplement 1.[3,17] We empirically drafted a decision tree, first attempting prenatal ultrasound-guided puncture (USGP); if not feasible or successful, we resorted to fetoscopy. Feasibility of USGP was left to the clinician's discretion. Ex utero removal was considered as a final strategy, preferably on placental circulation.

The obstetrical, fetal, and maternal data retrieved from hospital records are detailed in Supplement 2. Balloon removals were categorized as either prenatal, during delivery or postnatal, emergency or elective, by the method used, and by additional procedures to facilitate balloon removal (amnioinfusion, external version, or vaginal upwards pushing of the fetal head). Also, the interval between balloon removal and delivery was noted. First, descriptive statistics were done in terms of technique of removal in elective or emergency circumstances. We also tried to define conditions associated with impossible or problematic balloon removals. When referring centers chose to remove the balloon themselves, we retrieved information regarding the extraction and neonatal outcome.

FIGURE 1
Overview of procedures to remove 292 balloons at 3 centers



FETO, fetoscopic endoluminal tracheal occlusion; *IUD*, intrauterine demise; *US*, ultrasound.

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Statistical methods and ethics

Statistical analysis was performed with GraphPad Prism 7 (GraphPad Software, La Jolla, CA), using a two-tailed *t* test or analysis of variance (or Kruskal-Wallis test for nonparametric data) to compare them. For categorical variables the Fisher exact test and χ^2 were used. Values are expressed in mean, standard error of the mean and range when suitable. Descriptions were performed with differences of means or proportions with 95% confidence intervals for continuous and categorical data respectively. This study was approved by the Ethics Committee of the University Hospitals Leuven in document ML980. Next to this specific study, the clinical in utero treatment program of fetuses with isolated CDH has been approved by the Ethics Committees of the participating centers. Following counseling, participants give an informed consent for the procedure.

Results

Study population

A total of 351 balloon insertions were done over a 144-month period (Figure 1). Thirteen procedures were excluded from analysis either because there was no need for balloon removal (2 deliveries within 1 week after insertion, and 11 in whom free airways could be confirmed before birth, suggesting spontaneous dislodgement). In 9 cases (1.1%), the balloons were removed outside the FETO center at a median gestational age (GA) of 32.1 ± 0.6 weeks (range 28.0−36.1), one electively by USGP, and 8 emergency perinatal attempts. Four of these were removals on placental circulation and all were successful. In 4 cases, there was mention of primary removal in the postnatal period only. Three of them failed, with the consequent death of the newborn with the balloon still in situ. In 37 cases, the balloon removal detailed outcome data were missing. These observations were scattered along the experience of the Brazilian team. Those cases were excluded from further analysis, leaving 329 cases (Figure 1).

This resulted in 302 in-house balloon removal procedures in 292 fetuses, including 10 patients in whom 2 attempts were needed. There were no maternal complications observed. The overall GA at balloon removal was 33.4 ± 0.1 weeks (range, 28.9−37.1), with an interval between FETO and removal of 34.7 ± 0.8 days (range, 3−70) and an interval between removal and delivery of 16.6 ± 0.8 days (range, 0−85). In 81 attempts (26.8%) the membranes were ruptured before balloon removal. In 135 (44.7%) procedures, the placenta was reported as anterior. All balloons eventually were removed successfully, most primarily, although a second attempt in 10 of 292 (3.4%). Eight of the latter 10 that initially failed were USGP (8/62; 12.9%). Of those, 5 balloons were removed eventually by fetoscopy and 2 on placental circulation by tracheoscopy, because fetoscopy was judged impossible because of the fetal position. In another one, a second attempt by USGP later was successful. At that time, the fetal position was more favorable.

There were 2 failed fetoscopic attempts of 196 (1.02%), followed immediately thereafter by retrieval on placental circulation, which was successful. One fetus died in utero 10 days after balloon removal (failed USGP first attempt followed by a successful fetoscopic removal). Necropsy was done and no obvious cause was identified; therefore, we classified the cause of death as most likely unrelated to the removal procedure (Figure 1). Of all the endoscopic balloon retrievals, in only 2 cases minor tracheal epithelial defects were described during the tracheoscopy. In neither of the 2 did this have postnatal clinical consequences.

Elective removal was done in 217 attempts (71.9%) at 33.7 ± 0.1 weeks (range, 31−37.1 weeks) and in 85 attempts (28.1%) the removal was in an emergency setting at 32.7 ± 0.2 weeks (range, 28−35 weeks) after threatened preterm labor was diagnosed. Accordingly, tracheal occlusion duration was shorter at the time of emergency removal than electively (29.9 ± 1.4 and 36.6 ± 0.9 days, respectively; difference of means: 6.7 ± 1.7 weeks; 95% confidence interval [95% CI], −10.2 to −3.4; $P < .05$). The mean GA at delivery for elective removals was 36.6 ± 0.1 weeks (range, 31−40 weeks) and for emergency removals was 33.3 ± 01 weeks (range, 28−40 weeks). Fetoscopy was apparently the preferred method of removal during elective procedures (Table 1). Emergency procedures were distributed among removal on placental circulation, fetoscopy, and USGP. Postnatal removal was done only in an emergency setting (Table 1). Polyhydramnios was more frequent in elective removals and oligohydramnios was more frequent when the balloon was removed as an emergency (Appendix 1). Additional procedures were performed in 6 cases, all of them to create access to the mouth for fetoscopic removal. Amnioinfusion was done in 3 because of oligohydramnios and during an emergency removal. We performed 2 external versions, both elective. In one case, the same goal was achieved by gentle upward pushing through the vagina (elective removal; 35 weeks).

Elective balloon removal

Fetoscopic balloon removals were done slightly later than USGP (clinically not relevant) (Table 2). The postoperative course following both procedures seemed very comparable, with no differences between the 2 techniques in the interval between balloon removal and delivery for both methods (fetoscopy: 21.4 ± 1.1 days, range 0−85; USGP: 18.1 ± 1.9 days, range 0−49), without a major influence of the intervention on immediate onset of the delivery (Figure 2). On placental circulation, removal was only done in one case, in which other techniques were not possible because of fetal position, and it was successful and excluded from the aforementioned analysis. Anterior placenta was more frequent when USGP was chosen and polyhydramnios was more frequent when fetoscopy was used. No other differences were found in maternal characteristics or pregnancy-related variables between the chosen techniques (Table 2). The overall failure rate in elective cases was 3.2% (7/217).

TABLE 1
Balloon elective or emergency removals by technique

Balloon removal procedure	Elective (n = 217; 71.9%)	Emergency (n = 85; 28.1%)	Difference of proportions, % (95% CI)	Total (n = 302)
Ultrasound-guided puncture	45 (20.7%)	18 (21.2%)	0.5 (−0.1 to 0.1)	63 (20.8%)
Fetoscopic[a]	171 (78.8%)	30 (35.3%)	43.5 (0.3 to 0.5)	201 (66.6%)
On placental circulation[a]	1 (0.5%)	33 (38.8%)	38.3 (0.3 to 0.5)	34 (11.3%)
Postnatal[a]	0 (0%)	4 (4.7%)	4.8 (−0.03 to 0.09)	4 (1.3%)

Balloon removals by technique, further broken down by the elective or emergent nature of the removal. Differences of proportions and 95% CIs are presented.

CI, confidence interval.

[a] Fisher exact test *P* value <.05.

Jiménez et al. Balloon removal in diaphragmatic hernia. Am J Obstet Gynecol 2017.

TABLE 2
Elective balloon removals maternal characteristics or pregnancy-related variables by technique

Parameter	Ultrasound-guided puncture (n = 45; 20.7%)	Fetoscopy (n = 171; 78.8%)	On placental circulation[a] (n = 1; 0.5%)	Difference of means or proportions (95% CI)	*P* value
Maternal age, y	30.0 ± 0.9	31.3 ± 0.4	35.0 ± 2.9	1.3 ± 0.9 (−0.5 to 3.2)	.2
Maternal BMI	25.6 ± 0.6	25.9 ± 0.3	27.8 ± 2.1	0.3 ± 0.8 (−1.2 to 1.9)	.7
GA removal, wk	33.3 ± 0.1	33.9 ± 0.2	34.0	0.5 ± 0.1 (0.2−0.8)	.001
Occlusion days	39.6 ± 1.7	36.0 ± 1.0	41	3.6 ± 2.2 (−7.9 to 0.8)	.1
Anterior placenta	25/45 (55.6%)	63/171 (36.8%)	1/1 (100%)	18.7 (0.01 to 0.3)	.02
Oligohydramnios	4/45 (8.9%)	5/171 (2.9%)	0/1 (0%)	6 (−0.01 to 0.2)	.9
Polyhydramnios	10/45 (22.2%)	78/171 (45.6%)	1/1 (100%)	23.4 (0.1 to 0.4)	.006
Breech position	6/45 (13.3%)	29/171 (16.9%)	1/1 (50%)	3.6 (−0.07 to 0.2)	.7

Elective balloon removals by technique, further broken down by maternal characteristics or pregnancy-related variables. Differences of proportions or means and 95% CIs are presented. Student *t* test or Fisher exact test was used to calculate *P* values.

CI, confidence interval; *BMI*, body mass index; *GA*, gestational age.

[a] Excluded from analysis; only 1 case.

Jiménez et al. Balloon removal in diaphragmatic hernia. Am J Obstet Gynecol 2017.

The failure rate of USGP by these operators was 11.1% (5/45), which is significantly greater than for fetoscopy (1.2%; 2/171) (difference of proportions = 9.9%; 95% CI, 0.02 to 0.2; $P < .05$). There were no fetal complications observed with either method.

Emergency balloon removal

Oligohydramnios was more frequent for on placental removals and breech position more frequent during postnatal removals (Table 3). The overall failure rate in emergency cases was 3.5% (3/85). The failure rate of USGP was 16.6% (3/18), which is significantly greater than the other techniques, where there were no failed attempts.

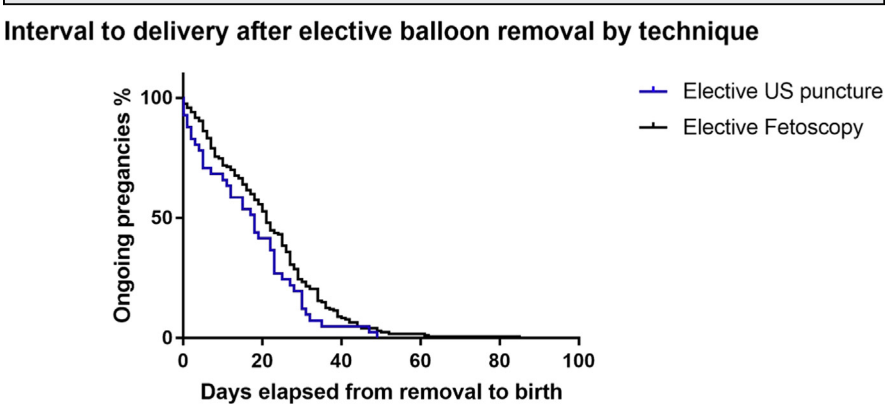
Preferred technique for balloon removal

Preferred primary removal technique at each center is described in Table 4. In São Paulo, the preferred technique was USGP. In both Leuven and Barcelona, the preferred technique was fetoscopy. The Barcelona team even decided not to use USGP after 6 cases (2 failed first attempts followed by fetoscopic removal).

Technique of fetoscopic balloon removal

In total, there were 196 primary and 5 secondary fetoscopic removals at a mean GA 33.8 ± 0.1 weeks, which took on average 18 ± 0.7 minutes (range, 3−60). Twenty-six attempts were categorized as difficult (12.9%). The reasons why removal was classified as difficult are displayed in Table 5. Most difficulties (12/26; 46.2%) were related to fetoscopic balloon extraction using only the forceps. When the balloon could not be dislodged, operators resorted intuitively to puncture, at that time using a laser fiber. Based on that observation, an adjustable stylet (11506P; Karl Storz, Tuttlingen, Germany) was developed and introduced in first in Leuven in 2008 (case 58 Leuven; case 13 Barcelona; case 3 Sao Paulo). Beyond that point, fetoscopic retrieval time significantly decreased (from 21.5 ± 1.3 to 15.0 ± 0.9 minutes [difference 6.5 minutes]; 95% CI, −9.6 to −3.5; $P < .05$) and the linear time trend was inverted (ie, time trend was increasing before the introduction of the stylet; after that, time trend decreased). Also, the number of attempts

FIGURE 2
Survival curves of ongoing pregnancies after the elective balloon removal by US-guided puncture or by fetoscopy



US, ultrasound.

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TABLE 3
Emergency balloon removals maternal characteristics or pregnancy-related variables by technique

Parameter	Ultrasound-guided puncture (n = 18; 21.2%)	Fetoscopy (n = 30; 35.3%)	On placental circulation (n = 33; 38.8%)	Postnatal (n = 4; 4.7%)	*P* value
Maternal age	30.4 ± 1.4	31.3 ± 1.1	30.0 ± 0.8	31.7 ± 1.5	.8
Maternal BMI	25.4 ± 1.2	25.5 ± 1.3	25.0 ± 0.8	23.4 ± 1.3	.9
GA removal	32.4 ± 0.5	33 ± 0.2	32.6 ± 0.27	27.6 ± 1.2	.3
Occlusion days	30.7 ± 3.8	31.9 ± 2.01	29.1 ± 2.2	16.5 ± 7.1	.2
Anterior placenta	12/18 (66%)	15/30 (50%)	16/33 (48.5%)	2/4 (50%)	.7
Oligohydramnios	6/18 (33.3%)	5/30 (16.6%)	17/33 (51.5%)	1/4 (25%)	.03
Polyhydramnios	3/18 (16.6%)	10/30 (33.3%)	3/33 (9.1%)	0/4 (0%)	.07
Breech position	2/18 (11.1%)	5/30 (16.6%)	7/33 (21.2%)	3/4 (75%)	.04

Emergency balloon removals by technique, further broken down by maternal characteristics or pregnancy related variables. Analysis of variance or Fisher exact test was used to calculate *P* values.

BMI, body mass index; *GA*, gestational age.

Jiménez et al. Balloon removal in diaphragmatic hernia. Am J Obstet Gynecol 2017.

categorized as difficult dropped significantly from 26.8% to 5.4%. (19/71 to 7/130; difference 21.4%; 95% CI, 0.2 to 0.6; $P < .05$) (Figure 3). When we identified factors associated difficult fetoscopic removal the availability of the stylet was the strongest factor (Table 6).

Ultrasound-guided puncture removal

There were 62 primary and one secondary USGP balloon removals at a mean GA of 33.7 ± 0.2 weeks. The intrauterine time of these were not recorded accurately enough to allow further analysis. When we compared the maternal characteristics or pregnancy-related variables, USGP was performed earlier than other technique, less likely to be used when there was polyhydramnios or in breech. It was more used when placenta was anterior (Appendix 2). Given the limited number of cases and brief procedure description in the records, no further attempts were made to describe difficulties or failure and associated maternal characteristics and pregnancy-associated variables.

Removal on placental circulation and postnatally

Extraction of the balloon on placental circulation was used primarily in 30 cases and 4 times secondarily after failed USGP or failed fetoscopy (2 each) at a mean GA 32.6 ± 0.3 weeks. This technique was more used in an emergency setting and earlier than the other techniques, with consequent shorter occlusion duration. When we compared the maternal or pregnancy-related characteristics of primary removals on placental circulation vs the other primary used techniques (Appendix 3), oligohydramnios was more frequent when this technique was used and polyhydramnios was less frequent. Postnatal balloon removal was used in 4 cases, always in an emergency setting, at a mean GA of 31.7 ± 0.7 weeks. All of these were done in Leuven.

Comment

This triple case series leads us to four conclusions. First, in patients purposely managed outside the FETO center, 3 of 9 balloons could not be removed. This was associated with neonatal death. Second, for on-site fetoscopic removals the introduction of a stylet dramatically facilitated retrieval and lowered the operation time. Third, the exact method for balloon removal seems to be, at least in part, function of operator preference as in all 3 centers balloons could be removed safely and effectively, yet by different techniques. Fourth, in utero airway re-establishment, either by percutaneous puncture or fetoscopy, does not precipitate immediate membrane rupture, labor, or delivery.

This study represents the historical development and evolution of a procedure that had no upfront standardized protocol but was managed initially

TABLE 4
Balloon removals primary attempts technique preferences by center

Balloon removal procedure ratio	Leuven	Barcelona	São Paulo	Total
Ultrasound-guided puncture	17 (12.0%)	6 (9.0%)	39 (47.0%)	62 (21.2%)
Fetoscopic	104 (73.2%)	57 (85.1%)	35 (42.2%)	196 (67.1%)
On placental circulation	17 (12.0%)	4 (5.9%)	9 (10.8%)	30 (10.3%)
Postnatal	4 (2.8%)	0 (0.0 %)	0 (0%)	4 (1.4%)
Total	142 (48.6%)	67 (23.0%)	83 (28.4%)	292

Balloon removals primary attempts technique preferences by center. No comparisons were done as the centers have different clinical approaches to select the technique.

Jiménez et al. Balloon removal in diaphragmatic hernia. Am J Obstet Gynecol 2017.

TABLE 5
Categorization of difficulties reported during fetoscopic balloon removal

Difficult fetoscopic removals	26/201
Criteria	
Longer than 90th percentile	21
Difficult balloon traction/puncture	9
Difficult airway access	8
Fetal movements	3
Difficult access to amniotic cavity	1
Operator reporting as "difficult"	5
Difficult balloon traction/puncture[a]	3
Fetal movements[b]	1
Unable to remove	1

Categorization of difficulties reported during fetoscopic balloon removal. Each case was assigned only once, according to the principal difficulty.

[a] Other than long operation time; [b] In the absence of a long operation time.

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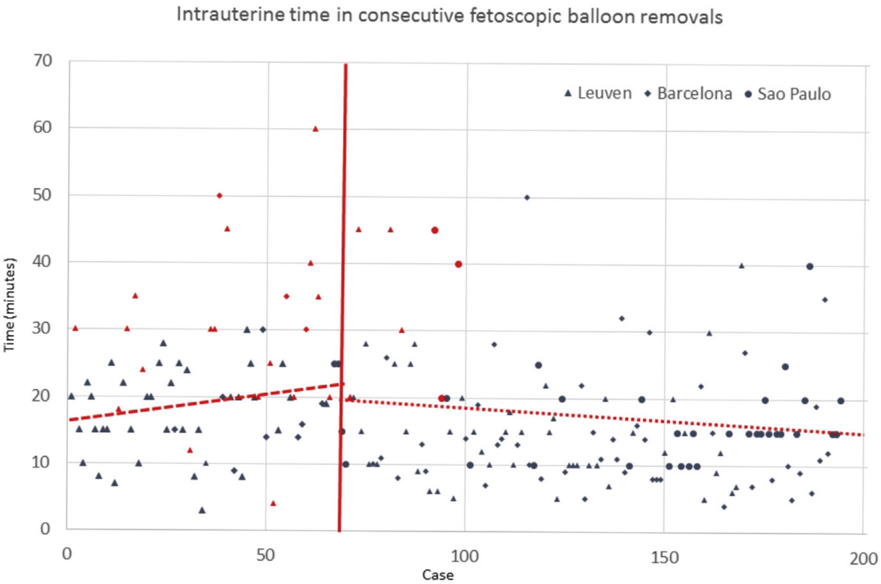
FIGURE 3
Operation time vs case number for fetoscopic balloon removals



▲, Leuven case; ◆, Barcelona case; ●, Sao Paulo case. Difficult fetoscopic removals are shown by a *red symbol. Red vertical line* depicts the introduction of the stylet; *dashed line* shows the linear trend of operative time before introduction of the stylet ($y = 0.0936x + 17.696$; $r^2 = 0.04$) and the *dotted line* shows the linear trend of operative time after this ($y = -0.0359x + 20.868$; $r^2 = 0.02$).

Jiménez et al. Balloon removal in diaphragmatic hernia. Am J Obstet Gynecol 2017.

using an empirical decision tree. Furthermore, it shows the experience of 3 different centers, 2 of which were among the pioneers of this procedure. At the onset of this study, we wanted to describe these 2 centers' experiences. On analysis, we suspected that operator preferences were biased towards fetoscopic balloon removal, as at some stage one team de facto abandoned ultrasound-guided puncture. Therefore, we asked for data from São Paulo, a team in which the lead member was trained in London, the third member of the FETO consortium.[17] We were aware that their preference was to remove the balloon by percutaneous ultrasound-guided puncture. The data herein confirm this personal bias towards a certain technique. Given that there was no standardized management, we did not embark on formal statistics to extract factors predicting the (successful) use of one or the other technique. Therefore, our study reflects a procedure in progress, which has stabilized, yet with a different preference for each surgeon.

Despite the aforementioned limitations, a number of other clinical conclusions can be drawn, which may be relevant now that FETO is becoming implemented more widely in a multicenter randomized controlled trial.[17] Based on these 3 cohorts, we propose a decision tree and give indicative numbers for the entire experience (Figure 4).

In total, 9 non-FETO centers took the responsibility of having the patient return after balloon insertion, and to remove it themselves. In 3, the managing team failed to do so, and this was the most likely the direct cause of neonatal death. Whether the inability to re-establish the airways was due lack of appropriate instrumentation or the method chosen (all were ex utero) is unclear. Extraction on placental circulation was successful in 4 of 4 cases in which this was the method chosen. Therefore, we now ask upfront that patients remain on site for as long as the balloon is in situ. We can guarantee 24/7 availability and all methods and instruments.

Forty percent of removals were done under local anesthesia (ie, in utero, not in labor) with fetal analgesia and immobilization. This number in the later experience is even greater, as initially loco-regional anesthesia was the anesthetic of choice. This was done out of precaution, to enable immediate delivery if fetal distress would occur. Because3 this never materialized, we moved away to local anesthesia.

All removal techniques are successful and safe, and they are not exclusive. Ultrasound-guided puncture failed in ~10%, yet with a range from 5% to 33% according to the center. Fetoscopy, which was used in both elective and emergency settings, had a very low failure rate (1%; 0%−1%). For the 40% of cases in which in utero freeing of the airways failed, postnatal alternatives were used. The most comfortable one is tracheoscopic removal on placental circulation, which we did under

TABLE 6
Maternal characteristics or pregnancy-related variables in difficult and not-difficult fetoscopic balloon removals

Parameter	Difficult (n = 26; 12.9%)	Not difficult (n = 175; 87.1%)	Difference of means or proportions (95% CI)	*P* value
Maternal age, y	31.5 ± 1,3	31.4 ± 0,4	0.1 ± 1.3 (−2.4 to 2.6)	.9
Maternal BMI	27.9 ± 1.6	25.4 ± 0.5	2.4 ± 1.4 (−0.3 to 5.3)	.08
GA at removal, wk	33.5 ± 0.1	33.64 ± 0.1	0.09 ± 0.2 (−0.5 to 0.3)	.5
Occlusion days	34.6 ± 2.3	31.1 ± 0.9	3.5 ± 2.4 (−1.2 to 8.2)	.1
Anterior placenta	11/26 (42.3%)	67/175 (38.3%)	4.0 (−0.2 to 0.3)	.8
Oligohydramnios	2/26 (7.7%)	8/175 (4.6%)	3.1 (−0.04 to 0.2)	.6
Polyhydramnios	12/26 (46.2%)	76/175 (43.4%)	2.7 (−0.2 to 0.2)	.8
Breech position	2/26 (7.7%)	32/175 (18. 3%)	10.6 (0.01 to 0.3)	.3
Emergency removal	5/26 (19.2%)	25/175 (14.3%)	4.9 (−0.1 to 0.3)	.6
Stylet introduction	19/26 (73.1%)	53/175 (30.3%)	42.9 (0.2 to 0.6)	.0001

Maternal characteristics or pregnancy-related variables in difficult and not difficult fetoscopic balloon removals. Differences of proportions or means and 95% CIs are presented. Student *t* test or Fisher exact test was used to calculate *P* values.

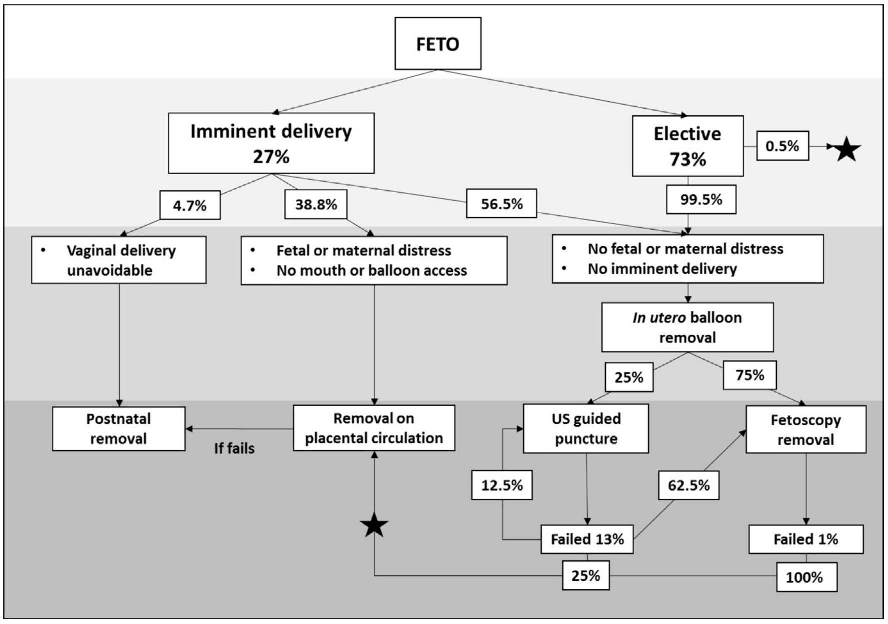
BMI, body mass index; *CI*, confidence interval; *GA*, gestational age.

Jiménez et al. Balloon removal in diaphragmatic hernia. Am J Obstet Gynecol 2017.

locoregional anesthesia, hence not as an ex utero intrapartum treatment procedure.[18] We dare to do without general anesthesia and a formal ex utero intrapartum treatment protocol, because the nature of the tracheal obstruction is well known, and removal of the balloon can be done quickly. In the rare case in utero removal was not possible (4.7%), the balloon was extracted successfully or punctured, without compromised umbilical cord blood gas levels at birth. Despite all that, balloon removal remains one of the limitations of the procedure. When doing it in utero, there is the inherent risk that the second procedure causes membrane rupture and/or preterm labor. It is very difficult to assess the effect of in utero balloon removal, yet when done electively at ≥34 weeks in patients without membrane rupture, only 23% of patients go into labor or rupture their membranes within 1 week. Actually, in this series the mean GA at birth after elective removals was 36.6 ± 0.1 weeks. This is 1 week later than what was reported in FETO patients expectantly managed using a strategy of balloon removal by ex utero intrapartum treatment, yet the data from the paper do not allow to extract raw data.[15] Fortunately, noninvasive techniques are under development, such as bursting of the balloon by high-frequency ultrasound or opening of the valve via a magnetic field.[19] The reliability of this, and the absence of fetal side effects remain to be proven.

Lastly, it needs to be acknowledged that it remains uncertain whether prenatal removal improves outcome as compared with postnatal removal, as suggested by others.[20] We have chosen this strategy, based on the extrapolation of the experimental protocol [11] and the clinical observation that prenatal

FIGURE 4
Proposed decision tree; team preferences



FETO, fetoscopic endoluminal tracheal occlusion; *US*, ultrasound.

Jiménez et al. Balloon removal in diaphragmatic hernia. Am J Obstet Gynecol 2017.

balloon removal is associated to a greater survival and lesser morbidity.[3,13] Apart from that, it has logistic consequences: it avoids unplanned, emergency balloon retrieval procedures and it permits in utero return to the referring tertiary center. The clinical consequences from our observations are that attempting tracheal balloon removal puts a tremendous responsibility on the operators. Teams have to provide the necessary skills and equipment for all available techniques, and these need to be permanently available. Access method for balloon removal may be a matter of preference. Although all are reliable, these techniques are complementary. ■

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Supplement 1

Criteria and technique for balloon occlusion

The endovascular balloon occlusion system is used off label. The Food and Drug Administration approved the use of these customized endoscopic instruments for this purpose.

Technique of balloon removal and decision tree

Balloon retrieval can be done in various ways. In utero, the balloon can be punctured by ultrasound-guided puncture, which we did with a 20-G needle, using fetal immobilization and analgesia. Following that, the balloon exits the airway together with entrapped lung fluid. Fetoscopic balloon extraction is done with similar instruments as for balloon insertion, yet using a 3 Fr forceps (11510C; Karl Storz, Tuttlingen, Germany). Because it turned out to be difficult to pull out the balloon when inflated, we designed an adjustable stylet (11506P; Karl Storz,). It is inserted through an operative channel, with its length is adjusted such that it exits the scope only a few millimeters, avoiding inadvertent trauma. Under viewing, the balloon tail can be grasped; the balloon is punctured, and retrieved. This device was used from case 71 onwards (case 58 in Leuven, 13 in Barcelona and case 3 in São Paulo).

In case in utero retrieval is not possible, the balloon can be removed by tracheoscopy during a modified cesarean section, with the fetal head and shoulders delivered, yet with the umbilical cord inside and the fetus remaining on placental circulation. Finally, the balloon can also be removed postnatally, which also is done by video laryngo-tracheoscopy and purpose-designed instruments.[1] The 3 participating centers never used ex utero blind or ultrasound-guided postnatal tracheal puncture with a short needle above the manubrium sterni, as described previously.[2] At the onset of the program, the empirically drafted decision tree was to first attempt ultrasound-guided puncture; if not feasible or successful, to resort to fetoscopic retrieval. This decision was always left to the clinician's discretion. Ex utero removal was always considered as a final strategy, preferentially on placental circulation. Also in terms of timing, the preferred scenario was to remove the balloon in utero and allow the lungs to mature, based on experimental data and later confirmed to be clinically relevant.[3-5]

Supplement 2

Data retrieved from hospital records

The following data were retrieved from hospital records. Maternal data were confined to age (years) and body mass index. Prenatal measures were gestational age (GA; weeks) at the time of endoscopic tracheal occlusion, anterior placenta (yes/no), presence of poly- or oligohydramnios (>8 cm or <2 cm) (yes/no), spontaneous balloon deflation (yes/no), duration of the tracheal occlusion period (in days), the occurrence of preterm prelabor rupture of the membranes and the GA at which this occurred (weeks); for balloon removal: time point in relation to delivery (prenatal, during delivery or postnatal), the GA at removal (weeks), the method used, and fetal position during the procedure (cephalic, breech, or transverse), success (yes/no), and any additional procedure done before or during to facilitate balloon removal (amnioinfusion, external version or upwards pushing of the fetal head through the vagina), duration of in utero fetoscopy (minutes), presence of uterine contractions (yes/no), use of tocolysis (yes/no) at the time of removal, and any description of difficulties or problems during balloon removal. Other parameters were interval between balloon removal and delivery, GA at birth (weeks), death events in relationship with the balloon removal, and any tracheal damage diagnosed at any time point.

Data analysis

First, balloon removal procedures were categorized according to the circumstances of the removal procedure (elective or emergency). Procedures were categorized by the method used (ultrasound-guided puncture, retrieval by fetoscopy, on placental circulation or postnatal). For those where an initial attempt failed, the secondary procedure(s) also were reported.

The second goal of this study was to define conditions associated with impossible or problematic balloon removals. Balloon removal attempts were for that purpose post hoc categorized as either "smooth" or "problematic." The latter was if any of the following events occurred: Failure to remove the balloon with the planned method OR the specific mention by the clinician that the removal was problematic OR time required for removal >90th percentile of the entire cohort (ie, 30.0 minutes) for fetoscopic removals.

APPENDIX 1

Comparison of maternal characteristics and pregnancy associated variables of elective balloon removal

Parameter	Elective (n = 217; 71.9%)	Emergency (n = 85; 28.1%)	Difference of means or proportions (95% CI)	*P* value
Maternal age, y	31.1 ± 0.4	30.1 ± 0.6	0.4 ± 0.7 (−1.8 to 1.1)	.5
Maternal BMI	25.8 ± 0.3	25.2 ± 0.6	0.6 ± 0.6 (−1.9 to 0.6)	.3
GA removal, wk	33.7 ± 0.1	32.7 ± 0.2	1.1 ± 0.1 (−1.4 to −0.8)	.0001
Occlusion days	36.6 ± 0.9	29.9 ± 1.4	6.7 ± 1.7 (−10.2 to −3.4)	.0001
Anterior placenta	90/217 (41.5%)	40/85 (47.1%)	5.6 (−0.07 to 0.2)	.3
Oligohydramnios	9/217 (4.2%)	29/85 (34.1%)	29.9 (0.2 to 0.4)	.0001
Polyhydramnios	88/217 (40.6%)	16/85 (18.8%)	21.8 (0.09 to 0.3)	.0004
Breech position	36/217 (16.6%)	17/85 (20.0%)	3.4 (−0.08 to 0.1)	.5

Comparison of maternal characteristics and pregnancy-associated variables of elective balloon removal. Differences of proportions or means and 95% CIs are presented. Student *t* test or Fisher exact test were used to calculate *P* values.

BMI, body mass index; *CI*, confidence interval; *GA*, gestational age.

Jiménez et al. Balloon removal in diaphragmatic hernia. Am J Obstet Gynecol 2017.

APPENDIX 2

Comparison of maternal characteristics and pregnancy-associated variables of primary ultrasound-guided punctures, with the others

Parameter	Ultrasound-guided puncture	Other	Difference of means or proportions (95% CI)	*P* value
Maternal age	30.1 ± 0.7	31.1 ± 0.4	1.1 ± 0.8 (−2.6 to 0.5)	.2
Maternal BMI	25.5 ± 0.5	25.7 ± 0.3	0.2 ± 0.7 (−1.6 to 0.7)	.8
GA removal	33.06 ± 0.2	33.54 ± 0.09	0.4 ± 0.2 (−0.8 to 0.2)	0.01
Occlusion days	37.03 ± 1.7	34.15 ± 0.9	2.9 ± 1.9 (−0.9 to 6.7)	.14
Anterior placenta	37/63 (58.7%)	99/239 (41.4%)	17.3 (0.03 to 0.3)	.01
Oligohydramnios	10/63 (15.8%)	28/239 (11.7%)	4.1 (−0.05 to 0.2)	.4
Polyhydramnios	13/63 (20.6%)	83/239 (34.7%)	14.1 (0.03 to 0.3)	.03
Breech position	1/63 (1.6%)	39/239 (16.3%)	14.7 (0.1 to 0.2)	.001
Emergency	18/63 (28.6%)	58/239 (24.3%)	4.3 (−0.08 to 0.2)	.5

Comparison of maternal characteristics and pregnancy associated variables of primary ultrasound guided punctures, with the others.

BMI, body mass index; *CI*, confidence interval; *GA*, gestational age.

Jiménez et al. Balloon removal in diaphragmatic hernia. Am J Obstet Gynecol 2017.

APPENDIX 3

Comparison of maternal characteristics and pregnancy-associated variables of primary removals on placental circulation, with the others

Parameter	Placental circulation	Other	Difference of means or proportions (95% CI)	*P* value
Maternal age	30.3 ± 0.8	31.0 ± 0.35	0.7 ± 1 (−1.3 to 2.7)	.5
Maternal BMI	25.2 ± 0.8	25.7 ± 0.3	0.5 ± 0.9 (−2.3 to 1.3)	.6
GA removal	32.6 ± 0.3	33.55 ± 0.07	0.9 ± 0.23 (0.5 to 1.5)	.0001
Occlusion days	28.8 ± 2.2	35.5 ± 0.8	6.6 ± 2.5 (1.7 to 11.5)	.008
Anterior placenta	18/34 (52.9%)	118/268 (47.1%)	8.9 (−0.1 to 0.2)	.4
Oligohydramnios	17/34 (50%)	21/268 (7.8%)	42.2 (0.2 to 0.6)	.0001
Polyhydramnios	3/34 (8.8%)	101/268 (37.7%)	28.9 (0.2 to 0.5)	.001
Breech	8/34 (23.5%)	45/268 (16.8%)	6.7 (−0.06 to 0.3)	.34
Emergency	33/34 (97%)	48/268 (17.9%)	79.1 (0.6 to 0.8)	.0001

Comparison of maternal characteristics and pregnancy associated variables of primary removals on placental circulation, with the others.

BMI, body mass index; *CI*, confidence interval; *GA*, gestational age.

Jiménez et al. Balloon removal in diaphragmatic hernia. Am J Obstet Gynecol 2017.

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