Title: Balloon removal after fetoscopic endoluminal tracheal occlusion for congenital diaphragmatic hernia

Keywords: Congenital diaphragmatic hernia, fetal therapy, fetoscopic endoluminal tracheal occlusion

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Condensation:

Endoluminal tracheal balloon removal in fetuses with congenital diaphragmatic treated in utero can be done safe and effectively by a prepared and experienced team.

Short title: Balloon removal in diaphragmatic hernia

Abstract:

Background: Isolated congenital diaphragmatic hernia (CDH) 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 (FETO) under local anesthesia. This *in utero* treatment requires a second intevention to reestablish the airway, either before birth or at delivery.

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

Methods: This is a retrospective analysis of prospectively collected data on consecutive patients with congenital diaphragmatic hernia (CDH) treated *in utero* by fetal endoluminal tracheal occlusion (FETO) from three 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 (USGP); fetoscopy; *ex utero:* on placental circulation or postnatal tracheoscopy).

Results: We performed 351 balloon insertions over a 144 months period. In nine cases removal was attempted outside FETO centers, being impossible in three leading to neonatal death. We attempted 302 *in house* balloon removals in 292 fetuses (217 elective (71.8%), 85 emergency (28.2%)) at 33.4±0.1 weeks (range: 28.9-37.1), with a mean interval to delivery of 16.6±0.8 days (0-85). Primary attempt was by fetoscopy in 196 (67.1%), by USP in 62 (21.2%), by tracheoscopy on placental circulation in 30 (10.3%) and postnatal tracheoscopy in 4 cases (1.4%), needing a secondary attempt 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 USP removals. Difficulties during fetoscopic removals led to the development of a stylet to puncture the balloon leading to shorter operating time and easier reestablishment of airways.

Conclusions: In these fetal treatment centers, the balloon could always be successfully removed. In 90% this was *in utero*, fetoscopy being preferred over USP. *Ex utero* removal was a fall back procedure. *In utero* removal, does not seem to precipitate immediate membrane rupture, labour or delivery though the design of the study does 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.

INTRODUCTION:

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]. In comparison to historical controls of similar severity, FETO apparently increases survival rate from 24% to 49% in LCDH, and from 17% to 42% in RCDH with observed/expected LHR <45%[9,10]. Currently two parallel randomized clinical trials are being done to investigate if 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 can also leave the occlusion till 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.

METHODS:

This is a three-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 Sao Paula 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, resorting 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.

Statistical methods and ethics

Statistical analysis was done using GraphPad Prism 7 (GraphPad Software, La Jolla, USA), using a two-tailed t test or ANOVA (or Kruskal-Wallis test for non-parametric data) to compare them. For categorical variables Fisher's exact test and Chi-square were used. Values are expressed in mean, standard error of the mean (SEM) and range when suitable. Descriptions are done using 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 months' period (Figure 1). Thirteen procedures were excluded from analysis either because there was no need for balloon removal (two deliveries within one week after insertion, and eleven in whom free airways could be confirmed prior to birth, suggesting spontaneous dislodgement. In nine cases (1.1%) the balloons were removed outside the FETO center at a median GA of 32.1±0.6 weeks (range 28.0-36.1): one electively by USGP, and eight emergency perinatal attempts. Four of these were removals on placental circulation and all were successful. In four 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 was missing. These observations were scattered

along the experience of the Brazilian team. Those cases were excluded from further analysis. This leaves 329 cases (Figure 1).

This left 302 in house balloon removal procedures in 292 fetuses, including therefore 10 patients where two attempts were needed. There were no maternal complications observed. The overall gestational age at balloon removal was 33.4±0.1 weeks (range 28.9 to 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 prior to balloon removal. In 135 (44.7%) procedures the placenta was reported as anterior. All balloons were eventually successfully removed, most primarily, yet requiring a secondary attempt in 10/292 (3.4%). Eight of the latter 10 initially failed were USGP (8/62; 12.9%). Of those, five balloons were eventually removed by fetoscopy, and two on placental circulation by tracheoscopy, as 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 two failed fetoscopic attempts out 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; so we classified the cause of death as most likely unrelated to the removal procedure (Figure 1). Out of all the endoscopic balloon retrievals in only two cases minor tracheal epithelial defects were described during the tracheoscopy. In none of the two this had 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% CI: -10.2 to -3.4; P<0.05). The mean gestational age 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 done in six cases, all of them to create access to the mouth access for fetoscopic removal. Amnioinfusion was done in three because of oligohydramnios and during an emergency removal. We performed two 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 two 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, being successful and excluded from the above-mentioned analysis. Anterior placenta was more frequent when USGP was chosen and polyhydramnios was more frequent when using fetoscopy. 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). The failure rate of USGP by these operators was 11.1% (5/45), which is significantly higher than for fetoscopy (1.2%; 2/171) (difference of proportions=9.9%; 95% CI= 0.02 to 0.2; P<0.05). 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 higher 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 already after 6 cases (two failed first attempts followed by fetoscopic removal).

Technique of fetoscopic balloon removal.

In total, there were 196 primary and five secondary fetoscopic removals at a mean GA 33.8±0.1 weeks, which took on average 18±0.7 min (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 intuitively resorted to puncture, at that time using a laser fiber. Based on that observation an adjustable stylet (Karl Storz, 11506P) was developed and introduced in 2008 (case 58 Leuven; case 13 Barcelona; case 3 Sao Paulo). Beyond that point, fetoscopic retrieval time significantly dropped (from 21.5±1.3 to 15.0±0.9 minutes (difference 6.5 min.; 95% CI -9.6 to -3.5; $P<0.05$) and the linear time trend was inverted (i.e. time trend was increasing before the introduction of the stylet; after that, time trend decreased). Also, the number of attempts categorized as difficult dropped significantly from 26.8% to 5.4%. (19/71 to 7/130; difference 21.4%; 95% IC: 0.2 to 0.6; $P<0.05$) (Figure 3). When identifying 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 accurately enough recorded to allow further analysis. When comparing the maternal characteristics or pregnancy related variables, USGP was done 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 nor 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 four times secondarily after failed USGP or failed fetoscopy (two 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 comparing the maternal or pregnancy related characteristics of primary removals on placental circulation versus 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 four 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, three out of nine 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 three centers balloons could be safely and effectively removed, yet by different techniques. Fourth, in utero airway re-establishment, either by percutaneous puncture or fetoscopy, does not precipitate immediate membrane rupture, labour or delivery.

This study represents the historical development and evolution of a procedure which had no upfront standardized protocol, but where initially managed using an empirical decision tree. Furthermore, it shows the experience from three different center, two of them being among the pioneers of this procedure. At the onset of this study, we wanted to describe these two centers experience. 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 where 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 above limitations, a number of other clinical conclusions can be drawn, which may be relevant now that FETO is becoming more widely implemented in a multi-center RCT[17]. Based on these three cohorts, we propose a decision tree and give indicative numbers for the entire experience (figure 4).

In total, nine non-FETO centers took the responsibility to have the patient return after balloon insertion, and to remove it themselves. In three, 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 four out of four cases where 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 (i.e. *in utero*, not in labour) with fetal analgesia and immobilization. This number in the later experience is even higher, 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. Since 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 where 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 loco-regional anesthesia, hence not as an EXIT procedure [18]. We dare to do without general anesthesia and a formal EXIT 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 successfully extracted or punctured, without compromise 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 labour. 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 labour or rupture their membranes within one week. Actually, in this series the mean gestational age at birth following elective removals was 36.6±0.1 weeks. This is one week later than what was reported in FETO patients expectantly managed using a strategy of balloon removal by EXIT, yet the data from the paper do not allow to extract raw data[15]. Fortunately, non-invasive 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 to 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 balloon removal is associated to a higher 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. Though all are reliable, these techniques are complementary.

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Tables

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 (-0.1-0.1)	**63 (20.8%)**
Fetoscopic *	171 (78.8%)	30 (35.3%)	43.5 (0.3-0.5)	**201 (66.6%)**
On placental circulation *	1 (0.5%)	33 (38.8%)	38.3 (0.3-0.5)	**34 (11.3%)**
Postnatal *	0 (0%)	4 (4.7%)	4.8 (-0.03-0.09)	**4 (1.3%)**

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 * (n=1; 0.5%)**	**Difference of means or proportions (95% CI)**	**P value**
Maternal age (years)	30.0 ± 0.9	31.3 ± 0.4	35.0± 2.9	1,3 ± 0,9 (-0,5-3,2)	0.2
Maternal BMI	25.6 ± 0.6	25.9 ± 0.3	27.8 ± 2.1	0,3 ± 0,8 (-1,2-1,9)	0.7
GA removal (weeks)	33.3 ± 0.1	33.9 ± 0.2	34.0	0,5 ± 0,1 (0,2-0,8)	0.001
Occlusion days	39.6 ± 1.7	36.0 ± 1.0	41	3,6 ± 2,2 (-7,9-0,8)	0.1
Anterior placenta	25/45 (55.6%)	63/171 (36.8%)	1/1 (100%)	18,7 (0.01-0.3)	0.02
Oligohydramnios	4/45 (8.9%)	5/171 (2.9%)	0/1 (0%)	6 (-0.01-0.2)	0.9
Polyhydramnios	10/45(22.2%)	78/171(45.6%)	1/1 (100%)	23.4 (0.1-0.4)	0.006
Breech position	6/45(13.3%)	29/171(16.9%)	1/1 (50%)	3.6 (-0.07-0.2)	0.7

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	0.8
Maternal BMI	25.4 ± 1.2	25.5 ± 1.3	25.0 ± 0.8	23.4 ± 1.3	0.9
GA removal	32.4 ± 0.5	33 ± 0.2	32.6 ± 0.27	27.6 ± 1.2	0.3
Occlusion days	30.7 ± 3.8	31.9 ± 2.01	29.1 ± 2.2	16.5 ± 7.1	0.2
Anterior placenta	12/18 (66%)	15/30 (50%)	16/33 (48.5%)	2/4(50%)	0.7
Oligohydramnios	6/18 (33.3%)	5/30 (16.6%)	17/33 (51.5%)	1/4 (25%)	0.03
Polyhydramnios	3/18 (16.6%)	10/30 (33.3%)	3/33 (9.1%)	0/4(0%)	0.07
Breech position	2/18 (11.1%)	5/30 (16.6%)	7/33 (21.2%)	3/4 (75%)	0.04

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**

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*	3
Fetal movements**	1
Unable to remove	**1**

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 (years)	31.5 ± 1,3	31.4 ± 0,4	0.1 ± 1.3 (-2.4-2.6)	0.9
Maternal BMI	27.9 ± 1.6	25.4 ± 0.5	2.4± 1.4 (-0.3-5.3)	0.08
GA at removal (weeks)	33.5 ± 0.1	33.64 ± 0.1	0.09 ± 0.2 (-0.5-0.3)	0.5
Occlusion days	34.6 ± 2.3	31.1 ± 0.9	3.5 ± 2.4 (-1.2-8.2)	0.1
Anterior placenta	11/26 (42.3%)	67/175 (38.3%)	4.0 (-0.2-0.3)	0.8
Olygohidramnios	2/26 (7.7%)	8/175 (4.6%)	3.1 (-0.04-0.2)	0.6
Polihidramnios	12/26 (46.2%)	76/175 (43.4%)	2.7 (-0.2-0.2)	0.8
Breech position	2/26 (7.7%)	32/175 (18. 3%)	10.6 (0.01-0.3)	0.3
Emergency removal	5/26 (19.2%)	25/175 (14.3%)	4.9 (-0.1-0.3)	0.6
Stylet introduction	19/26 (73.1%)	53/175 (30.3%)	42.9 (0.2-0.6)	0.0001

Table and figure legends

Table 1: Balloon removals by technique, further broken down by the elective or emergent nature of the removal. Differences of proportions and 95% confidence intervals are presented. *= Fisher's exact test P value <0.05

Table 2: Elective balloon removals by technique, further broke down by maternal characteristics or pregnancy related variables. Differences of proportions or means and 95% confidence intervals are presented. T-student test or Fisher's exact test were used to calculate P values. *=excluded from analysis; only 1 case. BMI: body max index, GA: Gestational age

Table 3: Emergency balloon removals by technique, further broke down by maternal characteristics or pregnancy related variables. ANOVA or Fisher's exact test were used to calculate P values. BMI: body max index, GA: Gestational age

Table 4**:** Balloon removals primary attempts technique preferences by center. No comparison were done as the centers have different clinical approaches to select the technique

Table 5: Categorization of difficulties reported during fetoscopic balloon removal. Each case was assigned only once, according to the principal difficulty. * Other than long operation time; ** in the absence of a long operation time.

Table 6: Maternal characteristics or pregnancy related variables in difficult and not difficult fetoscopic balloon removals. Differences of proportions or means and 95% confidence intervals are presented. T-student test or Fisher's exact test were used to calculate P values.

Figure 1: overview of procedures to remove 292 balloons at three centers.

FETO: Fetoscopic endoluminal tracheal occlusion; IUD: intrauterine demise.

Figure 2: Survival curves of ongoing pregnancies after the elective balloon removal by ultrasound guided puncture or by fetoscopy.

Figure 3: Operation time versus 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; dash-line shows the linear trend of operative time before introduction of the stylet ($y = 0.0936x + 17.696$; $r^2 = 0.04$) and the dot-line shows the linear trend of operative time after this ($y = -0.0359x + 20.868$; $r^2 = 0.02$).

Figure 4: Proposed decision tree; team preferences

FETO: Fetoscopic endoluminal tracheal occlusion; US: ultrasound

Appendixes

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 ± ,7 (-1.8 to 1.1)	0.5
Maternal BMI	25.8 ± 0.3	25.2 ± 0.6	0,6 ± 0,6 (-1.9 to 0.6)	0.3
GA removal (wks.)	33.7 ± 0.1	32.7 ± 0.2	1,1 ± 0,1 (-1.4 to -0.8)	0.0001
Occlusion days	36.6 ± 0.9	29.9 ± 1.4	6,7 ± 1,7 (-10.2 to -3.4)	0.0001
Anterior placenta	90/217 (41.5%)	40/85 (47.1%)	5.6 (-0.07 to 0.2)	0.3
Oligohydramnios	9/217 (4.2%)	29/85 (34.1%)	29.9 (0.2 to 0.4)	0.0001
Polyhydramnios	88/217 (40.6%)	16/85 (18.8%)	21.8 (0.09 to 0.3)	0.0004
Breech position	36/217 (16.6%)	17/85 (20.0%)	3.4 (-0.08 to 0.1)	0.5

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 (%)**	**P value**
Maternal age	30.1 ± 0.7	31.1 ± 0.4	1.1 ± 0.8 (-2.6 to 0.5)	0.2
Maternal BMI	25.5 ± 0.5	25.7 ± 0.3	0.2 ± 0.7 (-1.6 to 0.7)	0.8
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	0.14
Anterior placenta	37/63 (58.7%)	99/239 (41.4%)	17.3 (0.03 to 0.3)	0.01
Oligohydramnios	10/63 (15.8%)	28/239 (11.7%)	4.1 (-0.05 to 0.2)	0.4
Polyhydramnios	13/63 (20.6%)	83/239 (34.7%)	14.1 (0.03 to 0.3)	0.03
Breech position	1/63 (1.6%)	39/239 (16.3%)	14.7 (0.1 to 0.2)	0.001
Emergency	18/63 (28.6%)	58/239 (24.3%)	4.3 (-0.08 to 0.2)	0.5

Appendix 3: Comparison of maternal characteristics and pregnancy associated variables of primary removals on placental circulation, with the others.

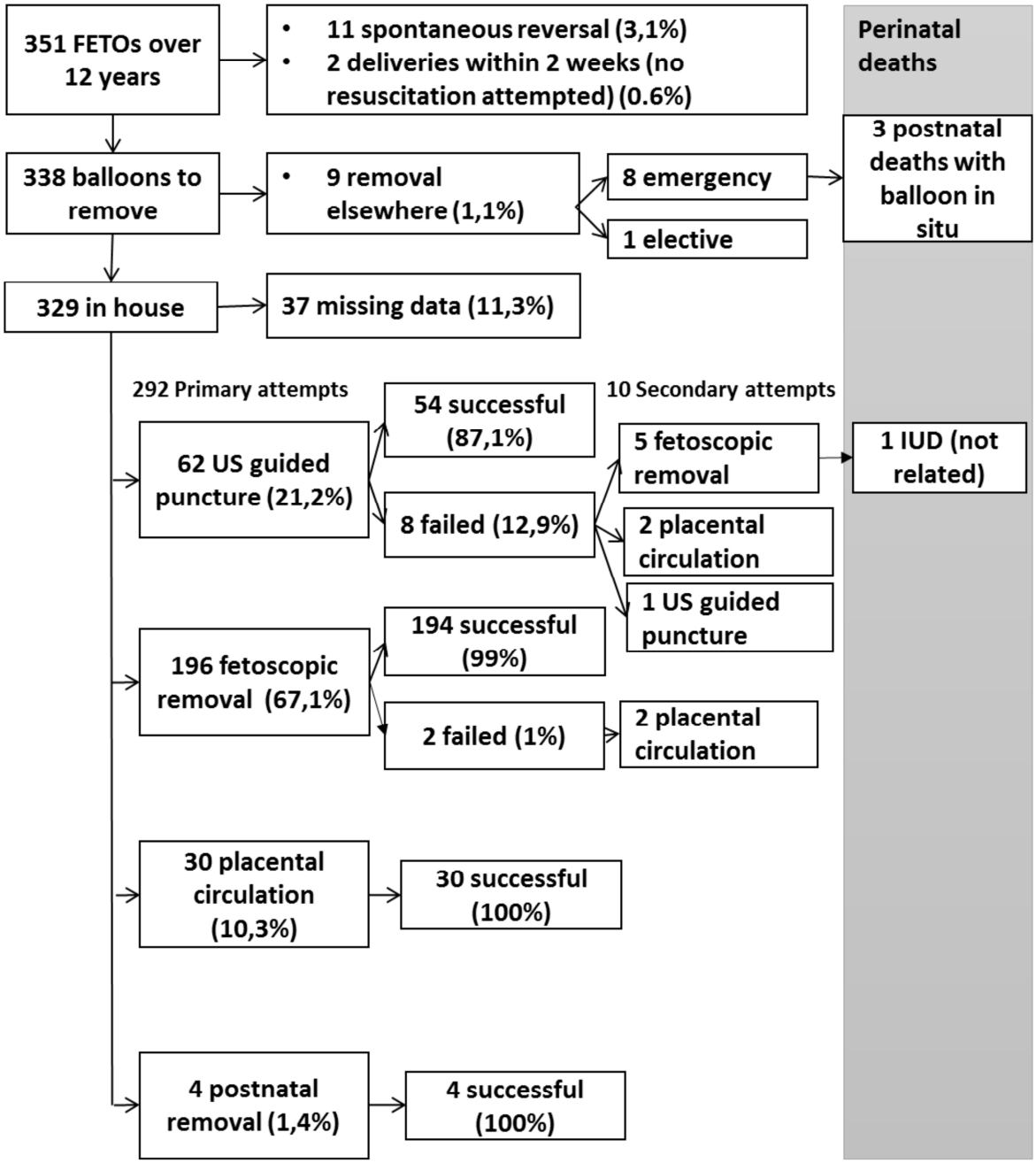
Parameter	**Placental circulation**	**Other**	**Difference of means or proportions (95% CI)**	**P value**
Maternal age	30.3 ± 0.8	31.0± 0.35	0.7 **±** 1 (-1.3 to 2.7)	0.5
Maternal BMI	25.2 ± 0.8	25.7 ± 0.3	0.5 ± 0.9 (-2.3 to 1.3)	0.6
GA removal	32.6 ± 0.3	33.55 ± 0.07	0.9 ± 0.23 (0.5 to 1.5)	0.0001
Occlusion days	28.8 ± 2.2	35.5 ± 0.8	6.6 ± 2.5 (1.7 to 11.5)	0.008
Anterior placenta	18/34 (52.9%)	118/268 (47.1%)	8.9 (-0.1 to 0.2)	0.4
Oligohydramnios	17/34 (50%)	21/268 (7.8%)	42.2 (0.2 to 0.6)	0.0001
Polyhydramnios	3/34 (8.8%)	101/268 (37.7%)	28.9 (0.2 to 0.5)	0.001
Breech	8/34 (23.5%)	45/268 (16.8%)	6.7 (-0.06 to 0.3)	0.34
Emergency	33/34 (97%)	48/268 (17.9%)	79.1 (0.6 to 0.8)	0.0001

Appendixes legends

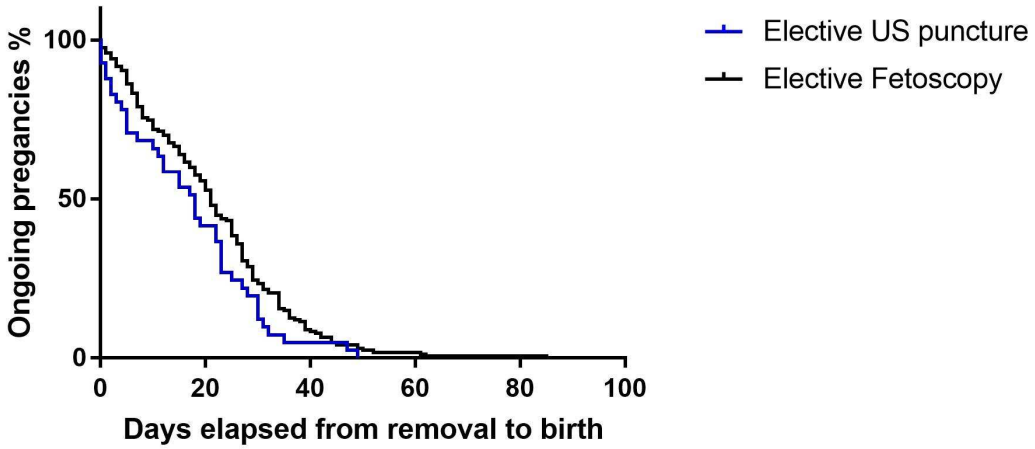
Appendix 1: Comparison of maternal characteristics and pregnancy associated variables of elective balloon removal. Differences of proportions or means and 95% confidence intervals are presented. T-student test or Fisher's exact test were used to calculate P values. BMI: body max index, GA: Gestational age

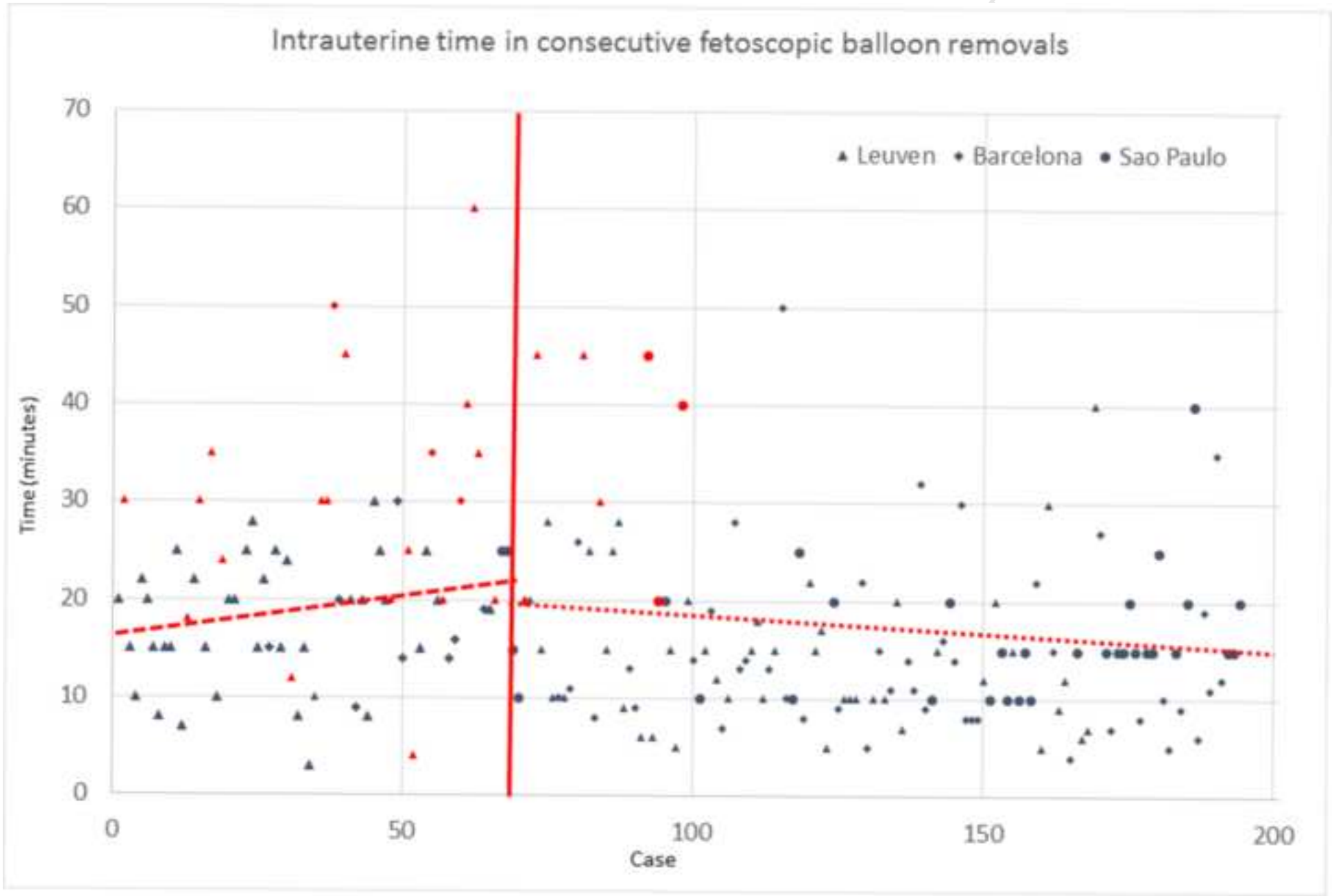
Appendix 2: Comparison of maternal characteristics and pregnancy associated variables of primary ultrasound guided punctures, with the others. BMI: body max index, GA: Gestational age

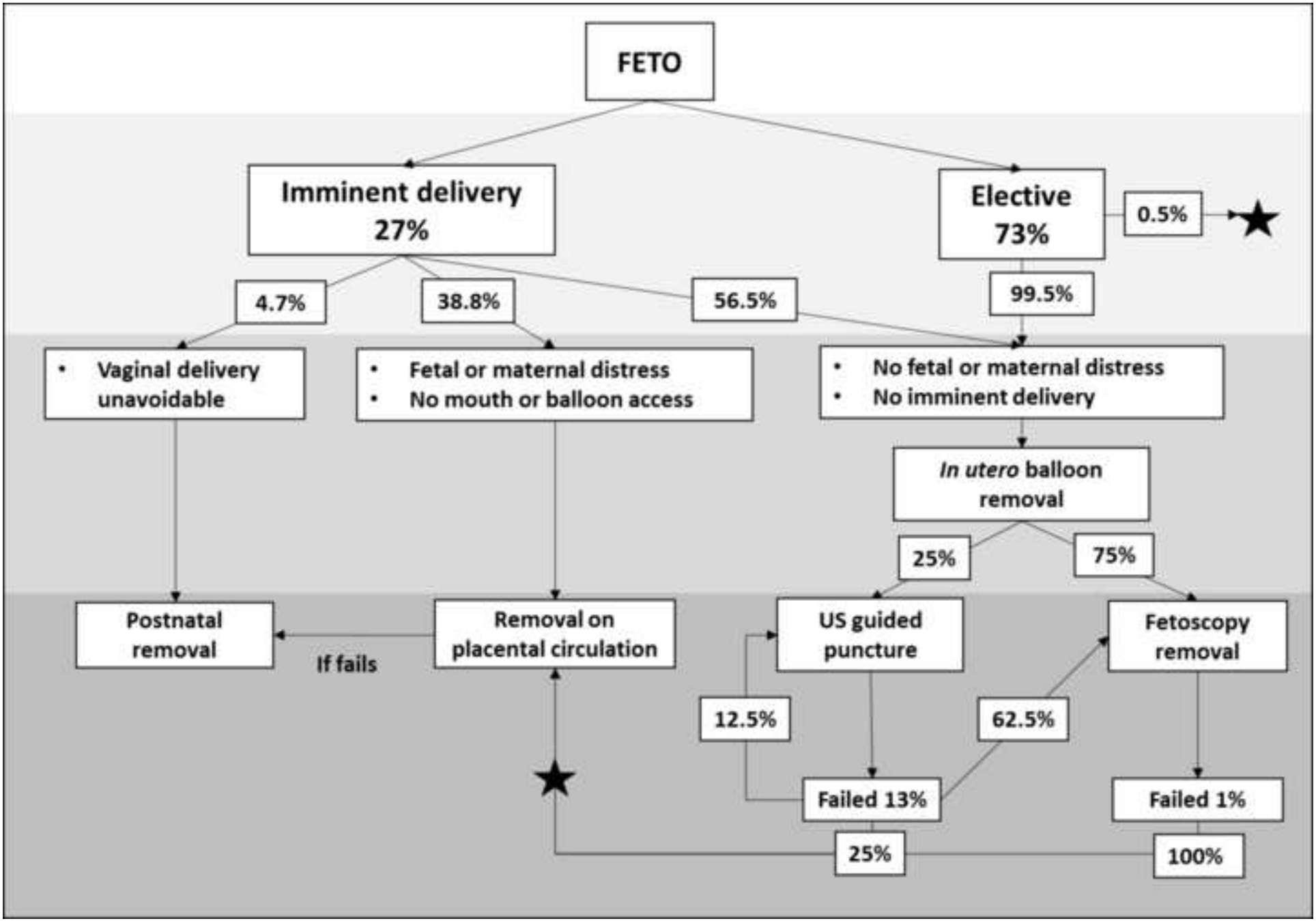
Appendix 3: Comparison of maternal characteristics and pregnancy associated variables of primary removals on placental circulation, with the others. BMI: body max index, GA: Gestational age


351 FETOs over 12 years
• 11 spontaneous reversal (3,1%)
• 2 deliveries within 2 weeks (no resuscitation attempted) (0.6%)
Perinatal deaths
338 balloons to remove
• 9 removal elsewhere (1,1%)
8 emergency
1 elective
3 postnatal deaths with balloon in situ
329 in house
37 missing data (11,3%)
292 Primary attempts
10 Secondary attempts
62 US guided puncture (21,2%)
54 successful (87,1%)
8 failed (12,9%)
5 fetoscopic removal
2 placental circulation
1 US guided puncture
1 IUD (not related)
196 fetoscopic removal (67,1%)
194 successful (99%)
2 failed (1%)
2 placental circulation
30 placental circulation (10,3%)
30 successful (100%)
4 postnatal removal (1,4%)
4 successful (100%)

Interval to delivery after elective balloon removal by technique




Intrauterine time in consecutive fetoscopic balloon removals
Leuven
Barcelona
Sao Paulo
Time (minutes)
Case
0
10
20
30
40
50
60
70
0
50
100
150
200


FETO
Imminent delivery 27%
Elective 73%
0.5%
4.7%
38.8%
56.5%
99.5%
• Vaginal delivery unavoidable
• Fetal or maternal distress
• No mouth or balloon access
• No fetal or maternal distress
• No imminent delivery
In utero balloon removal
25%
75%
Postnatal removal
If fails
Removal on placental circulation
US guided puncture
Fetoscopy removal
12.5%
62.5%
Failed 13%
Failed 1%
25%
100%