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## SCIENTIFIC ARTICLE

# Fetoscopic tracheal occlusion for severe congenital diaphragmatic hernia: retrospective study<sup>☆</sup>



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### KEYWORDS

Congenital diaphragmatic hernia;  
Prenatal diagnosis;  
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Fetoscopy;  
Fetal surgery;  
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### Abstract

**Background and objectives:** The temporary fetal tracheal occlusion performed by fetoscopy accelerates lung development and reduces neonatal mortality. The aim of this paper is to present an anesthetic experience in pregnant women, whose fetuses have diaphragmatic hernia, undergoing fetoscopic tracheal occlusion (FETO).

**Method:** Retrospective, descriptive study, approved by the Institutional Ethics Committee. Data were obtained from medical and anesthetic records.

**Results:** FETO was performed in 28 pregnant women. Demographic characteristics: age  $29.8 \pm 6.5$ ; weight  $68.64 \pm 12.26$ ; ASA I and II. Obstetric: IG  $26.1 \pm 1.10$  weeks (in FETO);  $32.86 \pm 1.58$  (reversal of occlusion);  $34.96 \pm 2.78$  (delivery). Delivery: cesarean section, vaginal delivery. Fetal data: Weight (g) in the occlusion and delivery times, respectively ( $1045.82 \pm 222.2$  and  $2294 \pm 553$ ); RPC in FETO and reversal of occlusion:  $0.7 \pm 0.15$  and  $1.32 \pm 0.34$ , respectively. Preoperative maternal anesthesia included ranitidine and metoclopramide, nifedipine (VO) and indomethacin (rectal). Preanesthetic medication with midazolam IV. Anesthetic techniques: combination of 0.5% hyperbaric bupivacaine (5–10 mg) and sufentanil; continuous epidural predominantly with 0.5% bupivacaine associated with sufentanil, fentanyl, or morphine; general. In 8 cases, there was need to complement via catheter, with 5 submitted to PC and 3 to BC. Thirteen patients required intraoperative sedation; ephedrine was used in 15 patients. Fetal anesthesia: fentanyl  $10\text{--}20 \text{ mg} \cdot \text{kg}^{-1}$  and pancuronium  $0.1\text{--}0.2 \text{ mg} \cdot \text{kg}^{-1}$  (IM). Neonatal survival rate was 60.7%.

<sup>☆</sup> This work realized at the Departamento de Anestesiologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brasil.

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**PALAVRAS-CHAVE**

Hérnia diafragmática congênita;  
Diagnóstico pré-natal;  
Oclusão traqueal;  
Fetoscopia;  
Cirurgia fetal;  
Anestesia

**Conclusion:** FETO is a minimally invasive technique for severe congenital diaphragmatic hernia repair. Combined blockade associated with sedation and fetal anesthesia proved safe and effective for tracheal occlusion.

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### Oclusão traqueal por fetoscopia em hérnia diafragmática congênita grave: estudo retrospectivo

#### Resumo

**Justificativa e objetivos:** A oclusão traqueal fetal temporária feita por meio da fetoscopia acelera o desenvolvimento pulmonar e reduz a mortalidade neonatal. O objetivo deste trabalho é apresentar experiência anestésica em gestantes cujos fetos eram portadores de hérnia diafragmática e foram submetidos à oclusão traqueal por fetoscopia (FETO).

**Método:** Estudo retrospectivo, descritivo, aprovado pelo Comitê de Ética da Instituição. Os dados foram obtidos das fichas anestésicas e dos prontuários.

**Resultados:** A FETO foi feita em 28 gestantes. Características demográficas: idade  $29,8 \pm 6,5$ ; peso  $68,64 \pm 12,26$ ; ASA I e II. Obstétricas: IG  $26,1 \pm 1,10$  semana (na FETO);  $32,86 \pm 1,58$  (desocclusão);  $34,96 \pm 2,78$  (parto). Via de parto: cesárea, parto vaginal. Dados fetais: peso (g) nos momentos da oclusão e nascimento, respectivamente ( $1.045,82 \pm 222,2$  e  $2294 \pm 553$ ); RPC na FETO e desocclusão:  $0,7 \pm 0,15$  e  $1,32 \pm 0,34$ , respectivamente. Anestesia materna: pré-operatório incluiu ranitidina e metoclopramida; nifedipina (VO) e indometacina (retal). Medicação pré-anestésica com midazolam EV. Técnicas anestésicas: bloqueio combinado com bupivacaína 0,5% hiperbárica 5-10 mg associada ao sufentanil; peridural contínua predominantemente com bupivacaína 0,5% associada a sufentanil, fentanil ou morfina; geral. Em oito casos houve necessidade de complementação pelo cateter, cinco nas submetidas a PC e três a BC. No intraoperatório 13 pacientes necessitaram de sedação; efedrina foi usada em 15 pacientes. Anestesia fetal: fentanil 10 a 20 mg.kg<sup>-1</sup> e pancurônio 0,1-0,2 mg.kg<sup>-1</sup> (IM). A taxa de sobrevivência neonatal foi de 60,7%.

**Conclusão:** A FETO constitui técnica minimamente invasiva para correção de hérnia diafragmática congênita grave. O bloqueio combinado associado à sedação e anestesia fetal se mostrou seguro e eficaz para a oclusão traqueal.

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## Introduction

Advances in prenatal diagnostic tools, such as high-resolution ultrasound and biochemical and cytogenetic analysis of fetal amniotic fluid and blood, more often have enabled the diagnosis and early correction of birth defects, delayed its evolution and prevented it from becoming irreversible.<sup>1-4</sup>

Numerous studies have shown that the main causes of death in fetuses with diaphragmatic hernia are pulmonary hypoplasia and pulmonary hypertension, but they can benefit significantly with intrauterine therapy. However, problems of open surgery, such as preterm labor and premature rupture of membranes, are obstacles to the success of this procedure and resulted in the development of minimally invasive techniques performed by fetoscopy.<sup>5-9</sup>

The aim of this paper is to present the initial experience and viability of fetoscopic tracheal occlusion (FETO) and anesthetic experience in pregnant women whose fetuses had severe diaphragmatic hernia.

## Method

Retrospective descriptive study performed at the *Hospital da Mulher Professor Doutor José Aristodemo Pinotti* (CAISM – Unicamp). After approval by the institutional Ethics Committee, data collection was based on review of anesthetic and obstetric records. The waiver of informed consent was requested from the aforementioned committee (Code of Medical Ethics – Resolution 196). From May 2007 to May 2012, pregnant women whose fetuses presented with congenital diaphragmatic hernia (CDH) were included in the study. The procedure performed was the temporary fetoscopic tracheal occlusion (FETO) with inflatable balloon, and the inclusion criteria for the procedure indication were: fetuses with severe diaphragmatic hernia characterized by liver herniation into the chest, lung-to-head ratio (LHR < 1); gestational age less than 27 completed weeks at the time of the diagnosis confirmation; no other major fetal structural anomalies (requiring postnatal surgical repair); and absence of fetal chromosomal abnormalities incompatible

with prolonged postnatal survival, detected by conventional karyotype analysis.

Determination of liver herniation into the chest was performed by identifying the liver parenchyma and vessels into the chest with ultrasound guidance (color Doppler). The lung-to-head ratio (LHR) was initially achieved with an ultrasound transverse cross-section of the fetal chest at the level of the cardiac four-chamber. In this image, the lung area contralateral to the CDH was drawn manually (dotted line method) and expressed in mm<sup>2</sup>. This area was divided by measuring the head circumference (expressed in mm) in cross-section of the fetal head.<sup>10,11</sup>

Demographic (age, weight, physical status) and obstetrical (gestational age at the time of tracheal occlusion, balloon withdrawal and delivery) characteristics of pregnant women were recorded, as well as fetal data (weight at the time of tracheal occlusion and birth, LHR at the time of tracheal occlusion and removal of the balloon, maternal and fetal anesthesia, procedure duration, and neonatal outcomes).

## Results

During the study period, 28 pregnant women, ASA physical status 1–2, mean age of  $29.89 \pm 6.57$  (16–38) years, whose fetuses had severe diaphragmatic hernia, and eligible for prenatal endoscopic therapy were selected. Tracheal balloon insertion was successful in 22 patients (78.5%) with mean gestational age of  $26.1 \pm 1.10$  (26–30) weeks, and procedure duration was  $53.39 \pm 26.38$  (20–120) min. There was failure in six cases: tracheal occlusion was not possible and patients did not accept new intervention. Mean values and standard deviation of LHR and fetal weight at the time of tracheal occlusion were  $0.70 \pm 0.15$  (0.33–0.94) and  $1045.8 \pm 222.2$  (644–1464) g, respectively.

All procedures were performed in the operating room under the same recommended antisepsis conditions for laparoscopic surgeries.

At admission, the patients underwent to the following preparation before the procedure: fasting for at least 8 h; oral nifedipine (20 mg); rectal indomethacin (50 mg) 8 h before surgery; intravenous cefazolin (1 g); oral nifedipine (20 mg); ranitidine (50 mg); and metoclopramide (10 mg) 1 h before intervention.

Seventeen patients (60.7%) received intravenous midazolam (1–3 mg) as premedication. Most procedures were performed with spinal block: continuous epidural (10 cases) and combined block (17 cases); in one case, the patient had von Willebrand's disease and general anesthesia was indicated. In this case, the anesthesia was induced with fentanyl, propofol and rocuronium and maintained with sevoflurane in 100% oxygen. In the continuous epidural technique, 0.25% bupivacaine was used in two cases ( $43.75 \pm 8.83$  mg) and 0.5% bupivacaine in eight cases ( $80 \pm 8.86$  mg). In all cases, the local anesthetic was associated with an adjuvant: morphine (2 mg) or fentanyl (100 µg) or sufentanil (20 µg). Combined blockade was performed using 0.5% hyperbaric bupivacaine (5–7.5 mg) associated with sufentanil (5–7.5 µg). In 50% of patients (five cases) who received continuous epidural, there was need for supplementation with 2% lidocaine (100 mg) or 0.5% bupi-

vacaine (35–40 mg) via catheter. Of the 17 patients who underwent the combined blockade, supplementation with local anesthetic via catheter was necessary in one case (0.5% bupivacaine – 50 mg). There was a need for sedation during surgery in 13 cases, achieved with midazolam alone (3.1 mg) or combined midazolam (1–3 mg) and fentanyl (25–75 µg), intravenously. Of the 13 patients who required intraoperative sedation, 11 also received midazolam as preanesthetic medication. In all cases, fetal anesthesia was achieved with fentanyl ( $15\text{--}20 \mu\text{g}\cdot\text{kg}^{-1}$ ), pancuronium ( $0.1\text{--}0.2 \text{mg}\cdot\text{kg}^{-1}$ ), intramuscularly with 20G or 22G needle, guided by ultrasound, at a total dose based on estimated fetal weight.

There were no hemodynamic and respiratory changes or maternal complications related to the anesthesia. Regarding the surgical procedure, the most common complications were loss of amniotic fluid into the maternal peritoneal cavity (one case) and premature rupture of membranes (three cases) to withdraw the balloon.

In all cases, the patients were hydrated with Ringer's lactate solution ( $10 \text{mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ).

After surgery, pregnant women stayed in the hospital for at least 24 h, at relative rest, taken oral nifedipine (20 mg; every 8 h) and analgesics, as needed. After discharge, the patient returned to the hospital for weekly or biweekly prenatal visits and ultrasound examinations.

The balloon withdrawal was performed using a fine needle aspiration guided by ultrasound; gestational age at that time was  $32.8 \pm 1.58$  (28–34) weeks, and fetal LHR was  $1.32 \pm 0.34$  (0.5–1.8), with an increase of about 100% compared to that observed at tracheal occlusion.

Mean gestational age at birth was  $34.96 \pm 2.78$  (27–39) weeks and the average weight of newborns was  $2294 \pm 553$  (920–3495) g.

In the six cases in which tracheal occlusion was not possible, there was one case of intrauterine death, three cases of death after birth who did not undergo CDH surgical repair, and two newborns survived after surgery (primary closure and patch placement due to extensive defect). Of the 22 cases of tracheal occlusion, 15 newborns (68%) survived after surgery (primary closure or patch) and seven died—four cases after surgery and, in three cases, the surgical repair was not possible. Of the 28 cases of severe CDH selected in the study period, 17 newborns (60.71%) survived, 10 (35.7%) died after birth, and there was one case of intrauterine death.

## Discussion

About half of fetuses with congenital diaphragmatic hernia survive after postnatal surgery. The other half dies of pulmonary hypoplasia. Due to the high postnatal mortality (>90%) associated with hypoplasia and pulmonary hypertension present in fetuses with severe congenital diaphragmatic hernia, early intrauterine treatment techniques have been described to promote prenatal lung development and greater chance of survival after birth.<sup>12</sup>

Initially, the treatment was performed by open surgery (hysterotomy), but due to problems associated with the technique, such as preterm labor and premature rupture of membranes, the development of minimally invasive techniques (fetoscopy) was encouraged to enable temporary

tracheal occlusion in order to minimize or reverse pulmonary hypoplasia.<sup>12–15</sup>

Fetal surgery in humans was preceded by extensive animal studies and demonstrated that tracheal occlusion promotes lung growth and development through an effective and sustained obstruction that can be done endoscopically with a detachable balloon without tracheal injury, and the subsequent intrauterine reversal of this obstruction allows in utero pulmonary recovery of type II pneumocyte and production of surfactant.<sup>16–20</sup>

Animal studies in which CDH was experimentally developed demonstrated that intrauterine tracheal occlusion allows the retention of pulmonary secretions—the likely mechanism of action responsible for lung development and growth, pulmonary hypoplasia reversal, and LHR normalization.<sup>15,20,21</sup>

This study performed at a university center in Brazil shows the preliminary results of the anesthetic techniques used in fetoscopy and reversible tracheal occlusion with a balloon and the feasibility of a minimally invasive technique (FETO) in fetuses with severe CDH, intrathoracic liver herniation, and LHR <1.

If we consider mortality greater than 90% in fetuses with severe CDH, our results were satisfactory in relation to maternal safety and the possibility of fetal lung development, with a survival rate of 60.7% for fetuses that would have a poor prognosis in the presence of severe CDH. In 2004, Deprest et al.<sup>22</sup> reported survival and hospital discharge in 48% of the 20 cases submitted to FETO. In a European multicentre study, which included 210 cases, Jani et al.<sup>23</sup> reported results of 38% and 49% survival in right and left CDH, respectively. Manrique et al.<sup>24</sup> performed FETO in nine cases with CDH, with a survival rate of 45.5% compared with 0% in control group who underwent watchful waiting. In Brazil, a study by Peralta et al.<sup>25</sup> showed survival of 46.2% in 13 cases evaluated.

In this study, the inclusion criteria for liver herniation into the chest and LHR < 1 are widely accepted as life treating indicators in CDH.<sup>26</sup> Jani et al.<sup>26</sup> observed that the LHR is directly proportional to the survival rate. The authors investigated the correlation between LHR and survival and found survival of 17%, 62%, and 78% in cases with LHR of 0.4–0.5, 0.6–0.7, and 0.8–0.9, respectively, undergoing tracheal occlusion. It was significantly higher than in those who underwent watchful waiting, with a survival rate of 0%, 0%, and 16%, respectively.

These results are similar to those of other authors who reported a lifespan shorter than 10% in watchful waiting cases and 50% in prenatal intervention cases.<sup>22</sup>

The right time for intervention and occlusion duration is essential to ensure the quality of pulmonary vessel and airway responses. The best results are seen in surgery performed as early as possible, with increased survival even in FETO performed between the 25th and 29th week of pregnancy.<sup>7,22,27,28</sup>

Unplugging should preferably be done between the 32nd and 34th weeks of gestation, as studies have shown that prolonged tracheal occlusion leads to decreased alveolar type II pneumocyte and decreased lung surfactant, which can lead to the development of hyaline membrane after birth.<sup>19,29</sup>

The fetal surgery anesthesia involves two patients, mother and fetus, and therefore care to ensure maternal

and fetal safety should be considered. Among the maternal care, in addition to those related to the specific changes of pregnancy, there are: prevention of premature labor using pre-, intra-, and postoperative tocolytic agents and postoperative analgesia. Regarding fetal care, attention should be paid to anesthesia, immobility, and prevention of fetal asphyxia.<sup>1,2</sup>

Preterm labor is the result of stimulation and uterine contraction caused by manipulation and uterine incision. This manipulation may cause placental detachment with decreased placental blood flow and fetal anoxia. Prevention and treatment of preterm labor are essential to the success of the surgery and include the use of pre-, intra-, and postoperative tocolytic drugs.<sup>30</sup> However, its use has been associated with maternal complications, such as hypotension, cardiac arrhythmias, pulmonary edema and metabolic changes; the choice will depend on the maternal side effects. Prostaglandin-synthetase inhibitors (such as indomethacin), beta-adrenergic drugs (such as terbutaline), and calcium channel blockers (such as nifedipine) are among the most commonly used agents. Fetal side effects have also been described after using these agents. The long-term use of indomethacin may be associated with renal dysfunction, necrotizing enterocolitis, intracranial hemorrhage, especially in preterm infants (<30 weeks). Regarding nifedipine, there are no reports of adverse effects in humans, although reduction in uterine blood flow and fetal acidosis have been demonstrated in animals.<sup>1,2</sup>

Regarding anesthetic technique, the physiological respiratory disorders of pregnancy contribute to the increased risk of hypoxia, which can be minimized by O<sub>2</sub> administration.<sup>1,2</sup> Hyperventilation may be aggravated by anxiety and stress, with consequent hypocapnia, oxyhemoglobin curve shift to the left, and decreased availability of oxygen to the fetus. Additionally, there is a decrease in venous return, maternal cardiac output, and uterine blood flow, the main determinant of placental flow.<sup>1,31</sup> Thus, it is important to prevent anxiety and pre- and intraoperative stress, maintaining the respiratory rate to avoid P<sub>ET</sub>CO<sub>2</sub> values below 30 mmHg.<sup>1,2</sup>

Gastrointestinal changes increase the risk of gastric content aspiration, and preventive measures such as intravenous metoclopramide (10 mg) and ranitidine (50 mg) and rapid sequence induction and intubation should be considered.<sup>1,2,30–32</sup>

Regarding cardiovascular stability, hypotension and hypertension and noradrenergic activity with myometrial vasoconstriction should be avoided, as they cause decreased uterine blood flow with loss of fetal well-being. The lower vena cava compression by the gravid uterus during supine position causes a decrease in venous return and maternal hypotension; it is mandatory to deviate the uterus to the left to prevent fetal asphyxia.<sup>31–33</sup>

These procedures usually do not require general anesthesia, which is associated with a higher incidence of maternal morbidity and mortality; regional anesthesia is used in most centers. However, regional anesthesia techniques may present some difficulties due to maternal anxiety, and does not provide fetal immobility, with endoscope displacement, bleeding, fetal trauma, cord compression, and fetal death.<sup>1–3,31,32</sup> Alternatively, local infiltration of the skin and subcutaneously with 2% lidocaine, supplemented with

maternal sedation, can be used. Some authors performed these procedures with combined blockade and maternal sedation and found that remifentanyl in continuous infusion provided maternal sedation and fetal immobilization equal to or higher than that obtained with diazepam.<sup>34</sup>

Deprest et al.,<sup>14</sup> in a study performed in 2011, recognized the spinal technique as more advantageous compared with general anesthesia, as it is an easy to handle and short surgical procedure. Leo et al.<sup>35</sup> found that low doses of 0.5% hyperbaric bupivacaine (7 mg) provided a rapid blockade and effective anesthesia for cesarean section with reduced incidence of hypotension compared with doses of 8 and 9 mg. However, due to its short duration, the use of an epidural catheter would not be feasible for a possible need for supplementation.

As described in previous studies,<sup>22,25</sup> the anesthetic technique most used in this work was the spinal block, particularly the combined blockade. Low doses of local anesthetics and adjuvants were used, which was effective for the procedure without maternal hemodynamic changes and with less need for catheter supplementation compared with epidural block.

Although in 53.6% of patients undergoing spinal block ephedrine has been used in low doses, the analysis of the anesthetic records showed hemodynamic stability throughout the surgical procedure. This can be justified by the criterion adopted, considering "zero tolerance" for reduced blood pressure and assuming the use of vasopressors for any decrease in systolic blood pressure below the baseline pressure levels (pre-anesthetic). The crystalloid and colloid administration to treat hypotension in these patients should be controlled, as the routine use of tocolytic agents may increase the risk of acute pulmonary edema. Regarding the use of pressor amines, ephedrine, although it can cause fetal acidosis, it is still the most used vasopressor due to its beta-adrenergic effect and minimal action on uterine blood flow.<sup>1,30,36</sup>

There is evidence that the fetus can experience pain, and the surgical manipulation of an unanesthetized fetus results in the autonomic nervous system stimulation, with effects on heart rate, increased hormone levels and fetal motor activity, changes that can be eliminated with proper fetal anesthesia.<sup>1,31,37</sup> Among the opioids, the option for fentanyl (5–20  $\mu\text{g}\cdot\text{kg}^{-1}$ ) due to the efficacy and safety observed in premature infants undergoing anesthesia.<sup>1,30,37</sup> Fetal movements have been safely managed with pancuronium (0.2–0.3  $\text{mg}\cdot\text{kg}^{-1}$ ) or pipecuronium (0.2  $\text{mg}\cdot\text{kg}^{-1}$ ) or vecuronium (0.2  $\text{mg}\cdot\text{kg}^{-1}$ ).<sup>1,8,30,37,38</sup> The choice of pancuronium in this study was due to its vagolytic activity, with increased heart rate, desirable to maintain fetal cardiac output.<sup>31</sup> Fetal heart rate monitoring was performed using ultrasound, the use of atropine was not needed.

Adequate postoperative analgesia has been achieved with local anesthetics and morphine administered through a catheter in the epidural space that extremely important for the fetal surgery success due to its role in preterm labor prevention.<sup>1</sup> The study results allow concluding that FETO is a minimally invasive technique for severe congenital diaphragmatic hernia repair and provides lung development and postnatal survival. This anesthetic technique selection should be considered for a successful procedure, and the

combined blockade associated with sedation and fetal anesthesia proved to be safe and effective for tracheal occlusion.

## Conflicts of interest

The authors declare no conflicts of interest.

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