

Two Cases of Ex Utero Intrapartum Treatment (EXIT) in UP-PGH

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ABSTRACT

The survival rate and prognosis for neonates with airway obstruction is poor if not managed immediately after delivery. Ex utero intrapartum treatment (EXIT) is indicated for cases in which airway obstruction is anticipated. The procedure establishes the fetal airway prior to complete delivery while maintaining an intact uteroplacental circulation. Maintaining uteroplacental circulation, ensuring uterine relaxation, and temporizing placental detachment during the EXIT procedure are achieved by administering a higher dose of inhalation anesthetic and intravenous nitroglycerine. However, this can lead to maternal hypotension and compromised fetoplacental perfusion, reduced fetal cardiac output, and acidosis. It is therefore essential that these be managed using vasopressors and inotropes. This paper reports the first institutional experience with the EXIT procedure in the Philippines, presenting two cases of neonates with large cystic hygroma. One case was performed as an elective procedure, the other as emergency treatment.

Key Words: EXIT procedure, Obstetric Anesthesia

Introduction

The Ex Utero Intrapartum Treatment (EXIT) procedure is performed to improve the survival rate during delivery of fetuses with life-threatening airway obstructions.¹ This procedure is indicated when difficulty in establishing and securing fetal airway is anticipated, such as in cases of large lingual cysts,² teratomas,^{3,4} skeletal dysplasia and micrognathia,⁵ cystic hygromas, thyroid goiters, and neuroblastomas.⁶

The EXIT procedure is performed immediately before the complete delivery of the baby and placental separation, while the uteroplacental circulation remains intact.⁷ The airway is secured during partial delivery of the head and neck or upper body in a planned cesarean section.

Preserving uteroplacental circulation buys the neonatal airway specialist (an anesthesiologist or otorhinolaryngologist) time to secure the airway⁸ before the newborn shifts to extrauterine circulation, thus

preventing neonatal hypoxemia, acidosis, and their adverse sequela.⁷ The airway may be secured by laryngoscopy, bronchoscopy, intubation, tracheostomy, tumor decompression and resection, and cannulation for extracorporeal membranous oxygenation (ECMO).

Cases of airway obstruction are now easily detected and anticipated due to advances in prenatal diagnosis and imaging technology, making EXIT an option for avoiding post-delivery neonatal respiratory distress and compromise.⁷

EXIT requires a closely coordinated, multidisciplinary team consisting of perinatologist-obstetricians, pediatric and obstetric anesthesiologists, neonatal otorhinolaryngologists, radiologists, pediatric surgeons, and ICU and surgical nurses.^{6,9} Planning conferences and simulation drills must be conducted in preparation for the procedure.

A review of international literature revealed few reports of EXIT. Most reported cases were performed in North America^{10,11,12,13,14} and in Europe^{15,16}, although EXIT cases have also been reported in Asia.^{1,8,17,18,19,20} In most reports, the maternal anesthesia of choice was general anesthesia (inhalational with intravenous opioid supplements), with a few cases performed with regional anesthesia (combined spinal-epidural anesthesia).¹⁶ All reported successful outcomes.

No reports of EXIT in the Philippines were found on review of records. Here we present two cases of EXIT, both performed in the University of the Philippines-Philippine General Hospital (UP-PGH), the first to be documented in the Philippines. One was performed as an elective procedure, the other as emergency treatment. Both procedures were performed without incident and with successful outcomes.

We report these cases from the perspective of the obstetric anesthesiologist, highlighting the implications of the anesthetic technique on both the mother and the fetus.

Case 1: Elective Scenario

The first case involved a 25-year-old (ASA I) primigravida with no co-morbidities weighing 60 kg. At 30 weeks AOG, the fetus was found to have an anterior neck mass, detected during a routine prenatal ultrasound. The mass grew progressively, observed to be 10.1 x 9.9 x 9.1 cm, multilobulated, multiseptated, and located on the left anterolateral portion of the neck. The largest locule was

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located inferiorly and measured 8.4 x 7.8 x 5.6 cm. With a prenatal impression of cystic hygroma, airway obstruction and difficulty of securing airway patency upon delivery were anticipated. An EXIT procedure was contemplated at 37 weeks 4 days age of gestation.

On the day of the procedure, the mother was premedicated with intravenous omeprazole (0.8mg/kg) and metoclopramide (0.02mg/kg). She was received in the operating room, BP=130/70, HR=85, RR=16, afebrile, awake, and calm. She was premedicated with midazolam IV (1 mg) at the OR. Her vital signs were monitored using pulse oxymetry, ECG, capnography, and both noninvasive blood pressure and continuous arterial pressure monitors. An epidural catheter (gauge 18) was inserted at the L4-L5 interspace.

After preoxygenation, rapid sequence induction, and intubation, intravenous fentanyl citrate (1 mcg/kg), atracurium (0.1 mg/kg), propofol (2 mg/kg), and succinylcholine (2 mg/kg) were administered. General anesthesia was maintained with sevoflurane of at least 2 MAC



Figure 1. Elective EXIT procedure: Neonate with a large cystic hygroma on the left anterolateral portion of the neck. Tracheostomy performed before complete delivery.



Figure 2. Emergency EXIT procedure: Neonate with large cystic hygroma on the right anterolateral portion of the neck, with macroglossia. Tracheostomy performed before complete delivery.

with intravenous fentanyl (1 mcg/kg) every hour and atracurium (0.2 mg/kg) every 30 minutes. Prior to ultrasound-guided aspiration of the fetal neck mass, a bolus of nitroglycerine (1.0 mcg/kg) was administered intravenously, followed by an infusion at 0.5-1.0 mcg/kg/min to maintain uterine relaxation. Initially, 10 ml of cystic aspirate was obtained.

Initially, the end tidal concentration of sevoflurane was maintained at least 2 MAC for proper uterine relaxation. Maternal systolic blood pressure was maintained at 100-130 mmHg through a continuous infusion of phenylephrine at 0.5-1.0 mcg/kg/min and intermittent infusion of dopamine at 5 mcg/kg/min, as needed. The initial phase of the procedure, from skin incision to uterotomy, lasted 7 minutes. The cyst was again aspirated, obtaining 90 ml of fluid. With an adequately relaxed uterus, slow amnioinfusion with NSS was performed to prevent placental separation, with an initial 300-cc bolus followed by infusion at 10 ml/minute via gauge 18 needle. The fetal head and the torso just above the nipple were partially delivered through a gentle scooping maneuver.

Several unsuccessful attempts at establishing the airway through intubation were made using an endotracheal tube size 2.5 under direct visualization (Miller 1) and video laryngoscopy (C-MAC). Failure was attributed to the large cystic mass occluding the passage of the tube toward the glottic opening. A tracheostomy was thus performed by a pediatric otorhinolaryngologist. Once the fetal airway was secured and equal air entry in both lungs was ascertained, the fetus was completely delivered from the uterus and the umbilical cord severed. Further resuscitative maneuvers were performed by the neonatologists. The first-minute APGAR score was 3, becoming 5 at 5 minutes, and finally 7 at 10 minutes. The time from uterine incision to cord clamping was about 15 minutes, including the EXIT procedure, which lasted 13.5 minutes.

After delivery, the inhalational anesthetic (sevoflurane) was gradually lowered to the sleep/hypnotic dose of an end-tidal concentration of 0.5 MAC. Simultaneously, epidural anesthesia was initiated with 20 ml of 0.5% levo-bupivacaine with 1:200,000 epinephrine. The infusions of nitroglycerin, dopamine, and phenylephrine were all discontinued.

Adequate uterine contraction after placental expulsion was induced by a slow intravenous bolus of carbetocin (100 mcg) and continuous infusion of oxytocin 30 U/li. Thereafter, neither uterine atony nor bleeding were observed. The total operation time was 2 hours and 10 minutes. Throughout the operation, the end-tidal CO₂ was maintained within normal limits. No significant hypotension was observed both through the arterial line and the NIBP monitor. The estimated blood loss was 1,100 ml and there was no need for transfusion of blood products. After the full reversal of the neuromuscular blockade with neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg), the patient was extubated fully awake. Initial doses of epidural morphine (3 mg) and

intravenous ketorolac (0.6 mg/kg) were administered. Subsequently, the patient was transferred to the post-anesthesia care unit (PACU) while the newborn was admitted to the neonatal intensive care unit with the tracheostomy tube in place, mechanically ventilated. The immediate postoperative course for both mother and newborn were unremarkable.

Without any postpartum complications 4 days postoperatively, the mother was discharged from the ward and sent home. The newborn remained admitted at NICU and underwent sclerotherapy 2 weeks post-delivery.

Case 2: Emergency Scenario

The mother was a 31-year-old (ASA I) G2P1 (1001) with no co-morbidities weighing 55 kg. At 34 weeks and 5 days AOG, she was admitted for preterm labor. An internal examination revealed 4-cm cervical dilatation and 80% effacement. Fetal ultrasound revealed an 8.4 x 8.4 x 5.0 cm multicystic, multiseptated anterolateral neck mass with facial involvement, the tongue protruding from the oral cavity. The radiological impression was cystic hygroma and macroglossia.

The EXIT procedure and cesarean delivery were planned for the 37th week AOG. However, at 35 weeks and 3 days AOG, due to the progression of labor on the day of the scheduled fetal MRI, an emergency cesarean section with EXIT procedure was performed.

The patient was brought to the operating room fully awake, not in distress but in active labor. Two large-bore intravenous lines were in place. Her ECG, blood pressure, and oxygen saturation were monitored noninvasively. Initial vital signs were: BP=100/60, HR=108, RR=18, with 99% O₂ saturation at 40%FiO₂. She was premedicated with intravenous midazolam (0.02 mg/kg) and nitroglycerin (0.5 mcg/kg). A nitroglycerin infusion at 0.5–1.0 mcg/kg/min was initiated to abate uterine contraction. An epidural catheter (gauge 18) was inserted at the L4–L5 interspace. This was followed by rapid sequence induction and intubation. Nitroglycerin (0.5 mcg/kg) was given intravenously followed by an infusion at 0.5–1.0 mcg/kg/min. After preoxygenating the patient, she was pretreated with atracurium (0.1 mg/kg), and fentanyl (1 mcg/kg) and propofol (2 mg/kg), given in increments of 20 mg, were administered. Once full hypnosis was achieved, Sellick's maneuver was performed and intravenous succinylcholine (100 mg) was administered. After 60 seconds, the patient was intubated under direct visualization. One dose of atracurium IV (0.5 mg/kg) was administered.

General anesthesia was maintained using sevoflurane at 2–3 MAC with hourly supplement of fentanyl (1 mcg/kg). A phenylephrine infusion at 0.05–0.10 mcg/kg/min was initiated and titrated to maintain systolic BP above 100 mmHg, with intermittent bolus of intravenous ephedrine (0.2 mg/kg), as needed.

Nitroglycerin infusion (0.5–1.0 mcg/kg/min) was maintained to induce continuous uterine relaxation. The baby was partially delivered by gentle scooping of the head up to the level of the shoulder. Amnioinfusion was performed using a French 16 feeding tube with a 300-cc slow bolus and maintenance rate of 10 ml/minute of plain NSS.

Two minutes after delivery of the head, the baby was successfully intubated by the pediatric anesthesiologist using a videolaryngoscope (C-MAC, Miller blade 1, ETT size 2.5). A sterile pediatric pulse oximeter was attached to the left earlobe, reading O₂ saturation at 65 to 70%. A tracheostomy was then performed successfully by the pediatric otorhinolaryngologist. The total EXIT procedure time was 14 minutes.

Upon establishment of the airway with a tracheostomy tube, the baby was delivered completely. The live baby weighed 2,510 grams, 36 weeks by pediatric aging and appropriate for gestational age. APGAR score was 4 at 1 minute, 4 at 5 minutes, and 4 at 10 minutes. Resuscitative maneuvers were continued by the neonatology team.

Upon delivery of the baby, the nitroglycerin infusion was discontinued. The sevoflurane concentration was lowered to 0.5 MAC. Oxytocin 30 mg incorporated in 1 L of crystalloid levo-bupivacaine was initiated as an intravenous drip, and methergine (50 U) IM was administered to ensure uterine contraction; 70-cc of 2% lidocaine with 1:200,000 epinephrine was administered via the epidural catheter, followed by 10 cc of 0.5% levo-bupivacaine. The phenylephrine infusion was tapered off. A propofol bolus (20 mg) was administered as needed to maintain adequate depth of anesthesia. Estimated blood loss was 800 cc, mainly from placental separation. Replacement with blood products was not necessary. Maternal vital signs remained stable during the 3-hour surgery.

At the end of the operation, the patient was given a dose of epidural morphine sulfate (3 mg) and intravenous ketorolac (0.6 mg/kg). The patient was extubated fully awake with adequate pain control. She was then transferred to the PACU and eventually to the regular ward, where she remained admitted for 4 days.

The newborn was admitted at the neonatal ICU with tracheostomy tube in place, mechanically ventilated. Further workup revealed multiple congenital heart disease (patent ductus arteriosus, patent foramen ovale) with cystic hygroma and macroglossia.

Discussion

The anesthetic management of mothers bearing fetuses with certain congenital anomalies is crucial to the success of the EXIT procedure. The anesthesiologist should have a thorough understanding of both fetal and maternal physiology as well as the effects of the anesthetic agents that will be used. There is a misconception that the EXIT procedure is the same as a cesarean section. However, more

correctly the EXIT procedure is an extension of a cesarean section, with unique features and different goals. The goal of the EXIT procedure is to maximize uterine relaxation for partial delivery of the baby, allowing fetal anesthesia and surgical intervention. In contrast, the goal of cesarean sections is prompt access to and evacuation of the uterine cavity (fetal and placental delivery) while maintaining uterine tone and minimizing fetal sedation.

The EXIT procedure was originally intended to allow removal of tracheal clips that were placed in utero to treat fetuses with severe congenital diaphragmatic hernia. However, today the indication is not only airway compromise but also other fetal anomalies in which neonatal resuscitation and survival could be improved through surgery performed while the fetus is still receiving placental support, at the same time providing optimally safe anesthesia to the parturient.^{2,4} Fetal conditions that may be indications for this procedure include large fetal neck masses which distort the airway anatomy and result in difficult laryngoscopy; lung or mediastinal masses that can result in cardiac compression and arrest upon institution of positive pressure ventilation and are managed with thoracotomy before delivery; severe congenital diaphragmatic hernias, requiring extracorporeal membrane oxygenation; and congenital high airway obstruction syndrome, such as laryngeal atresia.⁵ In the cases presented, the attending physicians anticipated potentially catastrophic situations in which establishing an airway would be difficult due to the large cystic hygromas. The EXIT procedures performed prevented unwanted hypoxia and acidosis in the neonates and improved their chances of survival.

There are three important requisites for a successful EXIT procedure: complete relaxation of the uterine muscles, maintenance of uterine volume, and intact uteroplacental circulation.⁶ Among these requisites, complete uterine relaxation is of paramount importance as the fetus continues to rely on the intact uteroplacental perfusion for oxygenation throughout the EXIT procedure. Complete relaxation allows adequate maternal-fetal gas exchange at the placental interface.

In addition to the usual anesthetic management of obstetric patients, management of fetal anesthesia and analgesia during the EXIT procedure should be considered. This can be accomplished through maternal transfer of anesthetic agents across the placenta or through direct injection of the anesthetic into the fetus.⁷ Volatile anesthetic agents of low solubility are well suited for fetal surgery as they permit rapid placental transfer, rapid dose adjustment, and rapid elimination. Inhaled anesthetics with low blood/gas partition coefficient such as desflurane and sevoflurane are ideal as they allow immediate response to changes in concentration and rapid elimination and recovery.⁷

In animal models, placental transfer of volatile anesthetic can reach as high as 78%,²¹ while the fetal MAC is

less than half of the maternal MAC (0.33% vs. 0.69%, respectively). The administration of 2–3 MAC of any volatile anesthetic to the mother would certainly anesthetize the fetus as well. Furthermore, propofol, a sedative-hypnotic agent, can potentiate the effect of volatile anesthetics on the fetus as it readily crosses the placenta. This is shown by an umbilical-to-maternal venous ratio of 0.76.^{22,23} Propofol also induces vasodilation without reducing placental blood flow.²⁴ Opioids such as fentanyl and remifentanyl also cross the placenta rapidly because of high lipid solubility, providing fetal immobilization and analgesia.⁷ The administration of the aforementioned does not preclude the use of additional analgesia (ketamine) and muscle relaxant to the fetus if needed.

In both cases, the complete uterine relaxation was well provided by the adequate depth of volatile anesthesia (sevoflurane) at 2–3 MAC along with intravenous nitroglycerine²⁵ (boluses and infusion). However, the high concentration of sevoflurane combined with the vasodilating effect of nitroglycerine can result in maternal hypotension and subsequently a decreased uterine blood flow and compromised uteroplacental perfusion. These can lead to decreased fetal cardiac output and reduced fetal oxygenation. Furthermore, maternal hypotension can potentially lead to uterine atony and post-delivery hemorrhage. These sequelae were prevented by careful titration of sevoflurane and nitroglycerine, as well as the administration of vasopressors, ephedrine boluses (5–10 mg), phenylephrine infusion (0.05–0.1 µg/kg/min) and dopamine drip (5 µg/mg/min). Ephedrine, a mixed α - and β -agonist, increases maternal cardiac output with mild vasoconstriction. It crosses the placenta more than phenylephrine and increases fetal heart rate. Phenylephrine, on the other hand, is a direct-agonist and produces vasoconstriction. Neither affects umbilical blood flow, thus maintaining adequate uteroplacental perfusion.

Nitroglycerin was the tocolytic used instead of magnesium sulfate because it is easily titratable, short acting, and rapid in onset. The onset of uterine relaxation using nitroglycerin is 30–60 seconds, and a loading bolus of 100 µg with continuous dosing of 0.5–1 µg/kg/min is recommended to maintain effective uterine relaxation.²⁶

When nitroglycerin infusion with a deep level of volatile anesthetic is utilized, it is essential that accurate, real-time monitoring of maternal hemodynamics, especially the blood pressure, be taken continuously through an arterial line. Ideally, a continuous end tidal monitoring of expired sevoflurane should be performed to measure anesthetic depth. However, due to time constraints, the insertion of an arterial line was not performed, and a gas analyzer was not available for the emergency EXIT procedure. A fetal pulse oximeter probe was used in both fetuses in order to measure the oxygen saturation and heart rate. Initial readings usually range from 60 to 70%, rising

once the airway is established and supplemental oxygen is initiated.

Preservation of uterine volume during the EXIT procedure is crucial for the maintenance of the placental flow. Loss of amniotic fluid may occur during the hysterotomy and sudden decrease of intrauterine pressure will lead to uterine contraction, fetal asphyxia, cord compression, and placental detachment. In order to maintain the uterine volume, an amnioinfusion of 300 ml NSS slow bolus and infusion at 10 ml/minute was administered during the Exit procedure.

The critical stage in the EXIT procedure is securing the fetal airway. In both cases, the time-motion profiles approximated each other (13.5 minutes vs. 14.0 minutes). Although no specific time restriction is imposed on the performance of the EXIT procedure, prolonged exposure to high concentrations of volatile anesthetic agents induces fetal hypoxia and acidosis.²⁷ Literature on the EXIT procedure reports that continued uteroplacental circulation has been maintained from 30 minutes to 45 minutes without fetal compromise.^{28,29,30}

The anesthetic technique utilized for both procedures was sequential general anesthesia–epidural anesthesia. This technique has provided the anesthesia team the opportunity to shift anesthetic technique once the EXIT procedure was completed. The epidural anesthesia in both cases was initiated at the end of the EXIT procedure and after delivery of the neonate and placenta were completed. The concentration of the inhalational anesthetic (sevoflurane) was then gradually decreased to a sleep dose (<0.5 MAC) in order to taper its tocolytic effect. Shifting the general anesthesia to a regional anesthesia, discontinuation of the short-acting nitroglycerine, and the immediate use of uterotonics (oxytocin, methergine, and carbetocin) prevented uterine atony and postpartum hemorrhage.³¹ Uterine atony and postpartum bleeding did not occur in either case.

There are alternatives to the EXIT procedure, such as neuraxial anesthesia and regional techniques; however, these alternatives have their own indications and limitations. Neuraxial anesthesia has been used during the EXIT procedure in place of general anesthesia with an accompanying nitroglycerine infusion to achieve uterine relaxation.⁵ Adequate uterine relaxation, however, may be difficult to attain and to titrate in this technique in comparison with volatile anesthetics. Limitations of the regional technique during an EXIT procedure have been reported, including increased risk of severe hypotension, increased fetal movement requiring adjunct anesthetics, and the possibility of fetal demise.^{20,32}

The two cases presented were successfully managed by the same team of healthcare providers, applying the same therapeutic principles and using the same anesthesia technique. A good maternal outcome was achieved in both

cases, though they differed in neonatal outcome. The team had more difficulty in establishing the airway in the elective EXIT procedure; nevertheless, they achieved a better APGAR score over the 1st, 5th, and 10th minutes with the elective procedure than with the emergency procedure (3-5-7 vs. 4-4-4, respectively). This was attributed to the coexisting multiple congenital heart anomalies (patent ductus arteriosus and patent foramen ovale) in the neonate in the emergency EXIT procedure. Both infants were admitted at the neonatal ICU with a working impression of Lymphangioma-Hemangioma Mass Complex (Lymphatic-Venous Malformation). Both have started undergoing sclerotherapy using doxycycline. The plan was to shrink the mass complex with sclerotherapy, followed by embolization and ultimately surgical excision.

As of this writing, the infant who underwent the elective EXIT procedure is on his 8th week post-delivery. He is stable and responding well to sclerotherapy. On the other hand, the infant who underwent the emergency EXIT procedure expired 6 weeks post-delivery due to overwhelming sepsis.

Despite the poor outcome in one of the two scenarios, the EXIT procedure remains a promising option for newborns with an anticipated airway obstruction. Currently, it is still the most rational and acceptable way of improving the chances of survival chances of such neonates. No other alternatives effectively and efficiently provide the necessary time for securing the airways in such cases. These two cases demonstrate that, barring maternal and fetal comorbidities, favorable outcomes can be attained utilizing the previously described anesthesia technique (sequential general anesthesia–epidural anesthesia) and ancillary hemodynamic support.

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