

From ‘OOPS to EXIT’: A Review of the Origins and Progression of Ex Utero Intrapartum Treatment

Nwamaka Nnamani*

UTSW Anesthesiology, 5323 Harry Hines Blvd, Dallas, Texas 75390-9068, USA

*Corresponding author: Nwamaka Nnamani, Assistant Instructor, UTSW Anesthesiology, 5323 Harry Hines Blvd, Dallas, Texas 75390-9068, USA, Tel: 773-749-2220; E-mail: nwamaka411@yahoo.co.uk

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Abstract

Advancement in the safety of obstetric anesthesiology has largely been due to better pharmacotherapy, monitoring devices and airway adjuncts. Similarly, the rate of fetal mortality has declined in the last two decades particularly due to improved neonatal intensive care and the wide-spread use of surfactant for premature births. The field of perinatology has long recognized that certain high-risk fetal anomalies, which previously carried significant mortality rates may now be amenable to the Ex Utero Intrapartum Treatment (EXIT). This review discusses the history of EXIT and focuses on the role of the anesthesiologist during this procedure; with emphasis that the successful outcome of many EXIT procedures is a testament to the advancements in obstetric anesthesiology, our understanding of maternal and fetal physiology, safer anesthetic agents, and improved overall safety of general anesthesia in parturients.

Keywords: EXIT procedure; Obstetric anesthesia; Fetal anesthesia

Key points

- EXIT enables the anatomically compromised fetus to retain its maternal blood supply throughout delivery whilst interventions to optimize its survival are performed.
- EXIT can be viewed as a modified cesarean delivery and creates a challenge for the obstetric anesthesiologist who has to manage two anesthetized patients concurrently.
- Most interventions are performed under general anesthesia, but cases done with regional anesthesia have been described.
- The role of the obstetric anesthesiologist is paramount in ensuring a coordinated, multidisciplinary team and favorable outcome.

It is speculated that approximately 1000 fetal surgeries were performed in the United States in 2012 [1] and the incidence of these interventions will continue to rise. In most instances fetal surgeries are performed in the late 2nd trimester or early 3rd trimester but Ex Utero Intrapartum Treatment (EXIT) is carried out at the delivery of the baby and can be viewed as a modified cesarean section (Table 1). This procedure enables the anesthesiologist to manage two anesthetized patients concurrently on utero-placental bypass in a laboring operating room; and is arguably one of the most challenging types of cases an obstetric anesthesiologist will encounter. EXIT has the potential to avert catastrophic events by allowing the anatomically compromised fetus to retain its maternal blood supply throughout delivery.

Numerous interventions and pharmacotherapy advancements in obstetric anesthesiology have led to a significant reduction in overall maternal mortality. Similarly, the rate of fetal mortality has likewise declined in the last two decades particularly due to improved neonatal intensive care and the wide-spread use of surfactant for premature births [2]. Certain high-risk fetal anomalies, which previously carried high mortality rates may now be amenable to the EXIT intervention.

	Fetal Surgery	EXIT procedure
Gestational Age	Late 2 nd /early 3 rd trimester	Late 3 rd trimester
Maternal Anesthesia	General/Regional	General Regional ±
Fetal Anesthesia	Transplacental/intramuscular	Transplacental
Type of surgery	Open/Minimally invasive	Open
Desired Uterine Tone	Complete relaxation	Complete relaxation

Table 1: Comparison of fetal surgery with EXIT procedure.

EXIT is a novel technique which provides a therapeutic option for fetuses with a variety of potentially fatal anomalies, particularly airway anomalies [3]. Two decades ago, these infants would have been diagnosed on prenatal imaging and would have had a low probability of survival with conventional treatment. Like other types of fetal intervention, the EXIT procedure requires the anesthesiologist or anesthesia team to care for two patients at once, often with different and at times conflicting anesthetic requirements [1]. However, unlike other fetal surgeries the goal of the EXIT procedure is a planned healthy delivery. The successful outcome of many EXIT procedures is a testament to the advancements in obstetric anesthesiology, our understanding of maternal and fetal physiology, safer anesthetic agents, and improved overall safety of general anesthesia in parturients.

The role of the obstetric anesthesiologist is paramount in ensuring a coordinated, multidisciplinary team comprising of obstetricians (usually perinatologists), pediatric surgeons, pediatric anesthesiologists, radiologists, neonatologists, nurses and surgical technicians who provide optimal care for both mother and fetus.

History

Operation on placental support (OOPS) was initially coined to describe the intervention to maintain utero-placental bypass whilst intervening on the fetus. However in the early use of the technique no attempt was made to prevent normal uterine contraction during the procedure. The first published report of the OOPS procedure for airway management was in 1989 by Norris [4]. The preterm fetus had a large neck mass, prenatally diagnosed as a cervical teratoma. Attempts at intubation were made but despite maintenance of fetoplacental circulation for 10 minutes, the fetus ultimately succumbed.

Langers [5] described the next EXIT case and stressed the importance of delivering the upper half of the fetal body to better stabilize the incision and avoid manipulation of the umbilical cord. Consequently, Schwartz [6] detailed two EXIT procedures for one fetus with cervical hemangioma and another with epignathus, an oropharyngeal teratoma. Tanaka [7] describes a similar experience as Schwartz [6] performing the EXIT procedure on a fetus with cystic hygroma and adapted fetal monitoring by using Doppler in lieu of pulse oximetry, which proved to be challenging on the moist infant.

Mychaliska [8] described the first series of 8 successfully treated cases. The author was the first to coin the acronym EXIT for this intervention. In contrast to earlier cases, Schwartz [6] and Mychaliska [8] emphasized that the central principle of the EXIT procedure is controlled uterine hypotonia to preserve uteroplacental circulation.

The largest published series to date is by Bouchard and colleagues [9] who described a total of 31 EXIT procedures. This was also the most complete description of the anesthetic management to date. The cases were performed at The Children's Hospital of Philadelphia. This series had good outcomes and reported only two maternal complications: one due to limited ultrasonography and failure to identify the placenta edge in the case of polyhydramnios, and the second due to dehiscence of the hysterotomy incision during a subsequent C-Section, but without long-term morbidity or mortality.

The EXIT procedure has also been performed in twin pregnancy, Liechty [10] described 35-week gestation twins, one with a large neck mass. The anatomically normal twin was delivered first and an EXIT procedure was performed in the twin with the neck mass. Midrio [11] reported a similar case of twin pregnancy at 36 weeks gestation. Here, the twin with the large neck mass was delivered first by the EXIT procedure, and subsequently the anatomically normal twin was delivered.

Indications for EXIT

EXIT enables the processes required for fetal survival to be carried out before clamping the umbilical cord and completing delivery. It was initially employed for cases with potential airway compromise and allowed adequate uteroplacental perfusion and oxygenation of the fetus until a definite airway was established. It was used primarily for the reversal of tracheal occlusion in the fetus with prenatally diagnosed severe congenital diaphragmatic hernia who had undergone uterotracheal clip application during pregnancy [12]. However, as anesthesiology and surgical techniques have advanced, it is now being utilized for the delivery of fetuses with cervical teratoma, cystic hygroma, oral tumors, and CHAOS (Congenital High Airway Obstruction Syndrome) (Table 2). CHAOS is a prenatally diagnosed clinical syndrome characterized by extremely echogenic lungs, dilated airways, flattened or inverted diaphragms with associated fetal ascites

and non-immune hydrops. Other fetal anomalies where EXIT has been employed include congenital goiter, as a bridge to ECMO (EXIT to ECMO), and resection of large chest masses such as congenital cystic adenomatoid malformation (CCAM) or mediastinal tumor that compress the intrathoracic trachea, as well as in the separation of conjoined twins [12] (Figure 1).

S.No	Indications for EXIT
1.	Tracheal occlusion
2.	Fetal neck mass
3.	CHAOS
4.	Unilateral pulmonary agenesis
5.	Thoracic abnormality
6.	EXIT to ECMO
7.	Conjoined twins

Table 2: Indications for EXIT.



Figure 1: EXIT to ECMO in 36 week gestation baby [9].

Physiology of EXIT

The success of the EXIT procedure can be attributed to improved understanding of maternal and fetal physiology and consequently the ability to take advantage and manipulate certain parameters to achieve an ideal state. In the EXIT procedure, it is of primary importance to ensure complete uterine relaxation throughout the duration of ureteroplacental support. This will preserve the maternal-fetal gas exchange at the placental interface, ensuring fetal oxygenation and avoiding potentially life-threatening hypoxia. Complete relaxation using inhaled anesthetic agents is preferred for several reasons:

1. Surgical manipulation often requires delivering the fetal head and shoulder and often times an abnormal neck mass through the hysterotomy incision; this is typically not possible with a normal low transverse segment incision.

2. The fetus may undergo a surgical procedure and will benefit from adequate anesthesia that it receives via transplacental transfer.
3. Maintaining fetal oxygenation is dependent on uterine perfusion and low uterine vascular tone. Any alteration in maternal mean arterial pressure or uterine vascular resistance will affect fetal oxygen delivery.

A good understanding of maternal hemodynamic changes during pregnancy and delivery is paramount to ensuring a good outcome. It is important to appreciate that pregnancy maximally dilates the uterine vasculature and as autoregulation is lacking, the uterine blood flow is entirely pressure-dependent. To complicate matters, hemodynamic measurements may not accurately reflect the uteroplacental circulation [13].

Unlike routine obstetric anesthesia practice where regional anesthesia is the rule, the use of inhalational agents is the technique of choice for patients undergoing EXIT. In effect this exposes the mother to surgical and postpartum risk without providing any health benefit directly to her. With a general anesthetic, she is at increased risk of aspiration due to obliteration of protective airway reflexes and full stomach conditions as a result of reduction of lower esophageal sphincter pressure and increased pressure of the gravid uterus on the stomach. In addition, pregnancy decreases Functional Residual Capacity (FRC) making hypoxemia more likely. For these reasons, maternal anesthesia is induced through a rapid sequence technique after adequate preoxygenation.

The favorable outcomes in most of these cases are due to enhanced knowledge of maternal and fetal physiology and the meticulous planning of the entire medical team.

Anesthetic Management of EXIT

Very few reports detail the anesthetic management of the EXIT procedure. This creates an impetus for better reporting by the obstetric anesthesiologist and will enable collaboration and exchange of ideas that could result in safety improvements and longer utero-placental bypass time.

S.No	Considerations for parturient undergoing EXIT
1.	Comprehensive preoperative visit with anesthesiologist
2.	Aspiration prophylaxis
3.	Left Uterine displacement to prevent aortocaval compression
4.	Invasive blood pressure monitoring
5.	Rapid Sequence Induction
6.	Maintenance of end tidal CO ₂ in normal pregnancy range 30-34 mmHg
7.	Aggressive blood pressure control to maintain uteroplacental perfusion
8.	Post-operative pain control

Table 3: Considerations for parturient undergoing EXIT.

Preoperative evaluation by the obstetric anesthesiologist

A detailed obstetric history is obtained, particularly in the case of an amnioreduction, the volume withdrawn and the presence of uterine contractions should be noted. Polyhydramnios is one consequence of fetal airway anomalies for which most EXIT procedures are performed [14].

A detailed history of preterm labor provides insight into the degree of uterine irritability and may indicate the need for additional tocolysis during the EXIT procedure. The preoperative visit also provides an avenue to alleviate the patient's anxiety and describe the events that are likely to occur during the perioperative course (Table 3). The importance of a good airway examination and plans for airway management should be established at this time.

The proposed Intraoperative and post-operative events for EXIT procedures

Preoperative indomethacin is usually administered prophylactically to the mother as a tocolytic. Most providers advocate placement of a lumbar epidural catheter for intraoperative and post-operative pain relief [15].

The operating room should be warmed to 85°F in preparation for the exposed neonate. The overall goal of anesthetic management is to maintain the mother and her baby (until the umbilical cord is severed) in the best possible physiological condition. This requires that the parturient and her fetus are effectively monitored in the perioperative period, including blood pressure, electrocardiography, respiratory rate, temperature, pulse oximetry, and end tidal CO₂ [16]. Tight hemodynamic control is critical, the possibility of significant blood loss should be anticipated, and invasive blood pressure monitoring employed. This will enable the early recognition of maternal hypotension that may compromise fetal oxygen delivery. Continuous end tidal monitoring is vital to prevent overventilation and hypocarbia which leads to alkalosis and a decreased uterine blood flow. Rapid sequence induction is usually employed with propofol and succinylcholine. Endotracheal intubation is usually achieved using video laryngoscopy. Monitoring of the fetus can either be done using pulse oximetry or doppler which also provides fetal heart rate and may detect early signs of placental shut down. Aortocaval compression can usually be minimized with a left uterine displacement device such as a wedge. After the induction of anesthesia, additional large-bore intravenous access is obtained, a nasogastric/orogastric tube is placed and a temperature probe is usually inserted.

The inhalational anesthetic regimen used during the EXIT procedure passes through two discrete stages. Anesthesia is first maintained with 0.5 Minimum Alveolar Concentration (MAC) of volatile agent and is then increased to 2-3 MAC before maternal incision. It is subsequently increased as needed before hysterotomy to achieve the desired relaxation of uterine tone. Once the placental location is identified by ultrasound the uterine incision is made and surgical palpation is then performed to assess the degree of uterine relaxation. Maintenance of uterine blood volume is also important to prevent uterine contraction. This is accomplished by preventing the fetus from complete delivery and by the use of amnioinfusion to prevent cord compression.

During the EXIT procedure hysterotomy is usually performed with a uterine stapler to provide hemostasis for a prolonged period and thus decreases the incidence of bleeding. After the hysterotomy site

has been created and hemostasis has been achieved, the fetal head, neck and shoulders are delivered into the operative field [12] (Figure 2).

Adequate pain control is paramount postoperatively. In addition, adequate counseling regarding subsequent pregnancies is advised. Patients with anterior placentas are at increased risk of uterine rupture in subsequent pregnancies.



Figure 2: Exposure of fetal head during EXIT procedure [15].

The most detailed anesthetic management is described by Bouchard et al [9]. This report of 31 cases maintained anesthesia with either isoflurane or desflurane. Desflurane appeared to be favorable due to its low blood-gas partition coefficient, which allows more rapid titration and thus the ability to control uterine tone better than when isoflurane was used. To supplement placental transfer of inhalational agents, the fetus also received analgesia and paralysis with intramuscular fentanyl (10 mcg/kg), vecuronium (0.2 mg/kg) as well as intramuscular atropine (20 mcg/kg) to prevent the expected bradycardic response to surgical stimulation. Immediately prior to umbilical cord clamping and delivery of the baby, the inhalational agent was reduced to 0.5 MAC and intravenous oxytocin (20 units in 500 mls) was administered to prevent serious uterine atony and subsequent maternal hemorrhage.

Gagnon et al [16] is amongst the few reports that mention the use of regional anesthesia for the EXIT procedure. The fetus had a neck mass which was operated on. In lieu of volatile anesthetics, magnesium and nitroglycerin were used to maintain uterine relaxation. The case had a favorable outcome.

Summary

Major advancements in obstetric anesthesiology have markedly reduced the mortality associated with childbirth. Some of these include the routine use of regional anesthesia, video laryngoscopy for endotracheal intubation, improved medication safety, and multidisciplinary care of the patient. Most recent advancements aim to reduce morbidity, but EXIT is an intervention which can be employed for the delivery of infants that would otherwise have had a dismal survival rate.

EXIT procedure is a testament to our advancement in the field of perinatology. Furthermore, improved outcome in general anesthesia of the parturient and coordination of the various medical disciplines in a multidisciplinary fashion have played vital roles. The adequate preparation and vigilance associated with the EXIT procedure has resulted in the outcome of EXIT being comparable to a cesarean delivery [3]. As the anesthetic and surgical techniques employed for the EXIT procedure are further refined, the indications will be broadened and complications further reduced. Hence EXIT may be considered in many fetal conditions where cardiorespiratory instability will occur if standard delivery techniques were utilized [9]. As obstetric anesthesiologists we can educate others that the EXIT procedure is strikingly different than a conventional Caesarean delivery. During a conventional Caesarean delivery performed under general anesthesia, a major goal is to minimize the exposure of the fetus to inhalational anesthetic and thus minimize the depression of the newborn. In addition a lower agent MAC will minimize the expected decrease in uterine tone and reduce maternal hemorrhage. In sharp contrast, during EXIT, deep inhalational anesthesia is required to maintain uterine relaxation and thus preserve utero-placental gas exchange.

The EXIT procedure presents a huge avenue for research. Previously the longest duration for the EXIT procedure was an hour but recently Hiorse [15] published the successful resection of a cervical teratoma in a full term infant with favorable outcome following 2.5 hours of uterine relaxation and placental circulation. Further research is required to determine optimal utero-placental perfusion, necessary uterine relaxation, adequate fetal anesthesia and immobility, minimal fetal myocardial depression and adequate blockade of the fetal stress response.

The positive outcome described in various EXIT procedures is a direct result of the meticulous planning and execution by the multidisciplinary team, and in particular the obstetric anesthesiologist who has to anticipate events preceding, during and immediately after the surgical procedure. Thus as we celebrate a process which amalgamates the advancement in our knowledge and techniques whilst reducing fetal mortality in certain conditions we have to harness the opportunity it provides to increase our understanding of the unknowns which still plague us.

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