

# Case Scenario: Anesthesia for Maternal-Fetal Surgery

## *The Ex Utero Intrapartum Therapy (EXIT) Procedure*

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**F**ETAL anomalies such as giant neck masses can result in perinatal death or hypoxia and anoxic brain injury due to inability to secure an airway in a timely fashion after delivery. Modern technology, ultrasound, and ultrafast magnetic resonance imaging have enabled intrauterine diagnosis and fetal interventions as a mode of therapy, thereby giving such affected fetuses a chance at survival.

Initially, the *Ex Utero* Intrapartum Therapy (EXIT) procedure was exclusively performed in large tertiary children's hospitals because of the easy availability of pediatric practitioners who can adequately manage the baby-related issues. These hospitals are often in close proximity to or affiliated with maternal obstetric units and involve a multidisciplinary team approach to provide care for both mother and baby. However, these types of procedures are increasingly being performed in diverse hospital settings<sup>1</sup>; therefore, adequate knowledge about the related intricacies of these cases is warranted.

We present the case of a mother carrying a fetus of 37 weeks' gestation with a giant cervical teratoma who underwent the EXIT procedure for fetal airway access. This discussion will focus on the multiple management issues and concerns to be contemplated before embarking on the care of a pregnant mother whose child may need surgery shortly before delivery to ensure neonatal survival.

### Case Report

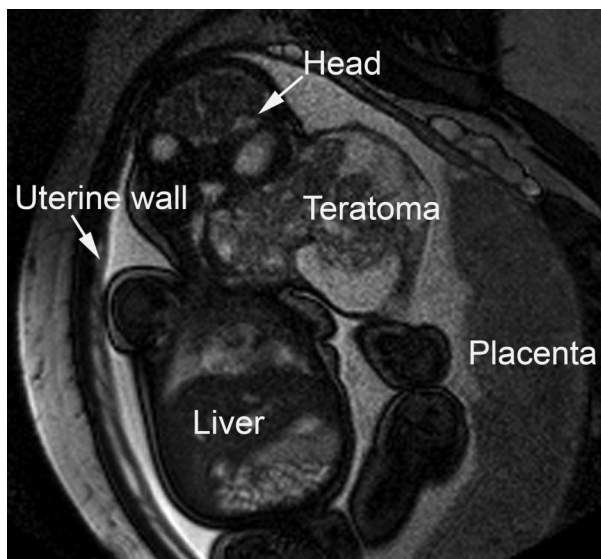
A 35-yr-old healthy, uniparous woman, gravida 2, was referred to our institution's fetal center at 21 weeks' gestation after diagnosis of a giant neck mass with associated moderate polyhydramnios on a routine obstetric ultrasound examination. Fetal magnetic resonance imaging revealed findings consistent with a cervical teratoma and significant airway compromise (fig. 1). Given the degree of airway compromise and distortion of the fetus' anatomy, a multidisciplinary meeting that included anesthesiologists, pediatric surgeons, maternal-fetal medicine specialists, obstetricians, neonatologists, cardiologists, operating room nurses, and labor and delivery room nurses was organized to discuss the fetal anomaly and management approach to delivery of the fetus. Conventional delivery followed by airway maneuvers to intubate the trachea or place a tracheostomy after delivery were thought to be the least favorable options for management given the gross anatomic distortion and potential for hypoxia associated with prolonged attempts at intubation. The EXIT procedure offered the ability to maintain neonatal oxygenation *via* placental support while trying different approaches to secure a definitive airway, and therefore seemed most favorable after reviewing the fetus' anatomy. Once the plan was concluded by the specialties involved, the family was invited to the meeting for an update on the deliberations and concerns and also to meet members of the team. The questions the family had were also addressed at this time, and appropriate counseling was given. The patient was to be monitored until the fetus was closer to term, at which time the EXIT procedure would be performed. It was also emphasized at this meeting that maternal safety was most important, and

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**Fig. 1.** Prenatal magnetic resonance image showing fetal cervical teratoma causing significant airway compromise.

the procedure would be aborted if the parturient's health appeared to be at risk at any time.

#### **What Is the EXIT Procedure and Why Is It Performed?**

Originally designed to allow removal of tracheal clips that were placed *in utero* to treat fetuses with severe congenital diaphragmatic hernia, the EXIT procedure has expanded to include indications for not only airway compromise, but also other fetal anomalies in which neonatal resuscitation and survival could be improved with life-saving fetal surgery during placental support.<sup>2–4</sup> While uteroplacental support is maintained, the baby is partially delivered (head and part of upper torso) and procedures critical for the baby's survival are performed. These may include direct visual laryngoscopy, bronchoscopy, tracheal intubation, tracheostomy, tumor decompression and resection, or placement on extracorporeal membranous oxygenation.<sup>4</sup>

#### **What Fetal Conditions Can Be Considered for This Procedure?**

Current indications for the EXIT procedure include large fetal neck masses, which distort the airway anatomy and result in difficult laryngoscopy; large lung or mediastinal tumors, which can result in cardiac compression and arrest upon institution of positive pressure ventilation and are therefore managed with thoracic decompression *via* thoracotomy before delivery; severe congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation; and congenital high-airway obstruction syndrome such as laryngeal atresia.<sup>5</sup>

Recently, the EXIT procedure and creation of a tracheostomy in the EXIT-to-airway procedure has been performed in fetuses with severe retrognathia or micrognathia with a jaw index of less than the fifth percentile with associated polyhydramnios<sup>6</sup> (table 1).

**Table 1.** Indications for the EXIT Procedure

Fetal cervical masses	Lymphangioma Teratoma Hemangioma Neuroblastoma Goiter
Fetal lung masses	Congenital cystic adenomatoid malformation Bronchopulmonary sequestration
Fetal mediastinal masses	Teratoma Lymphangioma
Congenital high airway obstruction syndrome	Tracheal atresia Laryngeal atresia
EXIT to extracorporeal membrane oxygenation	Severe congenital diaphragmatic hernia with liver herniation into chest cavity Congenital heart disease Hypoplastic left heart syndrome with intact/restrictive atrial septum Aortic stenosis with intact/restrictive atrial septum
Reversal of tracheal occlusion after tracheal clip or endoluminal balloon procedures	

EXIT = *Ex Utero* Intrapartum Therapy.

#### **Goals of the EXIT Procedure**

**Maintenance of General Anesthesia for the Mother with Maximal Uterine Relaxation to Facilitate Delivery of the Fetal Head while Minimizing the Risk of Placental Separation.** In addition to routine volatile anesthetic concentrations for maintenance of anesthesia in the mother, an increase in the inspired concentration of volatile anesthetic, up to two to three times the minimal anesthetic concentration, is required during the EXIT procedure to provide maximum uterine relaxation.

**Maintenance of Uteroplacental Blood Flow.** This is accomplished with the maintenance of maternal blood pressure within 20% of baseline values. Intermittent bolus administration of vasoactive agents such as ephedrine or phenylephrine or a phenylephrine infusion is frequently used during the procedure to counteract the decreased systemic vascular resistance that occurs due to the high volatile agent concentration.

Historically, ephedrine had been considered the gold standard for the treatment of hypotension in obstetric anesthesia due to its good safety record, familiarity,<sup>7</sup> and preservation of uteroplacental blood flow, which was initially demonstrated in animal studies.<sup>8</sup> The use of pure  $\alpha$ -agonists such as phenylephrine had been previously discouraged because of concerns about decreased uteroplacental blood flow.<sup>9</sup> However, recent evidence shows that ephedrine crosses the placenta to a greater extent than phenylephrine and also under-

goes slower metabolism and redistribution in the fetal circulation.<sup>10</sup> The resulting  $\beta$  stimulation in the fetus is thought to be responsible for the increased incidence of neonatal acidosis observed with its use.<sup>10,11</sup> In addition, a meta-analysis of studies comparing ephedrine and phenylephrine did not provide any evidence to suggest that phenylephrine decreased uterine blood flow.<sup>12</sup> Therefore, ephedrine is no longer considered to be preferred over phenylephrine, and both agents are now considered the vasopressors of choice for the treatment of hypotension in obstetric anesthesia.<sup>7,12</sup>

**Adequate Fetal Anesthesia.** Although volatile anesthetics administered to a mother may cross to the fetus,<sup>13</sup> supplemental intraoperative anesthetics, especially muscle relaxants and opioids, may be required for the fetus once direct access is obtained.<sup>14</sup>

### Differences between the EXIT Procedure and a Cesarean Section

The goal of the cesarean section is prompt access to and evacuation of the uterine cavity while maintaining uterine tone and minimizing fetal sedation.<sup>5</sup> In contrast, uterine relaxation is the goal during the EXIT procedure, allowing prolonged intrauterine access to the fetus. The high concentration of anesthetic gas required for uterine relaxation decreases uterine vascular tone and increases the risk for maternal blood loss.<sup>15</sup> Other differences are itemized in table 2.

### Preoperative Considerations for the Mother

A thorough medical history must be taken and complete physical examination performed in the mother. Significant cardiac or pulmonary coexisting diseases may exclude the mother from being an ideal candidate for the EXIT.<sup>16</sup> Polyhydramnios is a common finding in fetuses in whom the

trachea and esophagus are compressed by a neck mass; therefore, a detailed obstetric history including the number of amnioreductions, volume withdrawn, and presence of uterine contractions at the time of reduction should be obtained. Massive polyhydramnios can lead to premature labor requiring amnioreduction and/or tocolytic therapy. Tocolytic therapy can affect anesthetic management during the EXIT procedure.<sup>16</sup> Magnesium sulfate, used for tocolysis, has several additional effects that include increasing the patient's sensitivity to both depolarizing and nondepolarizing muscle relaxants and depression of the central nervous system, and at toxic concentrations it can lead to pulmonary edema, respiratory paralysis, myocardial depression, and cardiac arrest.

The physiology of pregnancy itself, including concerns for delayed gastric emptying, should be considered, with adequate precautions taken by administering preoperative sodium citrate and citric acid, a histamine-2 antagonist, and metoclopramide.<sup>17,18</sup>

### Preoperative Considerations for the Fetus

Amniocentesis can rule out the presence of major underlying chromosomal abnormalities. In addition, fetal imaging including echocardiography is critical to assess ventricular function and the development of heart failure. Heart failure in the fetus may present as hydrops fetalis (accumulation of fluid in one or more fluid cavities, such as the scalp, subcutaneous tissue, pleura, pericardium, or abdomen). Cervical teratomas or congenital cystic adenoid malformations may be associated with hydrops, and this worsens the prognosis of the fetus. The fetal weight is estimated by ultrasound and is used for calculation of any intravenous drugs administered intraoperatively.

**Table 2.** EXIT Procedure vs. Cesarean Section

	EXIT	Cesarean Section
Uterine tone	Goal: maximum uterine relaxation for partial delivery of baby and fetal surgical intervention	Goal: minimal uterine relaxation with rapid return of hypertonic uterus after delivery of baby
Preferred anesthetic	General	Regional
Anesthetic plane	Deep	Minimal to avoid neonatal depression
Infusion of warm fluid into uterus	Required	Not required
Number of anesthesiologists	2; 1 for mother and 1 for fetus	1 for mother

EXIT = Ex Utero Intrapartum Therapy.

### **Intraoperative Management Anesthetic Considerations for the Mother.**

**Monitoring and Access.** Large-bore intravenous access and an arterial line in addition to routine monitors are indicated. The patient is positioned with left uterine displacement in order to avoid aortocaval compression. Blood products for both the mother and baby should be in the room, ready for administration.

**Induction.** Preoxygenation followed by rapid sequence intubation with either propofol or thiopental, fentanyl, and succinylcholine or rocuronium is performed in order to secure the mother's airway. After tracheal intubation, an ultrasound of the fetus is repeated to confirm fetal well-being and to verify position.

### **Maintenance**

High-volatile anesthetic concentrations required to provide adequate uterine relaxation for fetal manipulation result in hypotension. However, normotension is necessary to maintain adequate uteroplacental perfusion; therefore, intermittent administration of vasoactive drugs such as ephedrine is imperative. Infusions of phenylephrine are also useful in maintaining uteroplacental perfusion. Desflurane, isoflurane, or sevoflurane may be used for maintenance of anesthesia.

### **Alternative Anesthetic Regimens**

The technique previously described is the anesthetic management used for most EXIT procedures. However, other anesthetic regimens that have their own special considerations and limitations have been described.

A recent retrospective study by Boat *et al.*<sup>19</sup> found that early institution of high concentrations of volatile agents for long periods of time before hysterotomy was performed resulted in the development of intraoperative fetal bradycardia, especially when desflurane was used as the maintenance agent. Based on their findings, the authors of this study suggest the utilization of supplemental intravenous anesthesia with propofol and remifentanyl until just before the hysterotomy incision is made, at which point high volatile anesthetic concentrations are used to achieve the desired uterine relaxation.<sup>19</sup>

Neuraxial anesthesia has been administered as an alternative to general anesthesia for the EXIT procedure with an accompanying infusion of nitroglycerin to achieve uterine relaxation.<sup>20,21</sup> This can be used in parturients in whom volatile anesthetics are contraindicated. The myometrial relaxation effect of nitroglycerin, however, may not be easily titrated in comparison with volatile anesthetics, and its use may be associated with hypotension, reflex tachycardia, tachyphylaxis, methemoglobinemia, and headaches in the awake patient. The most appropriate anesthetic regimen should be individualized for each patient.

### **Intraoperative Anesthetic Considerations for the Fetus Operating Room Preparation**

The anesthesiologist dedicated to the baby's care ensures there is a separate pulse oximeter monitor, labeled specifically

for intraoperative monitoring of fetal oxygen saturations during the EXIT procedure in the mother's operating room. This anesthesiologist is also responsible for preparing a separate, adjacent room specifically for the newborn baby. This second operating room may become necessary if additional surgery is required on the fetus after separation from the mother; for example, if immediate resection of the neck mass is required. Both operating rooms should be warmed to 80°F just before delivery of the baby to ensure normothermia. In addition, the infant resuscitation area (or adjacent operating room) is equipped with a radiant warmer and/or forced air warming blanket.

**Fetal Monitoring.** Before hysterotomy, continuous fetal monitoring can be provided by the cardiologist *via* echocardiography with precise information on the heart rate, cardiac filling, and contractility. Once access to a fetal extremity is obtained, a pulse oximeter probe is applied to encircle the hand, and information on oxygen saturation and heart rate can be obtained and recorded. Interference from excessive ambient light may necessitate covering the pulse oximeter probe with foil or towels. Initial fetal pulse oximeter readings usually range between 60–70% and will rise as the fetus receives supplemental oxygen following intubation.

**Fetal Equipment.** The required equipment should be obtained and placed on a sterile table in the mother's room before the EXIT procedure (table 3).

Intravenous catheter placement in the fetus, while occasionally challenging due to the fetus being covered in vernix, is helpful as fluid administration (albumin or lactated Ringer's solution) may be necessary if the cervical mass resection actually begins on the mother's sterile field.

In preparation for care of the newborn baby, the adjacent room is equipped with an intravenous fluid warmer and arterial line transducer, and drugs are prepared based on estimated birth weight.

### **Continued Management of Our Patient**

The EXIT procedure was scheduled for a date at which the mother was 35 5/7 weeks' gestation in order to preempt premature labor. On the day of surgery, following adequate preoxygenation, the mother underwent rapid sequence induction and easy tracheal intubation. An additional peripheral intravenous catheter was placed as well as an arterial line for hemodynamic monitoring. The concentration of sevoflurane was gradually increased to 5.5%, at which point adequate uterine relaxation was confirmed by manual palpation after laparotomy. Hysterotomy was performed with a uterine stapling device (U.S. Surgical Corporation, Norwalk, CT). Continuous irrigation of warm lactated Ringer's solution into the uterus was instituted and the fetus' left upper extremity was exposed in order to administer a combination of intramuscular fentanyl, pancuronium, and atropine.

The anesthesiologist dedicated to the baby's care placed a pulse oximeter probe on the left hand of the fetus as well as a 24-gauge peripheral intravenous catheter. The catheter



**Table 3.** Fetal Equipment

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Pulse oximeter monitor and probe for monitoring of fetal oxygenation during procedure
Sterile self-reinflating bag valve mask connected to oxygen source
End-tidal carbon dioxide indicator
Several 24-gauge intravenous catheters
Saline flush with extension for intravenous catheter
Penrose drain to use as tourniquet for intravenous catheter placement
Resuscitation medications:
Three 1-ml syringes of epinephrine 1 µg/kg (for intravenous or umbilical cord administration)
Two 1-ml syringes of calcium gluconate 30 mg/kg (for intravenous administration)
Fetal medication syringes with 27-gauge subcutaneous needles attached for intramuscular administration:
Three syringes of unit doses of atropine, fentanyl, and pancuronium all combined in one syringe
Two 1-ml syringes of unit dose of atropine 0.02 mg/kg
Array of different-size endotracheal tubes with stylettes
Two 10-ml syringes of saline
Two 10-ml syringes of albumin
60 ml of packed erythrocytes (type O-) for fetus

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placement was easily accomplished because the baby was near term and had adequate peripheral veins.

After placement of the pulse oximeter probe and intravenous catheter, the fetal head, neck, and shoulders were delivered, and the head was positioned for direct visual laryngoscopy. Laryngoscopy revealed a grade 4 view and inability to pass the endotracheal tube. Subsequent bronchoscopy performed by the surgeons allowed for successful placement of the endotracheal tube through the distorted airway. Adequate endotracheal tube placement and ventilation was confirmed with a colorimetric end-tidal carbon dioxide detector and fetal chest auscultation, after which the umbilical cord was clamped, and the baby was transferred to the neonatal intensive care unit. The mother received 20 units of oxytocin in a lactated Ringer's solution infusion, which was sufficient to return the uterine tone to normal. The mother was extubated uneventfully and transferred to the recovery room.

The baby subsequently underwent appropriate imaging studies and evaluation of the neck mass within the next few days in order to delineate vascular structures, and was returned to the operating room 4 days after delivery for successful resection of the neck mass.

### **Concern after Delivery**

Maternal hemorrhage is a real concern in these patients considering the amount of uterine relaxation required for surgery. The staples applied during hysterotomy prevent severe bleeding but an inappropriately applied or loose staple could result in massive bleeding. Hence, adequate preparations should be made for possible intraoperative transfusion, and cross-matched blood should be readily available. The blood bank should be notified that more units may be necessary. Uterotonic agents including oxytocin, methylergonovine, carboprost tromethamine, and misoprostol should be available to induce uterine contraction following delivery.

### **Comments from a Fetal Surgeon (0.0.0.)**

Anesthesia for maternal-fetal surgery, in particular the EXIT procedure, is a critical part of the operation. It requires particular attention to detail and coordination between the surgeons and the anesthesiologists. Effective uterine relaxation is crucial to maintaining uteroplacental flow for the duration of the procedure. This is best monitored by manual palpation on the operating field. The adequacy of uterine relaxation is communicated to the anesthesiologist. Furthermore, restoration of uterine tone at the conclusion of the procedure is imperative to prevent excessive bleeding from the placental bed. The surgeons and anesthesiologists must communicate effectively to coordinate the duration of the procedure and the timing of reduction of volatile anesthetic concentration to allow for uterine contraction. This is typically done just before the baby is ready to be separated from the mother. If increase in uterine tone occurs too soon, uteroplacental flow may be impaired. If it occurs too late, excessive bleeding may occur.

The duration of the fetal procedure may vary depending on the complexity of the airway anatomy. The procedure may be short if a direct laryngoscopy or bronchoscopy is all that is required to access the airway. Occasionally, a tracheostomy or even partial resection of the neck mass may be required to identify the location of the trachea when antegrade access is impossible. Ongoing dialogue with the anesthesiologists during these maneuvers is very important. Once access to the airway is obtained and the baby is being ventilated, the anesthesiologist assigned to the baby takes over the airway while the surgeons proceed with umbilical vascular access as needed. We have found that securing umbilical vascular access on the surgical field is easier because the vessels are still engorged. The umbilical cord is then clamped, and the baby is separated from the mother and carried to the resuscitation station or to an adjacent operating room for

further surgery if indicated. Transporting the baby at this point requires both the pediatric surgeon and the anesthesiologist to ensure the critical airway remains secure during transport.

Maternal fetal surgery is a truly multidisciplinary effort that requires a skilled team of physicians and nurses and excellent team communication.

### **Comments from an Obstetrician (R.T.I.)**

Indications and utilization of the EXIT procedure continue to evolve. We now have infants who survive conditions that were previously considered lethal. Although the use of placental bypass has provided another tool in obstetric care, it should be noted that it requires a multidisciplinary approach and meticulous planning. Temporal integration of services involving anesthesia, obstetrics, fetal surgery, cardiology, and neonatology is essential for optimal patient outcome.

Careful consideration must be given to the timing of delivery. The EXIT procedure is ideally performed before the onset of labor. The goal is to extend the pregnancy close to term to decrease the complications of prematurity. However, delivery is often done preterm because of the onset of labor or the development of maternal and/or fetal compromise.

Ultrasonography is performed in the immediate preoperative period to confirm presentation and placental location. In most cases, the lower uterine segment is of sufficient width to perform a transverse uterine incision. In cases of preterm gestation, large masses, or difficult fetal access, a vertical uterine incision may be required. The possibility of a vertical incision should be discussed with the patient during the preoperative period because it increases the risk of complications with future pregnancies. It should also be discussed with the team, particularly the anesthesiologist, because vertical uterine incisions are associated with increased blood loss compared with transverse uterine incisions in both EXIT procedures as well as conventional cesarean deliveries.

Control of maternal hemorrhage requires careful coordination between the anesthesiologist and the obstetrician. After delivery, the concentration of the anesthetic gases is decreased and uterotonic medications are administered. The placenta should be allowed to spontaneously separate and deliver as uterine tone increases. Manual manipulation of the placenta before this point greatly increases the risk for hemorrhage.

### **Epidemiology**

Although the number of EXIT procedures performed annually is unknown, several case series have been reported in the literature. The largest case series is reported by Hirose *et al.* in 2004 in which 52 EXIT procedures were performed at the University of California, San Francisco between 1993 and 2003.<sup>2</sup> Forty-five patients underwent the EXIT procedure for reversal of tracheal occlusion performed for congenital diaphragmatic hernia, five occurred in patients with neck masses, and two were in patients with congenital high airway

obstruction syndrome. The second largest case series was reported by Hedrick *et al.* from the Children's Hospital of Philadelphia in which 43 patients underwent the EXIT procedure between 1996 and 2002.<sup>22</sup> In this retrospective review, 19 patients underwent the EXIT procedure for a neck mass, 13 for reversal of tracheal occlusion, 5 for congenital cystic adenomatoid malformation, 3 for congenital high airway obstruction syndrome, and 1 patient each for EXIT-to-extracorporeal membrane oxygenation, pulmonary agenesis, and as a bridge to separation for conjoined twins. Since these initial reports of relatively large series from busy fetal treatment centers, the EXIT procedure has been increasingly performed in diverse hospital settings. Table 1 lists indications for the EXIT procedure.

Fetal laryngotracheal obstruction is a life-threatening condition, which if unrecognized before delivery has a reported mortality of 80–100%.<sup>23</sup> Obstruction can be classified as extrinsic or intrinsic. Extrinsic obstruction includes compression by a cervical teratoma, lymphatic malformation, or a vascular ring.<sup>23</sup> Intrinsic compression is comprised of the congenital high airway obstruction syndrome.

Specific to this case discussion, the incidence of teratomas is between 1 in 20,000 and 1 in 40,000 live births, with both sexes affected equally.<sup>24</sup> Cervical teratomas are germ cell tumors that comprise 1.5–5.5% of pediatric teratomas.<sup>25</sup> They usually have mixed solid and cystic components. Prenatal diagnosis is important because they can obstruct the airway. Severe airway compromise occurs in 50% of neonates with large cervical teratomas, with mortality approaching 43%.<sup>26</sup> However, mortality is low if an airway can be secured at time of delivery. Cervical teratomas may also be associated with lung hypoplasia and cardiovascular compromise, the latter resulting in high-output heart failure.<sup>26</sup> Polyhydramnios is a common associated finding because of difficulty swallowing as a result of its mass effect. The findings of polyhydramnios and a large neck mass suggest airway obstruction.<sup>27</sup> In one study by Wagner *et al.*, an airway was established in 79% of 29 fetuses with head and neck masses undergoing the EXIT procedure with an overall survival rate of 69%.<sup>28</sup>

### **Knowledge Gap**

The effect of anesthetic inhalational agents on the developing brain is a concern at this stage of life. The EXIT procedure is still fairly new, and information is being gathered about the possible long-term effects of these procedures, particularly of the high concentration of inhalational agents received in the first few hours of life. Lymphangiomas or cystic hygromas, another common indication for the EXIT procedure, are often treated after delivery, with multiple rounds of sclerotherapy, and many of these instances require a separate anesthetic. Although evidence from animal studies shows that anesthetic drugs given to an immature brain cause neuronal apoptosis and subsequent learning problems, this evidence is weak and mixed in humans.<sup>29</sup> It is difficult to determine whether the anesthesia itself or the underlying condition is

the factor that contributes to learning disabilities.<sup>30</sup> Babies who have undergone the EXIT procedure are being followed for neurologic assessment, but it is still too early to make any conclusive statements regarding the effect of anesthesia, if any, on these children. This is an area of ongoing research.

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