Anaesthesia for the EXIT procedure: A review

Olutoye OA, MD
Department of Anesthesiology and Paediatrics, Baylor College of Medicine, Texas Children's Fetal Center, Texas Children's Hospital, Houston, Texas

Correspondence to: Dr Olutoyin Olutoye, e-mail: oao@bcm.edu

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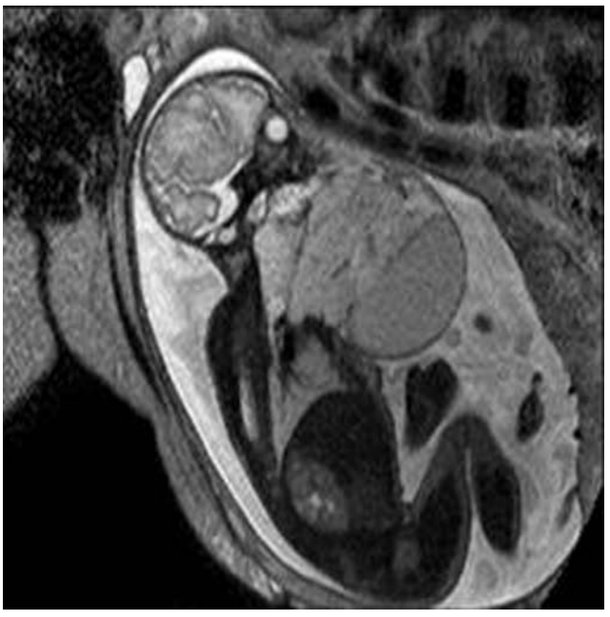
Introduction

The increased use of ultrasound during pregnancy has allowed early diagnosis of fetal abnormalities including life-threatening conditions affecting the airway. Detection of these anomalies enables advanced planning and coordination of resources to optimise the outcome for the fetus at birth and thereafter. Ultrafast magnetic resonance imaging (MRI), can delineate fetal masses more definitively than ultrasound (Figure 1) and can be used to identify those that will benefit from intervention.[1]

Figure 1: Prenatal ultrafast MRI image of cystic hygroma



The concurrent advancement of surgical techniques has made intrauterine procedures on the fetus possible during pregnancy or at the time of delivery. These recent advances have resulted in improved survival for babies with fetal airway obstruction caused by large intra-oral or neck masses that would make spontaneous ventilation or placement of an endotracheal tube with direct laryngoscopy impossible. Babies with large lung masses or pleural effusions that impair adequate lung expansion following delivery have also benefited from these procedures.

The acronym EXIT stands for Ex-utero Intrapartum Therapy. This procedure involves partial delivery of a fetus' head and upper body for management of life-threatening conditions while maintaining placental circulation. It eliminates immediate concern for hypoxia as the placenta continues to provide oxygenation while the airway is being secured or surgery is being performed on the fetus.[1-4] Historically, the EXIT procedure was first described for removal of tracheal clips in babies near term who had clips placed in utero to encourage lung growth in cases of severe congenital diaphragmatic hernia (CDH).[2] While this mode of management for CDH has not been widely accepted, the EXIT procedure is now gaining popularity as the standard of care for fetuses with particular congenital anomalies.

Fetal conditions that may require the EXIT procedure include masses obstructing the airway, space occupying lesions in the thorax, and conditions that require extracorporeal membrane oxygenation upon delivery.

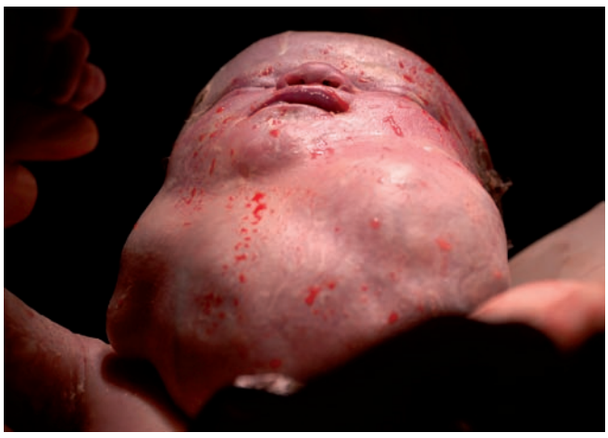
EXIT for airway obstruction

Anomalies that can present as newborn airway obstruction include cervical teratomas, cervicofacial lymphovenous malformations, intraoral masses, congenital goiter and congenital high airway obstruction syndrome (CHAOS) e.g. laryngeal atresia. The presence of these tumors limits the ability of the neonate to breathe after birth. The resulting anatomical distortion makes placement of an endotracheal tube extremely challenging and perinatal asphyxia is a significant threat. Babies with severe micrognathia also fall into this category.[5, 6]

Cervical teratomas

The first reported EXIT procedure with an indication unrelated to congenital diaphragmatic hernia was for the management of a fetus with a giant cervical teratoma.[3] Cervical teratomas are composed of tissue from all germ cell layers and can be very extensive. They are extensive, firm, and well-circumscribed tumors which may displace and compress the trachea (Figure 2). Hyperextension of the neck and traction on the carina may occur and the upper lobes of the lung may become hypoplastic as they are compressed against the apex of the thorax during fetal development.

Figure 2: Large, well circumscribed cervical teratoma

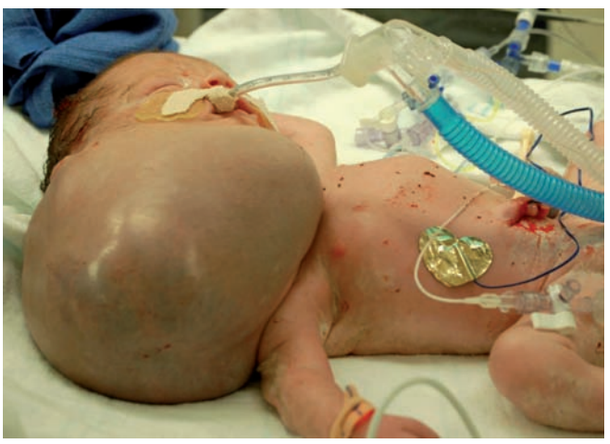


Cervical teratomas have varying presentations depending on the size and degree of compression of surrounding structures. Oesophageal compression may result in polyhydramnios that can precipitate pre-term labour. In very rare cases, large cervical teratomas with high vascularity may result in hydrops foetalis,

the result of high output cardiac failure in the fetus. Hydrops foetalis is characterised by the presence of excess fluid in two or more body cavities i.e. abdomen, pericardium, thorax or skin and may also be associated with placental thickening. The development of hydrops increases the urgency of intervention as the danger of fetal demise becomes imminent. Occasionally, it becomes necessary to drain pleural effusions to improve pulmonary function during an EXIT procedure.

Cystic hygromas or cervical lymphangiomas
These cystic masses develop as a result of failure of the jugular lymph sacs to join the lymphatic system early in fetal development. The sacs become filled with lymph-like fluid, gradually distend and compress surrounding structures. They may involve the floor of the mouth, pharynx, larynx and extend into the mediastinum or can extend from the mastoid process to the sternal notch inferiorly and the trapezius muscle posteriorly (Figure 3). Some hygromas regress spontaneously but the natural history of cystic hygromas in the prenatal period tends to be more dismal than that of hygromas diagnosed postnatally. Those diagnosed early in gestation are more likely to be associated with other structural or chromosomal abnormalities, and hydrops.[4] They are also associated with an increased mortality rate. Isolated fetal cystic hygroma and those developing later in life have a better prognosis. For large masses, the immediate challenge in the perinatal period is the potential for airway obstruction. Imaging with ultrafast fetal MRI carefully delineates the extent of these lesions and suggests the degree of airway distortion or compression.

Figure 3: Cervical hygroma

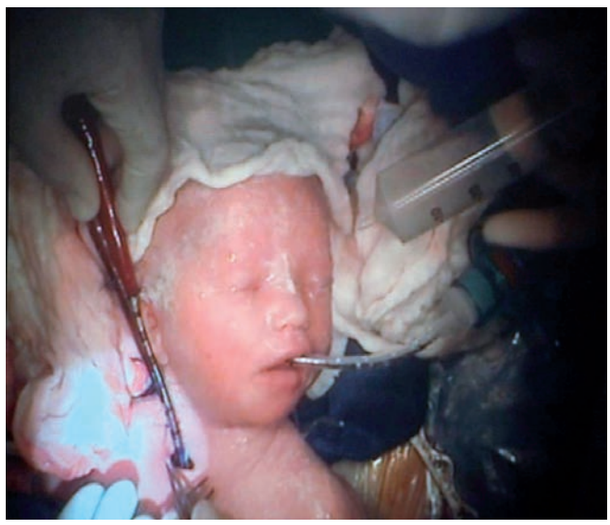


Congenital goiter
A diffuse enlargement of the thyroid may occur in the fetus of mothers with Graves disease as result of the transplacental passage of thyroid-stimulating immunoglobulin G antibody. Other causes of congenital goiter include: iodine deficiency or iodine intoxication (latter condition seen in the fetus of mothers with hypothyroidism). Markedly enlarged goiters may cause airway obstruction.

Congenital high airway obstruction syndrome (CHAOS)
This condition encompasses varying degrees of abnormal or arrested development of the larynx i.e. laryngeal or tracheal atresia and laryngeal cysts. These abnormalities result in hyper-inflated lungs, an everted diaphragm, dilated tracheobronchial tree and ascites. These fetuses may also develop non-immune hydrops. Fetal MRI studies characteristically show very large lungs with high signal intensity. While a tracheotomy and multiple airway operations are inevitable in the long term management of these fetuses following delivery, the EXIT procedure offers the slightest chance of survival for a condition that otherwise has a dismal outcome at birth.[7, 8]

Conditions that will necessitate emergent extracorporeal membrane oxygenation (ECMO)
When difficult transition from fetal to neonatal circulation is anticipated as in some congenital cardiac lesions or severe congenital diaphragmatic hernia (CDH),[9] the fetus can be placed on ECMO (extracorporeal membrane oxygenation) before placental support is discontinued to prevent haemodynamic and cardiorespiratory compromise (Figure 4). This approach has also been used in some fetuses with large intrathoracic masses.[10]

Figure 4: Fetus still covered in vernix with ECMO cannulae being inserted while on uteroplacental bypass



Intrathoracic masses requiring advanced cardiopulmonary resuscitation
Fetuses with large intrathoracic masses (mediastinal teratomas or large lung lesions) that can cause haemodynamic compromise and difficulty with ventilation at the time of delivery may undergo resection during the EXIT procedure i.e. EXIT-to-resection. In this scenario, the fetus would undergo a sternotomy or thoracotomy while still on placental support. The mass is then exteriorised and resected thereby reducing the compressive effect on the lungs and mediastinum prior to initiating ventilation and delivery of the infant.[11]

Severe micrognathia
There are reports of the EXIT procedure being performed on babies with severe micrognathia or retrognathia. Endotracheal intubation in these babies can be quite challenging and requires specialised equipment. In some institutions, performing the EXIT procedure as a means of establishing an adequate airway in a controlled fashion is becoming the standard of care for severely affected babies. However, the criterion to determine which of these babies would require airway establishment via the EXIT procedure has not yet been defined. Majority of EXIT procedures to date have been performed for neck masses.

Preoperative preparation
The multidisciplinary facets of this procedure mandates that all physicians involved in the management of the mother and the baby have an understanding of the prenatal history, maternal and fetal concerns and the necessary steps to ensure a smooth execution of the procedure.

Preoperative multidisciplinary meetings, that may include the parents, have become a mainstay in the preparation for these procedures and are of extreme importance as the indication for each EXIT procedure is different. The sequence of events also differs depending on the fetus' pathophysiology. Disciplines

involved in these meetings should include the obstetricians, paediatric surgeons, anaesthesiologists, paediatric cardiologists, neonatologists, radiologists, respiratory therapists, ethicists, operating room, and labour and delivery nurses as well as representatives from the pharmacy and blood bank. Each of these disciplines is introduced and their role in the procedure is explained in detail for the understanding of the family as well as other practitioners present.

The obstetrician and/or paediatric surgeon introduce the case explaining the nature, pathophysiology of the lesion and the indication for intervention. At our institution, we have discovered that a thorough understanding of the nuances of the condition and the proposed procedure fosters team building and ensures a clear delineation of the role of each team member.

Maternal perioperative considerations

A thorough medical history and physical examination must be performed in all patients scheduled for a proposed EXIT procedure. Significant cardiac or pulmonary co-existing diseases that increase maternal morbidity can preclude the mother from being an ideal candidate for this procedure. In cases of suspected or confirmed Graves's disease, the mother's thyroid function should be assessed to ensure a euthyroid state.

A history of polyhydramnios is important as this is a cause of premature labour and may warrant frequent amnioreductions in the mother prior to the EXIT procedure. The frequency of amnioreductions, amount of fluid obtained, and the presence of uterine contractions at time of reduction should be noted. Tocolytic therapy may be necessary, particularly if repeated amnioreductions have resulted in an irritable uterus. Recent tocolytic therapy with magnesium sulphate or nifedipine prior to surgery, can impact the anaesthetic as magnesium prolongs the duration of muscle relaxant agents and nifedipine may lower maternal blood pressure.

The ideal timing for the EXIT procedure is close to term but prior to the onset of labour. While, the onset of labour is not an absolute contraindication to an EXIT procedure, it mandates accelerated implementation of the preparatory steps for the procedure. In institutions in which these procedures do not occur on a regular basis, it is always beneficial if a dry-run or team meeting has taken place prior to emergently carrying out this procedure. However, depending on the situation, this may not always be feasible. There is always a risk of placental abruption if uterine contractions cannot be suppressed and this will obviate the need for the EXIT procedure if it occurs.

Concerns for delayed gastric emptying in a pregnant woman having surgery require the administration of metoclopramide and sodium citrate prior to surgery. Effective uterine relaxation is necessary for the success of this procedure hence tocolytic agents like nitroglycerine should be readily available if needed to supplement the relaxation that is primarily induced by inhalation agents.

Fetal perioperative considerations

The presence of a chromosomal anomaly is a relative contraindication to the EXIT procedure and it is usually ruled out by karyotyping performed on a sample obtained during amniocentesis.

Echocardiography plays a pivotal role in the assessment of a fetus for this procedure as the development of hydrops foetalis can be detected and monitored prior to intervention. In addition, ventricular volume status and ventricular function can be assessed. As some degree of myocardial depression can be anticipated with inhalational anaesthetic agents, an appreciation of baseline fetal cardiac function is helpful prior to commencing surgery. An estimate of the fetal weight, which is prudent for the anaesthetic management of the baby, is determined pre-operatively from the ultrasound.

Preparation of the operating room

In most cases, therapeutic management during the EXIT procedure is fully accomplished during uteroplacental circulation. In some instances however, the process may begin while the fetus is attached to the placenta but it may be necessary for the neonate to have the procedure completed in an adjacent room. Therefore, two adjacent operating rooms with separate operating room personnel (anaesthesiologists and nursing staff), must be prepared in advance; one for mother and baby respectively.

Table I: Maternal and fetal requirements specific for the EXIT procedure

Maternal
1. High concentration of volatile agents and tocolytics to provide uterine relaxation
2. Warmed lactated Ringers infusion to maintain amniotic fluid volume
3. Ephedrine and phenylephrine to maintain maternal blood pressure (consider continuous infusions depending on patient requirements)
4. Invasive continuous BP monitoring
Fetal
1. Type O negative packed red cells in split aliquots
2. Pre-prepared syringes of fentanyl, vecuronium or pancuronium and atropine in unit doses for intramuscular administration
3. Pre-calculated unit doses of epinephrine, calcium for resuscitation if necessary
4. Pulse oximeter dedicated for baby monitoring
5. End-tidal carbon-dioxide detector to confirm endotracheal intubation
6. Array of different size, styletted paediatric endotracheal tubes
7. Sterile ambu bag with manometer attached to oxygen source
8. Foil for placement over fetal pulse oximeter probe to decrease ambient light interference
9. Plastic bag to cover baby's head upon partial delivery if feasible

Unit doses of drugs available for the fetus based on a pre-determined weight should be readily available on the sterile field during the EXIT. Fentanyl (20 mcg/kg), vecuronium (0.2 mcg/kg) or pancuronium (0.1mg/kg) and atropine (0.1–0.2 mg/kg) should be available to provide anaesthesia to the fetus. Atropine is necessary to prevent vagal responses to stimulation. Epinephrine at 1–10 mcg/kg and calcium gluconate, both in unit doses, should also be available for resuscitation. An array of sterile endotracheal tubes and stylettes should also be available. Packed red blood cells should be available for both mother and baby. O negative irradiated blood in split units should be available for the baby in the event that a transfusion is required.

In preparation for the partially delivered fetus, the operating room should be warmed to approximately 85 degrees Fahrenheit in order to reduce heat loss during partial exposure of the baby. Depending on the surgical site, plastic wraps can be placed on the baby's head in order to minimise heat loss. See Table I for pre-operative check list.

Intraoperative considerations

Maternal induction of anaesthesia

Left uterine displacement in order to avoid aorto-caval compression is mandatory. General anaesthesia is commonly performed using a rapid sequence induction method with either propofol or thiopental and succinylcholine to secure the airway after adequate pre-oxygenation.

Monitoring

Large bore intravenous access and radial arterial line in addition to routine monitors are indicated. Monitoring of the blood pressure with the use of an arterial line allows prompt management of maternal hypotension caused by the increased concentration of inhalational agents and /or nitroglycerine required for uterine relaxation. Following induction of anaesthesia, a repeat ultrasound is performed to assess fetal well-being as well as placental location and fetal lie. The latter two are important as they dictate the location of the uterine incision.

Maternal maintenance of anaesthesia

Uterine relaxation

Following skin incision, the anaesthetic agent is maintained at 1–2 times minimal alveolar concentration (MAC) to achieve profound relaxation of the uterus at the time of hysterotomy. The resulting vasodilatation causes hypotension. Due to the proportional relationship of maternal mean arterial pressure and uterine blood flow which in turn determines umbilical venous flow, fetal cardiac output and oxygenation, maternal blood pressure must be maintained as close to awake values as possible.

Sympathomimetic agents, e.g. ephedrine and phenylephrine, are frequently used to maintain the blood pressure, depending on the maternal haemodynamic status.

Uterine relaxation is the single most important factor that determines the success of this procedure. No particular halogenated agent has any benefit over the other in terms of inducing uterine relaxation. Sevoflurane, isoflurane and desflurane all have been used. However, a retrospective study looking at fetal haemodynamic effects of desflurane when used for uterine relaxation during the EXIT procedure suggests that there is a high incidence of fetal bradycardia with high desflurane concentrations.[12] Ethical considerations will preclude a prospective randomised study to evaluate the validity of this finding. Intravenous agents such as nitroglycerin (boluses of 50–100 mcg) can also be used to augment uterine relaxation.

In contrast to a routine Caesarean section, a short induction to delivery time is not the goal during an EXIT procedure. What is of importance with the EXIT procedure is that adequate uterine relaxation occurs before the uterine hysterotomy is performed in order to prevent uterine contractions and placental abruption while the baby is partially delivered and being operated upon. Therefore, hysterotomy is not performed until an acceptable level of uterine relaxation is appreciated by manual palpation of the uterus by the surgeons. Incision of a relaxed uterus can result in massive blood loss, therefore a special hysterotomy stapling device is used to minimise blood loss. This device clips the myometrium and amniotic membrane together establishing a bloodless field as it cuts.

EXIT procedures with a combined-spinal-epidural (CSE) anaesthetic technique using intrathecal bupivicaine and opioids have been reported, but not widely used. In these patients, uterine relaxation was provided by an initial bolus of nitroglycerin (50–100 mcg) followed by an infusion at 0.5–1.5 mcg/kg/min.[6] In the cases of EXIT under CSE the reported duration of uteroplacental bypass was approximately 10 minutes and they involved quick fetal direct laryngoscopies and endotracheal intubation. However, it is difficult to predict ahead of time, the duration an EXIT procedure will last. Therefore combined spinal-epidural anaesthesia should not be considered the anesthetic method of choice.

Pharmacokinetic studies have demonstrated placental transfer of nitroglycerin and no significant haemodynamic effects in the fetus were detected. This is most likely related to rapid placental metabolism, short half-life, and high maternal-fetal gradient of nitroglycerin.[13] Nitroglycerin use may be associated with increased capillary leak in the mother and this is a potential disadvantage.

In addition to nitroglycerin, magnesium sulphate and calcium channel antagonists also provide uterine relaxation but their effects are not easily reversible and they may complicate the anaesthetic with adverse effects such as prolonged muscle relaxation. Therefore, they are not routinely utilised for the provision of uterine relaxation during this procedure.

Administration of 100% oxygen to the mother is recommended till baby is delivered in order to maximise fetal oxygenation although oxygen/air combinations have been used. Nitrous oxide does not cause uterine relaxation and may augment maternal hypotension so it adds no benefit to the procedure especially prior to complete delivery of the baby.

Another consideration during this surgery is loss of amniotic fluid during the procedure. Marked loss of fluid and decrease in uterine volume may result in contractions and inadvertent fetal expulsion or placental separation during the procedure. Decreased amniotic fluid volume may also result in umbilical cord compression by the fetus or surgical instruments. In order to prevent this, continuous replacement of amniotic volume with infusion of warmed lactated Ringer's solution is mandatory. This has the added benefit of keeping the fetus in a warm moist environment.

Maintenance of anaesthesia for the fetus

Monitoring

Fetal oxygenation is monitored via a dedicated pulse oximeter for the baby. A sterile sheath should be available for placement of the pulse oximeter cable onto the surgical field. Once hysterotomy is performed and there is access to the fetus, the right upper extremity or extremity that is readily accessible, is quickly identified and exteriorised for application of a pulse oximeter. Challenges to adequately placing this monitor include vernix and ambient light. Vigorous drying of the hand or extremity prior to placement of the pulse oximeter is helpful. The hand and monitor are then covered with small foil wrap and an overlying sterile towel to fully prevent ambient light interference. Saturations in the order of 70% are normal; bradycardia or saturations below 50% indicate significant hypoxia. If pulse oximetry cannot be established, ultrasound or Doppler are alternatives for fetal heart rate monitoring.

Endotracheal intubation is attempted by direct laryngoscopy. For babies with airway obstruction, bronchoscopy or tracheotomy may be required. A carbon dioxide colorimetric device should be available for confirmation of endotracheal tube placement once the airway has been secured. Once placement is confirmed, the tube is typically secured to the gums with sutures by the surgeon.

Despite the baby being anesthetised by halogenated agents received through uteroplacental blood flow, occasional movement may occur. Opioids and muscle relaxants may be administered intramuscularly to provide additional analgesia and muscle relaxation prior to any instrumentation or incision. Atropine administration helps prevent a vagal response.

A well coordinated effort to achieve completion of the procedure in the shortest possible time is the goal. Initial studies in mammals in which periodic fetal blood gases were obtained on the partially delivered fetus have shown that fetal acidosis does not occur until after about one hour on uteroplacental bypass.[14] Human studies also suggest that prolonged duration of general anaesthesia activates the sympathoadrenal system of the fetus resulting in fetal acidosis.[15] EXIT procedures have been reported in which

the duration of mass resection lasted approximately 2.5 hours with no untoward effects in either baby or mother.[16]

Maternal anaesthesia after delivery of baby

The post delivery phase is another important step in which effective communication between the surgeon and anaesthesiologist is imperative. Once the baby has been fully delivered, uterine tone needs to be rapidly restored in order to prevent massive maternal haemorrhage from uterine atony. Just before umbilical cord clamping or as the cord is being clamped, the concentration of inhalational agents must be reduced and uterotonic medications administered. Oxytocin as an initial slow intravenous bolus and subsequently as an infusion in crystalloid is started. Depending on the duration of uterine relaxation that was required, additional agents may be needed such as methylergonovine 0.2 mg IM or IV, carboprost 250 mcg IM, misopristol 600 mcg PR, and calcium carbonate 100–200 mg IV boluses. In addition some obstetricians may preferentially administer intramyometrial oxytocin (10U). The delivery of the placenta is delayed until adequate uterine contraction is achieved allowing the placenta to be spontaneously expelled. Blood products available in the room should be administered if necessary.

At this time, the rest of the anaesthetic may proceed with nitrous oxide in oxygen. Additional opioids may be administered or if an epidural had been placed preoperatively, it may be dosed at this stage. Use of regional anaesthesia as a supplemental anaesthetic prior to this point is not recommended as the sympathectomy-induced hypotension will accentuate the hypotension resulting from the high concentration of anaesthetic agents required for uterine relaxation.

Management of baby following delivery

The baby is carried to the adjoining room, warmly swaddled and hand ventilated during transfer with an ambu bag. The surgical procedure is completed in the adjacent room at this time if necessary or the baby is prepared for transfer to the NICU for ventilator management as necessary. Venous access may be secured at this time

Management of mother for future deliveries

There is no contraindication to vaginal delivery following the EXIT procedure provided a lower uterine segment incision is made. In situations where a lower uterine segment incision cannot be made, the uterus is at risk for rupture during subsequent pregnancies and most especially during labour. In these cases therefore, a vaginal birth after Caesarean would not be an option and subsequent deliveries by Caesarean section is recommended.

Conclusion

The EXIT procedure has become mainstay in the treatment of certain fetal life-threatening conditions. It is responsible for the increased survival of such affected fetuses that previously would have died or suffered perinatal asphyxia and become neurologically devastated for life. A thorough understanding of the different steps involved will allow for a smooth execution of this procedure. A commitment of resources and dedicated personnel to both the mother and the baby is critical to ensure a smooth execution of the procedure in its entirety. Many more institutions are becoming involved in EXIT procedures, and a full understanding of the anaesthetic requirements and necessary equipment can make an otherwise daunting procedure very smooth. SAJAA

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