Four cases of the ex utero intrapartum treatment (EXIT) procedure: anesthetic implications

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SUMMARY. The ex utero intrapartum treatment (EXIT) procedure is a method of maintaining utero-placental circulation during cesarean section to gain time to secure a potentially obstructed fetal airway. Four cases of the EXIT procedure are described with special reference to the maternal anesthetic technique. Deep volatile anesthesia (approximately 2 MAC) with isoflurane or sevoflurane for a prolonged period of time, in three cases in combination with an intravenous nitroglycerin infusion, was used to ensure a fully relaxed uterus during the procedure. All mothers were maintained hemodynamically stable with preserved utero-placental perfusion. It was possible to intubate the tracheas of two fetuses, whereas in the other two tracheostomies had to be performed. Fetal gas exchange was not negatively affected during the EXIT procedure as evidenced by normal blood gas values in the umbilical artery at the time of delivery. After reducing the concentration of volatile anesthetic, delivery of the neonate and administration of oxytocin, uterine contractility was promptly re-established and there were no signs of uterine atony in the postoperative period. All four neonates survived the procedure without complications.

INTRODUCTION

The ex utero intrapartum tracheoplasty procedure was originally developed for the fetus with severe congenital diaphragmatic hernia treated in utero with temporary tracheal occlusion to enhance lung growth. With this technique utero-placental circulation could be maintained during removal of the tracheal clips immediately followed by cesarean delivery. The technique has since been used also for fetuses with giant neck masses and other diseases with an increased risk for airway management problems directly after delivery. It has for this reason been renamed ex utero intrapartum treatment (EXIT) or operation on placental support (OOPS). After the first EXIT procedures were reported in the mid-nineties many case reports and case reviews have been published of which the review of 31 cases from the Children’s Hospital of Philadelphia is the largest. The EXIT procedure is performed in conjunction with an elective cesarean section. The fetus is only partially delivered from the uterus with maintenance of the utero-placental circulation allowing for diagnostic and/or therapeutic procedures to the fetal airway. Commonly, the fetus has been anesthetized and immobilized by the intramuscular route before the start of airway manipulations. When the airway is secured the fetus is delivered and the umbilical cord clamped. Main prerequisites during the EXIT procedure include complete uterine relaxation and maintained uterine volume and utero-placental circulation. Uterine relaxation has in most published cases been accomplished by deep volatile anesthesia but other means of treatment are also available. Uterine volume is preserved by the fact that the main part of the torso and the lower part of the fetus are retained in the uterus during the procedure. In many centers warmed Ringer’s lactate solution is also infused into the uterine cavity. In order to maintain the utero-placental blood flow, maternal cardiac output and blood pressure have to be kept at acceptable levels.

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Between 1998 and 2002 four EXIT procedures have been performed at the Karolinska Hospital, Stockholm. Case number one has previously been published in detail. The aim of this case review is to highlight the maternal anesthetic technique and also to discuss possible implications for the use of volatile anesthesia during the EXIT procedure.
anesthetics during general anesthesia for standard cesarean section.

CASE PRESENTATIONS

Relevant maternal and neonatal data are summarized in Tables 1 and 2.

Case one was a healthy 28-year-old primigravida. In week 27 the fetus was found to have a laryngeal stenosis/atresia. An EXIT procedure was performed at 35 weeks’ gestation. The patient was placed supine with left lateral tilt to avoid aortocaval compression. General anesthesia was then induced with thiopentone 400 mg, fentanyl 200 µg and succinylcholine 100 mg. After endotracheal intubation anesthesia was maintained with isoflurane and nitrous oxide in oxygen (50-50) combined with additional doses of fentanyl and vecuronium for muscle relaxation. The nitrous oxide was discontinued before uterine incision and the FiO2 was increased to 1.0. End-tidal (ET) isoflurane concentration was increased to 2.2% during 10–15 min before uterine incision. At the time of uterine incision the obstetrician confirmed that the uterus was fully relaxed. During the EXIT procedure ET isoflurane concentration was kept between 1.8 and 2.2%. Bleeding was controlled by a continuous suture around the uterotomy. The head, right arm and part of the torso of the fetus were then delivered. Based on the estimated fetal weight an intramuscular injection of fentanyl 10 µg/kg, vecuronium 0.2 mg/kg and atropine 10 µg/kg was given to the fetus. A sterile pulse oximetry probe was positioned on the right hand but a reliable reading could not be obtained. The fetal heart rate was monitored with ultrasonography. A direct laryngoscopy confirmed the diagnosis of laryngeal atresia and a tracheostomy was performed. Manual ventilation was started and surfactant instilled into the tracheostomy tube after which the fetus was delivered and the cord clamped. ET isoflurane was reduced to 0.9% and oxytocin 5 units was administered i.v. followed by slow infusion of 50 units. The recovery of uterine contractility was indeed very quick (within minutes) and there were no problems with uterine atony postoperatively. Maternal hemodynamics remained stable throughout the procedure and blood loss was moderate. At four years of age the child is doing fine with a normal clinical and neurological status, although still breathing via a tracheostomy.

Case two was a healthy 29-year-old multiparous woman. In week 28 the fetus was found to have a large oral cyst. An EXIT procedure was performed at 37 weeks’ gestation. The patient was placed supine with left lateral tilt to avoid aortocaval compression. General anesthesia was then induced with thiopentone 500 mg, fentanyl 100 µg and succinylcholine 100 mg. After intubation, anesthesia was maintained with sevoflurane in oxygen-air with FiO2 0.5. Vecuronium was administered for muscular relaxation together with additional small doses of fentanyl. The sevoflurane concentration was increased to 4.5% ET for 10 min to achieve full uterine relaxation. Nitroglycerin 1 µg·kg⁻¹ min⁻¹ was infused i.v. beginning before uterine incision and running until clamping of the cord. During the EXIT procedure ET sevoflurane concentration was kept between 2.8 and 4.5%. Bleeding was controlled by a continuous suture around the uterotomy. The fetus was anesthetized intramuscularly and monitored as in case 1. The fetus could be intubated nasally after aspiration.

### Table 1. Maternal data

<table>
<thead>
<tr>
<th>Case</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthetic agent</td>
<td>Isoflurane</td>
<td>Sevoflurane</td>
<td>Sevoflurane</td>
</tr>
<tr>
<td>Additional tocolytic</td>
<td>No</td>
<td>Nitroglycerin</td>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>Skin incision to uterotomy (min)</td>
<td>11</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>700</td>
<td>200</td>
<td>1700</td>
</tr>
<tr>
<td>Post partum uterine atony</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

### Table 2. Neonatal data

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Laryngeal atresia</td>
<td>Dermoid cyst</td>
<td>Lymphangioma</td>
</tr>
<tr>
<td>Airway procedure</td>
<td>Tracheostomy</td>
<td>Intubation</td>
<td>Tracheostomy</td>
</tr>
<tr>
<td>Uterotomy to cord clamp time (min)</td>
<td>24</td>
<td>14</td>
<td>62²</td>
</tr>
<tr>
<td>Umbilical artery pH</td>
<td>7.30</td>
<td>7.30</td>
<td>7.16</td>
</tr>
<tr>
<td>Umbilical artery PO₂ (kPa)</td>
<td>5.5</td>
<td>8.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Umbilical artery PCO₂ (kPa)</td>
<td>6.9</td>
<td>7.0</td>
<td>9.1</td>
</tr>
<tr>
<td>Umbilical artery base deficit (meq/L)</td>
<td>2.8</td>
<td>2.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Umbilical artery lactate (mmol/L)</td>
<td>Not analyzed</td>
<td>2.3</td>
<td>6.0</td>
</tr>
</tbody>
</table>

²See text Case three for comments.
of liquid contents from the sublingual cyst. After clamping of the cord oxytocin 10 units was given i.v. followed by a slow infusion of 100 units. Prostin fenem (15-metyl prostaglandin F2α) 0.25 mg was given into the uterine wall. Within a minute after clamping the cord and reducing the ET sevoflurane concentration to 1.4%, the uterus started to contract. Maternal hemodynamics remained stable throughout the procedure and bleeding was minimal. The sublingual cyst which turned out to be a dermoid cyst increased in size postoperatively; it was marsupialised the day after delivery and resected surgically two months later. The neonate developed normally and had no airway symptoms at one year of age.

**Case three** was a 37-year-old multiparous woman who had two years earlier been successfully treated for a malignant mediastinal lymphoma. At 17 weeks’ gestation the fetus was found to have a tumor anteriorly in the neck. In the following weeks the tumor showed substantial growth and at 33 weeks had a diameter of 10.5 cm. An EXIT procedure was performed at 36 weeks’ gestation. The patient was placed supine with left lateral tilt to avoid aortocaval compression. General anesthesia was then induced with thiopentone 400 mg, alfentanil 1 mg and succinylcholine 100 mg. After intubation, anesthestia was maintained with sevoflurane in oxygen-air with FiO2 0.7. Vecuronium was used for muscular relaxation. Nitroglycerin 1 μg·kg⁻¹·min⁻¹ was infused i.v. beginning before uterine incision and running until clamping of the cord. Sevoflurane concentration was increased to 4% ET for 8 min before the completely relaxed uterus was incised. During the EXIT procedure ET sevoflurane concentration was kept between 1.9 and 4%. The fetus was anesthetized intramuscularly and monitored as in case 1. The fetus was successfully intubated. After ventilation of the fetus was established, the placental circulation seemed to cease as manifested by disappearing pulsations in the umbilical cord. Due to the huge size of the tumor and the risk for dislocation of the endotracheal tube postoperatively the situation was reconsidered and a tracheostomy performed. A total time of 62 min passed between uterotomy and clamping of the cord. Of these 62 min we roughly estimate that the fetus depended on utero-placental perfusion only during the first 30 min. The blood sample from the umbilical artery at the time of cord clamping is therefore difficult to interpret. After delivery and cord clamping, the sevoflurane concentration was decreased and oxytocin 5 units was given i.v. followed by a slow intravenous infusion of 100 units. Blood loss was fairly high despite the continuous suture around the uterotomy but blood transfusion was not considered necessary. The maternal circulation was maintained by intermittent injections of ephedrine. Uterine contractility was quickly reestablished after delivery of the neonate and from that point on there were no bleeding problems. The fetal tumor was a lymphangioma which was to be treated with injections of the sclerosing agent OK-432 (Picibanil). At one year of age the child was normally developed although still breathing through the tracheostomy.

**Case four** was a 24-year-old healthy nulliparous woman with a history of three missed abortions. She was pregnant in week 29 when the fetus was found to have a tumor on the left side of the face and neck. At 31 weeks the tumor measured 7 x 8 cm. An EXIT procedure was performed at 35 weeks’ gestation. The patient was placed supine with left lateral tilt to avoid aortocaval compression. General anesthesia was then induced with thiopentone 425 mg, fentanyl 100 μg and succinylcholine 100 mg. Following intubation anesthesia was maintained with sevoflurane in oxygen-air with FiO2 0.7. Vecuronium was used for muscular relaxation. Nitroglycerin 1 μg·kg⁻¹·min⁻¹ was infused i.v. beginning before uterine incision and running until clamping of the cord. The sevoflurane concentration was increased to 3.5% ET for more than 10 min before incision of a completely relaxed uterus. During the EXIT procedure sevoflurane concentration was kept between 1.8 and 3.5%. The fetus was anesthetized intramuscularly as in case 1. Fetal heart rate was monitored by ultrasonography and oxygen saturation was successfully monitored via the right hand. Fetal oxygenation was normal throughout the procedure. The fetal airway could be secured with a nasal endotracheal tube. After delivery of the neonate and clamping of the cord the sevoflurane concentration was decreased and oxytocin 5 units was given i.v. followed by a slow intravenous infusion of 50 units. Uterine contractility was quickly re-established. Blood loss was considerable despite the continuous suture around the uterotomy and three units of packed red cells were transfused. Maternal hypotension was, however, well controlled with small ephedrine boluses and a low-dose phenylephrine infusion. There were no bleeding problems after the delivery of the neonate. The fetal tumor turned out to be a lymphangioma. The neonate could be extubated after three days. At 7 months of age a facial nerve palsy was present but the child was otherwise fine and did not require an artificial airway.

**DISCUSSION**

The dose of volatile anesthetics required for EXIT procedures is quite different from that for standard cesarean section. In the 1960s a thiopentone/nitrous oxide/muscular relaxant technique of anesthesia was in general use for cesarean section. In 1970 it was shown that the addition of a small amount of halothane (0.5% inspired concentration) to 2–3 mg/kg thiopentone and 50% nitrous oxide in oxygen decreased the incidence of maternal awareness with postoperative recall from 4 to 0%.
Blood loss was not increased and Apgar scores were improved compared to the old combination of thiopentone and 70% nitrous oxide. Many textbooks still recommend the use of such a low dose of volatile agent (corresponding to 0.5–0.7 MAC inspired concentration) to decrease the risk for maternal awareness without inducing neonatal depression, uterine atony and increased maternal blood loss. It is, however, important to realize that higher concentrations of volatile anesthetics could be necessary to eliminate the risk of awareness and also to counteract the negative effects on uteroplacental perfusion from the maternal autonomic stress response. During an EXIT procedure the ET concentration of the volatile agent is kept very high (approximately 2 MAC) in order to keep the uterus fully relaxed, provided that maternal hemodynamics and hence uteroplacental flow are not jeopardized. In standard cesarean section, the time from uterine incision to clamping the umbilical cord is usually intended to be well below three minutes, in order to avoid the assumed deterioration of fetal acid-base status with time. In contrast, during the EXIT procedure the uterine incision to clamping the cord time is as long as is needed for the fetal diagnostic/therapeutic interventions to take place.

There are many studies comparing the effects on the neonate of general versus regional anesthesia for standard cesarean section in terms of Apgar scoring and fetal blood gases and acid-base status. It seems obvious that general anesthesia with a combination of thiopentone and volatile anesthetic, compared to regional anesthesia, may induce transient sedation associated with decreased one-minute Apgar values. The exact role of the volatile agent in this respect is not known. Unfortunately randomized studies on neonatal outcome comparing different ET concentrations of modern volatile anesthetics during general anesthesia for cesarean section are lacking. In contrast to the possible effect of general anesthesia on one-minute Apgar scores, two large epidemiological studies suggest that fetal acidosis is more common after regional than general anesthesia in elective cesarean section. It should not be forgotten, however, that surgical management also has an impact on the status of the neonate. The time from uterine incision to delivery may even be a factor of greater importance for neonatal well-being than the type of anesthetic.

In healthy sheep, utero-placental blood flow, fetal blood acid-base status and fetal oxygen saturation remain well preserved with 1.0 and 1.5 MAC halothane and isoflurane, although 2 MAC caused a deterioration in these parameters due to maternal circulatory depression. In the asphyxiated lamb fetus a 15-minute exposure to 2 MAC halothane did not cause further deterioration in fetal status. In longer fetal operations halothane may, however, be associated with fetal blood acidosis. Generally, during anesthesia for fetal procedures lasting less than one hour in animal models, 1–1.5 MAC of a potent agent seem to be well tolerated. This dose-range is also used for human fetal surgical procedures. In our cases all four neonates were anesthetized and given muscle relaxants by the intramuscular route during the EXIT procedure, in addition to the volatile agent given through the mother. After delivery the neonates were mechanically ventilated until the effect of the anesthetics wore off. Assessment of the neonatal effects of the volatile anesthetic was therefore not possible at the time of birth. We can nevertheless conclude that neither prolonged deep volatile anesthesia (approximately 2 MAC) nor uterine incision and manipulating of the fetus caused any serious disturbances in fetal gas exchange as evidenced by the blood gas values. This finding is in line with others.

Maternal intraoperative blood loss during the EXIT procedure is exacerbated by the relaxed state of the uterus and surgical bleeding from the uterine incision in combination with the duration of the procedure. In the present cases, bleeding from the edges of the uterine incision was minimized by application of a continuous suture. A uterine incision stapling device developed and used for this purpose may, however, be more effective in this respect. Except for the first case, our patients received a nitroglycerin infusion in addition to the volatile anesthetic. In two of these patients blood loss was greater than with a standard cesarean section, although maternal hemodynamics remained well preserved. In retrospect the nitroglycerin treatment in our patients was probably unnecessary; it may be more useful for rescue if uterine relaxation is insufficient, or as an alternative to high-dose volatile anesthesia.

In-vitro measurements using pregnant human uterine muscle strips show a dose-dependant decrease in contractility with increased MAC values (0.5–1.5). This is true for the older agents halothane and enflurane as well as for the modern agents isoflurane, sevoflurane and desflurane. The uterine responsiveness to oxytocin, as investigated in patients after vaginal delivery, is however maintained up to 0.8 and 0.9 MAC for halothane and enflurane respectively. In this study it was also shown that “with both agents there was a rapid recovery of spontaneous uterine activity when deep planes of anesthesia was lightened.” The risk of increased blood loss from prolonged use of high doses of volatile anesthetics is obvious, but as our four patients clearly show, the depressed state of uterine contractility could be quickly reversed at the time of delivery without any signs of intra- or postoperative recurrence. These findings are in keeping with the results from 31 consecutive EXIT procedures where blood loss not was increased compared to standard cesarean sections.
In conclusion, four cases of the EXIT procedure are described with special reference to maternal anesthetic technique. Based on this experience and the literature, it seems that the fear of sustained uterine atony intra- or postoperatively from high doses of modern short-acting volatile anesthetics used for a short period during a standard cesarean section under general anesthesia, may be exaggerated. From a fetal point of view the EXIT procedures were well tolerated in terms of acid-base status and blood gas values indicating a well preserved utero-placental perfusion despite the prolonged use of high ET concentration of volatile agents.

REFERENCES