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# Multimodal general anesthesia approach for Ex Utero Intrapartum Therapy (EXIT) procedures: two case reports

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## ABSTRACT

High-dose volatile anesthesia is the most common method of achieving uterine relaxation for Ex Utero Intrapartum Therapy (EXIT) procedures. Other methods employ nitroglycerin for additional uterine relaxation with or without remifentanyl for additional fetal analgesia. We report a combination approach including one minimum alveolar concentration of volatile anesthetic plus nitroglycerin and remifentanyl infusions, to provide timely uterine relaxation under general anesthesia for both mother and fetus, during two EXIT procedures.

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**Keywords:** Ex Utero Intrapartum Therapy; General anesthesia; Regional anesthesia; Transversus abdominis plane block

## Introduction

Ex Utero Intrapartum Therapy (EXIT) procedures are performed when the fetus has a severe airway abnormality potentially compromising ventilation at birth, or more rarely severe cardiothoracic abnormalities.<sup>1</sup> Different anesthesia strategies for EXIT procedures have been described. The largest published series used two to three minimum alveolar concentration (MAC) volatile anesthetic to achieve uterine relaxation,<sup>1</sup> while others used nitroglycerin infusions (0.5–1.5 µg/kg/min) for optimal uterine relaxation under neuraxial anesthesia.<sup>2</sup> Fetal analgesia and immobility has been typically achieved by intramuscular fentanyl and neuromuscular blockers,<sup>1</sup> but some substituted remifentanyl.<sup>3</sup> One report combined two approaches, using one MAC volatile anesthetic with nitroglycerin.<sup>4</sup> We report two

cases using a combination of three techniques: one MAC volatile anesthetic, nitroglycerin, and remifentanyl to provide concurrent uterine relaxation, maternal anesthesia and analgesia, and fetal analgesia and immobility.

## Case reports

### Case 1

A 65 kg, 32-year-old gravida 3 para 2 woman presented at 35 weeks' gestation. Maternal history included scant prenatal care, psychosocial disarray, unstable housing, intimate partner violence, methamphetamine and heroin use, depression, anxiety, hepatitis C with undetectable viral load, and polyhydramnios requiring multiple amnioreductions. Fetal anomalies included severe micrognathia, narrow oropharynx and larynx, situs inversus, and low-set ears. Prior to delivery, obstetric, obstetric anesthesiology, pediatric anesthesiology, and pediatric otolaryngology teams held planning sessions and assembled necessary equipment.

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Initiation of general anesthesia by rapid sequence induction and placement of an arterial line were uneventful. One MAC sevoflurane and remifentanyl (0.1  $\mu\text{g}/\text{kg}/\text{min}$ ) provided maintenance anesthesia and fetal analgesia. Ketamine was given (30 mg bolus then 100 mg/h) for prevention of opioid-induced hyperalgesia<sup>5,6</sup> and to assist with postoperative pain control, given her polysubstance abuse.

Surgery proceeded uneventfully with up-titration of remifentanyl (0.3  $\mu\text{g}/\text{kg}/\text{min}$ ) due to maternal tachycardia. Prior to hysterotomy, nitroglycerin was started (100  $\mu\text{g}$  bolus twice, then 1  $\mu\text{g}/\text{kg}/\text{min}$ ) to obtain the obstetricians' desired degree of uterine relaxation. Phenylephrine (0.5  $\mu\text{g}/\text{kg}/\text{min}$ ) maintained blood pressure within 20% of preoperative values.

The fetus was delivered to its shoulders after stapled uterotomy. The otolaryngologists discovered an absent mandible, absent tongue, small mouth, and low-set ears. Fiberoptic bronchoscopy showed the mouth and nares ended blindly. Pediatric anesthesiologists administered fentanyl (30  $\mu\text{g}$ ), vecuronium (0.6 mg), and atropine (100  $\mu\text{g}$ ) intramuscularly prophylactically despite absent fetal movement, and placed intravenous (IV) access. An amnioinfusion (600 mL warmed fluid on a separate IV pole) helped to maintain intrauterine volume. Intermittent transthoracic echocardiography confirmed a normal fetal heart rate. Tracheostomy was performed (Fig. 1). The EXIT procedure time was 45 minutes, dur-



**Fig. 1** Fetus one at time of delivery, showing visible facial abnormalities and completed tracheostomy

ing which time maternal vital signs were stable and there was minimal bleeding.

After cord clamping, an oxytocin infusion was started as per the institutional protocol, nitroglycerin and phenylephrine were discontinued, and a bispectral (BIS) index-guided propofol infusion was started in place of sevoflurane. Methylergonovine (0.2 mg intramuscularly) was given per obstetrician's request, because of mild uterine atony, and with good effect. At the conclusion of surgery, remifentanyl and ketamine were stopped, and hydromorphone (1 mg), ketorolac, ondansetron, neostigmine, and glycopyrrolate were administered. Bilateral continuous transversus abdominis plane (TAP) blocks were established by the anesthesiologists prior to emergence, under ultrasound guidance and injecting 0.375% ropivacaine 15 mL bilaterally. Catheters were threaded and secured with transparent film dressing. Extubation was uneventful.

Multimodal postoperative pain control was provided with TAP catheter boluses (15 mL 0.375% ropivacaine each side every eight hours for 48 hours), scheduled acetaminophen and ibuprofen, and as needed oxycodone. We offered TAP catheters instead of our usual neuraxial analgesia to enable her desired freedom of movement postoperatively. Before bolusing the TAP catheters, testing with a blunt needle revealed numbness in the T10–12 dermatomes limited to near the midline. After bolusing, she reported numbness in the same distribution, but across her entire abdomen. Her recovery was routine and she was discharged home on postoperative day three and lost to follow-up. Unfortunately, the infant did not fare well. Despite normal cord gases (Table 1), his Apgar scores remained 1. Pulmonary hypoplasia was confirmed radiologically. Despite all efforts, he died in his mother's arms after six hours. Autopsy showed agnathia-otocephaly complex (OMIM #202650).

## Case 2

A 26-year-old nulliparous woman was transferred at 37 weeks' gestation for delivery of a fetus with a neck mass. Her maternal history included pre-eclampsia without severe features, obesity (body mass index 38), hypothyroidism and anxiety. Ultrasound imaging showed that the right-sided neck mass (10.4  $\times$  4.9 cm) approached the midline. After expedited multidisciplinary planning and preparation, the patient was taken

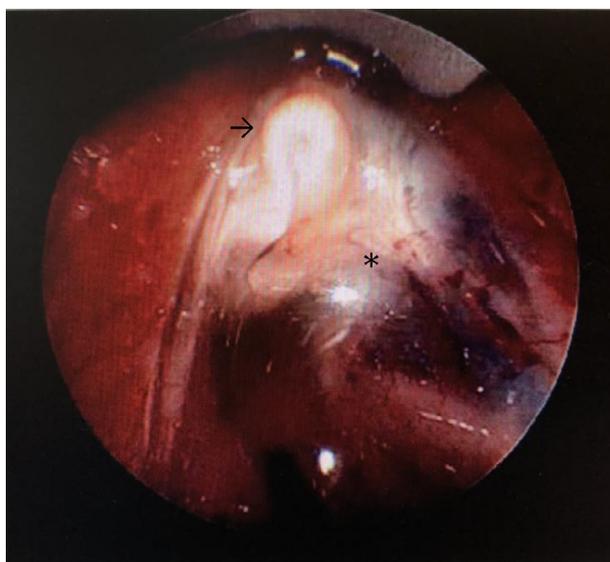
**Table 1** Umbilical cord blood gas values

	Case one		Case two	
	Umbilical artery	Umbilical vein	Umbilical artery	Umbilical vein
pH	7.15	7.27	7.21	7.29
pCO <sub>2</sub> (mmHg)	76	49	70	50
pO <sub>2</sub> (mmHg)	14	31	16	36
HCO <sub>3</sub> (mEq/L)	26	22	28	24
Base deficit (mEq/L)	4.1	4.7	0.6	2.5

to the operating room. A low thoracic epidural (T10–11) was placed for postoperative pain control and she underwent uneventful rapid sequence induction of general anesthesia and arterial line placement. One MAC of sevoflurane and remifentanyl (0.1  $\mu\text{g}/\text{kg}/\text{min}$ ) were used to provide maintenance anesthesia and fetal analgesia.

Prior to stapled uterotomy, nitroglycerin was started (100  $\mu\text{g}$  bolus then 0.5  $\mu\text{g}/\text{kg}/\text{min}$ ) to obtain the obstetricians' desired degree of uterine relaxation. Phenylephrine was titrated (to 0.6  $\mu\text{g}/\text{kg}/\text{min}$ ) to maintain blood pressure within 20% of her preoperative baseline. Fiberoptic examination of the fetus after delivery to the mid-thorax showed the mass extended to the right piriform sinus causing an obvious mass effect, sparing the vocal cords (Fig. 2). The otolaryngologists intubated the trachea fiberoptically using Seldinger's technique. Using ultrasound, a radiologist confirmed a normal fetal heart rate and correct endotracheal tube location. The EXIT procedure time was five minutes. Maternal vital signs were stable and there was minimal bleeding.

After cord clamping, an oxytocin infusion was started as per the institutional protocol, nitroglycerin and phenylephrine were discontinued, and a BIS-guided propofol infusion was started in place of sevoflurane. There was no uterine atony. The thoracic epidural was bolused (0.125% bupivacaine 5 mL) and an infusion initiated (0.0625% bupivacaine with 2  $\mu\text{g}/\text{mL}$  fentanyl at 10 mL/h, our institutional standard). At the conclusion of surgery she received ketorolac, ondansetron, dexamethasone, sugammadex, and labetalol (10 mg) for peri-emergence hypertension. The epidural was bolused (bupivacaine 0.125% 5 mL) in the post anesthesia care unit to manage moderate pain.



**Fig. 2** View of epiglottis ( $\rightarrow$ ) and encroaching piriform sinus mass (\*) on fiberoptic examination of fetus two

Postoperative multimodal analgesia also included scheduled acetaminophen and ibuprofen. Her epidural catheter was removed on postoperative day one and she received as needed oxycodone (5–10 mg every three hours). Her recovery was uneventful and she was discharged home on postoperative day three. The 4.1 kg neonate had Apgar scores of 2, 2, and 6 at 1, 5, and 10 minutes, respectively; and normal cord gas values (Table 1). After ten minutes the neonate began to emerge from anesthesia, and was extubated on day-of-life four. Biopsies showed a lymphatic malformation.

## Discussion

The precursor to EXIT procedures was first attempted in the late 1980s, after advances in diagnostic imaging made it possible to prenatally diagnose rare airway anomalies.<sup>7,8</sup> Anesthesia for EXIT procedures includes the provision of both maternal and fetal anesthesia and analgesia, as well as uterine relaxation to prevent premature placental separation. We performed two EXIT procedures for airway pathologies, using a multimodal technique of one MAC sevoflurane with remifentanyl for maternal and fetal analgesia, and nitroglycerin for uterine relaxation. Post-cesarean analgesia was provided by regional analgesia.

We chose a volatile-sparing technique instead of the traditional high-dose volatile anesthetic technique for several reasons. Given our first patient's substance use, we chose sevoflurane to avoid confusing tachycardia from abrupt changes in desflurane levels with nociception requiring more analgesia. In human myometrium, relaxation is equivalent for similar MACs of desflurane and sevoflurane.<sup>9</sup> Limiting fetal exposure to high-dose volatile anesthetics could also be beneficial for two reasons. First, volatile anesthetics can cause fetal cardiac depression.<sup>4</sup> Given the tenuous situation of the first fetus especially, it was advantageous to minimize this exposure, particularly when using fetal transthoracic echocardiography to assess the adequacy of uteroplacental perfusion during the EXIT procedure. Second, preclinical studies have shown evidence of neurotoxicity from volatile anesthetics and propofol in the developing brain. While these studies have failed to translate consistently in human outcome studies,<sup>10</sup> and it is premature to state early exposure to anesthetics causes harm,<sup>11</sup> it seems that reducing exposure to excess volatiles might be prudent while this important issue is under investigation.

When using a volatile-sparing technique, other medications are necessary to achieve uterine relaxation. Nitroglycerin is familiar to obstetric anesthesiologists from its use to abort tetanic contractions<sup>12,13</sup> and to assist with difficult cesarean deliveries.<sup>14</sup> Unlike high-dose volatile anesthetic, magnesium or terbutaline, nitroglycerin allows for very rapid initiation (30–120 s)

and termination (3 min half-life) of profound uterine relaxation.<sup>14</sup> Transient hypotension is treated with phenylephrine. Normal cord gases showed both fetuses remained well-perfused during their procedures. The dose of nitroglycerin our patients required (0.5–1 µg/kg/min) matches the doses used in other EXIT procedures utilizing nitroglycerin.<sup>2,4</sup>

After the deliveries had been completed, total intravenous anesthesia minimized the risks of volatile anesthetic-induced atony and postoperative nausea and vomiting (PONV). Lin et al.<sup>1</sup> used nitrous oxide after cord clamping to hasten the removal of volatile anesthetic and reduce the incidence of volatile anesthetic-induced atony. Nitrous oxide is associated with increased PONV<sup>15</sup> while propofol is used to both prevent<sup>16</sup> and treat PONV.<sup>17</sup> Additionally, propofol is much more environmentally friendly than nitrous oxide,<sup>18</sup> an increasingly important consideration.<sup>19</sup>

Remifentanyl, in addition to providing maternal and fetal analgesia, attenuates the stress response of both patients to surgery.<sup>3,20</sup> By crossing the placenta more than other opioids,<sup>20</sup> at maternal doses of 0.1–0.2 µg/kg/min it provides fetal immobilization and excellent surgical conditions for fetal airway manipulation.<sup>3,21</sup> Remifentanyl's short context-sensitive half-life in both the mother and newborn<sup>22</sup> allows quick recovery from anesthesia without the side effects of long-acting opioids. While controversial, we used ketamine to reduce the risk of postoperative hyperalgesia from remifentanyl in our first patient, who had opioid tolerance. Ketamine may also have effects on the developing brain,<sup>23</sup> but we considered that benefits to the mother outweighed risks to the fetus.

We describe the different anesthetic management of two EXIT procedures under general anesthesia using a multimodal approach, minimizing fetal volatile anesthetic exposure while achieving uterine relaxation and intraoperative analgesia, as well as post-cesarean analgesia using regional analgesia. Further studies focusing on fetal outcomes and patient satisfaction are warranted.

## Funding

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