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Anesthesia for fetal surgery

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ABSTRACT

Fetal surgery pushes the limits of knowledge and therapy beyond conventional paradigms by treating the developing fetus as a patient. Providing anesthesia for fetal surgery is challenging for many reasons. It requires integration of both obstetric and pediatric anesthesia practice. Two patients must be anesthetized for the benefit of one, and there is little margin for error. Many disciplines are involved, and communication must be effective among all of them. Conducting anesthetic research with vulnerable populations, such as the pregnant woman carrying a fetus with a birth defect is difficult, and many questions remain to be answered. Work is needed to study possible neurotoxicity caused by exposure of the developing brain to anesthetic agents. The effects of stress on the developing fetus also must be further delineated. Anesthetic techniques vary by institution, and prospective studies to determine optimal anesthetic regimens are warranted.

Introduction

Fetal surgery is a rapidly evolving discipline. The idea of treating the fetus as a patient is not intuitive and has its roots in the 1960s when intraperitoneal blood transfusions were performed for the treatment of erythroblastosis fetalis. Invasive surgical therapies in humans took place in the 1980s after rigorous study in animal models. These operations involved maternal laparotomy and hysterotomy to access and treat fetuses at varying gestational ages. The anesthetic techniques developed to facilitate these invasive procedures are based on the physiology of the pregnant woman and fetus and also on an understanding of the procedure to be performed.

Physiology

Maternal physiology

The physiologic changes of pregnancy impact anesthetic management. While many organ systems are affected, the most relevant are the neurologic, respiratory, cardiovascular, gastrointestinal, and hematologic systems.

Generally, maternal sensitivity to anesthetic agents is increased.[1] Minimum alveolar concentration (MAC) for isoflurane and halothane is lower during pregnancy. Increased dermatomal spread of epidural anesthetics is likely due to increased nerve sensitivity, hormonal changes in pregnancy, reduced protein levels, and pH changes in the cerebrospinal fluid. Pregnancy also increases sensitivity to nondepolarizing muscle relaxants.

Management of the airway of a pregnant woman may be difficult. Engorgement of the airway mucosa has multiple implications. Smaller endotracheal tubes must be used, and nasal intubation may cause epistaxis. The potential for difficult intubation is increased and airway complications are a significant factor in anesthesia-related morbidity and mortality.[2–5] Oxygen consumption increases and functional residual capacity (FRC) decreases during pregnancy, increasing the risk for hypoxia.

Pregnancy is a high cardiac output state. At term cardiac output is increased approximately 50% from nonpregnant values.[1] Systemic vascular resistance is decreased by about 20% secondary to vasodilation and the addition of the placenta, a low resistance circuit. Supine hypotension may result from aortocaval compression by the gravid uterus. Plasma volume increases relatively more than red blood cell volume increases, and thus hemoglobin concentrations fall during pregnancy.

The pregnant patient is at risk for aspiration of gastric contents due to displacement of the stomach and decreased lower esophageal sphincter tone. Intragastric pressure is highest in the third trimester. Gastric emptying of solids and liquids is slowed during labor.[1]

The coagulation system is in a state of accelerated, compensated intravascular coagulation. This hypercoagulable state is suggested by an increase in the majority of coagulation factors, a decrease in prothrombin and partial thromboplastin times, and a decrease in antithrombin III. Increased fibrinolysis is suggested by an increase of fibrin degradation products. Attention must be paid to thromboprophylaxis.

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Fetal physiology

Fetal physiology is complex. Neurologic pathways for cortical transmission of noxious stimuli in humans are still developing into the third trimester.[6] With both isoflurane and halothane, anesthetic requirements of fetal lambs are lower than that of a pregnant ewe.[7,8] Perception and processing of pain is controversial, but noxious stimuli will elicit a physiologic response in the human fetus, as evidenced by increases in cortisol, β-endorphin, and decreases in the pulsatility index of the fetal middle cerebral artery.[9]

The placenta acts as the organ of respiration, while a major function of the lung *in utero* is the production of amniotic fluid. Restriction of egress of this fluid results in pulmonary hyperplasia, while continuous drainage results in hypoplasia.[10]

The fetal circulation is notable for being a parallel system prior to transitioning to a serial circulation at birth. The fetal myocardium has a higher proportion of noncontractile elements, and is also stiffer than adult myocardium.[11] Increases in preload will provide minimal, if any, incremental increases of stroke volume and cardiac output.[12] Variation in heart rate provides a relatively greater contribution to variation in cardiac output compared to stroke volume. A lack of response to preload has been attributed to poor compliance of the myocardium, but may also be due to extrinsic compression of the fetal heart that is relieved with aeration of the lungs and clearance of lung fluid after birth.[13]

The blood volume of a fetus varies over gestation. At 16–22 weeks, blood volume of the fetoplacental unit has been estimated at 120–162 ml/kg of fetal weight.[14,15] It is important to note that about two thirds of the blood volume is contained on the placental side of the fetoplacental unit.[16]

The coagulation system evolves throughout the fetal and neonatal period. The fetus produces coagulation factors independently of the mother, and these factors do not cross the placenta.[17] The plasma concentrations of these proteins increase with advancing gestational age.

While *in utero*, fetal temperature is linked to maternal temperature. A fetus partially removed from the uterus during open surgery needs to increase heat production, but it cannot. Maintenance of normothermia in a fetus exposed during open surgery can be challenging due to the lack of shivering and nonshivering thermogenesis, immature skin barriers, and increased evaporative losses.

Fetal pharmacokinetics are not well understood. Historically, the dosing of medications given to the fetus for fetal surgery has been empiric based on data extrapolated from neonatal pharmacokinetic studies. However, a recent study quantifying the serum concentrations of fentanyl after IM injection during *ex utero* intrapartum therapy (EXIT procedure) at 34–37 weeks gestation showed that fetal fentanyl concentrations were higher than expected based on previous neonatal and minimally invasive fetal work and that the concentrations could be quite variable between fetuses.[9,18] Some of this variability may be explained by the immaturity of the hepatocytes, bypass of the liver and lungs during fetal circulation, and variations in the fetoplacental blood flow during open fetal surgery. However, further studies are needed to better understand fetal pharmacokinetics.

Uteroplacental blood flow

The fetus depends on uteroplacental blood flow and patent umbilical vessels for respiration. Uterine blood flow, while a surrogate for fetal oxygen delivery, correlates with fetal umbilical venous PO_2.[19] Uterine blood flow is directly related to uterine perfusion pressure (the difference between uterine arterial and venous pressure) and inversely related to uterine vascular resistance. For fetal surgical procedures, maternal hypotension, aortocaval compression, and uterine contractions decrease uterine blood flow. The effects of vasopressors, vasodilators, and anesthetic agents on uterine blood flow are variable because these agents affect uterine arterial pressure and uterine vascular resistance at the same time. Studies comparing ephedrine and phenylephrine for maintenance of blood pressure have shown no dramatic clinical differences in neonatal outcome and lend slightly more support to phenylephrine to support maternal blood pressure.[20–22] Ephedrine is a logical choice if the maternal heart rate is low, while phenylephrine could be used if the maternal heart rate is high.

Neuraxial and general anesthetics have variable effects on uterine blood flow. As long as maternal systemic pressure is maintained, epidural anesthesia does not alter uterine blood flow in elective cesarean sections.[23] Pain and stress will decrease uterine blood flow.[24] Relief of pain with an epidural may attenuate this reduction. Barring resultant hemodynamic changes, intravenous induction agents, (thiopental, propofol, etomidate, and ketamine) do not affect uterine blood flow dramatically. Volatile anesthetics decrease uterine tone and increase risk of bleeding.[25] Light and moderate levels of volatile anesthesia will slightly depress blood pressure, but uterine vasodilation maintains blood flow. In a sheep model of fetal surgery, with deeper levels of volatile anesthesia, uterine vasodilation cannot compensate for the reductions in blood pressure and cardiac output, and fetal acidosis occurs.[26] It is important to note, however, that no medications were given to the sheep to support their blood pressure while undergoing general anesthesia with high doses of volatile agent.

Maternal hypocapnia or hyperventilation with positive pressure will likely decrease uterine blood flow and fetal oxygen tension. Hypercapnia may increase fetal oxygen tension.[27]

Simple mechanical factors are important in the maintenance of uteroplacental perfusion and fetal oxygen delivery. Compression of the umbilical cord, either from loss of amniotic fluid or from surgical manipulation will cause rapid deterioration in the condition of the fetus. Likewise, integrity of the uteroplacental interface must also be maintained. Separation of the placenta from the uterus (placental abruption) is catastrophic.

Placental transport

Factors controlling placental drug transfer include size, lipid solubility, protein binding pKa, pH of fetal blood, and blood flow. High lipid solubility allows rapid transfer, but may result in trapping of drug in the placenta. Local anesthetics and opioids have higher acid dissociation constants and may be trapped in ionized form in the fetal circulation if the fetal pH is lower than the drug's pKa. Protein binding has a variable effect depending on the particular drug and protein interaction.

While the newer volatile anesthetics, desflurane and sevoflurane have not been studied as thoroughly as halothane and isoflurane, the low molecular weight and lipid insolubility of these medications should allow rapid transfer with relatively high fetal to maternal (F/M) ratios. Halothane and isoflurane have a F/M ratio of 0.7–0.9 and 0.7 respectively.[28,29] Nitrous oxide has a F/M ratio of 0.83.[30]

Thiopental crosses rapidly into the fetal circulation, but F/M ratios range widely, between 0.4 and 1.1.[31] Propofol has been studied at both term and midgestation and F/M ratios range between 0.5 and 0.85.[31] Propofol infusions may be used for maternal sedation in early pregnancy for minimally invasive operations. Diazepam is a commonly used drug for maternal and fetal sedation. Within minutes of injection the F/M ratio reaches unity and ratios approach two after an hour.[31] While midazolam has a F/M ratio of 0.76 at term,[31] it is gaining popularity in minimally invasive operations. Morphine is also