Anesthesia for Fetal Surgery
*Miles to Go before We Sleep*

Anesthesia for fetal surgery, that is, anesthetizing a pregnant woman so that surgery can be performed on her developing fetus, is a specialty that lies at the intersection of several clinical specialties, including, but not limited to pediatric and obstetric anesthesia, pediatric surgery, neurosurgery, otolaryngology, pediatric cardiology, maternal-fetal medicine, and neonatology. It is a specialty that is sometimes dismissed as too narrow or risky. Conversely, it may be sensationalized because of its perceived novelty or drama. It is, simply, a specialty and intervention that is necessary, and becoming more common, because more fetal procedures are being performed for more indications. Since the completion of the Management of Myelomeningocele Study trial,1 at least three additional centers in the United States, and two additional centers in Europe are now offering fetal surgery to repair myelomeningocele. A Web of Science search for “fetal surgery” shows publication of fewer than 20 articles in 1990, approximately 160 articles in 2000, and approximately 280 in 2010. A similar search for “fetal anesthesia” yields less than 10, approximately 60, and approximately 70 articles in the same years. Clinical care should rest on a foundation of both laboratory and clinical studies, and more work needs to be done to optimize anesthetic management of open fetal surgery. In this issue of *Anesthesiology*, Ngamprasertwong et al.2 have taken an important step forward in this field.

Current anesthetic management of open fetal surgery in humans is similar to the management initially developed in nonhuman primate models in the early 1980s.3 It is an anesthetic with many competing priorities. Two high-risk patients (a fetus and a pregnant woman) must be cared for simultaneously. The mother’s safety is paramount, but her anatomy and physiology must be manipulated aggressively to facilitate surgery on the fetus. Despite the “mom comes first” mantra, the needs of fetal surgery inevitably lead to situations where decisions are made and actions taken that put the mother at risk in an attempt to improve the condition and outcome of the fetus and neonate. The anesthesiologist must maintain adequate maternal and fetal perfusion and stable operative conditions. Profound uterine relaxation is essential to allow optimal fetal surgical exposure, lower the downstream resistance to uterine blood flow, minimize the risk of placental abruption, and allow better maintenance of amniotic fluid volume after the hysterotomy has been performed. If the amniotic fluid volume is not maintained, there is higher risk of umbilical cord compression.

Uterine relaxation is often achieved with high-dose volatile anesthetic agents. Intravenous nitroglycerin is occasionally needed to provide supplemental uterine relaxation, but relaxation by either pharmacologic strategy comes at a price. These medications may decrease maternal blood pressure, which will result in lower upstream perfusion pressure to the uterus, placenta, and fetus. Phentylephrine and ephedrine are commonly used to treat the hypotension. Intravenous administration of crystalloid is useful during near-term ex-utero intrapartum therapy, but attempts are made to limit fluids for midgestation open-fetal surgery as these mothers are at high risk for developing postoperative pulmonary edema.4 Fetal myocardial depression may also result from the high doses of volatile anesthetic.5 Ideal surgical conditions as defined by a relaxed uterus often come at the expense of stable maternal and fetal hemodynamics.

Ngamprasertwong et al.2 have performed a study in the instrumented pregnant sheep model comparing the fetal and maternal effects of high-dose volatile anesthetic...
with an alternative technique consisting of a lower dose of volatile anesthetic supplemented with intravenous infusion of propofol and remifentanil. The first part of their study involved a randomized controlled crossover trial, where sheep were exposed to high-dose desflurane (HD-DES) or lower dose desflurane with supplemental intravenous anesthesia. Maternal, uterine, umbilical, and fetal hemodynamics were compared. Blood gases and echocardiographic data were also obtained. The second part of the study involved tight control of maternal hemodynamics in sheep exposed to HD-DES. Not surprisingly, the maternal hemodynamics and fetal acidemia were worse in the HD-DES group. The fetal acidemia persisted in those sheep exposed to HD-DES even in the face of aggressive attempts to maintain maternal hemodynamics with vasopressors. Fetal cardiac function was similar between the groups compared.

The hypothesis of the Ngamprasertwong study (and the retrospective human study that preceded it) is that limiting fetal exposure to volatile anesthetic will improve fetal well being, with a purported mechanism being that high-dose volatile agents decrease fetal cardiac function. This premise is logical, but the findings of this study do not totally support the investigators’ hypothesis, because although there was more acidemia in the HD-DES groups, decreased fetal cardiac function per se could not be demonstrated by echocardiography. The clinical issue remains, however, that human myometrium must be relaxed to a level that is considered satisfactory by the criteria of the surgical team. This work has opened up potential avenues for investigation to achieve an anesthetic that is safe for mother and fetus, which concomitantly allows satisfactory conditions for surgery to occur.

For practical reasons, sheep models such as the one used in this study have a long history in maternal-fetal physiology and therapy, and have taught us much, particularly in the areas of pharmacokinetics and placental drug transfer, but these models may not be ideal for a variety of reasons including phylogenetic distance from humans, different placental anatomy, and different implantation characteristics. In one of the central issues in obstetric anesthesia, decades of sheep research suggested that treatment of maternal hypotension during spinal anesthesia should be treated with mixed α- and β-adrenergic agents (epinephrine) rather than pure α-1 agonists (phenylephrine) to avoid decreasing uteroplacental blood flow and compromising the fetus. Over the past decade and a half, studies have demonstrated that this is not the case in humans, where phenylephrine actually results in moderately better fetal pH status (and maternal hemodynamics), due to the fact that ephedrine crosses the placenta freely and results in many cases in fetal “hypermetabolism.” The history and lessons of this research may be relevant to the interpretation of the findings of Ngamprasertwong et al. The groups that received high-dose desflurane also received ephedrine to maintain maternal blood pressure, often receiving high doses. It is possible that some or much of the fetal acidemia is due to ephedrine administration, as opposed to or in addition to effects on uteroplacental perfusion or fetal cardiovascular function, especially in the absence of evidence of objective cardiac dysfunction in the HD-DES group. The dose of desflurane the authors used is approximately 50% higher than would be used in women, based on the minimal alveolar concentration in sheep being estimated at 9.5% compared with approximately 6% in humans. Although this is the ratio of anesthetic potency between sheep and humans, the cardiovascular potency could be more similar, with the result that these doses in sheep cause more hemodynamic instability than the comparable anesthetic doses would in women. These possibilities must be considered with any attempt to translate this work into recommendations for clinical management, and should be addressed in future animal or human research.

Human studies in fetal surgery are difficult, but the performance and results of the Management of Myelomeningocele Study show that there is value in conducting research in this arena. There are not many areas where it is suspected or demonstrated that “anesthetic technique” makes a difference in outcome, and if this is the case in fetal surgery, it is our opportunity and responsibility to determine the proper course forward through observational and interventional studies.

Pregnant mothers and fetuses are clearly vulnerable populations at risk for harm in biomedical research. To protect them, the Code of Federal Regulations (45 CFR 46.204) lays out conditions that must be met for such research to be conducted. The code does allow research that poses greater than minimal risk to the fetus to be performed. However, this research may only be conducted if the risk is caused by a procedure or intervention that holds the prospect of direct benefit to the fetus. This prospect clearly applied to the Management of Myelomeningocele Study trial. Ngamprasertwong et al. have now provided data in sheep, which suggest that high-dose volatile agents may not be the best anesthetic for fetal surgery. Although this should not immediately change clinical practice, at the minimum, this study suggests that we do not know what the best anesthetic is for open fetal surgery, the condition of equipoise that is essential to justify human clinical research.

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