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Review

Anesthesia for fetal surgery☆

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ABSTRACT

Introduction: Fetal surgery is making huge strides in medicine due to the breakthroughs in prenatal medicine that have opened a window into early diagnosis of abnormalities which may be subject to prenatal interventions. Fetal interventional procedures range from minimally invasive surgery on the fetus, the placenta or membranes, to open techniques requiring laparotomy and maternal hysterectomy.
Objective: A narrative review of anesthetic techniques used in fetal surgery. For that purpose, a non-systematic review of medical databases publications including MEDLINE, SciELO and EMBASE, was undertaken using the terms "anesthesia and fetal surgery" and restricted to the following types of publications: "Practice Guideline, Randomized Controlled Trial, Review".
Results: Minimally invasive procedures may be performed under local anesthesia or neuraxial techniques, with appropriate sedation of the mother, analgesia/anesthesia and fetal immobilization. The development of anesthetic techniques in this area should focus on minimizing maternal risk and preserving a normal neural development of the fetus.

Anestesia para cirugía fetal

Palabras clave:
Anestesia
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RESUMEN

Introducción: La cirugía fetal es un área de la medicina que progresa rápidamente, debido a los avances en el diagnostico prenatal se identifican precozmente anomalías susceptibles de intervención antenatal. Los procedimientos de intervencionismo fetal varían desde procedimiento mínimamente invasivos sobre el feto, placenta o membranas, hasta técnicas abiertas que requieren laparotomía e histerotomía materna.
Objetivo: Realizar una revisión narrativa de las técnicas anestésicas utilizadas para cirugía fetal. Para ello se realizó una búsqueda no sistemática de publicaciones en bases de datos médicas que incluyeron MEDLINE, SciELO y EMBASE, utilizando los términos «*anesthesia* y *fetal surgery*» y restringida a los siguientes tipos de publicación: «*Practice Guideline, Randomized Controlled Trial, Review*».

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Resultados: Las técnicas anestésicas en cirugía fetal pueden ir desde la sedación, técnicas neuroaxiales o anestesia general materna y la analgesia/anestesia con o sin inmovilización en el feto. El desarrollo de técnicas anestésicas en este campo se debe enfocar en la minimización de riesgos maternos y la preservación del neurodesarrollo normal en el feto.

Introduction

Fetal surgery is an area of medicine that progresses quite rapidly. Thanks to the advances in prenatal diagnosis, the anomalies susceptible to antenatal intervention are identified early. Fetal intervention procedures are varied and range from minimally invasive procedures (percutaneous, endoscopic) on the fetus, the placenta or the membranes, to open techniques requiring laparotomy and hysterectomy of the mother.[1–3] Anesthetic interventions are a clinical challenge because they demand a comprehensive knowledge of the maternal–fetal physiology and involve caring for both the mother and her fetus (fetuses).[4] The objective of this article is to do a descriptive review of anesthesia for fetal surgery.

Methodology

A non-systematic search of the publications in medical databases including MedLine, SciELO and Embase was done, using the terms "anesthesia AND fetal surgery" and restricted to the following types of publications: "Practice Guideline, Randomized Controlled Trial, Review".

Does the fetus feel pain?

To answer this question we shall review the development of pain pathways in the fetus. Peripheral pain receptors start developing during the seventh week of gestation; the afferent fibers that communicate those peripheral receptors are the gelatinous substance of the dorsal horn that develop during week 8; the spinothalamic connections are fully developed by week 20 and the thalamocortical connections present since week 17 are totally developed between weeks 26 and 30 of gestation.[5–7]

From the hormonal point of view, stress response (expressed as increasing levels of catecholamine, beta endorphins and cortisol) has also been identified in the fetus and it has been established that the hypothalamic-pituitary-adrenal system is functional since early in the second trimester.[8–10] Furthermore, hemodynamic responses to painful stimuli have been documented, characterized by the redistribution of blood flow to protect perfusion to vital organs[11]; additionally, the serotonin-mediated descending inhibitory system of pain only develops after birth; "clearly then, fetuses feel more pain that neonates".[12] All of these hemodynamic and hormonal responses to nociceptive stimuli during the synaptogenesis period may impact the neural development of the fetus and are attenuated by anesthetic agents.[13–16]

Recent studies in rodents have shown that inappropriate and high doses of anesthetic agent may result in neuronal apoptosis with the theoretical risk of long-term neurodevelopment problems; this is actually a controversial topic. It has been shown that neuroapoptotic effects are dose-dependent and the data obtained from rodents cannot be extrapolated to humans.[17,18]

The current consensus is to provide fetal analgesia/anesthesia in a judicious and proper manner during painful interventions that trigger noxious fetal responses.[19,20]

What is clear now and should be highlighted is that the long-term follow-up of new born babies from mothers who received neuraxial analgesia and anesthesia techniques for vaginal delivery or cesarean section did not result in neural development disorders.[21–24]

Anesthetic interventions in fetal surgery

Analgesia, anesthesia and fetal immobility may be provided by several means. The most common are: administration of agents to the mother that take advantage of their high transplacental passage (inhaled agents, Remifentanil type opiates); intramuscular or intravenous administration directly to the fetus or the umbilical cord (neuromuscular relaxants, fentanyl type opiates), and in some cases, administration of intra-amniotic anesthetics.[1–3]

Every patient considered for fetal intervention should be reported to the neonatology and anesthesiology departments and referred for pre-anesthetic evaluation. Informed consent should be obtained for anesthetic interventions and the fasting standards established for surgical procedures have to be followed[25,26]; in case of a gestational age within the range of fetal viability, the procedure must be performed in the operating room in case an emergency cesarean section is required.

There are two procedures currently supported by randomized clinical trials: one is the open correction of myelomeningocele[27,28]; and the second one is endoscopic laser therapy for twin-to-twin transfusion syndrome.[29]

The anesthetic techniques for fetal surgery will be described separating those procedures into three groups: *open fetal surgery*, *Placental support procedures* (EXIT, OPPS) and *minimally invasive procedures*.

Open fetal surgery

Some examples of open fetal surgery include: Correction of the myelomeningocele[27,30–33]; resection of cystic adenomatoid malformation of the lung[34]; and selected cases of sacrococcygeal teratoma.[30] All of these require laparotomy and hysterectomy of the mother, with of without fetal exposure, as the case may be; the mothers receive antibiotic prophylaxis in

addition to prophylaxis for bronchoaspiration and for thromboembolic venous disease. Blood is stored for the mother and 50 ml aliquots of O-negative leukocyte-free blood should be available for the fetus.

Most of the time general anesthesia with maternal endotracheal intubation is provided and it is suggested that prior to the induction of general anesthesia, an epidural catheter be provided for a balanced management of postoperative analgesia.

Maternal monitoring is key (non-invasive arterial pressure, pulse oximetry, continuous electrocardiographic monitoring, capnography/capnometry, temperature, vesical catheter and monitoring of neuromuscular relaxation); additionally, these patients need an arterial line for strict blood pressure control, anesthesia gas analyzer (high doses of 2 MAC inhaled agents are required for uterine relaxation), and a central venous catheter to use vasoactive agents.

Prophylactic tocolysis in these scenarios is multimodal, consisting of preoperative non-steroid anti-inflammatory agents, magnesium sulphate when starting the hysterectomy closure (6 g bolus and 3 g/h infusion), non-steroidal anti-inflammatory (NSAIDs) and nifedipine in the post-op.

Fluid management must be rational since intraoperative volumes exceeding 1 l are associated with pulmonary edema; similarly, due to the high doses of inhaled agents for achieving uterine relaxation (and occasionally due to the use of parenteral nitroglycerine), the use of vasoactive agents (phenylefrine, ephedrine) should be liberal and the hemodynamic control must be optimal; as a general goal, the systolic blood pressure should be kept above 100 mmHg.

Uterine bleeding is avoided with the use of metallic staples or suturing the margins of the hysterectomy during the fetal procedure. Fetal monitoring is done with continuous or intermittent ultrasound; in case of fetal exteriorization a sterile fetal oximeter may be used in the limbs of the fetus and eventually take measurements of umbilical artery blood gasses.

Sterile syringes and all the resuscitation and fetal anesthesia drugs (adrenalin, atropine, Fentanyl, pancuronium or vecuronium) should be available in the OR. Monitoring and reversal of the mother's neuromuscular relaxation are mandatory if indicated; however, keep in mind that the rapid injection of anticholinesterase agents trigger uterine contractions.

Nausea/vomiting and maternal hypothermia should be avoided and chills and vomiting must be managed aggressively at awakening and in the immediate postoperative period, in order to avoid leaking of amniotic fluid through the hysterorraphy. Adequate postoperative analgesia decreases oxytocin maternal levels and contributes to the prevention of preterm labor; most of these patients do not need any postoperative management in the ICU and continuous tocodynamometric monitoring is done during the first 12–24 postoperative hours.

Fetal hypothermia during its exposure may develop quickly: the thin and friable skin facilitates the temperature drop and, therefore, the irrigation fluids used in open surgery must be at body temperature to prevent such complication.

EXIT (ex utero intrapartum procedure)/OOPS (operations on placental support)[35]

Intrapartum *in utero therapy was initially* described in cases in which the airway was secured and surfactant was administered to patients in whom clip tracheal occlusion was practiced for managing congenital diaphragmatic hernia during the cesarean section under placental support. This therapy was later on adapted to manage patients with giant neck masses or congenital upper airway obstruction (CHAOS syndrome).[36]

The goals of anesthesia include: ensuring adequate uterine relaxation to externalize the fetal head and trunk and avoid premature placental abruption, in addition to maintaining the uterine volume, the placental support and the maternal hemodynamic stability, while securing the airway in a controlled manner in an anesthetized fetus. The premise is to convert the potential situation of crisis into a planned scenario.

Other indications for EXIT/OOPS are: Patients with giant chest masses, pulmonary agenesis and situations in which neonatal resuscitation is very complex. The strategy is further used occasionally for avascularities in placental support, as a transition to ECMO (extracorporeal membrane oxygenation).[37]

These cases, mostly elective, are done ensuring the fetal viability and maturity. The mother receives antibiotic prophylaxis as well as prophylaxis for bronchoaspiration and thromboembolic venous disease, ensuring blood reserves for the mother. Usually general anesthesia is administered with maternal endotracheal intubation; there are some case reports of patients with malignant hyperthermia and difficult airway that have been performed under regional anesthesia and intravenous nitroglycerin for neuromuscular relaxation.[38,39]

Maternal monitoring is of the essence (non-invasive blood pressure, pulse oximetry, continuous electrocardiographic monitoring, capnography/capnometry, temperature, vesical catheter, monitoring of neuromuscular realization), in addition to the implementation of an arterial line for strict blood pressure control, anesthetic gasses analyzer (high doses of 2 MAC inhaled agents are required for uterine relaxation); the decision of whether to use a central venous catheter is made according to maternal indications.

The use of vasoactive agents (phenylephrine, ephedrine) must be liberal; hemodynamic control shall be optimal. Uterine bleeding and the risk of after-birth uterine atony are important; consequently, adequate peripheral venous access shall be made available.

Fetal monitoring is done with continuous or intermittent ultrasound echocardiography and in the cases of fetal exteriorization; in anticipated extended procedures (tracheostomies, ECMO) a sterile fetal oximeter may be attached to the limbs of the fetus and then the umbilical artery blood gasses are measured and a peripheral vein of the fetus is catheterized.

All drugs required for resuscitation and fetal anesthesia (adrenalin, atropine, Fentanyl, pancuronium) must be available in the OR. Once the fetal airway is secured, the inhaled agent is reduced or closed and uterotonic agents are administered to prevent uterine atony. The surgery is then completed as if it were a conventional cesarean section; most

mothers have an adequate postoperative course; analgesia is managed with a multimodal approach. The hospital stay seldom exceeds 48 hours; neonates are managed by neonatology and pediatric surgery, in accordance with their underlying disease.[40]

Minimally invasive procedures

Several procedures are included in this classification and they involve placental, membrane or fetal interventions. Some examples are ultrasound-guided percutaneous punctures – such as in the case of intrauterine fetal transfusions and cardiac punctures for atrial septostomy[41] – and interventionist procedures in cardiac valves[42]; there are also fetoscopic procedures such as laser photocoagulation of placental anastomosis in cases of twin-to-twin transfusion syndrome (TTTS)[29,43,44] and *fetal endoscopic tracheal balloon occlusion* (FETO)[45–48] in cases of congenital diaphragmatic hernia. The TOTAL clinical trial is currently underway and it will provide the final recommendations for this latter procedure.[49]

These procedures are mostly done under locoregional anesthesia; the main role of the anesthesiologist is then to provide sedation analgesia and maternal hemodynamic stability with fetal immobility: this helps to shorten the surgical time, avoids fetal trauma, improves the technical conditions for adequate performance of the procedure and avoids the adverse consequences of fetal nociception in cases in which the fetus is operated on.[50,51]

Currently, the management of anesthesia in Clínicas Colsanitas is based on the neuraxial techniques (spinal and epidural combined) to the mother and the use of ultra short-acting opiates (remifentanil) that due to their high transplacental passage is titrated until the required fetal immobility is achieved.

Some specific situations such as those arising during FETO or percutaneous cardiac interventions require fetal neuromuscular relaxation which is obtained through intramuscular percutaneous administration to the fetus by a specialized fetal surgeon. These procedures are managed with very short hospital stays (24 h maximum) and exhibit very low rates of maternal and neonatal complications.

Conclusions

Anesthesia for fetal interventions is a challenge since care must be given to both the mother and the fetus. In multiple pregnancy cases any special needs and the maternal and fetal physiological conditions most be clearly identified. Pregnant women have increased anesthetic complications, particularly when general anesthesia is required.[52] While the discussion on fetal pain persists, the anesthesiologists' interventions must be judicious and promote adequate fetal neurological development.

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Conflicts of interest

None declared by the author.

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