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ANESTHESIA FOR FETAL SURGERY - PRINCIPLES AND CONSIDERATIONS: A CONCISE REVIEW.

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ABSTRACT Fetal surgery, an integral part of fetal therapy has undergone evolution since is conception, which was possible due to continuous refinements in surgical as well as anesthetic techniques The fetal surgery can be done in various stages of the gestation for corrective treatment. Time tested criteria have been laid down for patient selection which help improve the outcome of the whole exercise. The anesthesia concerns and considerations are unique as are the ethical issues involved in this treatment modality involving two patients with contrasting physiological needs. This article reviews salient aspects of fetal physiology in detail. Anesthesia for the fetal interventions is curated as per the invasive nature of surgical interventions. The type of fetal interventions are classified as minimally invasive procedures, Open mid gestation procedures and Ex-utero intrapartum treatment (EXIT) procedures. Preoperative evaluation is dictated by extent of gestation, and invasiveness of the surgical procedure apart from medical status of mother and fetus. This review also tries to enumerate number of clinically useful pharmacological agents in fetal anesthesia including essential tocolytic agents, in addition to management of common fetal complications with a separate section on fetal bradycardia.

KEYWORDS : Fetal Anesthesia, EXIT procedure, Fetal Surgery

Introduction:

Fetal surgery, an integral part of various available fetal therapies, evolved in the past three decades. Surgery on the fetus, intends to correct congenital anomalies in the fetus, thus preventing their severe consequences not only during later fetal development but also after birth. Continuous refinements in surgical and anesthetic techniques have resulted in a wide range of fetal interventions being performed at different stages of pregnancy, not only to save the life of the fetus but also to prevent permanent organ damage.[1] As the mother gains no direct benefit from surgical intervention, maternal safety is paramount and the inherent risk of maternal complications must be weighed against the potential benefits to the fetus.[2] Fetal Intervention can be ethically justified only if there is reasonable probability of benefit.

Materials and Methods

We have reviewed original research articles, case reports, meta-analyses, randomized control trials (RCTs), as well as reviews based on pain physiology in respect to preemptive analgesia from Medline, Medscape, and PubMed from the year 1997 to 2022. A broad free-text search with restriction to publications in English was undertaken with all variants of terms. “fetal surgery,” “anesthesia for fetal surgery,” “updates in fetal anesthesia,” and “fetal interventions” were entered as major keyword search. Reference lists of retrieved reports and reviews were searched for additional trials. Unpublished reports and abstracts were not considered.

Historical Facts:

Dr. Michael Harrison, presently the Director Emeritus, Fetal Treatment Center, University of California, San Francisco, is regarded as the father of fetal surgery[2]. He performed the first successful open fetal surgery in 1983 in the same hospital, which also holds the flag of being the first fetal treatment center in the United States. Lesser invasive fetoscopic procedures have replaced the traditional open fetal surgery, here a video camera is inserted inside the uterus under ultrasound guidance and surgery is performed through a working channel[3].

Criteria for fetal Surgery:

The time-tested criteria for successful fetal surgery are as follows[4]

a) Fetal anomaly: Singleton fetus with significant fetal anomaly that interferes with organ development, and whose treatment might allow further normal course of fetal development.

b) Maternal safety: Maternal risks should be minor and acceptable to mother and family.

c) Reporting requirement: All case material should be reported, regardless of outcome, to a fetal-treatment registry.

d) Oversight requirement: A multi-disciplinary team of specialists should make a cohesive plan for innovative treatment and obtain approval of an institutional review board. There should be access to a level III high-risk-obstetric unit, along with provision for ethical and psychological counselling.

Ethical Considerations:

The ethical issues in the field of fetal surgery are complex because medical intervention is invasive, often experimental, involves two patients, the mother and fetus, and the success rate is difficult to measure. Mother and fetus; undergoing these interventions must have equal protection, with detailed explanation of both short and long-term risks and benefits of these procedures on both the mother and the fetus. A multidisciplinary team of specialists including fetal surgeons, maternal–fetal medicine specialists, anesthesiologists, neonatologists, radiologists, nurses, and social workers must be actively involved in the counselling, planning, and preparation for all fetal interventions[5].

Salient aspects of fetal physiology which needs to be considered:

Fetal hemodynamics, oxygenation, pharmacodynamics and pharmacokinetics are important considerations that must be addressed during fetal surgery.

a) The fetal circulation is a parallel circuit with a normal total intravascular blood volume of 100– 110 ml/kg, cardiac output of 350 ml /kg/min and HR of 120-160/min (HR<100 is considered to be significant bradycardia, a strong indicator of fetal distress)

b) The fetal myocardium has greater proportion of noncontractile elements compared to full term heart and it functions close to the upper limit of the Frank–Starling curve. The fetal heart rate (FHR) is the most important determinant of cardiac output.

c) Common physiological stressors causing fetal distress include hypoxia, noxious stimuli and hypothermia. Fetal hypoxia occurs due to decreased uteroplacental circulation, diminished umbilical cord perfusion and decreased O2 delivery to fetal tissues.

d) The gestational age at which a fetus is aware of pain is strongly debated. The thalamocortical connections necessary for pain

perception do not develop until 23 to 30 weeks of gestational age. However, it has been noted that noxious stimuli can elicit neuroendocrine and hemodynamic responses as early as 18–20 weeks of gestations [6]. Procedures on non-innervated fetal tissues, such as the placenta and umbilical vessels, do not require fetal analgesia[7].

e) Drugs can be administered to the fetus by transplacental passage of maternal medications or by direct intravenous or intramuscular injection to the fetus. Transplacental passage of drugs requires maternal intravenous injection of the drug at a higher concentration than is clinically indicated for her own anesthetic needs. Hence, direct fetal drug administration not only allows more precise dosing but also eliminates the need for maternal drug exposure [7]. Common sites for iv access in fetus are umbilical vein, hepatic vein and relatively large peripheral veins. The shoulders and buttocks are used for intramuscular injection.

f) The majority of i.v anaesthetic agents easily cross the placenta except neuromuscular blocking agents. However, the uptake of volatile agents in the fetus is delayed compared to the mother, but a good clinical effect is achieved due to the lower MAC requirements of the fetus.

Anesthetic Considerations:

a) Anesthetic technique needs to be customized according to the surgical approach, extent of expected fetal surgical stimulation, maternal medical history, and patient - surgeon preference, if any.

b) The anesthesiologist provides care for two patients who have mutually conflicting anesthetic and hemodynamic requirements.

c) Challenges related to any anesthetic in a pregnant woman as well as maintaining adequacy of uteroplacental blood flow and appropriate uterine tone.

d) Prevention and treatment of inadvertent preterm labor situation.

e) Maintenance of feto-maternal homeostasis in the face of tocolytic techniques

Types of fetal interventions:

These can be broadly classified as

a) Minimally invasive procedures

- Needle-based ultrasound-guided procedures (e.g., percutaneous umbilical blood sampling, radiofrequency ablation, balloon valvuloplasty, shunt placement)
- Fetoscopic interventions under ultrasound guidance (laser ablation of blood vessels in twin to twin transfusion syndrome, umbilical cord coagulation, tracheal occlusion, amniotic band release, ablation of posterior urethral valves)

b) Open mid gestation procedures (18-28 weeks)

- Most common procedure is prenatal repair of myelomeningocele (MMC) defect.
- Others (resection of large fetal lung masses; debulking of sacrococcygeal teratomas)

c) Ex-utero intrapartum treatment (EXIT) procedures done during late gestation. (4 subtypes) [8]

- Exit to airway (most commonly performed) (e.g. Large oropharyngeal or neck masses; congenital high airway obstruction syndrome; severe micrognathia.)
- Exit to resection (Congenital pulmonary airway malformation; Thoracic or mediastinal tumors)
- Exit to ECMO (CDH with poor prognostic indicators; Hypoplastic left heart syndrome)
- Exit to separation (Bridge to separation in conjoined twins)

Preoperative evaluation and preparation:

- A multidisciplinary team ideally meets the mother and her family a few days prior to surgery in order to explain the planned fetal intervention, discuss surgical and anesthetic risks, address any concerns, and obtain informed consent[9].

- The preoperative anesthetic evaluation should include a detailed history of maternal comorbidities, previous anesthetics, and obstetric complications. Significant cardiopulmonary disease or increased anesthetic risk is a contraindication to fetal intervention.

- Laboratory investigations of mother include tests as dictated by the preanesthetic evaluation. For the mother, typing and screening is enough for minimally invasive procedures, while cross-matching is needed for open mid-gestation fetal surgeries and EXIT procedures. For the fetus, leukocyte reduced, irradiated, O-negative blood, cross-matched to mother should be readily available. Before the hysterotomy incision is given, the placental edges are mapped using a sterile USG probe.

- Important investigation relevant for the fetus are fetal imaging studies like ultrasonography, fetal MRI, and fetal echocardiography. Pertinent information for the anesthesiologist includes baseline FHR and cardiac function, estimated fetal weight for drug dosing and location of the placenta.

- It is ideal to have the anesthesiology team with an experienced obstetric anesthesiologist for maternal perioperative care (epidural analgesia, fluid management and general anesthesia) and a pediatric anesthesiologist with specialized training in neonatal/ fetal anesthesia (Sterile fetal IV access, administration of fluid/blood/drugs, prevent and treat stress response, bradycardia and cardiac depression). Both of these teams would be in communication with the pediatric surgeon, and cardiologists throughout the case[10].

- Estimated fetal weight-based resuscitation doses of epinephrine and atropine must be prepared in a sterile fashion and should be immediately available in the surgical field for intramuscular delivery.

Anesthesia for Minimally Invasive Procedures:

a) Maternal anesthesia in these procedures comprises of local/ neuraxial anesthesia +/- iv sedation. Uterine relaxation is usually not required intraoperatively; however, it may be required in the postoperative period. Maternal hemodynamic is managed with IV maintenance fluids +/-ephedrine/phenylephrine and standard ASA monitors is used for the mother

b) Fetal anesthesia technique depends on which type of procedure is being performed. If fetal surgery is done on non-innervated tissues (the placenta & umbilical cord), then no additional analgesia is required[7]. For fetoscopic procedures on fetus, analgesia and anesthesia are provided by i.m injection of a fetal cocktail, commonly comprised of fentanyl (10–20 mcg/kg; vecuronium (0.2 mg/kg); or rocuronium (2 mg/kg) and atropine (20 mcg/kg). FHR assessed once after induction and at the end of the procedure by echocardiography.

Anesthesia for Open Mid-gestation Procedures:

a) Maternal anesthesia of choice is general anesthesia with lumbar epidural analgesia . Due to anticipated intraoperative hemodynamic instability, local anesthetic infusion/bolus is not administered via the epidural catheter until the end of the surgery.

b) The basic principles of administration of general anesthesia in a pregnant woman needs to be followed (e.g. 15-degree wedge under right buttock; endotracheal intubation with RSI; keeping PETCO2 30–35 mmHg), two large bore IV access, etc . Goal directed judicious fluid management with the need of intraoperative and postoperative use of tocolytics. Vasopressor (Inj. Phenylephrine) to be used to prevent maternal hypotension. Standard ASA monitors and invasive BP measurement for close hemodynamic monitoring.

c) Profound uterine relaxation is required and maintained during hysterotomy by the supplemental intravenous anesthesia (SIVA) technique. Regime used is 2-3 MAC of inhalational agent (Desflurane/Sevoflurane)1-1.5 MAC + propofol infusion + remifentanil infusion). Uterine volume is maintained with continuous infusion of warm saline through a silicone catheter inserted into the uterine cavity. Since extensive uterine manipulation is required for these procedures, perioperative tocolysis (MgSO4/ NTG boluses i.v) is a must to prevent preterm labour[11].

d) Fetus is partially delivered within the uterus in a way to get direct access to surgical site. Minimal fetal exposure is essential to maintain uterine volume and prevent fetal hypothermia. Intramuscular injection of fetal cocktail is administered. Continuous fetal monitoring is done

with echocardiography every 3 to 5 mins till closure of the uterus.

e) Adequate postoperative analgesia can be achieved by continuous epidural infusion (patient-controlled analgesia), as pain induced maternal stress response can trigger preterm labour.

Anesthesia for EXIT Procedures:

a) Also known as operation on placental circulation, these interventions are performed while the fetus is still on placental bypass. Completion of surgery is followed by delivery of the baby by the termination of umbilical circulation (cord clamping and cutting). Principle is to perform controlled delivery once the oxygenation of the baby is assured without the need of maternal support. The anesthetic management is similar to that done in Open Mid-gestation procedures, except for a few cardinal differences.

b) The mother will not be started on a magnesium sulphate infusion or maintained on postoperative tocolytics rather she will need uterotonics after delivery of the baby. Uterine relaxation required during fetal procedure is achieved by Inj. Nitroglycerine boluses. Vasoactive medications will be necessary to maintain blood pressure.

c) Fetus is partly delivered, intramuscular cocktail is given, iv cannulation is done. Monitoring is done by sterile pulse oximeter and echocardiography in the operative field, every 3 to 5 mins till closure. Fetal echocardiography gives information about the FHR; ventricular function & volume; ductal patency and AV valve function.

d) Regardless of the indication for the EXIT procedure, securing the fetal airway by direct laryngoscopy/fiberoptic bronchoscopy is always the first step. Failed intubation may lead to a tracheostomy. However, the lungs are not ventilated until just prior to delivery, as that would begin the process of transitional circulation and placental separation[12].

Commonly used Tocolytic agents in the perioperative period:

1. Calcium channel blockers (nifedipine 10-20mg orally TDS/QDS)
2. Magnesium sulphate (4-6 gm loading i.m over 20 mins followed by 2gm /hour infusion)
3. Nitroglycerine (50-100 mcg iv bolus or 15-20 mcg/kg/min infusion)
4. Beta- adrenergic agonists (Terbutaline 250 mcg i.m/iv)

Management of Fetal bradycardia during Open mid-gestation and EXIT procedures:

a) Fetal bradycardia is a reliable indicator of fetal distress which needs to be treated urgently. Other presenting signs can be hypoxemia (Fetal SpO2 less than 30%; normal being 30-70%), impaired ventricular function, and decreased cardiac filling.

b) Umbilical cord compression must be ruled out by repositioning the fetus and increasing uterine volume with continuous infusion of warm saline.

c) Maternal FiO2 is increased and vasopressor administered to maintain adequate uteroplacental blood flow

d) In the presence of uterine contractions, the concentration of the volatile agent is increased and additional boluses of nitroglycerine administered for tocolysis.

e) If bradycardia still persists resuscitation is started with epinephrine(10mcg/kg) i.m, atropine (20mcg/kg) i.m, volume administration and chest compressions at 120– 150 b/min. If there is no improvement of fetal hemodynamics and the fetus is viable, emergent fetal delivery is done followed by neonatal resuscitation.

Complications:

a) Sudden onset persistent fetal bradycardia and cardiac dysfunction leading to fetal demise.

b) Failure to preserve uteroplacental perfusion and uterine relaxation during hysterotomy in open mid-gestation and EXIT procedures.

c) Maternal hemorrhage, preterm labour, premature rupture of membranes, chorio-amniotic membrane separation, chorioamnionitis, placental abruption, and increased need for maternal transfusion at the time of delivery.

d) Complications related to anesthesia in parturient and susceptibility towards postoperative pulmonary oedema due to tocolytic use.

e) The fetal exposure to painful stimuli and anesthetic medications is likely to have long-term effects on the developing nervous system.

Future of Fetal Surgery and Fetal therapy:

The concept of treating two patients at the same time is a challenging goal to achieve. Minimally invasive treatment is undoubtedly the future of fetal surgery, with the aim of providing the best possible outcome for the fetus, while minimizing the morbidity or mortality for the mother. At the moment, prenatal stem cell transplantation and gene therapy is under extensive research to treat a wide range of genetic conditions, and to go beyond fetal surgical interventions which are presently being performed only for correction of structural fetal anomalies. With significant advancement of fetal therapy, study of fetal gene therapy and gene-editing technology have risen in the horizon as treatment lines for fetal genetic disorders.

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