Introduction

Fetal surgery involves the performance of procedures on the fetus or the placenta, with the aim of altering the natural history of the disease that is diagnosed in utero. The first operation on a human fetus occurred in 1981 at the University of California San Francisco where a Fetal Treatment Centre was established. Prenatal imaging and invasive testing enable prenatal diagnosis and prognostic evaluation of fetal anomalies. Most fetal anomalies are amenable to therapy after birth however, sometimes therapy before birth is desirable to prevent permanent organ damage depending on the natural history and pathophysiology of malformation. The effectiveness of fetal therapies are being studied, especially those that result in better outcomes following fetal surgery, than if the defect corrected after birth.¹

Fetal surgery is a new and fast moving frontier of medicine. There are now a dozen centers worldwide performing these operations. With the development of minimal access surgical techniques, the indications for fetal surgery are on the increase. Surgical techniques range from minimal invasive to open fetal procedures with a trend towards less invasive fetoscopic procedures.² Providing anesthesia for these different procedures is a clinical challenge. Fetal interventions involve two or three patients simultaneously. Fetal surgery is performed in specialist centers and requires multidisciplinary teamwork. Anesthesiologists are involved to provide for the comfort and safety of pregnant mothers and their babies.

Ethical considerations

The fundamental conflict in fetal surgery is balancing the risks to both the mother and fetus against the potential benefit to only the fetus. As the mother is the innocent bystander in the endeavour her involvement involves only risk. A major intervention to save the life of a fetus appears to be warranted if maternal risks can be minimized and good fetal outcomes assured.³⁴ In view of the high fetal maternal risks, strict criteria for fetal surgery have been defined by the International Fetal Medicine and Surgery Society. Interventions are done within strict protocols by a trained multidisciplinary team.⁵ The practice of fetal surgery is different in USA and Europe. Open fetal surgery is rarely performed in Europe. In the USA on the other hand fetoscopy is performed less often.
Indications for fetal surgery

Table 1 Classification and Fetal Malformations Where Fetal Surgery are Indicated

<table>
<thead>
<tr>
<th>Noncorrectable Malformations incompatible with postnatal life</th>
<th>Life-threatening Malformations potentially correctable in utero</th>
<th>Malformation best corrected after birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
<td>Congenital diaphragmatic hernia(CDH)</td>
<td>Omphalocele</td>
</tr>
<tr>
<td>Renal agenesis</td>
<td>Congenital cystic adenomatoid malformation with hydrops (CCAM)</td>
<td>Gastrochisis</td>
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<tr>
<td>Severe chromosomal defects</td>
<td>Sacrococcygeal teratoma with hydrops, Meningomyelocele</td>
<td>Hydrocephalus</td>
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<tr>
<td>Lethal bone dysplasia</td>
<td>Twin-twin transfusion syndrome(TTTS) Twin reversed arterial perfusion sequence(TRAP)</td>
<td>Conjoined twins</td>
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Timing of fetal intervention

Typical gestational ages for surgery are between 21 to 27 weeks. Mid-gestational fetal surgery is performed for twin-twin transfusion syndrome and the twin reverse arterial perfusion syndrome (TRAP). In TRAP, one fetus has a lethal disease (acardiac or acephalic). The other fetus viability is threatened due to high output cardiac failure required to support both twins leading to hydrops fetalis. Severe congenital diaphragmatic hernia, spina bifida, myelomeningocele, heart failure from a tumor with large blood vessels like sacrococcygeal teratoma, obstructive uropathy and congenital cystic adenomatoid formation of the lungs are indications for surgery. The congenital cystic adenomatoid malformations (CCAM), sacrococcygeal teratoma and twin problems require fetal intervention only when the fetus develops hydrops and demise is imminent. Fetuses with these defects are closely followed ultrasonographically and criteria for fetal surgical intervention are being developed.

Types of fetal surgery

Fetoscopic surgery

Fetoscopic intervention involves minimal insult to the uterus while obtaining access to the fetus through surgical trocar insertion. The surgeons use small cameras placed through small incisions in the mother’s abdomen. Usually local anesthesia is used to keep
the mother comfortable or epidural anesthesia is administered in addition to intravenous sedation or anxiolysis. This technique is most commonly used to treat twin–twin transfusion syndrome and twin reversed arterial perfusion sequence. Pharmacological agents can be administered through the placenta avoiding direct access to the fetus. Injection of medication into the amniotic cavity or fetal blood transfusions administered via an 18-20 gauge needle with minimal risk.

**Open fetal surgery**
This surgery is performed in the fetus in which post-natal survival is considered unlikely. The long term outcome studies are underway in the three major centers in the USA where these operations are being conducted. Anesthesia for open fetal surgery involves maintenance of uteroplacental perfusion to maximize chances of a favorable outcome. This involves deep uterine relaxation with 2 MAC anesthesia, invasive maternal monitoring and additional intramuscular drug administration to the fetus.

**EXIT procedure**
The ex-utero intrapartum treatment procedure (EXIT) involves only partially delivering the fetus, thereby uterine volume, placental perfusion and oxygenation are maintained; allowing time to perform direct laryngoscopy, bronchoscopy, intubation and tracheotomy on the fetus. This technique is performed clinically to deliver term fetuses who would sustain a hypoxic event immediately after delivery e.g., fetuses with cervical teratomas, cystic hygromas, goiter, laryngeal webs and involving the fetal airway. Anesthesia for EXIT procedure requires several differences. Complete uterine relaxation is necessary to expose the operative fetal anatomy. In addition the fetus has to be maintained inside the uterus. Unlike open fetal surgery however, the fetus will be delivered at the end of the fetal intervention resulting in a completely flaccid uterus that must immediately involute or else massive maternal hemorrhage will occur. Obviously clear communication and coordination is required between the entire surgical and anesthesiology teams.

**Anesthetic Implications of fetal surgery**
It is important that the anesthesiologist understand the fetal lesion and the surgical approach as these factors determine the type of anesthetic care to the mother. Anesthesia for fetal surgery involves two patients simultaneously, the mother and the fetus. The problems in the anesthetic management differ form Caesarean sections or other non obstetric surgery in the pregnant patient and fetal surgery. In fetal surgery the fetus and mother are both active recipients of surgery however in maternal surgery the mother is an active recipient while the fetus is a bystander. Minimal access fetal surgery offers the option of regional anesthesia. Open fetal surgery involves maternal hysterotomy with the risk of blood loss, preterm labor and uterine rupture. The challenges that these procedures present to the anesthesiologist are described below.

**Problems related to anesthesia in a pregnant woman**
These procedures are performed most often in the second or third trimester. There are a number of physiological changes which occur during pregnancy as a result of hormonal
changes and the enlarging uterus. Cardiovascular, respiratory and gastrointestinal system changes are the most profound. Cardiac output increases by 50-100% due to an increase in heart rate and stroke volume. The blood pressure drops by 15% as a result of vasodilatation and the presence of a low resistance placental vascular bed. The large uterus increases the risk of supine hypotension syndrome. Intravascular blood volume increases by 40%; more than the red cell volume increase (20%) which alters the plasma concentration (lower total protein and albumin levels), thus altering the pharmacodynamic of drugs administered to these patients.

Higher oxygen consumption and a lower functional residual capacity results in rapid desaturation, the airway mucosa is swollen and bleeds easily making the pregnant patient more difficult to intubate. Minimum alveolar concentrations (MAC) values decrease by 40%. This may lead to a deeper level of anesthesia than predicted during surgery with a relative over dosage. Elevated gastric acid content is, delayed gastric emptying and lower gastro-esophageal sphincter tone, make these patients more prone to regurgitation and aspiration. All pregnant women should be treated as if they have a full stomach, especially in the latter half of pregnancy. The epidural space is narrowed by the epidural venous engorgement increasing the risk of intravascular catheter placement and a larger dermatomal spread of injected local anesthetics.

**Placental Transfer of drugs**

Substances like oxygen, carbon dioxide, fatty acids, sodium and glucose cross the placental membrane by five basic mechanisms i) diffusion, ii) active transport, iii) bulk flow, iv) pinocytosis and v)via breaks of the villa in the inter-villous space. Inhalation agents which are lipid soluble are not ionized and of low molecular weight and readily cross the placenta. Uptake of these agents is slower in the fetus than the mother. Fortunately since the fetal MAC is less than that of the mother this is well below that needed to obtain uterine relaxation. Therefore, adequate maternal anesthesia and uterine relaxation results in adequate fetal anesthesia.

**Techniques used to prevent preterm labor and the use of tocolytic techniques**

One of the requirements of fetal surgery is the avoidance of intraoperative and postoperative uterine contraction. For open fetal surgery and the EXIT procedures profound uterine relaxation is required for optimal surgical exposure. Volatile anesthetic agents at 2 MAC concentrations are potent uterine relaxants. During initial surgery in the 80’s, halothane was used but now isoflurane of sevoflurane are preferred. At these high concentrations significant reduction in cardiac output and resultant hypotension occur. This leads to decreased uteroplacental perfusion and fetal hypoxia. Appropriate monitoring of maternal circulation is essential and when inadequate, timely administration of fluid boluses or vasopressors like ephedrine or phenylephrine may be required. Alternatively to avoid high concentrations of volatile anesthetic agents, short acting but profound uterine relaxants like IV nitroglycerin. Intravenous infusion of magnesium sulfate towards the end of surgery, subcutaneously turbutaline and indomethacin are used postoperatively.
Adequate post operative maternal analgesia results in lower plasma oxytocin levels and also decreases uterine tone. Placement of an epidural catheter preoperatively and local anesthetic initiated postoperatively is an important measure to prevent preterm labor. A smooth anesthetic emergence and tracheal extubation is required to minimize tension on the uterine and abdominal suture line.

**Fetal Anesthetic Considerations**

*Maintenance of fetal homeostasis*

Fetal surgical patients at high risk because of immature organ system function. Hypothermia occurs rapidly from heat loss through the thin and easily bruised skin resulting in hypoperfusion. Poor compensatory vasoconstriction in the fetus is due to decreased baroreceptor activity. Hypovolemia easily occurs, as fetal blood volume is low (<50mL), there is a higher bleeding tendency with immature coagulation system and because of evaporative fluid loss. Therefore the fetus may require blood transfusion in procedures associated with a minimal loss of 10 mL. Decreased myocardial contractility also predisposes to hypoperfusion. Fetal hypoperfusion and uteroplacental hypoperfusion leads to fetal hypoxia.

Fetal oxygenation is a function of maternal oxygen content and placental blood flow. Maternal hypoxia should obviously be avoided. Maternal hyperoxia does not produce adverse effects. Maternal hyperventilation and hypocarbia results in respiratory alkalosis shifting the oxygen dissociation curve to the left. This therefore increases the affinity of hemoglobin for oxygen and reduces movement of oxygen across the placenta. In addition, hyperventilation may reduce maternal cardiac output and uterine blood flow. Any factor that decreases uterine blood flow; like maternal hypo or hypertension, increased uterine tone and myometrial vasoconstriction from noradrenergic activity, may jeopardize fetal wellbeing with the consequence of death of the fetus.

*Providing fetal analgesia during surgery*

Pain pathways and EEG activity are present in the fetus by midgestation. Fetal surgery requires anesthesia to prevent perception of pain and induce unconsciousness. When the mother is under general anesthesia, the volatile anesthetic will pass into the fetus providing anesthesia. Other analgesic drugs and muscle relaxants are administered to avoid fetal movement.

**Anesthetic management of fetal surgery**

**Preoperative evaluation and preparation**

An anesthesiologist experienced in fetal surgery, screens the mother at the time of surgical and obstetrical workup and informs the surgical team of any issues and discusses the anesthetic plan with the mother. On the morning of surgery, the obstetrician examines the mother for premature labor and fetal wellbeing. A tocolytic drug like indomethacin (50 mg rectal suppository) is administered to the mother either preoperatively or post
induction. In addition oral 30 mL of a 0.3 molar solution of sodium bicitrate and metoclopramide 10 mg IV is administered. Type specific blood for the mother and 50 mL aliquots of O-negative blood for the fetus, should be available. The operating room is warmed up to 26°C. Drugs for the fetus should include: atropine 0.02 mg kg\(^{-1}\), adrenaline 1 µg kg\(^{-1}\), vecuronium 0.2 mg kg\(^{-1}\) and fentanyl 20 µg kg\(^{-1}\) are prepared in a 1 mL syringe and handed over to the scrub nurse. A lumber epidural catheter is then placed for later management of postoperative pain.\(^{11}\)

**Intraoperative Anesthetic Management for Open Fetal Surgery**

The mother is positioned to achieve left uterine displacement, is preoxygenated and a rapid sequence is performed with thiopental 5 mg kg\(^{-1}\), succinylcholine 2 mg kg\(^{-1}\) and fentanyl 1-2 µg kg\(^{-1}\). Anesthesia is maintained with 0.5 MAC of isoflurane or desflurane or sevoflurane in oxygen. A second wide bored intravenous catheter, arterial catheter and nasogastric tube are inserted. An ultrasound examination is done to delineate the surface anatomy of the fetus and the placenta. The location of the placenta is important as surgical access to the fetus is more difficult if the placenta is attached to the anterior wall of the uterus. There is also an increases risk of bleeding and more manipulation of the uterus if the placenta is located anteriorly. Fetal hemodynamics is measured by continuous fetal echocardiogram.

Prior to skin incision the volatile agent is increased to 2 MAC and abdominal wall relaxation is achieved with vecuronium. The surgeon assesses uterine tone and if found to be high, the inhalation anesthetic is further increased to provide excellent uterine relaxation. A special stapling device is used to incise the uterus with minimal bleeding and to seal the amniotic membrane. Warm fluid is continuously infused into the uterine cavity. Because of slow uptake of volatile anesthetics by the fetus, there should be at least 20 minutes delay in timing of fetal surgical incision, after induction of anesthesia in the mother. Maternal systolic blood pressure is maintained above 100 mmHg systolic (within 10% of baseline value). If required IV ephedrine 5-10 mg or phenylephrine 1-2 µg kg\(^{-1}\) are administered to achieve this.\(^{13}\) Total intravenous fluid is limited to 500 mL of normal saline, to prevent postoperative pulmonary edema, unless blood loss exceeds 100 ml.

Fetal monitoring during fetal surgery has undergone changes as the techniques for intervention have developed. For EXIT procedure and other procedures with potential blood loss, the surgeon applies a pulse oximeter on the fetal forearm. Fetal hemodynamics is otherwise measured by continuous fetal echocardiogram. A blood sample from the umbilical artery can be taken to check fetal hemoglobin, pH and blood gases. Fetal desaturation (SpO2 < 50%) usually results from hypoperfusion, low cardiac output or kinking of the umbilical cord. The anesthesiologist infuses blood and medications as needed into an exposed fetal vessel e.g., superior vena cava, aorta or umbilical vein via a cannula or scalp vein needle.

As surgery proceeds the fetus is administered drugs and volume as required. When access to the fetus has been established in open procedures it is possible to administer different
injections of opioids, muscle relaxants, vagolytic or there drugs directly into the fetus either IV through the umbilical vein or IM or intra amniotic. Fentanyl $5-20 \mu g.kg^{-1}$ can be given. The fetus metabolizes opioids slowly (fentanyl half-life is $>12$ hours in a very premature baby). Atropine $20 \mu g.kg^{-1}$ is often given to prevent bradycardia during surgical stimulation. Vecuronium $0.2 \text{ mg} \text{ kg}^{-1}$ is injected IV or IM into the fetus.

During hysterotomy closure, intravenous IV magnesium sulphate 4-6 g bolus over a 20 minute period is followed by 2-3 g.hr$^{-1}$ infusion. Magnesium sulphate may potentiate neuro-muscular blockade by vecuronium and needs to be monitored. Volatile anesthetics are discontinued and the mother is allowed smooth tracheal extubation and emergence to minimize tension on the uterine and abdominal suture line. The epidural catheter is then activated with 15-20 mL of 0.25% bupivacaine and 3 mg morphine.

**Postoperative Problems and Concerns**

The primary goals for the postoperative management include prevention of premature labor and maintaining maternal comfort. Magnesium sulphate is the drug of choice in the early postoperative period (18-24 hours). Premature uterine contractions occur in most patients in the immediate postoperative period. Patient controlled epidural analgesia is used for postoperative pain; this assists in the prevention of preterm labor as well. Indomethacin is continued for 48 hours postoperatively. After discontinuing the epidural, the first line tocolytic drug is oral nifedipine. If this fails terbutaline is administered subcutaneously with a pump. The mother must undergo Caesarean section for the delivery and all subsequent deliveries because of the high uterine incision these surgeries require. Other serious postoperative concerns include pulmonary edema, amniotic fluid leak and fetal demise.

**Anesthesia for minimally invasive fetal surgery**

These procedures involve the use of a laparoscopic fetoscope and ultrasound. It is crucial that the anesthesiologist attends the preoperative team meetings to understand the surgical approach and select the most appropriate anesthetic. The surgical concerns include location of the placenta and umbilical cord, position of the fetus, relation of fetal lesion to other structures, and chance of converting to open surgery.

The preoperative evaluation is the same as mentioned above. A balanced general anesthesia technique is used. The inhalation agent is administered with 0.75- 1 MAC with fentanyl. Alternatively an infusion of remifentanil can be administered to the mother; the drug crosses the placenta, providing both maternal and fetal sedation. It also provides fetal immobilization during fetoscopy. Deep inhalational anesthesia is not used as profound uterine relaxation is not necessary. Skin, uterine and fetal incisions are small and postoperative epidural analgesia is generally not required. For these procedures an arterial catheter and nasogastric tube are not inserted. Tocolytic management is with magnesium sulphate and subsequently subcutaneous terbutaline or oral nifedipine. Epidural analgesia is recommended along with conscious sedation, if desired by the
patient. A level of T4 or higher is aimed at. Spinal anesthesia is avoided by some authors because of the potential of sudden hypotension and unpredictable duration of surgery.

Summary

Anesthesia for fetal surgery is an exciting new field; the whole effort is a team approach. Anesthetic techniques are being constantly refined and issues like tocolysis are being constantly readdressed. The anesthesiologist can play a vital role to help establish improvements in care and research for years to come.

References