Fetal Surgery: General Principles

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Fetal surgery has moved from the experimental model to the human condition and even the standard of care for certain diseases. However, despite developments in techniques and imaging, fetal surgery has only been shown to be beneficial in a small subset of patients and still carries significant morbidity risks.

60.1 Introduction

The first open surgery on a human fetus was performed for congenital bladder obstruction in 1981 by Michael R Harrison at the University of California, San Francisco (UCSF). Since then, advanced fetal imaging has dramatically improved our understanding of congenital anomalies and has opened the door to new treatments and minimally invasive techniques.

Human fetal surgery is now being performed for diseases such as:

- Congenital diaphragmatic hernia (CDH)
- Twin anomalies
- Mass lesions with hydrops fetalis

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- Early Pregnancy Renal Anhydramnios
- Spina bifida/Myelomeningocele
- Aortic valve stenosis
- Amniotic Band Syndrome
- Congenital high airway obstruction

60.2 Ethical Concerns

The welfare of both mother and fetus must be considered within fetal surgery. The treatment of a fetus with a congenital anomaly confers no direct physical benefit to the mother and subjects her to risk. The risk is primarily related to the high incidence of preterm labor and its corresponding morbidity, but as with any operation, fetal surgery also carries a risk of infection, bleeding, and damage to adjacent structures. Fetal surgical procedures should only be considered if the in utero anomaly has been shown to have severe irreversible consequences and the procedure is safe, superior to postnatal options, and beneficial to the fetus with low risk to the mother.

Further considerations must be taken when the fetal intervention addresses one pathophysiological process but necessitates postnatal interventions for another as in congenital renal agenesis. Amnioinfusions in cases of renal agenesis allow for lung development until delivery; however, once born, the child lacks kidneys thus requiring neonatal dialysis and renal transplant.

60.3 Accessing the Fetus

The gravid uterus can be accessed by open or minimally invasive (fetoscopic and percutaneous) techniques. In both approaches, ultrasound assessment for placental position, uterine anomalies, and fetal position are critical for successful intervention, and a skilled sonologist/ultrasonographer is a mandatory member of the operative team.

Open fetal surgery requires:

- Maternal low transverse incision.
- Exposure and intraoperative ultrasound of the uterus.
- Analgesia and paralysis of the fetus.
- Hysterotomy opposite placental location using a uterine stapler with absorbable staples thus providing hemostasis, and sealing membranes.
- Exposure of appropriate body part of the fetus.
- Repair of the defect.
- Return of fetus to uterus.
- Closure of hysterotomy with two running layers of absorbable suture and fibrin glue.

Endoscopic techniques for fetal surgery *(FETENDO)*, Figs. 60.1 and 60.2) have been adapted from laparoscopic surgery. A minimally invasive approach avoids the maternal morbidity incurred with a large open incision and hysterotomy (e.g., postoperative bleeding, adhesions, and the inability to deliver vaginally). Percutaneous interventions are usually directed at draining fluid-filled fetal structures or radiofrequency ablation of an anomalous twin. "Real-time" continuous ultrasound guides the placement of percutaneous instruments.

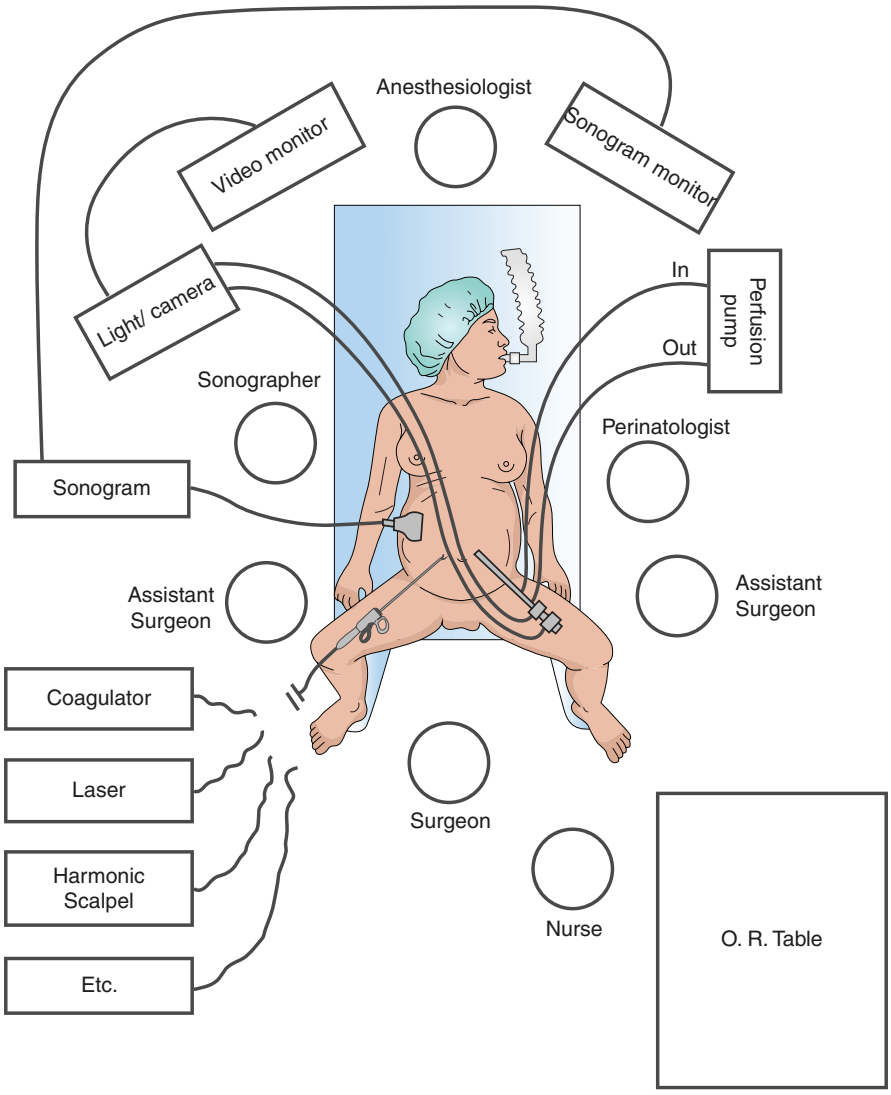

Fig. 60.1 Typical operating room setup for a fetoscopic procedure

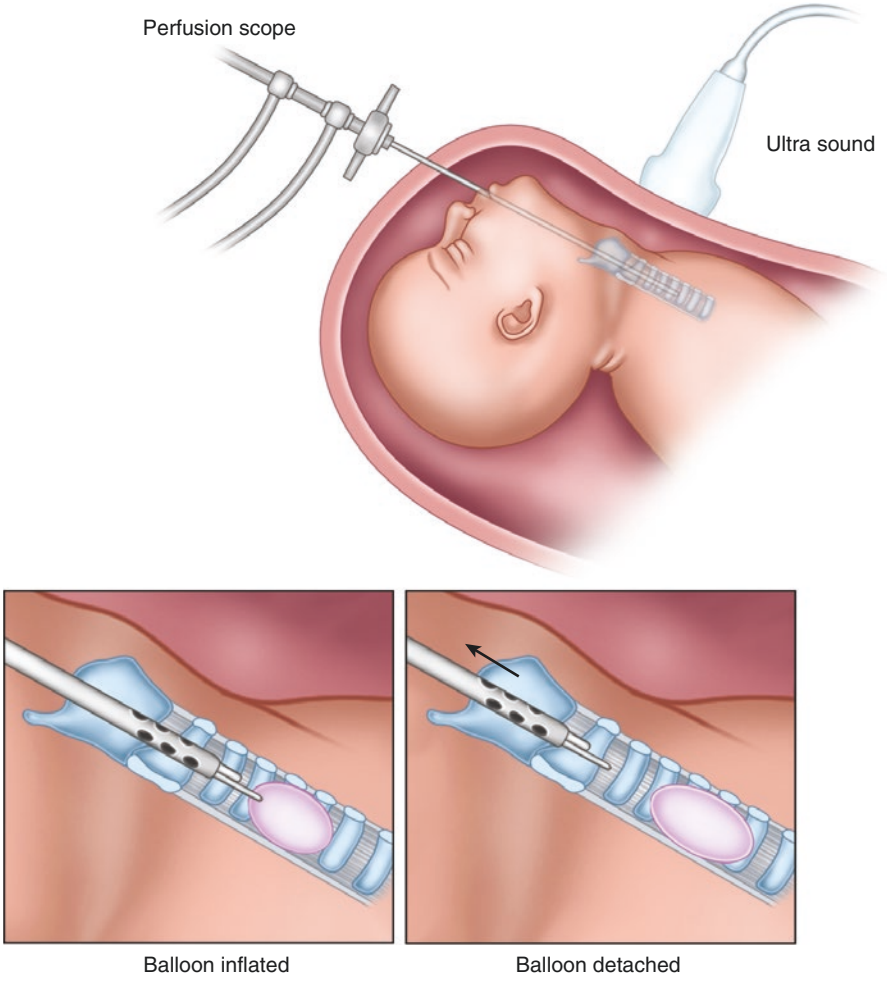

Fig. 60.2 Use of fetoscopy to place an inflatable balloon in the fetal trachea for CDH

60.4 Specific Conditions

60.4.1 Congenital Diaphragmatic Hernia

Principle
Fetal tracheal occlusion (FETO) promotes lung growth and thus improves postnatal lung function.

Fetuses with severe CDH and lung hypoplasia continue to have a dismal prognosis. For these selected patients, fetal surgery may improve survival and reduce postnatal morbidity.

FETO is performed by placing a balloon into the fetal trachea at 26–29 weeks' gestation. An early randomized control trial in 2003 comparing in utero FETO for CDH with standard postnatal care did not show improved survival in the TO group (both groups had a 90-day survival of 75%) (Harrison et al. 2003). However, the study had broad inclusion criteria and did not target the sickest subset of fetuses.

Consequentially, the *Tracheal Occlusion To Accelerate Lung growth (TOTAL)* trial was begun with more stringent selection criteria, randomization to expectant management or FETO, and two study groups consisting of patients with moderate or severe lung hypoplasia. Enrolment has been completed for patients with moderate lung hypoplasia while enrolment for patients with severe lung hypoplasia is near complete. The results have been recently reported (2021) showing significant improvement in survival in the most severely affected fetuses.

60.4.2 Twin Anomalies

This is directed at the abnormal circulation during multi-gestational pregnancies putting one or both fetuses at risk for disease and/or death.

Principle
Fetoscopic laser ablation of abnormal placental connections.

60.4.2.1 Twin-Twin Transfusion Syndrome

- Abnormal placental connections cause unequal sharing of blood between fetuses.
- Occurs in up to 15% of monochorionic twin pregnancies.

The condition is fatal in >80% of untreated cases and survivors face a risk of brain damage and morbidity.

A 2004 randomized control trial (Senat et al. 2004) of laser blood vessel ablation showed superiority compared to amnioreduction, the previous therapy of choice, in patients with severe Twin-twin transfusion syndrome (TTTS) (≤26 weeks gestation) Survival of at least one twin at 1 month was 76% (laser) vs. 56% (amnioreduction group). The procedure has been improved by the Solomon technique by reducing twin anemia polycythemia sequence (3% Solomon vs. 16% standard laser) and recurrence of TTTS (1% Solomon vs. 7% standard laser) (Slaghekke et al. 2014).

60.4.2.2 Twin Reversed Arterial Perfusion (TRAP) Sequence

- ~1% of monochorionic twins.
- Characterized by an acardiac and/or anencephalic twin whose blood flow is provided by reversed perfusion through the normal twin's umbilical cord. Fetal demise occurs in approximately 60% of cases and is more likely if the anomalous twin is large, well-vascularized, or both.

Fetal surgery consists of ablation of the blood vessels that supply the acardiac twin, either via fetoscopy with monopolar or bipolarly diathermy, YAG laser, radiofrequency ablation, or microwave. Survival rates for the normal twin after ablation are >90%, higher than treatment with cord occlusion which are higher than survival rates from conservative management.

60.4.3 Fetal Mass Lesions with Hydrops

Large, vascularized mass lesions cause heart failure and hydrops either by impairing venous return or arteriovenous shunting.

Principle
Reversal of fetal cardiac failure and hydrops by fetal mass excision.

The vast majority of mass lesions are benign and often spontaneously regress; however, some become so large that they cause high-output cardiac failure. The most common are *congenital pulmonary adenomatoid malformation (CPAM)* and *sacrococcygeal teratoma (SCT).* Fetal surgery for these lesions involves resection via an open approach (Fig. 60.3). A recent review showed improvement in survival of hydropic fetuses with mass lesions from <5% without intervention to 50% with resection. For microcystic or solid CPAMs with hydrops fetalis, survival is >80% with maternal steroid treatment. Fetal surgical resection should only be considered with persistent hydrops fetalis after 2 or more courses of steroids.

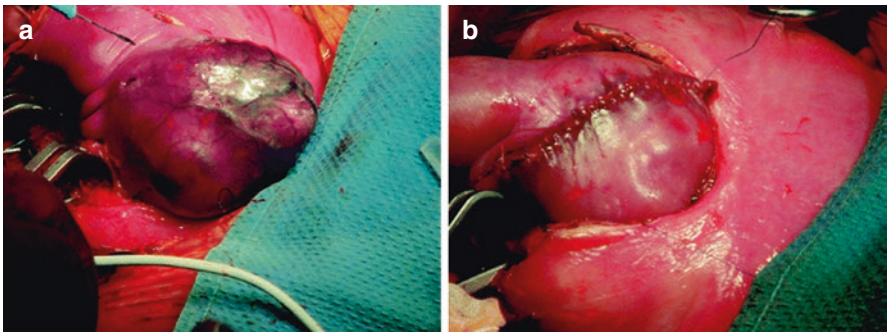

Fig. 60.3 Sacrococcygeal teratoma (**a**) before and (**b**) after fetal resection

60.4.4 Early Pregnancy Renal Anhydramnios

Early pregnancy renal anhydramnios (EPRA) occurs when fetal urine fails to enter the amniotic sac whether due to an obstruction or lack of production. The minimized amniotic fluid levels lead to pulmonary hypoplasia causing EPRA to be universally fatal as the fetus cannot develop functional lungs.

60.4.5 Bladder Outlet Obstruction (BOO) and Fetal Renal Failure

Principle
Relief of urinary obstruction may reduce renal failure and limit pulmonary hypoplasia.

When renal function is absent, amnioinfusions have the potential to recuse neonatal lung function.

Bladder outlet obstruction affects ~1 in 1000 live-births. The causes include:

- Posterior urethral valves (most common)
- Prune belly syndrome
- Urethral atresia

Congenital urinary obstruction leads to oligohydramnios, renal failure, and pulmonary hypoplasia. Insertion of a double-J pigtail vesicoamniotic shunt can prevent further deterioration and enhance lung growth; however, the *Percutaneous Lower Urinary Track Obstruction (PLUTO) trial* (Morris et al. 2013) was not able to detect a difference in survival when comparing vesicoamniotic shunts to conservative management. Despite poor recruitment and a low sample size, survival at 28 days was 50% after vesicoamniotic shunt treatment and 27% after conservative treatment. Only two children survived to 2 years of age, and both were treated with vesicoamniotic shunts. Some centers are now investigating the role of fetal cystoscopy to treat fetal bladder outlet obstruction (Ruano et al. 2015).

Fetuses with congenital bilateral renal agenesis or early renal failure are both conditions preventing the production of urine which leads to progressive oligohydramnios and eventually anhydramnios resulting in pulmonary hypoplasia. Pulmonary function in these pregnancies may be improved by an exogenous source of fluid.

Replacing fetal urine with normal saline may improve lung hypoplasia. However, success rates and longer-term outcomes for serial amnioinfusions to treat these diseases have not been fully and systematically explored.

The *Renal Anhydramnios Fetal Therapy (RAFT) trial* (O'Hare et al. 2019) is a current multicenter, prospective, non-randomized trial to assess the feasibility of serial amnioinfusions for maternal and fetal safety. Furthermore, survival to neonatal dialysis and possible biomarkers will be determined in addition to efficacy of amnioinfusions in relationship to morbidities from neonatal dialysis, future surgeries (e.g., urinary tract reconstruction), and renal transplant (Jelin et al. 2020).

60.4.6 Myelomeningocele (Spina Bifida)

Neural tube defects (e.g., myelomeningocele (MMC) or spina bifida) occurs in ~1 in 1000 live-births and is associated with debilitating neurologic injury (e.g., loss of hind limb function, bowel and bladder incontinence, hydrocephalus, and Arnold[1]-Chiari[2] malformation (condition where part of cerebellum herniates through foramen magnum causing hydrocephalus).

Principle
In utero repair of MMC may preserve peripheral neurological function and prevent Arnold-Chiari malformation.

Successful prenatal MMC repair rectifies error in neural tube development and minimizes damage to neural structures by the amniotic fluid. In the *MOMS trial*, repair consisted of open fetal surgery for neural tissue separation, dural suturing, and connection of myofascial tissue (Adzick et al. 2011). Despite prematurity, neonates receiving MMC repair in utero were less likely to die or require a cerebrospinal fluid shunt in the first year of life (68% prenatal MMC repair vs. 98% postnatal MMC repair). Advantages of prenatal MMC repair continued in the longer term with higher functionality of the prenatal group than postnatal at 30 months and 5–10 years of age (Houtrow et al. 2020).

Fetoscopic techniques for MMC repair have also been developed and tested through a Phase I trial called the *CECAM trial* (Pedreira et al. 2016). This utilized a one layer technique consisting of a simple skin closure over a biocellulose patch. The technique was improved to a 3-layer closure wherein a collagen patch is placed, dura-fascia or myo-fascia flaps are sutured to cover the patch, and the skin closed. Further studies are required to compare outcomes for fetoscopic and open techniques for MMC repair (Belfort MA et al. 2019).

[1] Julius Arnold (1835–1915)—German pathologist, published his case in 1894.

[2] Hans Chiari (1851–1915)—Austrian pathologist, published a series of cases, and a hypothesis concerning hydrocephalus in 1891.

60.4.7 Aortic Valve Stenosis

Prenatally diagnosed critical aortic valve stenosis leads to ventricular overload, chronic myocardial wall ischemia, and eventually hypoplastic left heart syndrome (HLHS). Postnatal therapy involves staged surgical repairs, but mortality is up to 25% after the first operation and survivors face a lifetime of cardiac and neurologic dysfunction.

Principle
In utero repair of valve stenosis may preserve ventricular function.

Percutaneous and open fetal aortic valvuloplasty have successfully relieved left ventricular obstruction and minimized left heart damage. The largest series from the Children's Hospital Boston (n = 100) reported a technical success rate of 77% (Freud et al. 2014). Of the surviving fetuses with successful interventions, 50% developed a functional left ventricle. At most recent follow-up, participant ages ranged from 2 months to 13 years wherein no cardiac deaths reported for participants with a functional left ventricle at birth. Despite the decrease in mortality, participants with a functional left ventricle experienced morbidities at similar rates to those with HLHS (e.g., interventional catheterizations and neurodevelopmental delay) (Laraja et al. 2013).

60.4.8 Amniotic Band Syndrome

Strands from the amniotic sac have the potential to separate from the sac and entangle portions of the fetal body. Severe malformations result from tight entanglements to the limbs and other parts of the body resulting in deformities or possible fetal death.

Principle
Removal of amniotic bands may prevent death or lessen deformity.

Fetoscopic techniques are used to release amniotic bands from their entanglement about the fetal structure (Derderian et al. 2014). Surgeons transect the bands mechanically or with a laser. Success rates have been cited >74% with reasonable functionality of affected structure postnatally; however, postnatal surgeries are often indicated (Iqbal et al. 2015).

60.4.9 Congenital High Airway Obstruction Syndrome

Congenital high airway obstruction syndrome (CHOS) is characterized by a stenosis or mass lesion that blocks the fetal airway. Fetuses with CHAOS that survive until birth face certain death secondary to airway obstruction.

Principle
Correction of airway occlusion while still on placental support.

The *EXIT (ex utero intrapartum treatment) procedure* is a specialized mode of surgical delivery developed for fetuses with airway obstruction (Fig. 60.4). EXIT maintains the fetus on placental support while an airway is established by orotracheal intubation or tracheostomy. Once oxygenation of the fetus is achieved, the cord is clamped and cut, and the baby is delivered.

Experimental techniques such as fetoscopic laser laryngotomy are being attempted at multiple centers.

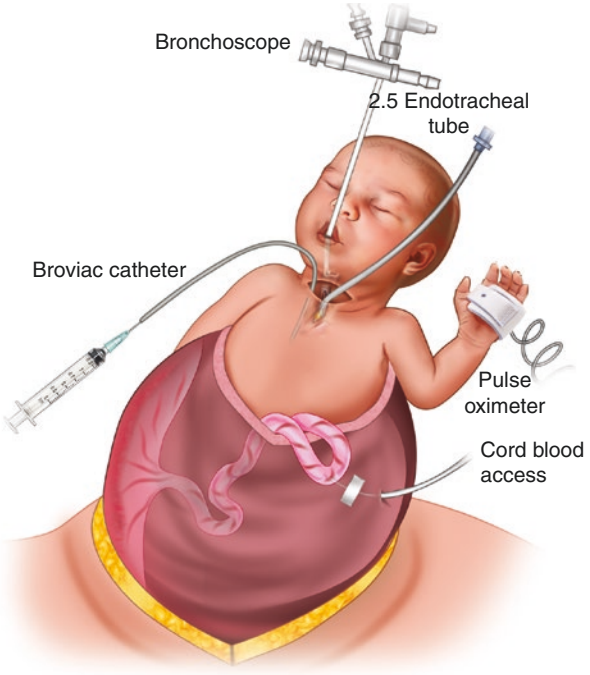

Fig. 60.4 Schematic of an "EXIT" procedure

60.5 The Future of Fetal Surgery

For many fetuses with severe disease, fetal surgery offers the best and sometimes only therapy. The efficacy of intervention is still greatly limited by high rates of preterm labor and preterm birth, but as more is learned about the underlying mechanisms of labor, strategies are being developed to combat it. Minimally invasive techniques will continue to improve and replace open techniques. In the near term, stem cell transplantations are being performed in utero. Clinical trials are currently underway. In utero hematopoietic stem cell transplantation for α-thalassemia major is currently recruiting patients at the University of California San Francisco. Another trial is the Boost *Brittle Bones Before Birth (BOOSTB4) trial*. BOOSTB4 is a European multisite Phase I/II trial for prenatal and/or postnatal allogenic expanded fetal mesenchymal stem cell transplantation for osteogenesis imperfecta. Future in utero interventions may also involve gene therapy via viral vectors or medication administration via microparticles for metabolic deficiencies, musculoskeletal anomalies, and neural defects with animal studies at Yale University and University College, London showing promise. The frontier of fetal therapy is with a nexus of multidisciplinary scientific and technological advancements; however, caution is warranted. It is uncertain how, or if, developments such as gene editing may impact fetal therapy in the distant future, but healthcare providers in the field are to remain cognizant of ethical considerations as steps forward are taken. Fetal therapy has evolved quickly since Dr. Harrison's first fetal surgery in 1981. Responsible and ethical research in the field will guarantee the next stage of fetal therapy to be as dramatic and promising.

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