Fetal Intervention

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Fetal conditions considered candidates for in utero intervention include fetal anemia, fetal arrhythmias, lower urinary tract obstruction (LUTO), congenital diaphragmatic hernia (CDH), chylothorax, congenital pulmonary airway malformation (CPAM), open spina bifida, and sacrococcygeal teratoma (SCT), among others. Fetal intervention in the management of complicated monochorionic twin pregnancies make up the largest group of in utero procedures. Indications for fetal therapy for complicated monochorionic twins include twin–twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR) with abnormal Dopplers, twin anemia polycythemia sequence (TAPS), twin reversed arterial perfusion (TRAP) sequence, and discordance for fetal anomaly (Table 9.1).

Fetal intervention techniques range from medical treatment to minimally invasive procedures to open maternal-fetal surgery and ex-utero intrapartum treatment (EXIT) procedures. Fetal therapy requires absolute certainty in diagnosis including skilled imaging and interpretation as well as fetal genetic evaluation. Because of the complexity of the procedures that involve the health and well-being of two (or more) patients, mother and fetus(es), the approach to management involves a large multidisciplinary team. The mother is often considered essentially the innocent bystander in fetal intervention, assuming risk for herself and her fetus, and should always be the primary consideration with regard to safety. Thorough counseling regarding risks and benefits to both mother and fetus must be a standard component of the fetal therapy care paradigm.

Fetal Interventions: Multiple fetal intervention techniques are currently employed based on fetal diagnosis, technical feasibility, and maternal-fetal safety profiles. Once the diagnosis is established, options for treatment must be presented to the patient in a non-directive manner with full disclosure of the team's experience and maternal-fetal risks and potential benefits described. Consideration of operative approach, anesthetic requirements, pregnancy outcomes, neonatal and long-term care, as well as the impact on future maternal reproduction must be discussed. Plans for fetal resuscitation or delivery must also be determined in conjunction with the expectant parents' wishes prior to any fetal intervention.

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P. Mattei (ed.), *Fundamentals of Pediatric Surgery*, https://doi.org/10.1007/978-3-031-07524-7_9

Table 9.1 Fetal interventions and indications

Intervention	Indication
Medical therapy	
Antiarrhythmic agents	Supraventricular tachycardia
Corticosteroids	Prevention of female virilization with CAH
Corticosteroids	Lung lesions
Ultrasound-guided procedures	
Amnioreduction	Polyhydramnios
Vesicocentesis	Lower Urinary Tract Obstruction
Thoracentesis	Cystic CPAM; Chylothorax
Percutaneous umbilical blood sampling (PUBS)	Genetic testing; Fetal anemia
Intrauterine transfusion (IUT)	Fetal anemia
Thoracoamniotic shunt placement	Cystic CPAM; Chylothorax
Vesicoamniotic shunt placement	Lower Urinary Tract Obstruction
Interstitial laser coagulation	TRAP sequence, BPS, SCT
Balloon valvuloplasty	Critical aortic stenosis/evolving HLHS
Selective cord occlusion	Complicated monochorionic twins (severe TTTS, sFGR, discordant malformation)
Radiofrequency ablation	TRAP sequence
Bipolar cord coagulation	Discordant malformation
Fetoscopy	
Laser coagulation of placental anastomoses	TTTS; TAPS; sFGR
Amniotic band release	ABS
Ablation of posterior urethral valves	LUTO
Fetoscopic endoluminal tracheal occlusion	CDH
Myelomeningocele/myeloschisis closure	MMC
Open maternal-fetal surgery	
	Myelomeningocele/myeloschisis closure
	Resection of fetal lung lesions—BPS/CPAM
	Resection/debulking of SCT
	Resection/debulking of mediastinal mass
EXIT procedure	
	Cervical mass: Teratoma, lymphangioma
	CHAOS
	Severe micrognathia
	Severe lung lesions—CPAM/BPS
	SCT

EXIT EX utero intrapartum treatment, *CAH* congenital adrenal hyperplasia, *CPAM* congenital pulmonary airway malformation, *TRAP* twin reversed arterial perfusion, *BPS* bronchopulmonary sequestration, *SCT* sacrococcygeal teratoma, *HLHS* hypoplastic left heart syndrome, *TTTS* twin–twin transfusion syndrome, *sFGR* selective fetal growth restriction, *ABS* amniotic band sequence, *LUTO* lower urinary tract obstruction, *CHD* congenital diaphragmatic hernia, *MMC* myelomeningocele, *CHAOS* congenital high airway obstruction syndrome

Medical Therapy

Medical fetal treatment is a non-invasive form of fetal intervention that relies on maternal-fetal physiology and transplacental passage of medications to achieve a fetal response. Typically, fetal loss is not an associated risk related directly to the treatment, contrary to the case with invasive procedures. Maternal risk is largely related to the side effect profile of the medication being administered. Medical fetal therapy is generally considered fairly benign as it does not require the use of anesthesia or invasive techniques.

Fetal medical treatment includes the administration of corticosteroids in the setting of impending preterm delivery to promote fetal lung maturity. This has been accepted as a global standard of care, although it is not often appreciated as a form of medical fetal treatment. Maternally administered corticosteroids are also used for fetal benefit in the management of congenital heart block related to maternally derived anti-SSA/SSB antibodies associated with systemic lupus erythematosus (SLE) or Sjogren syndrome, avoidance of female virilization in congenital adrenal hyperplasia (CAH), reduction in the size of rapidly involuting congenital hemangiomas (RICH), and stabilization/reduction in the size of microcystic congenital pulmonary airway malformations (CPAM).

In families at risk for classical CAH due to 21 hydroxyase deficiency, maternal treatment with dexamethasone beginning by the sixth week of gestation is used to avoid virilization of female fetuses by causing adrenal suppression. The treatment is controversial and the complete side-effect profile

on the developing fetus is unknown. Treatment must be started before invasive testing can be performed, either by chorionic villus sampling or amniocentesis, to confirm the diagnosis in the fetus. This means that many male fetuses and unaffected female fetuses are treated with dexamethasone unnecessarily. With the advent of cell-free fetal DNA screening, a non-invasive prenatal screening option that detects fetal DNA within the maternal plasma as early as 6 weeks' gestation, fetal gender determination can be used to guide treatment, selecting only those pregnancies with a female fetus for potential therapy.

Rapidly growing microcystic CPAM can result in significant mediastinal shift, cardiac compression, and decreased venous return that in turn can cause hydrops in affected fetuses. Treatment with betamethasone (2 doses of 12 mg IM given 24 h apart) has been shown to stabilize the rapid growth velocity of the CPAM and reverse the hydrops. Repetitive steroid dosing at intervals of at least 7–14 days apart for each course has been used to mitigate the growth velocity on a longer-term basis and avoid open maternal-fetal surgery.

Women with SLE or Sjogren syndrome are at risk for having circulating autoantibodies (anti-SSA/SSB) that cross the placenta and cause inflammation of the fetal conduction system with an otherwise structurally normal heart, resulting in congenital heart block. Affected fetuses are at risk for endocardial fibroelastosis (EFE), valvular insufficiency, and dilated cardiomyopathy. The fetus may also develop hydrops fetalis if the fetal heart rate is not maintained at an adequate level, typically above 50–55 bpm. The use of maternal dexamethasone has been used to minimize ongoing inflammation. Additionally, hydroxychloroquine and sympathomimetics are often used in combination to maintain an adequate fetal heart rate. Most affected neonates will require a pacemaker (~70%) and the mortality rate is nearly 20%.

Fetal arrhythmias are typically identified at the time of a routine prenatal visit when the fetal heart rate is auscultated. Further evaluation including a fetal echocardiogram is warranted to evaluate cardiac structure and define the arrhythmia. Fetal magnetocardiography can be used to define the specific arrhythmia, however this is not universally available. The majority of fetal rhythm differences are benign and are most commonly premature atrial contractions (PAC) that will resolve as the gestation progresses, requiring no intervention. Sustained tachyarrhythmias, such as supraventricular tachycardia, place the fetus at risk for the development of hydrops. First-line treatment is typically digoxin with conversion to normal sinus rhythm occurring in nearly two-thirds of affected fetuses. Route of administration can be either oral or intravenous. Intravenous dosing requires hospitalization while oral loading can be done as an outpatient. Maternal serum digoxin levels are used to guide treatment. Flecainide and sotalol are commonly used as second-line agents if monotherapy with digoxin does not result in return of sinus rhythm. The presence of hydrops can impact transplacental transfer of medication due to a thickened placenta and altered volume of distribution, leading to poor resolution of the fetal arrhythmia. For this reason, cordocentesis with direct fetal treatment is sometimes performed. For transplacental treatment, a maternal ECG is required prior to initiation of any anti-arrhythmic therapy to ensure that no underlying maternal electrophysiologic baseline differences exist. Patients must be closely monitored for any cardiac symptoms or side effects. Monitoring for fetal response can include close outpatient monitoring via serial ultrasound or echocardiogram or inpatient continuous fetal monitoring.

Ultrasound-Guided Procedures

US-guided needle procedures, such as amniocentesis, amnioreduction, vesicocentesis, and thoracentesis, are typically performed in the outpatient setting using only local anesthetic. Some providers may choose to use no anesthetic as this reduces the number of needle sticks. These procedures are performed using spinal needles ranging in size from 22- to 18-gauge, depending on the procedure. The smaller gauges should be used for procedures that will remove fluid from the fetus proper. For amnioreduction due to polyhydramnios, in which larger volumes of amniotic fluid are being removed, an 18-gauge needle attached to a vacuum bottle is often used so that the flow of fluid is steady. Fluid should not be removed too quickly and the volume removed should restore the fluid level to a high normal amniotic fluid index, as rapid decompression of amniotic fluid can result in placental abruption. Viable pregnancies are monitored as inpatients for at least 2 h with continuous fetal monitoring and tocodynamometer after amnioreduction for any clinical evidence of preterm labor or abruption. Potential post-procedure complications include rupture of membranes, membrane separation, placental abruption, preterm labor/delivery, infection, and possible need for delivery/loss of pregnancy, which occur in 1–3% of cases.

More complex US-guided procedures, such as shunt placement, selective cord occlusion, PUBS/IUT, interstitial laser and balloon valvuloplasty, are typically done in the OR. Even for those procedures performed using needle instrumentation, they last longer and require the patient to remain immobilized for a longer period of time. The instruments used for shunt placement and selective cord occlusion are larger caliber (up to 4 mm) and require a small skin incision typically made with an 11-blade scalpel and uterine puncture with a trocar. Intravenous sedation and local anesthetic are most commonly employed for maternal anesthesia. In some cases, regional anesthetic or general anesthesia are preferred based on maternal body habitus, anticipated length of procedure, or technical limitations. Patients are often posi-

tioned to allow direct access to the fetus and avoidance of the placenta. This positioning also impacts the decision regarding anesthetic choice. Perioperative prophylactic antibiotics are given intravenously. Preoperative prophylactic tocolytic administration of indomethacin or nifedipine is often used. Magnesium sulfate is used for break-through contractions/labor. Sequential compression devices (SCD) are used for prevention of perioperative deep vein thrombosis (DVT). Postoperative complications occur in ~10–15% of cases.

Fetoscopy

Fetoscopy is performed in the OR using maternal IV sedation and local anesthesia. Like US-guided procedures, regional anesthesia or general anesthesia may be preferred depending upon maternal factors, positioning needs, and anticipated length of the procedure. Perioperative prophylactic antibiotics are given intravenously and prophylactic tocolytics (indomethacin or nifedipine) are given. Intraamniotic installation of antibiotics using oxacillin or clindamycin is commonly used. Magnesium sulfate is used for breakthrough contractions/labor. The operative ports vary in size depending on the fetoscope diameter used and range from 2 to 4 mm. These require a small skin incision and uterine puncture for placement. Methods for insertion include direct trocar insertion of the operative port or insertion using the Seldinger technique that is performed initially with a needle and introduction of the operative port over a guidewire and dilator. Depending on the procedure, multiple operative ports may be needed. SCDs are used for prevention of perioperative DVT. Postoperative complications occur in 10–30% of cases.

Open Maternal-Fetal Surgery

Open maternal-fetal surgery (OMFS) represents the most complex end of the fetal surgery spectrum (Fig. 9.1). OMFS is performed under general anesthesia involving high-dose volatile anesthetics to achieve adequate uterine relaxation. This regimen can cause maternal hypotension, poor uteroplacental perfusion, and impaired fetal cardiac function. Maternal status is monitored closely and ephedrine and phenylephrine are used to maintain blood pressure. An arterial line is used to invasively monitor blood pressure and guide treatment. The hypotension is not treated with aggressive fluid replacement as this can lead to postoperative pulmonary edema. Preoperatively, an epidural is placed for postoperative pain control. Supplemental intravenous anesthesia (SIVA) is also used in some centers in which remifentanil infusions with or without propofol allow a lower amount of volatile anesthetic agent to achieve uterine relaxation to

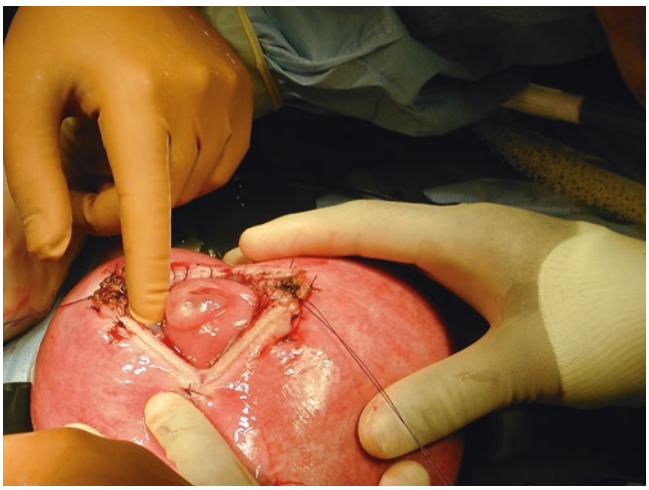

Fig. 9.1 Open maternal-fetal surgery for myelomeningocele closure. Stay sutures are visible on either side of the hysterotomy which is bloodless. The fetus is positioned within the hysterotomy for surgical closure

counteract maternal hemodynamic and fetal cardiac function concerns. Perioperative prophylactic antibiotics are administered intravenously in conjunction with intraamniotic installation of antibiotics at the conclusion of the fetal surgery. Prophylactic tocolytics include a combination of indomethacin, nifedipine and magnesium sulfate. Typically, the indomethacin is initiated preoperatively and continued for completion of a course of 48 h, with a 50 mg loading dose followed by 25–50 mg every 4–6 h. This can be given per rectum or orally. Magnesium sulfate is infused intravenously with a 6 g bolus followed by 2–4 g per hour continuous infusion for the first 24 h postoperatively. The infusion is titrated depending upon uterine activity and maternal status. The magnesium sulfate is typically started at the conclusion of the fetal surgery but can also be initiated during the surgery to maintain uterine relaxation throughout the case. Nifedipine is started once the magnesium sulfate is discontinued using a regimen of 10–20 mg by mouth every 4–6 h titrated to uterine activity. Nitroglycerin and terbutaline can be used for additional intraoperative uterine relaxation if needed. A Foley catheter is used to monitor maternal fluid status closely. SCDs are used for prevention of perioperative DVT. The fetus is monitored by US and echocardiogram for 2 days postoperatively to assess amniotic fluid levels, umbilical artery Dopplers, and evidence of ductal constriction due to exposure to indomethacin.

The skin incision is typically made in a transverse fashion, approximately halfway between the umbilicus and the pubic symphysis. The incision is wide in order to provide adequate access for uterine manipulation. If the indication for the fetal surgery is a large tumor, such as a giant SCT, a vertical skin incision may be required to provide adequate space to deliver the tumor. The subcutaneous adipose is dis-

sected off the fascia, again for the purpose of mobilization. The fascia is incised vertically and the rectus muscles separated. In the case of a posterior placenta, the hysterotomy is created on the anterior fundus and the uterus is left in its typical anatomic position. In the case of an anterior placenta, the hysterotomy is created on the posterior fundus. The uterus is brought forward and tilted onto the lower maternal abdomen, care being taken to avoid kinking or twisting of the lower uterine segment and broad ligaments. The placenta is mapped using US and demarcated on the surface of the uterus with the cautery. The goal is to create the hysterotomy incision at least 6 cm from the placental edge. A stay suture is placed under ultrasound guidance in a pocket of amniotic fluid free from placental edge, fetal parts, and umbilical cord. A second stay suture is placed approximately 1 cm apart in a similar fashion. The intervening uterine tissue is opened using the cautery with return of amniotic fluid. The uterine tissue is often thick at the fundus, and the use of bowel clamps to compress the uterine tissue can help to facilitate use of the uterine stapler. The uterine stapler with absorbable staples provides control of the membranes upon entry to the uterus (Premium Poly CS, Medtronic, Minneapolis, Minn.) and is fired in each direction as many times as needed to create an adequate hysterotomy for the planned fetal surgery. The fetus is then positioned in the hysterotomy as indicated by the procedure. Fetal intramuscular anesthetic is administered that includes Fentanyl (20 μg/kg), Vecuronium (0.2 mg/kg) and Atropine (20 μg/kg). Level 1 infusion tubing is inserted into the uterus, with care to avoid the placenta, and warmed lactated Ringer's solution is infused throughout the case to maintain uterine distension and avoid compression of the umbilical cord. The fetal surgical intervention is then carried out with continuous monitoring of fetal cardiac function. After the fetal procedure is completed, the uterus is closed in two layers, interrupted and continuous. The level 1 infusion is allowed to run in until an adequate amount of amniotic fluid has been re-established and the last suture is placed. An omental flap is created and tacked over the hysterotomy. The uterus is restored to its appropriate anatomic position and the laparotomy is closed. Postoperatively, the patient is awakened and extubated, and the arterial line is removed. The epidural and Foley catheter remain in place until the patient is able to transition to oral pain medications and able to ambulate to the restroom. Postoperative complications can be as high as 40%.

Ex-Utero Intrapartum Treatment

The EXIT procedure is used to support the fetus on placental bypass and create a smooth transition in cases of anticipated airway or cardiovascular compromise due to large neck masses, CHAOS, micrognathia, large lung lesions, or SCT. The procedure is technically similar to OMFS, except it is performed at or near term, and the fetus is delivered at the end of the case.

The EXIT procedure is also performed under general anesthesia with placement of an epidural catheter preoperatively for postoperative pain control. High-dose volatile anesthetic agents are used for uterine relaxation and to maintain placental blood flow. Additional intraoperative tocolytic use is limited to magnesium sulfate, nitroglycerin, and terbutaline because indomethacin is contraindicated due to the later gestational age and risk of premature closure of the ductus arteriosus. There is no need for tocolytic use postoperatively as delivery occurs. Perioperative prophylactic antibiotics are administered intravenously. A Foley catheter is used to monitor maternal fluid status. SCDs are used for prevention of perioperative DVT.

The decision regarding the skin incision is dependent upon the indication for the EXIT procedure. For large neck masses or SCT, a vertical skin incision may be needed. Otherwise, the skin incision is typically made similar to that in OMFS in a transverse fashion halfway between the umbilicus and pubic symphysis. The hysterotomy is created in a similar fashion to OMFS by placing stay sutures followed by the use of the uterine stapling device. Care must be taken to create a hysterotomy that is large enough to deliver the fetal head or SCT, such that the process of delivery does not sheer or tear the uterine staples or cause bleeding. If the placenta is posterior, the uterine incision is made anteriorly taking caution to avoid the placenta by a margin of at least 6 cm. If the placenta is anterior and there is enough room in the lower uterine segment to safely create a hysterotomy at least 6 cm from the placental edge, the incision can be created anteriorly. However, if the placenta covers the majority of the anterior uterine surface without an adequate window, a posterior hysterotomy will need to be planned. This involves delivering the uterus by tilting it forward onto the lower maternal abdomen, taking care not to kink the lower uterine segment or broad ligaments. Mapping is performed by US to determine the optimal site to create the hysterotomy in an amniotic fluid pocket free of fetal parts, umbilical cord and a distance of at least 6 cm from the placental edge. A level 1 infusion catheter is inserted, and warmed lactated Ringer's solution is continuously infused to maintain uterine distension.

The fetus is partially delivered in order to facilitate the indicated procedure. Fetal positioning is key to a successful EXIT procedure. In order to facilitate an airway, the fetus should be delivered to the umbilicus with the arms positioned outside of the uterus. If the goal is debulking an SCT, the lower portion of the fetus is delivered, leaving the upper body and head in the uterus. Fetal status is monitored using a pulse oximeter or continuous fetal echocardiography. A fetal IV should be placed to administer medications and

blood products as needed. Once the airway is secured and the fetal portion of the case is completed, the fetus is ventilated until an adequate pulse oximeter reading is obtained. The cord is then clamped and cut and the neonate is taken to the stabilization room.

Attention is then turned to delivery of the placenta and achieving uterine tone. The volatile anesthetics are decreased and uterotonic agents are given. This is initiated just prior to complete delivery of the neonate. Uterotonic administration typically involves oxytocin initially with the addition of methylergonovine (Methergine®), carboprost tromethamine (Hemabate®), or misoprostol depending on uterine tone. Excision of the uterine staples from the hysterotomy allows for a clean re-approximation of the uterine incision. The remainder of the procedure and postoperative management are similar to a cesarean delivery. The EXIT procedure is associated with longer operative times and increased maternal blood loss/transfusion requirement compared to cesarean delivery.

Should maternal or fetal status become compromised during the EXIT procedure, alternative plans must be in place for complex neonatal resuscitation in the case of non-completion of the procedure. This requires the immediate availability of an additional OR or stabilization room and complete neonatal resuscitative staff. The team involved is quite large and involves multiple specialties including neonatology, surgery, maternal-fetal medicine, obstetrics, and anesthesia, among many more.

Indications for EXIT

There are relatively few indications for an EXIT procedure. Largely these include concerns for airway obstruction caused by a large oropharyngeal mass, compression from large neck masses such as cervical teratoma or lymphangioma or intrinsic obstruction caused by CHAOS (Congenital High Airway Obstruction Syndrome). Anticipated difficult neonatal transition in cases of large lung lesions or SCT causing hemodynamic compromise can also be indications for EXIT. In cases of large neck or oropharyngeal masses, establishing the airway on placental bypass can oftentimes require simultaneous resection of portions of the mass to facilitate access to the airway or a deviated trachea. Detailed imaging is warranted in cases of CHAOS to determine the extent of available patent trachea to access for the possibility of a successful EXIT procedure. This requires that an adequately patent trachea is identified at the level of the thoracic inlet in order to facilitate the establishment of a secure airway. In general, normal amniotic fluid and a normal appearing stomach on ultrasound are indicative of a patent fetal airway, and typically an EXIT procedure would not be indicated in that scenario. In the setting of large lung lesions the EXIT procedure is performed to allow resection of the lung mass while on placental bypass to achieve an optimal neonatal transition.

Maternal Considerations

Maternal safety and well-being are the primary consideration in any fetal intervention. A detailed maternal history and preoperative evaluation must be performed in order to rule out any contraindications to fetal therapy. Alterations in anesthetic management and medication management may be needed in certain maternal medical conditions or in women with higher BMI. Postoperative pharmacologic VTE prophylaxis using low molecular weight or unfractionated heparin might be considered based on clinical indication. Additionally, given the risk of maternal hemorrhage in any of the aforementioned circumstances, specifically with OMFS and EXIT procedures, clear protocols for hemorrhage, maternal resuscitation, and mass transfusion are recommended. Maternal psychosocial factors must also be explored in order to ensure that the patient has the resources to be able to remain compliant with postoperative recommendations and that her mental health is taken into consideration.

When making decisions about fetal surgery, patients are counseled regarding the potential risks and benefits not only to the current pregnancy, but also to any subsequent pregnancies. The most common complications with fetal surgery are related to the membranes and include membrane separation and premature rupture of membranes leading to preterm labor and delivery. Pulmonary edema can complicate any postoperative course but is more often associated with OMFS. Intraoperative need for fetal resuscitation and perinatal loss are uncommon but devastating complications of fetal surgery. The risk for any maternal complication after fetoscopy appears to be approximately 6%, with severe complications in 1–2%. For OMFS, the risk for any maternal complication is around 20%, with severe complications in 4–5% (Table 9.2).

Table 9.2 Maternal complications in OMFS and fetoscopy

	OMFS (%)	Fetoscopic procedures (%)
Intraoperative abruption	1.28	0.28
Intraoperative bleeding	1.97	1.74
Intraoperative transfusion	1.0	0.27
Abruption	1.8	1.29
Transfusion after surgery	3.36	0.32
Infection	4.13	1.45
Pulmonary edema	4.32	0.63
Uterine rupture	0.9	
Uterine dehiscence	3.67	
Transfusion at delivery	1.83	

Sacco et al. Prenat Diagn 2019;39(4):251–268

Maternal counseling must also include an assessment of her reproductive life plan. Based on available evidence, it does not seem that fetal intervention impacts fertility in subsequent pregnancies. However, the risk for uterine rupture and dehiscence are a concern not only for the index pregnancy, but for all subsequent pregnancies. This risk has been quantified in the range of 10–15%. Uterine rupture can be catastrophic, resulting in fetal loss and major maternal morbidity. For women who undergo OMFS, labor should be avoided and all subsequent pregnancies must be delivered via cesarean. Unfortunately, there is no reliable predictor for future uterine rupture and many cases have occurred in the preterm period prior to onset of labor. Repeat cesarean delivery is typically recommended after EXIT delivery unless the uterine incision is confirmed to be located completely within the lower uterine segment. Otherwise obstetrical providers must assume that the uterine incision was extended into the active portion of the uterus, increasing the risk for uterine rupture or dehiscence in subsequent pregnancies.

The presence of fetal hydrops imparts an increased maternal risk to develop *mirror syndrome*. This phenomenon, also known as Ballantyne syndrome and triple edema among others, is manifest by maternal edema, hypertension, and laboratory abnormalities in the setting of fetal hydrops, typically presenting in the mid-trimester. Mirror syndrome has features similar to preeclampsia and can result in major maternal morbidity if unrecognized. Treatment involves evacuation of the uterus, particularly in cases of maternal instability. Fetal therapy has been used to reverse fetal hydrops and improve maternal status in cases of early mirror syndrome. This should only occur in an inpatient setting under controlled circumstances, provided maternal status remains stable without evidence of pulmonary edema or significant laboratory abnormalities.

Complicated Monochorionic Twins

Complications of monochorionic twin pregnancies are the most common indication for fetal intervention. The underlying pathology involves vascular anastomoses within the shared placenta. There is often unequal sharing of the placenta that further contributes to the development of diagnoses unique to monochorionic twins. The largest risk in monochorionic twins involves the death of one which places the surviving twin at risk for neurologic injury due to profound hypotension at the time of the demise. This is essentially the equivalent of a fetal stroke and occurs in up to 30% of cases of co-twin demise.

Twin–twin transfusion syndrome (TTTS) occurs in 10–15% of monochorionic twins. The underlying pathophysiology is complex and not completely understood, but is thought to result from mostly unidirectional flow of blood through vascular anastomoses, creating a donor fetus and a recipient fetus. The severity of TTTS is designated through the use of a staging system (Table 9.3). Some centers employ echocardiography to delineate cardiovascular abnormalities in TTTS. Outcomes for advanced stage TTTS are dismal without intervention, particularly when it occurs early in gestation. For Stage I TTTS, defined by polyhydramnios-oligohydramnios sequence, varying rates of progression, regression, and stability have been reported. There appears to be no harm in conservative management for Stage I with the current recommendation to await intervention with laser therapy until there are signs of progression to Stage II.

The accepted intervention for Stages II-IV is fetoscopic laser photocoagulation of the placental communicating vessels if TTTS is diagnosed at less than 26 weeks. Laser coagulation of the placental communicating vessels functionally dichorionizes the placenta (Fig. 9.2). Laser therapy results in dual survival in the range of 50–70% and survival of at least one fetus of 75–90%. When laser is not feasible, amniore-

Table 9.3 Staging for twin–twin transfusion syndrome

Stage	Ultrasound findings
Stage I	Polyhydramnios with MVP >8 cm in recipient sac and oligohydramnios with MVP <2 cm in donor sac
Stage II	Non-visualized or small, non-cycling bladder in the donor
Stage III	Abnormal Doppler studies: Absent or reversed end diastolic flow in the umbilical artery, pulsatile umbilical vein, reversed a-wave in the ductus venosus
Stage IV	Hydrops in one or both twins
Stage V	Death of one or both twins

Quintero et al. J Perinatol 1999;19:550–5

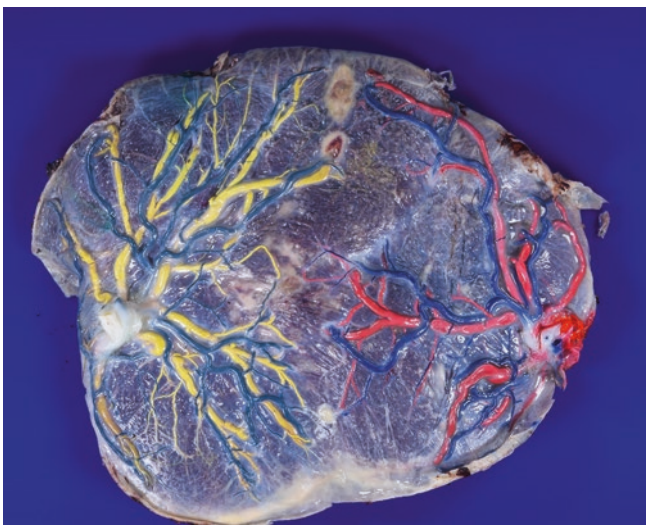

Fig. 9.2 Placenta post laser for TTTS. The photograph was taken after dye injection studies were performed—red/blue for one twin and yellow/aqua for the co-twin. Notice the blanched areas of ablation at the vascular equator (photo courtesy of Rebecca L. Linn, MD)

duction of the recipient sac can be curative in up to 20% of cases and is a worthwhile intervention in certain circumstances. Selective reduction via cord occlusion is a salvage procedure and can be an acceptable treatment in cases of advanced TTTS.

Selective fetal growth restriction (sFGR) is defined by an intertwine size discordance of ≥25% and an estimated fetal weight <10th percentile in one twin. sFGR occurs in up to 20% of monochorionic twins. TTTS and sFGR can occur simultaneously, clouding the choice for optimal treatment. Outcomes in pregnancies with sFGR are related to the Doppler flow studies in the umbilical artery of the growth restricted twin. Type I sFGR is characterized by normal umbilical artery flow and follows a benign course with delivery nearing 35 weeks. Type II sFGR is characterized by persistently abnormal flow in the umbilical artery and decompensation of the smaller twin in over 90% of cases. Type III sFGR is characterized by intermittent abnormal Doppler flow in the umbilical artery of the smaller twin with resultant decompensation/death in 10–20% of cases. For both type II and type III sFGR, delivery is typically indicated around 30 weeks. There is no agreement as to the optimal treatment for sFGR. However, laser has been attempted with a significant loss rate for both the smaller twin and the larger twin. Selective cord occlusion is commonly employed based on patient preference as a salvage technique to optimize the likelihood of a reasonable outcome for a singleton to achieve a term or near-term delivery. Outcomes for selective cord occlusion, most commonly performed using radiofrequency ablation, result in a singleton live birth in 85–90% of cases.

The hallmark of *twin reversed arterial perfusion* (TRAP) sequence is a normal twin that provides blood flow to a parabiotic, abnormally formed and usually acardiac co-twin by reversed perfusion via the umbilical vessels. It is a very rare complication of monochorionic twins. Parabiotic twins vary greatly in their development with some developing limbs and even rudimentary heart tubes. In general, they are acardiac masses of tissue that can achieve considerable size. Large parabiotic twins impact the healthy co-twin because of the large vascular demand that can result in the development of hydrops. Without treatment, reported fetal loss rates are as high as 50–70%. Improvement in outcome with pump twin survival of up to 85–90% has been reported with cord occlusion of the parabiotic twin, most commonly using radiofrequency ablation. Utilization of the parabiotic-to-pump twin size helps to guide intervention. For parabiotic-to-pump ratios over 70%, intervention is associated with improved outcomes. In cases of small parabiotic twins with ratios of 50% or less, conservative management with observation alone results in high pump twin survival. Currently, there is an ongoing trial investigating the potential benefit of first trimester intervention to improve outcomes for the pump twin.

Twin anemia polycythemia sequence (TAPS) can occur spontaneously or after laser therapy. TAPS is diagnosed prenatally when features of anemia indicated by increased middle cerebral artery peak systolic velocity (MCA-PSV) of one twin >1.5 MoM (multiples of median) is identified in conjunction with features of polycythemia, MCA-PSV <1.0, in the co-twin. Neonatal TAPS is defined by an inter-twin hemoglobin difference of >8.0 g/dL. Staging systems for both prenatally and postnatally diagnosed TAPS have been developed. Severe TAPS can lead to profound anemia and hydrops in one twin and devastating polycythemia resulting in neurologic injury and limb loss in the co-twin. There is currently no agreed upon optimal in utero intervention for TAPS. However, potential treatments include intrauterine transfusion/exchange transfusion, laser photocoagulation of placental vessels, selective cord occlusion as a salvage procedure, and, depending on gestational age, delivery.

Selective reduction via cord occlusion is a commonly utilized option based on patient preference in cases of discordant malformation in monochorionic twins. The goal of selective reduction in this setting is to reduce the associated risks of carrying an anomalous twin in order to optimize the outcome for the structurally normal twin. The method of cord occlusion is dependent upon the fetal anomaly and amnionicity. Radiofrequency ablation is commonly used for diamniotic twins and in the absence of a major abdominal defect. Bipolar cord coagulation is often utilized in cases of abdominal defects and in the setting of monoamniotic twins with cord entanglement in which cord transection is also employed to minimize cord accidents post reduction.

Congenital Diaphragmatic Hernia

Despite advances in neonatal treatment, overall survival with a diagnosis of CDH remains around 70%, mostly due to complications related to pulmonary hypoplasia and significant pulmonary hypertension. Tracheal occlusion in the setting of CDH has shown improvement of lung growth by obstructing the natural escape of lung fluid leading to stretching of the airways and lung growth. Early in the development of fetal intervention, tracheal occlusion was performed using OMFS techniques, then by fetoscopic tracheal occlusion, though outcomes were not improved, perhaps related to the lack of strict inclusion criteria. More recently, fetoscopic endoluminal tracheal occlusion (FETO) using a balloon has been employed as a minimally invasive technique for tracheal occlusion in cases of severe CDH. A randomized international trial comparing tracheal occlusion to expectant management in pregnancies complicated by severe left CDH defined as LHR O/E <25% with liver up position has shown benefit for select cases of severe left CDH (Deprest et al. 2021).

Lower Urinary Tract Obstruction

Lower urinary tract obstruction (LUTO), most commonly due to posterior urethral valves, leads to oligohydramnios or anhydramnios and resultant pulmonary hypoplasia that can be life-limiting. Diversion of fetal urine directly from the fetal bladder to the amniotic cavity through placement of a vesico-amniotic (VA) shunt can result in maintenance of amniotic fluid for lung development. Selection criteria for optimal candidates for VA shunting include singleton male fetuses with isolated LUTO with no evidence of cystic renal disease and a normal karyotype or microarray. Serial vesicocentesis with evidence of favorable urinary electrolytes are also used for determining optimal candidacy. Despite successful VA shunting, one-third of children will require dialysis and transplantation and another third will have some degree of renal dysfunction. Fetoscopic ablation of posterior urethral valves and OMFS to create a vesicostomy have also been proposed as alternative fetal interventions in the treatment of LUTO. The Renal Anhydramnios Fetal Therapy (RAFT) trial is currently ongoing to investigate the potential of serial amnio-infusions in the setting of fetal renal failure, as in some cases of LUTO, to avoid lethal pulmonary hypoplasia and allow for neonatal dialysis and eventual transplantation.

Lung Lesions

From a prenatal diagnosis and fetal treatment standpoint, congenital pulmonary airway malformations (CPAM) can be divided into microcystic and macrocystic lesions. Microcystic lesions appear echogenic, but largely solid, by ultrasound. Macrocystic lesions contain larger, more apparent fluid-filled cysts. Some lesions have mixed microcystic and macrocystic components. CPAM can grow very rapidly in the mid-trimester up until 26–28 weeks' gestation when they tend to plateau in size. During this rapid growth period, CPAM can cause significant mediastinal shift, cardiac compression, and reduced venous return that can lead to fetal hydrops. Additionally, lesions that are persistently large throughout gestation can lead to pulmonary hypoplasia. In general, large bronchopulmonary sequestrations (BPS) can act similarly to CPAM and can be treated similarly. Interstitial laser has also been used to ablate the feeding vessel in large BPS to inhibit growth of the lesion.

The CPAM volume ratio or CVR is used to stratify fetuses at high risk for developing hydrops. The CVR is calculated using 3-dimensional measurements of the CCAM by US using the formula for the volume of an ellipse and dividing by the head circumference (Length × Width × Depth × 0.523/head circumference in cm). A CVR of 1.6 or greater is associated with an increased risk for hydrops and is used to help guide management.

For a microcystic CPAM with a CVR ≥ 1.6, rapidly increasing CVR or presence of hydrops, betamethasone 12 mg IM × 2 given 24 h apart, can be used to mitigate growth and reverse hydrops if present. Multiple courses of betamethasone can be used at intervals of 7–14 days or more to stabilize growth and reverse hydrops. With this regimen we have been able to avoid OMFS in most cases. If the CPAM does not respond to steroid therapy, there is likely a bronchial atresia component present or an atypical histopathology.

For macrocystic lesions with a CVR ≥ 1.6, rapidly increasing CVR or presence of hydrops, needle drainage of the macrocysts is typically the initial first step. In many cases multiple honeycomb-type cysts are connected. Needle drainage allows the opportunity to confirm if this is the case, which can help guide later placement of a thoraco-amniotic shunt to provide longer-term drainage of the cysts and resolution of the hydrops. If one single dominant macrocyst is present, initial needle drainage is not required and management typically involves placement of a thoraco-amniotic shunt. Some CPAM contain a combination of microcystic and macrocystic components and can be treated using a combination of steroids, needle drainage, and shunt placement.

If steroids and minimally invasive treatments are not successful in reducing the size of the CPAM or reversing the hydrops, OMFS can be considered as a next step treatment. However, this aggressive treatment is very rarely needed. Delivery options can include the EXIT procedure with resection of the lung lesion on placental bypass to facilitate a smooth neonatal transition or cesarean delivery to immediate neonatal resection of the lung lesion. Cesarean delivery to immediate resection involves a complete second surgical team in an adjacent operating room to provide anesthetic and surgical care for the neonate.

Sacrococcygeal Teratoma

Sacrococcygeal teratomas (SCT) that are largely cystic in nature rarely result in fetal compromise. They can grow to considerable size, however, and result in a difficult cesarean delivery. US-guided needle drainage of the cystic component immediately prior to birth can facilitate vaginal delivery in select cases, or at least facilitate delivery through a low transverse uterine incision, allowing for vaginal births in future pregnancies.

Predominantly solid SCT and those that increase rapidly in size result in high-output cardiac failure and hydrops. Close sonographic surveillance in all cases of solid-appearing SCT is warranted to monitor the overall growth velocity of

Table 9.4 Fetal myelomeningocele closure—outcomes and techniques

	MOMS[a] *N* = 91 OMFS	Moldenhauer[b] *N* = 100 OMFS	Belfort[c] Single-layer closure *N* = 32 Fetoscopic	Belfort[c] 3-layer closure *N* = 18 Fetoscopic
Gestational age @ surgery (weeks)	24.2	23.3	25.0 (22.9–25.9)	25.0 (24.0–26.0)
Operative time (min)	105 + 23.2	78.5 (54–106)	260.7 ± 58.4	237.3 ± 47.0
Blood transfusion	1%	1%	0	0
Pulmonary edema	5.5%	2%	22%	0
Membrane separation	33%	22.9%	41%	39%
PPROM	44%	32.3%	28%	29%
Oligohydramnios	20%	6.3%	22%	6%
GA @ delivery	34.0 + 3.0	34.3 (22.1–37.6)	38.1 (26.0–40.7)	39.0 (31.1–40.9)
Cesarean delivery	100%	100%	50%	53%
Uterine status: Dehiscence/complete dehiscence	11.3%	8%		
Dehiscence of fetal repair	13%	3.6%	31%	6%

OMFS open maternal-fetal surgery
[a] Adzick et al. (2011)
[b] Moldenhauer et al. (2015)
[c] Belfort et al. (2020)

the tumor and monitor for evidence of secondary complications including bleeding into the tumor, dilated IVC, increasing combined cardiac output, and early signs of hydrops. Fetal intervention is aimed at debulking the SCT, thus minimizing the vascular steal phenomenon and allowing the fetus to recover in utero until birth weeks later. Fetuses with type I or II SCT with a narrow pelvic stalk are the optimal candidates for in utero resection. After birth, the remaining pelvic component of the SCT must still be resected. The optimal timing for OMFS for SCT debulking is prior to evidence of frank hydrops. Once the fetus becomes overtly hydropic, the success of OMFS decreases. Because of the significant vascularity of these tumors, the operative team must be prepared to perform fetal resuscitative measures, including availability of medications and blood products. After 28 weeks' gestation, preterm delivery prior to overt hydrops is associated with an improved outcome. Children are followed on surveillance programs that include serial physical examinations, imaging, and AFP levels.

Myelomeningocele/Myeloschisis

Since the publication of the Management of Myelomeningocele Study (MOMS), in utero closure of myelomeningocele (MMC) has become an accepted standard of care in affected pregnancies meeting selection criteria. The MOMS trial was a randomized trial comparing OMFS for fetal MMC closure compared to standard postnatal closure. The fetal closure is performed in a similar manner to surgery performed on the neonate, creating a water-tight multi-layer closure. The results were consistent with a reduction in need for shunting, reversal of hindbrain herniation, improved motor function, and higher likelihood for independent ambulation in the prenatal surgery group compared to the postnatal closure group. Despite these benefits, the prenatal surgery group had an increased risk for preterm delivery and uterine dehiscence at delivery. Since that time, multiple centers have published their independent data with results comparable to those of the MOMS trial (Table 9.4).

In order to minimize maternal morbidity, fetoscopic MMC closure has been explored. Initial techniques were fraught with issues related to membrane rupture and preterm delivery, and neonatal outcomes were not consistent with the MOMS trial data. Multiple groups developed various approaches to the fetoscopic MMC closure technique. Maternal laparotomy with fetoscopic MMC closure seems to be the most promising with regards to optimizing fetal benefit and minimizing maternal risk.

Summary

Advancements in the field of fetal medicine and surgery have revolutionized the ability to treat fetal conditions in utero to promote survival and decrease morbidity. With such advancements in care, it is critical that the original tenets of fetal therapy are followed. These include the ability to accurately diagnose the condition, adherence to selection criteria to determine optimal maternal-fetal candidates, technical feasibility of the procedures, and maintenance of maternal-fetal safety. Given the complex conditions and need for multidisciplinary care, fetal therapy is often reserved for specialized centers where fetuses are cared for throughout the pregnancy, neonatal period, and into childhood.

Editor's Comments

Centers that specialize in fetal diagnosis and intervention are increasingly common. As the technology advances rapidly, indications for actual in utero or antenatal fetal intervention, though still relatively few, are increasingly commonplace including laser ablation for twin–twin transfusion syndrome, drainage procedures for urinary obstruction and macrocystic lung lesions, surgical repair of myelomeningocele, surgical debulking of massive sacrococcygeal teratoma, EXIT procedures for airway lesions, and now fetoscopic balloon tracheal occlusion for CDH. Nevertheless, although most fetuses are not candidates for antenatal intervention, these centers serve several important roles and as such contribute greatly to the care of newborns with congenital anomalies by providing (1) genetic and obstetrical counseling, (2) state-of-the-art imaging and interventional diagnostics available in one location, (3) a source of reliable information for pregnant women and their families when a congenital anomaly has been identified antenatally, (4) the opportunity to pursue in utero intervention when indicated, (5) the ability to make plans for appropriate medical and surgical therapeutics for when the baby is born, and (6) the option of actually delivering the child in a children's hospital where care can be delivered without the delay associated with transfer.

Several technical problems encountered early on have been resolved, including achieving hemostasis of the hysterotomy incision, maintaining uterine volume and temperature during the procedure, balancing the needs of the mother and the fetus related to anesthetic issues, and avoiding injury to the placenta, which occupies a large proportion of the internal surface area of the uterus. Postoperative preterm labor remains a common and frustrating occurrence after fetal intervention. Nevertheless, it is inevitable that someday soon fetal surgery will become more routine as the few remaining hurdles are removed.

Fetal operations, including procedures performed using the EXIT approach, involve a large team of dedicated specialists all working together to maintain the health and well-being of the fetus and, more importantly, the mother. The planning and coordination of the team are clearly important to achieving this goal. During a typical fetal operation or EXIT procedure, the operating theater is filled with personnel, more than for any typical operation, each contributing something specifically important to the task at hand: pediatric surgeons, obstetricians, anesthesiologists, neonatologists, and nurses representing each of the specialties involved. Two operating rooms are usually required, one for the mother and another for the infant. The result is a tense but well-orchestrated process and more often than not a successful outcome. Eventually, it is likely that nearly every congenital anomaly will be detectable antenatally, in which case newer and better treatments will become available because of the ground-breaking work of the dedicated few who are today's fetal surgeons.

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