61 Recent developments in fetal therapy

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The developments of ultrasound imaging prenatally as well as the implementation of ultrasound screening in pregnancy in most developed countries lead to an increasing number of fetal anomalies to be diagnosed before birth. The issue of fetal treatment is raised when the anomaly is diagnosed at an early stage and when its natural history suggests that the most likely outcome is either perinatal death or severe handicap irrespective of pediatric management. The management of fetal anomalies is ruled in each country by different laws regulating the indications for termination of pregnancy (TOP). Since many women wish to carry on with their pregnancy and TOP cannot be performed either at all or above a certain gestational age, fetal therapy has gradually developed since the early 1980s. Fetal therapy or surgery can be implemented with the aim to stabilize the effects of the anomaly on fetal development or to cure the disease itself (1). This might be either by anatomical correction of the malformation or by arresting the progression of the disease, delaying its definitive repair until after birth (2).

Only few examples fulfill these criteria (Table 1) (2,3). Since most attempts of fetal surgery concern treating rare and severe fetal conditions, they carry a large component of medical innovation, scientific research, as well as technical prowess, which unfortunately sometimes leads to procedure-related complications.

The first invasive fetal intervention began in 1963 with Liley (4). It was a blind intrauterine intraperitoneal blood transfusion. The evolution of fetal surgery has progressed since then with historical surgeries and a countless number of animal experiments. Fetal surgery is now a clinical reality (3) validated by randomized trials for a number of fetal pathologies but remains investigational for many others. The concept of fetal surgery is subjected to skepticism due to lack of clinical evidence, ethical issues, and public perception (5). Clinical trials are ethically challenging and difficult to organize and finance. This, however, should be no excuse to address all pertaining relevant issues appropriately (6).

MULTIPLE MONOCHORIONIC PREGNANCIES

Specific complications related to monochorionicity are based on hemodynamic imbalance between the twins, which are essentially normal as in twin-to-twin transfusion syndrome (TTTS) or in cases with a normal twin and its abnormal co-twin with the extreme form of the acardiac twin (7). When TTTS develops in the second trimester, the natural history leads to intra- or perinatal death in 90% of the cases, and up to 50% of the survivors show impaired neurologic development as a consequence of the death of their co-twin in utero or in the context of extreme prematurity. In all cases, intrauterine fetoscopic selective occlusion of the vascular anastomoses is attempted on the

chorionic plate (Fig. 1). In more severe forms where one twin is normal and the other shows severely impaired development, selective feticide using umbilical cord occlusion of the affected twin appears to be the safest method to protect the normal twin (8–10).

The technique of selective laser coagulation of placental vessels has paved the way for fetal surgery in a minimally invasive way for the pregnant woman. Initially performed using a 5-mm hysteroscope inserted through a purse-stringed hysterotomy after exposure of the uterus with a small laparotomy (11), the technique was greatly simplified by a minimally invasive percutaneous approach under ultrasound guidance and under local or epidural anesthesia that has transformed the prognosis of the disease (8,12–15). An endoscope of 1.3 to 2 mm in diameter is introduced in a 3-mm trocar. A Nd:YAG or diode laser fiber is passed through the operative channel of the endoscope. It allows coagulation of the anastomotic vessels joining the two fetoplacental circulations (Fig. 2). This technique has been developed over 15 years and has proven to be the best first-line treatment with the highest degree of evidence, leading to survival rates of around 75% with severe morbidity in less than 10% of the survivors (9). These results are stable through to long-term follow-up and up to the age of 6 years (16).

Several techniques for selective feticide of a monochorionic fetus have been described and used, including ultrasound-guided fetal cord ligation or compression (17), bipolar coagulation, laser coagulation, transection with harmonic ultrasound scalpel (18), thermocoagulation (19), and radio-frequency ablation (20). Bipolar coagulation technique remains a gold standard for cord coagulation (21) because of the short duration of the surgery, its relative technical simplicity, and availability (21).

Bipolar umbilical cord coagulation is performed using a bipolar forceps (2.5-mm diameter). The procedure aims at coagulating the cord at placental or abdominal insertions, depending on their accessibility. A longitudinal portion of the cord is exposed to the bipolar forceps with its jaws perpendicular to the cord. After grasping the cord, an initial coagulation is performed using 15 W for 15 to 60 seconds. The efficacy of the procedure is judged by the appearance of echogenic steam bubbles and increased echogenicity of the coagulated portion of the cord. In the absence of bubbles, the power is increased in 5-W increments up to a maximum of 50 W. When the appropriate power is obtained, the coagulation is continued for 1 or 2 minutes, without releasing the cord. A second segment of the cord is then systematically coagulated following the same procedure. The interruption of blood flow in the coagulated cord is checked by ultrasound during the procedure.

Table 1 Criteria for Fetal Surgery (2,3)	
1	Accurate diagnosis and staging possible, with exclusion of associated anomalies
2	Natural history of the disease is documented, and prognosis established
3	Currently no effective postnatal therapy is available
4	In utero surgery proven feasible in animal models, reversing deleterious effects of the condition
5	Interventions performed in specialized multidisciplinary fetal treatment centers within strict protocols and approval of the local ethics committee with informed consent of the mother or parents

CONGENITAL DIAPHRAGMATIC HERNIA

Thoracic anomalies are the most illustrative to view fetal surgery in both historical and technical perspectives. These anomalies have in common to interfere with lung development through the mass effect leading to pulmonary hypoplasia that is often lethal when compression develops during the second trimester of pregnancy (22). Ultrasound screening in the second trimester depicts the majority of these severe anomalies at an early stage that is potentially amenable to fetal surgery. Thus fetuses with the most severe forms of congenital diaphragmatic hernia (CDH) can also benefit from intrauterine fetal surgery (10).

Figure 1 Vascular anastomoses between the circulations of the two twins in a monochorionic diamniotic pregnancy complicated: (A) and (C) nonselective anastomoses passing under the amniotic membrane; (B) and (D) selective. Laser fiber can be visualized at 12 o'clock in (A) and (B).

Figure 2 Selective laser coagulation of placental vessels in a twin-to-twin transfusion syndrome. Donor stuck twin in anhydramnios (A, B, C). Vascular anastomoses (D, E, F) coagulated with a laser fiber seen at 12 o'clock (D, F).

Figure 3 “Plug the lung until it grows” strategy. Fetoscopic access to the fetal trachea (A, B) reaching the carina (C), and inflating a balloon, 1 cm above the carina (D, E, F).

CDH of intra-abdominal organs in the thorax, when it is not associated with other anomalies, allows survival between 0% and up to 85% of the cases depending upon the degree of lung development. Prenatal evaluation of the volume of the contralateral lung has been the subject of continuous research for the last 20 years. To date, the simplest evaluation of the relative size of the lung mass to the head circumference [lung-to-head ratio (LHR)] has the best prognostic value. When expressed as a proportion compared with what is expected in a normal fetus (observed/expected LHR), this prediction is independent of gestational age (23). The presence of the liver in the thorax is another independent factor of poor prognosis. Fetuses with CDH and $LHR < 1$ with liver up in the thorax are almost certainly destined to die in the perinatal period despite advanced neonatal care (24).

History of fetal CDH surgery begins with pediatric surgeons who operated newborns. The initial prenatal approach consisted of patch closure of the diaphragmatic defect (25,26). Fetal surgery followed the rules of neonatal surgery with the aim of curing the defect through very invasive modalities for the pregnant woman, including laparotomy, hysterotomy, and aggressive tocolysis. Delivery was then doomed also to be performed by cesarean section at any gestational age, owing to the recent uterine scar, whether the child was dead or alive (27). This approach was based on successful sheep experimental surgery for 10 years but failed 20 years later for the very reason that the human uterus is far more sensitive to preterm labor triggered by uterine surgery than sheep. The natural history of yet another congenital malformation, tracheal atresia, showed the rationale for palliative intrauterine surgery in CDH. This condition causes pulmonary hyperplasia by increasing bronchial pressure and the possibility of a temporary obstruction proved successful to stimulate the growth of hypoplastic lungs in a sheep model (28).

Tracheal occlusion was first clinically achieved by laparotomy, hysterotomy, neck dissection, and tracheal clipping (29) with impressive results on lung growth in a subset

of fetuses but with a low survival rate. The first *percutaneous* endoluminal occlusion was reported by Quintero et al. (30). Unfortunately, the device failed to occlude and the baby died in the postnatal period.

In Europe, a clinical technique via a 3.3-mm percutaneous access was developed with balloon removal initially at the time of an ex utero intrapartum treatment (EXIT) procedure (31,32). General anesthesia was used at first but was soon replaced by regional and local anesthesia with fetal sedation and immobilization. This approach is often referred to as the “plug the lung until it grows” strategy (33). This surgery consists of accessing the fetal trachea using a 1.2-mm endoscope as described in placental surgery (see above) and inflating a balloon in the fetal trachea, 1 cm above the carina (Fig. 3). This is usually performed at 26 to 34 weeks and the balloon is removed 8 weeks later. Removal can either be performed following the same procedure, be deflated by needle puncture under ultrasound guidance or following neonatal intubation immediately after birth. Preliminary results in over 200 human fetuses with a poor prognosis where the expected survival was around 10%, the observed survival was 55% (24). The results depend upon estimated fetal LHR to reach 78% for LHR between 0.8 and 1 (34). However, although uterine tolerance to endoscopic fetal surgery is good, the risk of preterm rupture of the membranes in up to 20% before 32 weeks remains a challenge to the development of this surgery, which has to address at least two other issues: (1) to establish itself through a randomized study against postnatal management only. (2) to evaluate later intervention in the forms with less severe prospect based on $LHR > 1$ in order to decrease prematurity-related risks. In the latter group, a previous randomized study with suboptimal design suggested that prenatal management was not beneficial, but the suboptimal design significantly biased the result of the trial (35).

Jani et al. (36) recently reported results of 210 severe CHD treated with fetal endoscopic tracheal occlusion. They concluded that their treatment is associated with a high

incidence of preterm premature rupture of fetal membranes (PPROM) (16.7% cases) and preterm delivery (30.9% of patients delivered before 34 weeks) but a substantial improvement in survival. Forty-eight percent of infants were discharged from the hospital alive. They therefore increased survival in severe cases with left-sided CDH from 24.1% to 49.1%, and in right-sided CDH from 0% to 35.3% ($p < 0.001$) (37). The strongest predictors of survival are observed/expected LHR *prior* to the procedure, the absence of PPRM, and gestational age at delivery.

Although many recent nonrandomized reports of success with balloon tracheal occlusion (and release) are promising, prenatal therapy should not be widely adopted until a well-designed prospective randomized trial demonstrating efficacy is performed (38).

This surgery has also demonstrated that the fetal airways were directly accessible to prenatal local administration of drugs opening new perspectives for gene therapy in congenital severe respiratory diseases such as cystic fibrosis.

FETAL LOWER URINARY TRACT OBSTRUCTION (39)

Lower urinary tract obstruction (LUTO) encompasses different malformations of the urethra including posterior urethral valves (PUV) (60%), urethral agenesis, and atresia (40%) and has a prevalence of around 2/10,000 births. The related mortality and morbidity are high and related both to progressive renal dysfunction and/or to dysplasia secondary to parenchymal compression and pulmonary hypoplasia related to oligoanhydramnios in cases with complete urethral obstruction.

Symptomatic fetal treatment should optimally rely on vesico-amniotic shunting, as it proved to work in animal models. The use of a double pigtail catheter placed into the fetal bladder as a temporary therapeutic intervention to allow obstructed urine to flow into the amniotic space has met with inconsistent success. Anhydramnios often found in LUTO presents a technical challenge when placing a vesico-amniotic shunt because the distal end of the shunt catheter needs to be placed into a pocket of amniotic fluid. Amnioinfusion allows to re-expand the amniotic cavity with fluid for successful shunt placement.

Technically, the placement of a vesico-amniotic shunt is done under local anesthesia and continuous ultrasound guidance. The two-pushrod shunt procedure, which we describe here, is the most used technique nowadays. The fetal bladder is accessed lateral to the midline below the abdominal cord insertion. Doppler is used to localize the umbilical arteries and confirm that the trocar will not injure them on passage through the abdominal and bladder walls.

First, the trocar is introduced into the amniotic space close to the lower fetal abdomen. An adequate pocket of amniotic fluid needs to be present in which to drop the distal end of the double pigtail catheter on exiting the fetal abdomen. As indicated above, an amnioinfusion is done in case of anhydramnios or insufficient fluid space. The trocar is then inserted into the bladder and positioned into a central location. The double pigtail catheter is then completely threaded into the trocar sheath. A short push rod is introduced and used to push the proximal pigtail of the catheter

into the bladder. The shorter push rod is then removed and a long push rod is gently introduced until it comes in contact with the distal tip of the shunt catheter within the trocar sheath. The push rod is then held in place while the shaft of the trocar sheath is slowly pulled back about 2 cm. At this point, the trocar sheath should lie just outside the fetal abdomen, with the straight segment of the shunt catheter traversing the region of abdomen between the bladder and amniotic space. The trocar sheath is then tilted to direct it away from the insertion site and the long push rod advanced to displace the distal pigtail of the catheter into the amniotic space (40).

Although the overall benefit of bladder shunting seems to translate into increased survival (OR 2.5; 95% CI, 1.0–5.9; $p < 0.03$) especially in the most severe cases (OR 8; 95% CI, 1.2–52.9; $p < 0.03$) (41), this hardly translates into improved renal function. Several potential explanations have recently been identified:

1. Shunting is performed under local anesthesia to the mother as well as fetal analgesia and curarization. Shunts most commonly used are 2.5 mm in diameter and placed through a 3.5 mm trocar introduced percutaneously into the uterus and into the fetal bladder. It is not an easy procedure to perform and one-fourth to one-third of shunts get displaced.
2. Shunting should optimally be performed when renal function is still normal. The best single parameter seems to be beta-2-microglobulin in fetal blood since fetal urine analysis and ultrasound assessment of the kidneys have a poor predictive value.
3. The diagnosis of PUV is the only one amenable to significant improvement in survival and renal function. However, the diagnosis is rightly made in only around 60% of the cases in experienced hands.
4. Overall, it is likely that shunting is too often being placed to late in the course of the natural history of the disease.

LUTO is yet another example of failed open surgery that has been abandoned in the late eighties. The encouraging results from meta-analysis on bladder shunting are calling for a randomized controlled trial that has been initiated as the PLUTO trial (percutaneous shunting in lower urinary tract obstruction: www.pluto.bham.ac.uk). Recruitment is slow and it is hoped that 200 cases could be included over a 5-year period to compare outcomes in fetuses with normal renal function and oligohydramnios at less than 26 weeks following either early bladder shunting or expectant management in utero.

A recent advance in this respect is in utero cystoscopy (42). Ruano et al. (43) recently reported a large series of PUV treated with fetal cystoscopy and laser fulguration. They proved it to be feasible and suggested that it might prevent renal function deterioration.

The same technique of shunt placement is also used for some compressive thoracic processes such as congenital hydrothorax or macrocystic congenital cystic adenomatoid malformation (CCAM) (40).

COMPRESSIVE FETAL PLEURAL EFFUSION AND OTHER COMPRESSIVE LUNG MALFORMATIONS

Fetal pleural effusions have a prevalence of 1/10,000 to 1/15,000 births. Irrespective of the underlying etiology, around one-fifth resolve spontaneously. However, compressive pleural effusion that is characterized by either mediastinal shift or compression in unilateral and bilateral effusions, respectively, is associated with a poor prognosis when it leads to polyhydramnios through esophageal compression and hydrops through impaired venous return and cardiac tamponade. Indeed, unilateral effusions, with spontaneous resolution and absence of hydrops, are associated with 100% survival but progressive hydropic cases are associated with less than 50% survival. Furthermore, other malformations can be found in 25% of the cases and prolonged compression during the canalicular phase can lead to pulmonary hypoplasia (44,45).

Although no randomized studies have been published, thoracentesis or thoracoamniotic shunting are likely to benefit hydropic cases by increasing survival in hydropic fetuses from roughly 40% to over 60% (46–48). This should apply at any gestation in order to facilitate neonatal resuscitation, even late in the third trimester. For non-hydropic fetuses, the benefit of shunting is less clear (49,50).

The technique is similar to that described for vesicoamniotic shunting in this chapter. Fetal anesthesia is mandatory and paralysis is optional. Ideally, the trocar should be inserted perpendicularly through the fetal chest wall into the effusion as close as possible to the mid-axillary line at the level of the base of the scapula. This should best prevent active removal of the catheter by the fetus. One half of the catheter is placed inside the effusion and the other half is left in the amniotic cavity.

In case of bilateral effusions, an attempt to rotate the fetus using the trocar loaded with a blunt stylet is made in order to avoid a second insertion in the maternal abdomen and uterus. The lower the gestational age, the easier this is (51).

Weekly ultrasound surveillance is recommended following shunt insertion. Technical failures are reported in 20% to 25% of the cases, including removal by the fetus within days after the procedure. Repeating the procedure may be justified in a large proportion of cases.

Macrocystic forms of congenital adenomatoid malformations of the lung when they are compressive are often associated with hydrops although does not usually develop when it is not present at the time of diagnosis. In these hydropic cases of CCAM, survival is around 25% if untreated, and nonrandomized studies suggest that cyst aspiration/shunting procedures could improve survival dramatically (52–54).

Although less frequent in cases of bronchopulmonary sequestration (BPS), shunting of the compressive associated pleural effusion also seems beneficial (55). In addition, two hydropic fetuses with large BPSs have been treated by ultrasound-guided Nd:YAG laser ablation of the feeding vessels with subsequent resolution of hydrops and delivery of healthy infants at term (56).

MYELOMENINGOCELE

Intrauterine surgery requesting maternal open surgery has not taken off anywhere in the world outside the United States not only in view of the poor results of CDH programs but also due

to the obvious conflict of interest between the pregnant woman and her fetus. This conflict relies largely on the risk of severe maternal morbidity in balance with mainly poor perinatal outcomes. It is also related to the laws regulating TOP for fetal indications in most countries. It is not surprising that this technique remains in a country where all forms of TOPs cannot be performed after 24 weeks, especially when fetal therapy has been initiated. Enrollment of women in these fetal surgery programs could be motivated by the potential fetal benefit, but the contradictory hope for the loss of a severely affected fetus cannot be entirely ruled out.

This apparent ambiguity is particularly questionable in a nonlethal condition such as spina bifida with an often-dismal neurologic motor development (57) and little prospect of improvements in postnatal management.

The rationale for in utero intervention is based on the “two-hit hypothesis” (58,59) that states that primary congenital abnormalities in anatomic development allow a relatively normal spinal cord to become secondarily damaged by amniotic fluid exposure, direct trauma, hydrodynamic pressure, or a combination of these factors. It is this secondary damage that may be ameliorated by early fetal surgical repair (60).

The National Institute of Child Health and Human Development decided to sponsor the Management Of Myelomeningocele Study (MOMS) trial, which involves three clinical centers: the Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania; the University of California at San Francisco, San Francisco, California; and Vanderbilt University Medical Center, Nashville, Tennessee (61). The future of open fetal surgery is therefore largely dependent upon the results of this unblinded randomized controlled trial (www.spinabifidamoms.com). This is evaluating the benefits of palliative intrauterine surgery covering the neural tube defect in order to protect the nerves from amniotic fluid detrimental effects (62).

Preliminary studies suggested that fetal surgery results in reversal of hindbrain herniation (the Arnold–Chiari malformation), a decrease in shunt-dependent hydrocephalus, and possibly improvement in leg function, but these findings might be explained by selection bias and changing management indications. The current study is experiencing difficulties to recruit patients due to the alternative of TOP but suggests that maternal morbidity can be safely handled. However, this study is somehow challenging several ethical principles including the confusion between evaluation and direct benefit when advertising for the study and therefore influencing the emotional component of the women’s decision to participate (63). If the “MOMS” trial demonstrates a decreased morbidity in survivors, open fetal surgery will inevitably be put back on the European agenda.

In brief, this fetal surgery is performed between 19 and 25 weeks of gestation. In the operating room, after laparotomy and hysterotomy, the fetus is positioned with the myelomeningocele (MMC) lesion visible through the uterine incision. The cystic membrane of the MMC is carefully excised and the attachments of the meninges to the skin and soft tissues are detached. If possible, native dura alone is closed over the spinal cord as a first layer, followed by closure of paraspinous myofascial flaps, and then the skin surrounding the lesion is

carefully mobilized and closed over to complete the repair. When the skin cannot be closed primarily, acellular human dermis graft can be used to complete the closure (60).

As an unanticipated side effect, the MOMS trial apparently slowed down the clinical development of minimally invasive techniques to perform this operation in the United States (3). Nevertheless, endoscopic coverage of the defect is currently explored by several teams, experimentally and also clinically (64,65).

CRITICAL AORTIC AND PULMONARY STENOSIS

Severe and complex cardiac malformations are among the most difficult situations to handle antenatally in making the diagnosis, in assessing the prognosis, and in the perspective of continuing the pregnancy with the prospect of difficult and often multiple surgical interventions that often lead to palliative care.

Left or right heart hypoplasias are currently associated with a 60% survival rate at 5 years with mostly univentricular cardiac function. A well-recognized common pathway leading to these conditions is the critical stenosis of the aorta or the pulmonary artery respectively. Although postnatal dilatation of the stenotic vessel improves the prognosis, the hypoplastic ventricle remains nonfunctional and a univentricular cardiac function is the rule. The hypoplasia-related hypertrophy of the affected ventricle alters the coronary circulation and pulmonary venous return, weighing heavily on the overall prognosis. The first attempt to catheterize a fetal critical aortic stenosis dates back to 1991. Since then, around 30 cases have been reported with much heterogeneity in the case-selection process as well as in their management and success rates (66,67). All procedures were performed no sooner than early third trimester, which is probably too late in the natural history of most cases but is the result of a technical compromise that is required to access the affected vessel and to keep procedure-related mortality and morbidity to an acceptable level (68).

Pulmonary or aortic valve perforation or dilation can be performed under local or general maternal anesthesia. The latter performed with inhalational agents promotes uterine relaxation and facilitates fetal manipulation for positioning. The fetus is premedicated with intramuscularly administered analgesics and curarization. Under continuous ultrasound guidance, manual version is performed to optimize the fetal position. If the optimal position is not achieved or imaging is inadequate, some authors perform a limited maternal laparotomy without uterine exteriorization or incision (69). The right ventricle (RV) or left ventricle (LV) outflow tract is accessed through direct puncture, by using a 19-gauge ultrathin-walled cannula. With the cannula tip in the RV or LV outflow tract, the atretic valve is perforated with the stylet of a 19-gauge cannula. A 0.014-inch floppy-tipped guidewire is then positioned, and a coronary angioplasty balloon is inflated across the valve. After the final balloon deflation, the wire, balloon, and cannula are removed. Color Doppler ultrasound flow imaging demonstrates the success of the valvuloplasty with an antegrade jet of flow across the patent valve.

This form of minimally invasive surgery is however questioning the issue of the learning process inasmuch as that of defining clear and indisputable indications (69). Answers

should ideally be reached through an exemplary collaboration between fetal medicine specialists and interventional pediatric cardiologists. This would ensure appropriate fetal access as well as adapted pediatric follow-up within an optimally run specialized perinatal network. Rather than await a proliferation of such procedures at centers that are unlikely to amass a critical volume of experience to ensure clinical competence, a prospective multicenter trial should be considered to address the nuances of technical performance of the procedure, to evaluate the short- and midterm results, and to compare these results with those of children undergoing various forms of palliation for hypoplastic left heart syndrome (70). Moreover, the perceived benefits of prenatal treatment have to be weighed against steadily improving postnatal surgical and hybrid procedures, which have been shown to reduce morbidity and mortality for these complex heart defects (71).

Furthermore, criteria to define a successful intrauterine procedure are still unclear: permeability demonstrated by Doppler flow through the valve is an immediate but incomplete one that hides somehow the significant perioperative short- and mid-term mortality and morbidity. Less than 30% of the cases reported to date following critical aortic stenosis dilatation in utero have a biventricular cardiac function. However, owing to the high incidence of TOP following prenatal diagnosis of these conditions, comparative studies are going to be difficult to set.

EXIT PROCEDURES

The EXIT procedure can somehow be considered as a fetal surgery. It is a procedure performed while the baby is still on placental support. Initially described in 1997 for the reversal of tracheal occlusion at the time of delivery in fetuses that had undergone in utero tracheal occlusion for severe CDH (72,73), its use has expanded to convert an emergent crisis (airway obstruction mainly) into a controlled situation (74). Its indications include now not only fetal neck masses, congenital high airway obstruction but also large thoracic lesions, CDH, conjoined twins, unilateral pulmonary agenesis, and cardiac lesions where neonatal resuscitation may be compromised (75–78).

In brief, a multidisciplinary team is implicated in an EXIT procedure (pediatric surgeons, obstetrician, neonatologist, anesthesiologist, and nurses).

In the EXIT procedure (74), high concentrations of inhalational anesthetics and additional tocolytics, if necessary, are used to provide uterine relaxation and preserve placental perfusion. The time between induction of anesthesia and cord clamping is kept as long as it is clinically required. A low transverse maternal laparotomy incision is performed allowing a quick assessment of placental position with a sterile intraoperative ultrasound. While one assistant stabilizes fetal position, hysterotomy is performed. Only the fetal head and upper torso are delivered through the hysterotomy in order to maintain uterine volume. Amniotic fluid volume is maintained with the infusion of warm Ringer's lactate. Fetal well-being is continuously monitored by a pulse oximeter and by continuous echocardiography. Fetal venous access can be obtained with a peripheral intravenous line for fetal volume loading or drug administration. The procedures that can be performed on the fetus during EXIT range from direct

laryngoscopy, rigid bronchoscopy, tracheostomy to secure the fetal airway, to resections of neck masses and thoracic masses, to the placement of extracorporeal membrane circulation cannulas. Prior to clamping of the umbilical cord and delivery of the baby, communication between the surgical and anesthesia teams is essential to prevent uterine atony and excessive maternal hemorrhage. The inhalational agent is decreased and oxytocic bolus followed by a continuous infusion is administered and titrated to uterine tone, and the umbilical cord is then clamped and divided and the newborn taken to a separate operating room for further management.

OPEN FETAL SURGERY

CCAM, bronchopulmonary sequestration (BPS), and sacroccoccygeal teratoma (SCT) are most frequently benign lesions managed expectantly during the prenatal follow-up. At present, the development of early fetal hydrops is considered by some authors to be the only criterion for fetal open surgery, because it is a predictor of extremely poor prognosis (55). For the fetus with a life-threatening malformation, the risk of the procedure is small when compared with the potential benefit of salvage. The risks and benefits for the mother are more difficult to assess. We provide in the following a general description of open fetal surgery as described by Adzick (79).

Patients are admitted immediately prior to the operation for obstetric monitoring and initiation of tocolysis. Indomethacin and antibiotics are given preoperatively. Maternal general and epidural anesthesia provides anesthesia for the mother and the fetus and ensures good uterine relaxation. The uterus is exposed through a low transverse abdominal incision. Sterile intraoperative ultrasound is used to delineate the fetal position and placental location. The position and orientation of the hysterotomy is planned to stay parallel to, and at least 6cm from, the placental edge and still allow exposure of the appropriate part of the fetus. For the fetal portion of the procedure, the fetus is positioned with the appropriate fetal anatomy visible through the uterine incision. Intraoperative fetal monitoring is provided by a miniaturized pulse oximeter and continuous intraoperative fetal echocardiography. The fetus is kept warm in the uterus by the continuous administration of 38–40°C Ringer's lactate solution. A fetal intravenous line is placed for infusion of fluid, blood, and/or medications. After the fetal procedure, a watertight two-layer uterine closure is performed with double-armed full-thickness 0 PDS interrupted stay sutures followed by a running 2-0 PDS suture. Approximately 400mL of warmed Ringer's lactate containing 500mg of oxacillin is instilled into the amniotic cavity just prior to completing the running layer and is continued until sonography shows an adequate amniotic fluid volume (79).

In SCTs, open fetal resection of predominantly extra-pelvic tumors has been reported in five cases (80). Mean age at birth was 30 weeks and four survived long term. There is also anecdotal experience of less invasive techniques, arresting flow in feeding vessels either by fetoscopic laser (81), interstitial thermocoagulation (82), or radiofrequency ablation (83). Needle-guided intravascular embolization with alcohol or histoacryl or coils has been reported, but without measurable success (84).

FETAL ANALGESIA

The issue of fetal analgesia touches on the surgical approach itself as much as the "primum non nocere" principle (85). It is well established that very preterm neonates experience pain, and related autonomous neural connections are operating from around 22 weeks of gestation. It is therefore important and beneficial that any directly invasive fetal procedure be preceded by appropriate fetal analgesia (86). Sufentanyl is the drug of choice and can be administered under ultrasound guidance either intravascular in the umbilical cord or intramuscular. Dose regimens are established in relation to fetal estimated weight. This should be considered independently of curarization that can be requested for technical considerations but is totally ineffective in relieving fetal pain or awareness in these situations (87).

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