

Recommendation and Guidelines for Perinatal Practice

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Is intrauterine surgery justified? Report from the working group on *ultrasound in obstetrics* of the World Association of Perinatal Medicine (WAPM)

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Abstract: Fetal surgery involves a large number of heterogeneous interventions that vary from simple and settled procedures to very sophisticated or still-in-development

approaches. The overarching goal of fetal interventions is clear: to improve the health of children by intervening before birth to correct or treat prenatally diagnosed abnormalities. This article provides an overview of fetal interventions, ethical approaches in fetal surgery, and benefits obtained from antenatal surgeries.

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Introduction

Fetal surgery involves a large number of heterogeneous interventions that vary from simple and settled procedures, such as as intrauterine transfusion for treatment of hydrops fetalis, to very sophisticated or still-in-development approaches, such as minimally invasive surgeries for treatment of congenital diaphragmatic hernia (CDH), open surgery for spina bifida correction and *ex-utero* intrapartum therapy procedure (EXIT). The single convergence point among all these fetal surgeries is that everything is done during the prenatal care, or at least, before the delivery itself.

Of course, the development of fetal surgery should not be disconnected from the general development of perinatal medicine. Considering this context, the tripod of i) glucocorticosteroid for fetal lung maturation, ii) the improvement of ultrasound equipment, and iii) the upgrade of neonatal intensive care unit (NICU) results deserves special reference. In 1972, Liggins first described the use of maternal glucocorticosteroids therapy in the prevention of respiratory distress of prematurity [1]. Ultimately, maternal use of glucocorticosteroids promotes fetal lung maturation, which is extremely desired in case of preterm labor and delivery, although there may

be possible complications after fetal surgery. The incorporation of routine ultrasound used in obstetric practice permits a safe, non-invasive approach both in the identification of fetal abnormalities potentially treated *in utero*, and can directly help fetal surgeons during the surgical act itself, which should be done under fulltime sonographic guidance. The development of a new standard of care in NICU, also greatly contributed to the changes in the limits of fetal viability. Viability itself is not an intrinsic characteristic of the fetus but a function of biology and technology, which may vary remarkably among regions, and can reach around 24 weeks of gestation in some developed countries. It promotes the fetus to a moral status of a “baby” or, in other words, a person [2].

Ethical and historical aspects

The ethical approach in fetal surgery is based on, a greater and central concept of obstetric ethics: the concept of the fetus as a patient [3]. In essence, this perception is not only therapeutic-health based but is also constructed socially. The idea of promoting an *in utero* intervention to potentially benefit the fetus, sometimes even increasing maternal risk, involves a pool of cultural, religious, legal, and technological factors.

The overarching goal of fetal interventions is clear: to improve the health of children by intervening before birth to correct or treat prenatally diagnosed abnormalities. Although, in the past, new interventions have been motivated by a special desire to help particular group of fetuses, good practice recommends that once feasibility and potential benefit have been identified, innovations should be subjected to systematic formal research. This permits the best evaluation of new procedures with introduction of “innovative therapy” as part of careful care and research [4]. Pregnant women and their fetuses that undergo these interventions must have at least the same protection afforded to other research participants, and studies should be designed to assess the full impacts of the risks and benefits of these interventions on both the woman and the fetus, for both short- and long-term outcomes. Any fetal intervention, however, has implications for the pregnant woman’s health and, necessarily, her bodily integrity; therefore, it cannot be performed without her explicit informed consent [4].

An important ethical landmark of fetal surgery was the first symposium congregating fetal experts in the world, carried out in Santa Ynez, California, in which the five main rules that guide the fetal surgical interventions until

Table 1: Criteria for fetal surgery [6].

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1. Accurate diagnosis and staging is possible, with exclusion of associated anomalies.
 2. Natural history of the disease is documented, and prognosis is established.
 3. Currently, there is no effective postnatal therapy reported.
 4. *In utero* surgery is proven feasible in animal models, reversing deleterious effects of the condition.
 5. There have been 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.
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the present days were introduced [5] (Table 1) [6]. Moreover, in the 1980s, a pioneer team led by Prof. Michael Harrison of the University of California at San Francisco (UCSF) proposed the use of the animal model (sheep) in experimental fetal surgeries and also established the basis for fetal surgery in humans. In 1981, the first surgical management in a human being, the placement of a double pigtail shunt in a case of urinary tract obstruction, inaugurated the use of a minimally invasive surgical approach in fetuses [7]. Fortunately, this patient and his parents continue to communicate with USCF center over 25 years after his birth [8]. The so-called “open surgery”, which required the performance of a large hysterotomy, was also first applied by the same center for the treatment of another patient with urinary tract malformation [5].

The growing popularity of videoendoscopic surgery in the 1990s, combined with earlier fetoscopic experience, paved the way for the concept of endoscopic fetal surgery, which is the most frequent fetal surgery performed in the world. The rationale was that a small puncture of the amniotic cavity would overcome the following limiting factors of fetal surgery: (1) preterm labor, which was believed to be activated more frequently by the large hysterotomy performed during an open fetal surgery; and (2) significant maternal morbidity associated with a large laparotomy.

Gaining a better understanding of the pathophysiologic mechanisms of some fetal diseases also contributed enormously to changing the prior aggressive, anatomical, and direct surgical approach of determining underlying defects into less invasive and safer procedures for both the mother and fetus. This paradigm transformation of fetal treatment may be clearly observed in the CDH approach. The initial primary open surgical repair of fetal diaphragm was abandoned in favor of fetal endoscopic tracheal occlusion (FETO), which gave importance to the physiologic changes of CDH [9]. The evolution of the laser coagulation of placental vessels in the treatment of

twin-twin transfusion syndrome (TTTS) for over a decade, which is based on a better understanding of pathophysiologic changes in the underlying disease, is another good example of real improvements in endoscopic techniques.

Another important step in ushering safer fetal surgery procedure in consonance with most modern practices is the publication in 2004 of the first randomized clinical trial (RCT) in this field by Senat et al. [10]. This RCT compared the use of laser coagulation of placental vessels vs. amnioreduction in TTTS treatment. However, even before this emblematic publication, isolated case reports and small series of cases reports have been reported in specialized maternal-fetal journals for more elaborated prospective cohort studies and other RCTs. Following the same trend, studies focusing on long-term outcomes are currently being privileged to be published in detriment of short-term results for mothers and fetuses.

Fetal surgery interventions

Currently, fetal surgery can be divided into three broader areas: i) open fetal surgery, ii) minimally invasive fetal surgery, and iii) EXIT procedures. Each procedure is subdivided into several others in an attempt to treat a wide number of severe pathologies that would compromise the fetus and newborn. However, not all of these attempts have succeeded. The sub-section below provides an overview of these state of the art fetal interventions.

Open fetal surgery

At present, it is mandatory to discuss with the parents the risks to the mother, the fetus and the pregnancy of open fetal surgery intervention whenever this is offered as an option. The risks to the mother are similar to any major abdominal surgery, although in this case, there is no direct physical benefit to her. In addition, there are risks associated with aggressive tocolytic therapy and bed rest in a hypercoagulable state. Postoperatively, the mother is usually given a 24-h course of tocolysis. Prophylactic antibiotics are continued for 24 h. The patient also undergoes daily ultrasound by which fetal well-being and fluid volume are assessed. Most patients recover in the hospital for 4–5 days after surgery. The patient is then seen on a weekly basis with ultrasound evaluation. Compared with early experiences with hysterotomy, some of the associated morbidities have now decreased. Significant pulmonary edema or blood loss is now relatively rare [11].

The risks to the fetus are primarily vascular instability and hypoperfusion, intraoperatively leading to organ injury or death, as well as prematurity due to postoperative complications. The risks to the pregnancy are primarily preterm labor and preterm premature rupture of the membranes (PPROM) and preterm delivery. Infectious complications are rare, except when premature rupture leads to prolonged latency. An important additional discussion point is that the real long-term impact of a fetal open surgery on fertility and the obstetrical future of this woman still cannot be asserted, but caesarian section will be the unique option in the index and upcoming pregnancies [12, 13]. Experience from the Children's Hospital of Pennsylvania (CHOP) suggests a concerning risk for uterine rupture/dehiscence in subsequent pregnancies, which may be as high as 6%–12% [14]; this is considerably higher than the risk after previous low transverse cesarean section (1% or less) [15]. Another potential risk in subsequent pregnancies is placenta accrete, which is due to the fact that the site of a hysterotomy performed in the second trimester is never in the same area of a term cesarean section.

In 2011, with the Management of Myelomeningocele Study (MOMS) publication, a high-quality RCT sponsored by the National Institute of Health (NIH) was conducted with the aim of observing the emergence of a new paradigm for spina bifida treatment, together with the rebirth of open fetal surgery. Since then, open fetal surgery has become a new standard of care for perinatal treatment of MMC for those mothers and fetuses that reach its specific criteria. The basic purpose of this trial was to compare the safety and efficacy of prenatal repair of MMC with the standard postnatal repair [16].

That study reported the decreased need for postnatal VP shunting as well as the reduction of the number of infants who had no evidence of hindbrain herniation and the proportion of infants who had moderate or severe hindbrain herniation. Other benefits were also obtained in this first analysis. Neurological mental and motor functions at 30 months were also significantly improved in the prenatal surgery group. The percentage of patients able to independently ambulate at 30 months increased from 21% to 42% after prenatal repair compared with postnatal surgery. However, the MOMS maternal results can be considered suboptimal. Although there was no maternal death reported, there was an increased risk of complications to the mother, such as spontaneous labor and rupture of membranes, pulmonary edema, blood transfusion, and dehiscence of hysterotomy.

Although other types of open fetal surgery have been historically well documented in medical literature, there is no recent publication involving other open surgeries apart from myelomeningocele correction (Table 2).

Table 2: Open fetal surgeries.

Type of surgery	Primary objective of surgery
Myelomeningocele ^a	Covering of exposed spinal cord Avoidance of “second hit” (additional neurological damage)
Sacrococcygeal teratoma ^b	Tumor resection
Congenital cystic adenomatoid malformation of the lung ^b	Tumor resection/lobectomy

^aClinical practice supported by randomized clinical trials.

^bClinical practice supported by low quality scientific studies.

Minimally invasive maternal-fetal surgery

Fetoscopy

Endoscopic fetal surgery developed as a result of the advancements in videoendoscopic surgery and experience with fetoscopy. Access to the fetus is achieved with a tiny puncture of the amniotic cavity. The idea is that with this less-invasive approach, some of the major limiting steps in fetal surgery can be overcome, including (1) preterm labor, which was believed to be triggered by the large uterine incision of open fetal surgery, and (2) significant maternal morbidity associated with a large laparotomy [11].

Although there are many differences among reference centers, generally, patients submitted for a fetoscopic procedure are often premedicated with a tocolytic agent. The surgeries are performed under local or regional anesthesia. Depending on the gestational age and the tradition of the center, the surgery may be performed in the surgical operating rooms, labor and delivery unit, or in an ultrasound suite. Cannulas, instruments, and particularly, endoscopes have undergone a tremendous evolution, based on prototypes developed in animal models. Purpose-designed embryoscopes or fetoscopes typically have remote eyepieces to reduce weight and facilitate precise movements. Bendable fiber-endoscopes rather than conventional rod lens scopes are being used, and as the number of pixels has increased over time, image quality has also improved. Typical diameters are between 1.0 and 2.0 mm. Sharp trocars have been developed to accommodate the wide range of diameters used for different operations. Meanwhile, the risks of fetoscopy are clearly associated with the uterine puncture and underlying pathology that is being treated.

Operative fetoscopy is a sonoendoscopic enterprise that has evolved so that the surgical team can see the

ultrasound and fetoscopic images simultaneously. Basically, the ultrasound is used to identify an appropriate entry point, which is then used to direct the trocar into the amniotic cavity, avoiding the placenta and the fetus as well as maternal organs, such as the bowel and bladder. One group has documented the safety, in their hands, of a transplacental approach [17]. Despite this experience, most operators still attempt to avoid the placenta. The trochar has thus been replaced by the fetoscope.

For cases of TTTS, the endoscope is in the sac of the recipient twin, the one with the polyhydramnios. The entry point is determined by the factors noted earlier; this process also allows for good visualization of the vascular equator of the twins. The whole equator is then explored, and any unpaired vessels consistent with abnormal communications are ablated using the laser fiber, which is advanced through the operating channel of the endoscope sleeve. After successful ablation, the endoscope is withdrawn, and the polyhydramnios drained through the cannula under ultrasound guidance. The cannula is removed once the fluid has reached a normal level (deepest vertical pocket of around 5–6 cm). This amnioreduction reduces the risk of port-site leaking and amniotic fluid irritation of the peritoneal cavity, which may be painful. It may also improve placental perfusion, thus making the patient more comfortable. In many cases, little or no tocolytic medication is needed, and patients are generally discharged within 24 h or less after the procedure is performed.

Shunts

Shunts are used for chronic drainage of fluid-filled fetal cavities, organs, and cysts. This is basically a double pigtail shunt that is introduced through a 14-gauge introducer (Cook Medical, Bloomington, IN, USA) [18]. The Rodeck shunt (Rocket Medical, Hingham, MA, USA) was developed during a similar time period in the UK. It is also a double pigtail shunt but is longer and has a greater diameter (Rocket Medical, UK). Obviously it uses a larger diameter introducer [19]. These catheters are used for draining obstructed bladders, pleural effusions, and large macrocystic lesions in the lung.

Radiofrequency ablation (RFA)

RFA is most commonly used for the destruction of tumor tissue in solid organs, such as the liver, of a nonobstetric patient. Initially, this was used in fetal surgery for ablating the feeding vessels to the anomalous fetus in twin-reversed

arterial perfusion (TRAP) [20]. Since then, the use of RFA has been expanded, especially for the selective reduction of one twin in cases of discordant severe anomalies or severe selective intrauterine growth restriction (SIUGR). RFA has also been used in procedures related to some fetal tumors.

Bipolar coagulation

In monochorionic twins, fetal death puts the healthy one at risk, due to the feto-fetal hemorrhage that may occur over the anastomoses. Patients may prefer selective feticide in such cases. In those cases, controlled feticide can be done with ultrasound-guided bipolar cord coagulation.

Another condition is TRAP. The normal “pump” twin perfuses the anomalous parasitic mass, leading to congestive heart failure and hydrops in >50%. Ultrasound-guided bipolar cord coagulation has a 78%–84% survival rate. When low flow conditions are present, interstitial coagulation may be done by alternative energy sources, such as laser, monopolar or radio-frequency energy used through 14–18 G needles. However a potential advantage of electrocautery usage is to section the umbilical cord in all cases of MC/MA pregnancies, to avoid the entrapment of the pump umbilical cord. Table 3 provides a general

overview of minimally invasive fetal surgery, considering the types and the primary objectives of the procedures.

Ex-utero intrapartum therapy procedure (EXIT)

EXIT was first employed in early 1990s to permit the reversal of tracheal occlusion performed *in utero* for the treatment of severe CDH [21]. The basic idea of EXIT is to maintain the uteroplacental blood flow for the fetus during a long period of time, allowing the execution of a surgical procedure or a lifesaving intervention on the fetus. Nowadays, EXIT is used to permit bronchoscopy, laryngoscopy, tracheostomy, cannulation for extracorporeal membrane oxygenation (ECMO), and even resection of lung masses/lobectomy [22]. As a treatment option, EXIT has been used in many different pathologies including CCAM, congenital high airway obstruction syndrome (CHAOS), ECMO for CDH, and in airway obstructing giant neck mass such as teratomas, lymphangiomas and goiter [22]. In case of CCAM pulmonary resection, the average time on EXIT has been described to be so long as 65 min [23] (Table 4).

In summary, EXIT technique is a complex approach with many different issues. Once the uterus is exposed, intraoperative ultrasound guidance is required to observe the placental and fetal positions. The hysterotomy should

Table 3: Overview of minimally invasive fetal surgeries.

Surgery intervention	Primary objective of the surgery
Complications of monochorionic pregnancy	
– Twin-twin transfusion syndrome (TTTS) ^a	Coagulation of anastomoses responsible for TTTS, preventing both fetal demise
– Selective intrauterine growth restriction ^b	Coagulation of anastomoses if TTTS is present, protection of the healthy twin
– Twin reverse arterial perfusion (TRAP) ^b	Protection of the healthy twin
– Twin anemia-polycythemia sequence (TAPS) ^c	Prevention of some cases of cardiac failure TAPS perinatal injuries
– Discordant anomalous twins ^b	Protection of the healthy twin
Congenital diaphragmatic hernia ^b	Reversal of pulmonary hypoplasia
	Avoidance of pulmonary hypertension
Lower urinary tract obstruction ^b	Prevention of renal failure and pulmonary hypoplasia
Pleural effusions ^b	Prevention of cardiac failure or pulmonary hypoplasia
Amniotic band syndrome ^c	Prevention of anatomic and functional damage
Cardiac abnormalities of the fetus ^c	Prevention of hypoplasia or other irreversible damage
Myelomeningocele ^c	Covering of exposed spinal cord, avoidance of “second hit” (additional neurological damage)
Sacroccygeal teratoma ^c	Prevention/reversal of cardiac failure, termination of the blood flow shunting to the tumor
Congenital cystic adenomatoid malformation of the lung ^b	Prevention of cardiac failure or pulmonary hypoplasia
Bronchopulmonary sequestration ^b	Prevention of cardiac failure or pulmonary hypoplasia
Chorioangioma ^c	Prevention/reversal of cardiac failure and hydrops fetoplacentalis

^aClinical practice supported by randomized clinical trials.

^bClinical practice supported by cohort studies or large series of cases.

^cClinical practice supported by low quality scientific studies.

Table 4: Overview of maternal-fetal surgeries.

Intervention	Primary objective of the surgery
EXIT Bronchoscopy, laryngoscopy, tracheostomy ^a Cannulation for (ECMO) ^b Resection of lung masses/ lobectomy ^b	Maintenance of the fetal-placental circulation during the delivery for different purposes

^aClinical practice supported by cohort studies or large series of cases.

^bClinical practice supported by low quality scientific studies. ECMO-extracorporeal membrane oxygenation.

be done while avoiding the placenta margins and preferentially on the lower segment. In order to prevent maternal bleeding, a uterine special stapling is fundamental in ensuring a bloodless hysterotomy. The maintenance of uterus size is achieved by the lower part of fetus body and by the introduction of a continuous amnioinfusion catheter inside the uterus. The fetal procedure itself is initiated only after obtaining a fetal peripheral intravenous access and with continuous monitoring through a pulse oximeter and echocardiography. Halothane, or the anesthetics derived from it, is used to achieve better uterine relaxation. Intramuscular vecuronium, fentanyl, and atropine are given to the fetus for adequate anesthesia [23–26].

The EXIT procedure must not be considered a simple variation of a cesarean delivery and should only be carried out in reference centers. The presence of a complete multidisciplinary team is required to perform a correct preoperative evaluation, including the diagnosis, counseling, and planning for the EXIT procedure. The intraoperative team includes a maternal and fetal anesthesiologist, an airway cart nurse, a maternal-fetal medicine specialist, a fetal cardiologist, pediatric surgeons, and an obstetrician, among others. Neonatologists and a second complete operative team should be prepared to receive the newborn and to act in case of potential complications, such as fetal distress as well as anesthetic complications on the mother, including placental abruption and hemorrhage [22].

Final considerations

Despite the heterogeneity of interventions and the difficulty of selecting the specific group of fetuses to obtain real benefits from antenatal surgeries, the significant changes in prognostic factors of some diseases after fetal

surgery highlight the relevance of antenatal intervention. A multidisciplinary approach is often fundamental in constructing an authentic empowered option, and the final decision of the parents must be based on adequate technical, emotional and social support. To protect the interests of the pregnant woman, these teams should include a specialist in maternal-fetal medicine [4], who are best suited to direct the care of pregnant women and to perform surgery on the fetus.

The maternal-fetal medicine team has an intrinsic responsibility to benefit the small patient, but not forgetting other values that involve mother autonomy and non-maleficence of mother and fetus [27]. To properly take advantage of these principles, parents should be given detailed information about the pathophysiology of fetal disease as well as perinatal treatments and prognosis factors. (Ville [28])

Many fetal and placental procedures can now be performed using micro-endoscopes. Hysterotomies are reserved only for a few rare indications. The wider use of minimally invasive approaches has improved the rate and severity of maternal complications. Nevertheless, these procedures are not completely risk-free and there have been intraoperative maternal deaths reported. Maternal complications from fetal surgery must, therefore, be discussed with a patient and her family to balance the risks and benefits of a prospective intervention [11].

To conclude, cooperation between the fetal care specialties and centers should be encouraged and strengthened to establish collaborative research networks and support studies that, in turn, can accumulate better data on long-term maternal and fetal outcomes in all categories of fetal intervention.

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