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Intrauterine fetal surgery

**Aleksandra Barbachowska¹, Mikołaj Baliś², Klaudia Krzanik³,
Mateusz Zamłyński, Piotr Bodzek, Anita Olejek**

Department of Gynecology, Obstetrics and Gynecologic Oncology in Bytom,
Medical University of Silesia, Bytom, Poland

¹⁻³E-mail addresses: aleksandrabarchowska@gmail.com , balismikolaj@gmail.com ,
klaudia.krzanik@onet.pl

ABSTRACT

The progress made in the past few years in prenatal medicine has led to the development of new diagnostic and surgical techniques that are used to treat congenital disorders during pregnancy. This stride also raises ethical questions, including the borderline between innovative treatment and experimental surgery. Surgical interventions on the fetus may be performed by amniotic shunting, open fetal surgery or fetoscopy. The choice of the method depends on the type of malformation. Intrauterine surgery is possible in selected cases e.g. congenital cystic adenomatoid malformation, diaphragmatic hernia, hydrocephalus, myelomeningocele, feto-fetal transfusion syndrome and others. The indications for fetal intervention are: the risk of fetal death, significant developmental disorders or the chance for reducing the disability. Both, amniotic shunting and fetoscopy, are performed by gynecologists, whereas open fetal surgeries require cooperation between gynecologists, pediatric surgeons and other medical specialists. Parents are informed about congenital defects, prognosis and treatment possibilities. Afterwards they discuss the treatment plan with doctors. Prenatal procedures are still relatively rare and require long-term observation, refinement in surgical techniques and guidelines for postoperative care. Current research focuses on gene therapy and use of stem cells in developmental defects treatment.

Keywords: perinatology, prenatal diagnosis, congenital disorders, fetoscopy

1. INTRODUCTION

Human fetuses have become patients, who can be operated while still in the uterus. Due to development of high resolution USG, congenital malformations can be easily detected in early gestation. That allows to make the best therapeutic decisions in early stage of pregnancy and choose the right way of treating the fetus.

There are a few fetal defects that can be treated surgically. There are also two major ways of approaching the fetus in the uterus: open fetal surgery and fetoscopy. Open fetal surgery is basically a laparotomy followed by hysterotomy, which allow to gain access to the uterus, amniotic sac and the fetus. Fetoscopy, however, uses laparoscopic-like equipment and gives the possibility to access the fetus under video supervision [1,2]. A special type of fetoscopy is amniotic shunting [3]. Some of possible defects that can be treated with intrauterine fetal procedures: myelomeningocele, diaphragmatic hernia, feto-fetal transfusion syndrome, congenital cystic adenomatoid malformation, hydrocephalus, aortic stenosis, obstructive uropathy and teratoma.

Before the operation, the mother and the fetus have to undergo special diagnostic procedures. It is necessary to determine fetal karyotype. It can be obtained by amniopunction or cordocentesis. To evaluate the exact form of nervous system malformation, USG and MRI needs to be performed [4].

The first open fetal surgery was performed in 1982 in USA by Michael R. Harrison and it was a cystotomy operation on fetus with posterior urethral valve. From that time, a vast array of new indications for fetal interventions have been invented. Some of them became popularized, but some remain forgotten, and are no longer in use anymore.

Fetal surgeries can lead to several serious complications like: premature rupture of membranes, premature birth, infection or pulmonary edema caused by magnesium sulfate intake in order to achieve tocolysis. The indications for fetal interventions are the threat of fetal death and essential developmental disorders. Fetal procedures also allow us to reduce fetal mortality and disability. Prenatal procedures remain at the stage of clinical studies and should be performed only in selected, highly specialized centers. In Poland, the only one is in Bytom, where multidisciplinary team successfully treats fetuses with myelomeningocele [5].

2. PRENATAL SURGICAL INTERVENTIONS

Fetal surgeries are a variety of medical interventions which can be performed *in utero* on the developing fetus aiming for repair congenital abnormalities. Nowadays fetal treatment can be performed by shunting, fetoscopic interventions and open fetal surgery, which means, by opening the uterus [6]. These methods are performed for a spectrum of fetal diseases that progress in severity during pregnancy and which influence on morbidity, perinatal mortality and long term prognosis [7]. The chosen method depends on the congenital abnormality of the fetus [8].

2. 1. Shunting

The shunting procedure is performed by percutaneous placement of catheters to drain body cavities to amnion. This method requires local anesthesia and ultrasound guidance. Through the mother's abdominal wall and uterine, a metal cannula on a trocar is inserted

into the amniotic cavity. Afterwards it is maneuvered into the right cavity, which may be e.g. bladder or brain chamber. Subsequently the trochar is removed and the drainage catheter is inserted into the cannula. One end is placed in the cavity and the other in the amniotic cavity. In the last step of this procedure, the cannula is removed and the final position is settled by ultrasound [8]. This method has found use in fetal treatment of bladder outflow obstruction or hydrocephalus.

2. 2. Fetoscopy

Fetoscopy is defined as the endoscopic diagnostic method of looking directly at the fetus [7]. The first attempts at fetoscopy were carried out by Westin in 1954 who inserted hysteroscope through the cervix of patients to perform therapeutic abortions. Subsequently in 1967 Mandelbaum used transabdominal approach during attempts at intrauterine fetal transfusion for hemolytic disease. In 1973 Scrimgeour introduced the term fetoscopy after uncovering the uterus at laparotomy and inserting a 2.2 needlescope in order to view the amniotic cavity and fetus [9]. Currently, fetoscopy is a minimally invasive method of treating the fetus using ultrasonography and advanced techniques [10]. Fetoscopic surgery can be performed by two methods. At the first method, after laparotomy, the trocars are introduced through the uterus wall to the uterine cavity. In the second, less invasive method, trocars are inserted into the uterine cavity through mother's abdominal and uterus wall. It is expected that this methods will decrease trauma to the fetus, the uterus and of course, the mother. After fetoscopy cesarean sections are not obligatory. Mothers can give birth by vaginal delivery also after subsequent pregnancies [11,12].

2. 3. Open fetal surgery

First fetal surgery with open hysterotomy was performed in early 1980's by pediatric surgeons Alfred de Lorimier and Michael R. Harrison at the University of California, San Francisco. The surgeons developed the technique as a new way of treating myelomeningocele [13]. OFS team should consist of perinatologists, obstetricians, pediatric surgeons or pediatric neurosurgeons, anesthesiologists and psychologists. Intrauterine MMC repair is divided into a few stages (Figure 1). During surgery mother is under general anesthesia. Under the control of ultrasonography, fetus and MMC are visualized. Obstetricians perform laparotomy and hysterotomy and attach fetal membranes to the uterine wall. After uterus is open and fetus is positioned pediatric surgeon may perform MMC repair. Subsequently fetal water is supplemented with a warm solution of 0,9% natrium chloratum and antibiotic. In the last stage layers of uterine and abdomen are closed.

MMC is not the only congenital abnormality that can be treated using this procedure. Open fetal surgery is moreover the only option that gives a chance to the fetus with small cystic type of *congenital cystic adenomatoid malformation* (CCAM). Unfortunately, the results are associated with high mortality [14-18]. Open fetal surgery gives also possibility to cure fetus with *sacroccoccygeal teratomas* (SCT) where the main indication is growing fetal edema before 32 week of pregnancy. The operation allows the identification of the tumor and removal of its major mass, however, these operations are very rare and come with high risk of failure [8,19]. Very common complication after open fetal surgery, which occurs in almost 50% cases, is amniotic leakage and preterm premature rupture of membranes (PPROM). For comparison, endoscopic fetal surgery is associated with average PPRM rates of 10 to 15%

[20-23]. Nevertheless, open fetal surgery gives us the opportunity to treat many congenital abnormalities and change the prognosis and mortality.

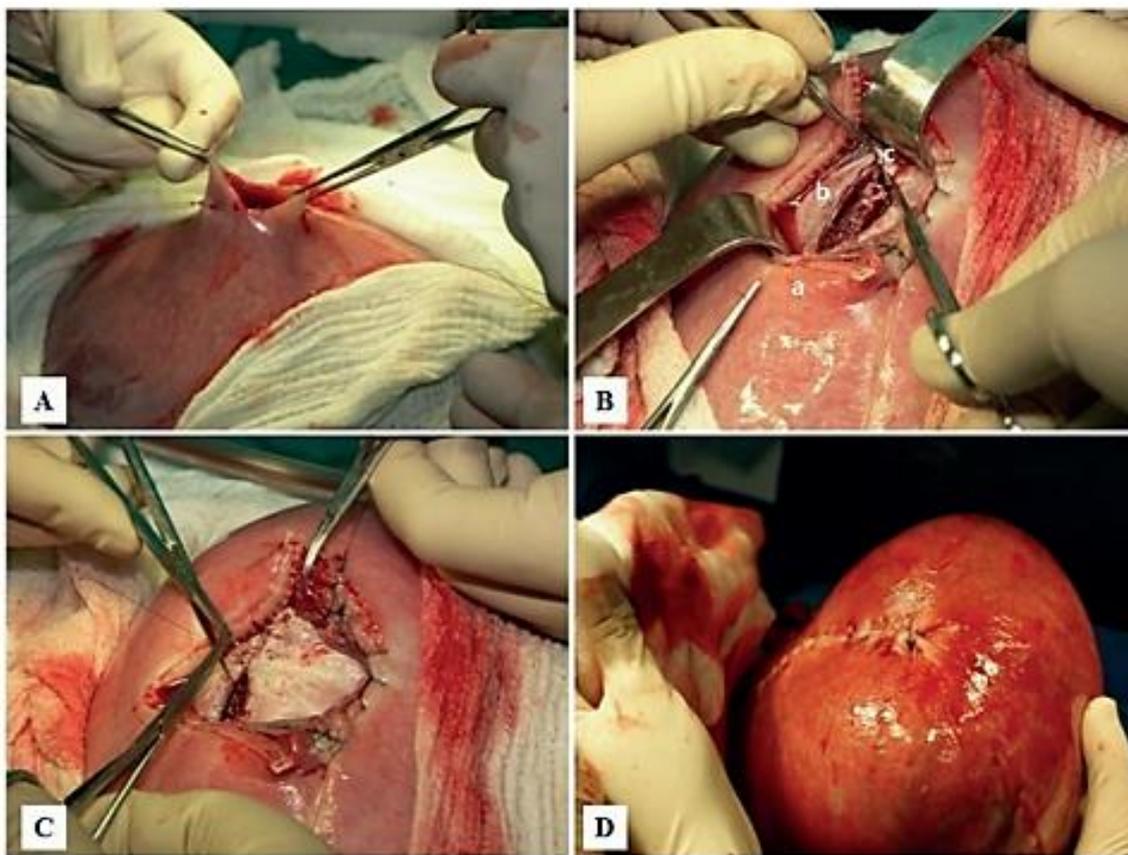


Figure 1. IUMR stages (A- hysterotomy; B- stabilization of the fetus with exposed MMC; C- closed MMC, D- closed uterus) [5].

3. CONGENITAL DISORDERS

3. 1. Myelomeningocele

Myelomeningocele (MMC) is one of the most common fetal neural tube defects [24]. The incidence of MMC in the USA is about 2/10 000 live births, whereas in Poland MMC affects 6/10 000 [25,26]. The occurrence of neural tube defects is connected with folic acid deficiency, however, folic acid supplementation has not eradicated MMC due to existence of other causes of defects, including exposure to drugs, toxins and genetic abnormalities [27].

“Two-hit hypothesis” of myelomeningocele explains the wide spectrum of neurologic deficits and associated morbidity. The first hit is the abnormality of the neural placode itself around 4-8 weeks of gestation. The second hit of myelomeningocele injury is the continued exposure of the neural tissue to neurotoxic amniotic fluid and intrauterine trauma throughout fetal development [28,29]. Reparation of the defect protects spinal cord and eliminates the second hit of myelomeningocele’s physiopathology [30].

Patients with myelomeningocele show abnormalities related to the severity of their neurologic defect. Nearly all newborns with a myelomeningocele defect develop an Arnold-Chiari II malformation, caused by a pressure gradient from the spillage of cerebrospinal fluid. It results in hindbrain herniation and frequently causes hydrocephalus [31,32]. Children with this defect might develop cerebellar and upper cervical nerve dysfunction, which result in difficulty in swallowing, vocal cord motion, upper extremity innervation and, in severe cases, central hypoventilation or apnea. Symptoms caused by spinal cord exposure to the amniotic fluid are paralysis of the lower extremities and bladder and bowel dysfunction [33].

Vast majority of patients with MMC require postnatal treatment including endoscopic third ventriculostomy (ETV) or insertion of the ventriculoperitoneal shunt (VPS), which allows drainage of cerebrospinal fluid to the peritoneal cavity [34]. VPS placement is associated with numerous complications concerning its obstruction or infection [35]. Despite intensive postnatal treatment, almost 14% of all children with MMC live less than 5 years.

The association of cerebellar dysfunction increases mortality rate to 35% [36]. About 70% of children reach the IQ level > 80 and only every other is self-reliant in adulthood [37].



Figure 2. MMC of three newborns delivered at 36–37 weeks for a scheduled operation after birth [5].

Surgical treatment of defects during pregnancy improves motor and urinary function and reverses the Arnold-Chiari II malformation with near normal hindbrain development in the animal model. Likewise, an experimental study in human fetus showed reversibility and even regression of hydrocephalus and hindbrain herniation [38].

One of the first reports of open fetal myelomeningocele repair was published by Vanderbilt University in 1999. VPS implantation rate was lower in the fetal surgery group as compared to the group treated postnatal (90% vs. 46%). Motor function of the lower extremities were similar to motor functions typical for the injury of two spinal segments below the actual anatomical MMC level [39]. The Management of Myelomeningocele Study (MOMS) in randomized research confirms advantages of prenatal surgery. Enrollment for the

study was closed in 2010 due to the efficacy of prenatal surgery shown in the first 183 patients [40].

Prenatal repair of a myelomeningocele with fetoscopy was initiated in Vanderbilt University as well. The results of fetoscopy in the treatment of MMC are not satisfactory. Report includes four cases of maternal laparotomy, three-port access to the uterus and application of a maternal skin graft over the defect. Both fetuses, who survived to birth, required reoperation. Other studies, at The University of California, reported three attempts at fetoscopic repair. Two of them were converted to open fetal surgery due to intraoperative complications and one patient had postnatal surgical intervention [41,42]. Fetoscopy is also performed in Germany. Professor Thomas Kohl accomplished coverage of the trocar insertion defects within the chorioamniotic membranes. As the result of this method, nearly 90% of fetuses have been delivered at or beyond 30 weeks of gestation and have avoided the complications associated with prematurity [44].

3. 2. Diaphragmatic hernia

Diaphragmatic hernia (CDH) is a congenital malformation of the diaphragm, in which abdominal organs are allowed to move into the chest cavity, hindering proper lung formation. CDH is a life-threatening pathology in infants and a major cause of death due to two complications: pulmonary hypoplasia and pulmonary hypertension.

It is usually detected in ultrasonography [45]. The lung-to-head ratio (LHR) is an important prognostic indicator. It is obtained by measuring the right lung area at the level of the four-chamber view of the heart and dividing by the head circumference. In multiple studies, an LHR <0.6 was associated with 100% mortality, while an LHR >1.35 was associated with 100% survival. The LHR (or variants of the LHR) has been widely accepted. Another diagnostic option is fetal magnetic resonance imaging. It allows to evaluate a measurement called percent predicted (expected) lung volume. Then the actual lung volume is measured and divided by the expected lung volume to create a percentage [46].

In 1990, Dr. Michael Harrison and his team performed the first successful open fetal CDH repair. Then, however this therapeutic method was abandoned. Nowadays, the first choice method of CDH treatment is fetoscopic tracheal occlusion. At first this operation was performed via an open hysterotomy with tracheal clip application, but now it uses fetoscopic bronchoscopy with tracheal balloon occlusion. Before the delivery, the balloon is broken during the second fetoscopic procedure or is pulled out by a neonatologist just after the labor [47]. In the majority of cases the fetus does not apply to fetal intervention, due to the excessive size of hernia. Overall survival is about 50%.

3. 3. Twin-to-twin transfusion syndrome

Twin-to-Twin Transfusion Syndrome (TTTS) occurs in 10-15% of all monochorionic pregnancies. Most of the monochorionic twins share blood flow via arteriovenous, and occasionally via arterio-arterial and venovenous anastomoses. Commonly, this transfusion is equitable, nonetheless in 10-15% of monochorionic pregnancies the transfusion can become unbalanced. The circulation of one of the twins, the so-called "Donor Twin" becomes compromised by blood and pressure loss via anastomoses toward its sibling twin, called "Recipient Twin". This leads to chronic hypovolemia, oliguria, and oligohydramnios in the donor, while the recipient becomes polycytemic and hypervolemic, leading to polyuria and polyhydramnios [48].

The diagnosis can be done by prenatal ultrasound findings. The initial staging system described by Quintero in 1999 is the one most commonly used. With increasing severity, the polyhydramnios–oligohydramnios (stage I) sequence is associated with a collapsed bladder in the donor (stage II), signs of cardiovascular strain and Doppler anomalies in either twin (stage III), fetal hydrops (stage IV) and single or dual fetal demise (stage V) [8]. In cases untreated and diagnosed before 20 weeks of gestation, mortality is close to 100%.

Among used treatments the most common was amnioreduction [48, 49]. Subsequently Julian DeLia in the early 1990s announced an endoscopic technique of laser ablation of communicating vessels (FLA). Nowadays this procedure with some modifications has become the definitive treatment for severe TTTS (\geq stage II). In 2004 Senaat et al. reported results of multicenter randomized control trial focused on comparison endoscopic laser surgery and serial amnioreduction for severe twin-to-twin transfusion syndrome. The study revealed a higher survival rate of neonates especially in group of patients with Stage 2 or higher that underwent FLA vs. amnioreduction (76% vs. 56%). The incidence of brain anomalies (as assessed by the presence of periventricular leukomalacia on imaging) was also lower in FLA group. Moreover patients after in utero laser ablation were delivered 4 weeks later than those after amnioreduction (33 vs 29 weeks) [50].

3. 4. Congenital cystic adenomatoid malformation

Congenital cystic adenomatoid malformation (CCAM) is a defect, in which usually entire lobe of lung is replaced by a cyst made of abnormal lung tissue. It occurs in 1 of 30 000 pregnancies. Not every case of CCAM is a life-threatening condition for the fetus [51]. Cystic volumes ratio is a measurement which allows to determine if CCAM is dangerous for the fetus. It is obtained by dividing cyst volume by head circuit. If it reaches higher value than 1,6 the risk of fetal death is significantly increased. If the cystic mass grows too large, it can limit the growth of the surrounding lung and cause pressure against the heart. There are two types of cysts found in lungs: single - chamber cysts, with better prognosis, and microcystic form, with considerably worse prognosis [52].

The defect is usually detected during prenatal ultrasound examination. In most cases the child is operated after birth, but in case of large CCAM or presence of other defects, fetal surgery needs to be performed. With fetoscopic approach a shunt between the lung cyst and amniotic sac is installed. It allows the cyst content to be evacuated to the amniotic cavity, and reduces the intrapleural pressure, which is necessary for proper lung development. Unfortunately, the microcystic form cannot be treated with fetoscopy. Open fetal surgery, hysterotomy and fetal thoracotomy with lobectomy is the only way of treating this specific condition [53]. Sometimes, undetected lesion remains asymptomatic after birth, until it is diagnosed as infection, emphysema or even neoplastic malformation. That is why every CCAM diagnosed prenatally should be treated as fast as possible after birth or even during pregnancy.

3. 5. Hydrocephalus

Hydrocephalus can be defined as any increase in amount of cerebrospinal fluid (CSF) within the skull, including brain edema, more precisely as ventricular enlargement that causes accelerated head growth or requires surgical intervention [54-56]. Prevalence evaluation for infantile hydrocephalus vary between one and 32 per 10,000 births, depending on the definition used and the studied population. Congenital hydrocephalus may be caused by an

infection in the mother during pregnancy, such as rubella or mumps, or a birth defect, such as spina bifida and is diagnosed during pregnancy, present at birth or developed during the time after labour.

Fetal hydrocephalus is diagnosed sonographically, by the demonstration of abnormally dilated ventricles. Presence of other malformations or chromosomal defects strongly influences the neurodevelopment in survivors and the chance of fetal or perinatal death. The attached hydrocephalus detected during pregnancy may be indication of the establishment of a shunt or valve. First shunt was founded in 1982 in USA [57].

Many trials of intrauterine shunting proved unsuccessful, mostly because of complications such as intra- or extracranial shunt migration, obstruction and infection. Another therapeutic option is valve implantation which requires hysterotomy. In this procedure catheter drains cerebrospinal fluid into amniotic fluid [58]. According to some studies progressive fetal hydrocephalus can obtain benefit from intraventricular decompression performed during the fetal period. The reason may be the fact that much enlarged and deformed shape of the skull developed during the gestation has small chances to achieve normal size [59]. The discussion on the benefits of hydrocephalus treatment during pregnancy is still open.

4. CONCLUSIONS

Fetal surgery is a multidisciplinary, collaborative medical specialty that strives to improve outcomes in patients diagnosed with fetal anomalies. Prenatal procedures are still relatively rare. The ethical issues, e.g. the right to expose a healthy mother to the risk of surgery and eligibility to abortion, accompany the fetal operation for the beginning. Requirements are long-term observation, refinement in surgical techniques and guidelines for pre-and postoperative care. For that reason, fetal surgery should be performed only in selected, highly specialized centers.

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