VIA MEDICA

RECCOMENDATIONS

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Fetal therapy guidelines of the Polish Society of Gynecologists and Obstetricians — Fetal Therapy Section

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INTRODUCTION

The last two decades have witnessed significant changes in the fields of fetal therapy and surgery. Owing to the latest advancements in ultrasound imaging techniques, it is currently possible to diagnose anatomical defects at the initial stages of pregnancy, while miniaturized surgical tools allow to perform increasingly complicated and complex procedures *in utero*.

Evidence-based medicine (EBM) has become a vital aspect of patient management in all surgical specialties. Compared to the results of large — often multicenter and randomized — studies, the impact of the reports and recommendations from individual clinicians has markedly decreased. The value of own experience has diminished when contrasted with the findings of large sample size studies which allow for comprehensive and reliable assessment of fetal anatomical defects and proper eligibility process for intrauterine interventions. Importantly, only those fetuses who will benefit from these procedures should be deemed eligible for surgery. Surgical approach is on a par with justifiable expectant management and

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Table 1. Ultrasonographic criteria for polyhydramnios

Polyhydramnios	Mild	Moderate	Severe
MVP	8.0–11.9 cm	12.0–15.9 cm	≥ 16.0 cm
AFI	24.0–29.9 cm	30.0–34.9 cm	≥ 35.0 cm

MVP — maximum vertical pocket; AFI — amniotic fluid index

the decision to forgo surgery. A medical intervention, defined as 'at least a break in the continuity of the skin', in a non-sick patient *i.e.* the mother of the affected fetus, represents a unique aspect of fetal therapy. The intervention aims at improving fetal prognosis but it may be associated with considerable discomfort and risk for complications in the mother. Therefore, it is crucial for all fetal therapy procedures to be merited and performed by experienced professionals at highly specialized healthcare centers, and only if these interventions might save fetal life or improve the prognosis. Evidence-based consultation, which allows the patient to make an informed decision, and professional psychological care are the two key elements of fetal therapy. It needs to be emphasized that centralized care benefits both, the woman and the child, as it ensures that a high number of intrauterine procedures are performed at a given center, enhancing the skill set and expertise of the medical professionals.

The goal of this guideline is to systematize intrauterine procedures and to recapitulate their applications and recommendations, in accord with the EBM standards. Most of the procedures described in this guideline have been organized by anatomical regions. Amniocentesis and chorionic villous sampling have been purposefully excluded as they are used in invasive prenatal diagnostics and have been extensively discussed elsewhere.

The authors wish to emphasize that this guideline was compiled based on the currently available and up-to-date findings. Future reports and data may change the recommendations presented below.

POLYHYDRAMNIOS

Polyhydramnios is defined as the excess of the amniotic fluid in the uterus and is diagnosed if the amniotic fluid index (AFI) is ≥ 24 cm, or the depth of the maximum vertical pocket (MVP) in the anterior-posterior view is ≥ 8 cm on ultrasound [1]. The prevalence of polyhydramnios has been estimated at 1–2% of all gestations. Polyhydramnios is either idiopathic (40–50%) or caused by congenital fetal defects or maternal diseases.

Fetal defects (including many genetic conditions, neurovascular, gastrointestinal diseases or vascular rings) are more often responsible for the development of severe polyhydramnios, whereas mild polyhydramnios is mostly associated with gestational diabetes, multiple gestation, or Rh incompatibility.

Detailed ultrasound screening and evaluation of the genetic risk factors, especially for trisomy 21 and 18, should constitute the first stages of the diagnostic process for polyhydramnios. There is no premise for routine genetic testing in idiopathic polyhydramnios [2, 3]. Likewise, there is usually no reason to screen for cytomegalovirus (CMV) infections and toxoplasmosis [4, 5]. Irrespective of the fetal evaluation, it is necessary to analyze maternal risk factors, especially to exclude diabetes or Rh incompatibility, and to collect and screen maternal medical history for medicine, substance and drug use [6].

Polyhydramnios can be classified as **mild, moderate and severe** (Tab. 1). Its severity correlates with the risk for the following complications: preterm labor, abnormal fetal presentation, placental abruption, or cord prolapse.

In mild and moderate polyhydramnios, the management typically consists in regular (every 1–2 weeks) monitoring for changes in the amniotic fluid volume (AFV), maternal wellbeing, and risk for preterm delivery. Nevertheless, due to the subjectivity and limitations of ultrasound evaluation of AFV, amnioreduction should always be considered if the pregnant woman reports clinical symptoms of polyhydramnios.

Amnioreduction

1. In severe polyhydramnios, amnioreduction is recommended in case of severe maternal dyspnea or discomfort which interferes with normal daily functioning [1].
2. In asymptomatic patients or those with well-tolerated symptoms and moderate dyspnea, as well as in mild polyhydramnios, amnioreduction is not recommended [1].
3. In patients < 32 weeks gestational age (GA) with uterine contractility present before the procedure, **indomethacin** may be considered before, during, or after amnioreduction, for example at the dose of 4 × 25 mg for 48 hours [1]; reports about short-term effects of using small doses of indomethacin before 32 weeks GA and the risk for premature closure of the arterial duct are conflicting [7–10]; still, it is necessary to take that risk into account when using indomethacin, especially > 3 days and monitor the patency of the arterial duct.
4. If the only goal of therapy is to decrease the volume of the amniotic fluid, **indomethacin** is not recommended in patients without concomitant clinical symptoms of polyhydramnios [1].

5. After amnioreduction, it is essential to monitor AFV every 1–2 weeks, and repeated amnioreduction should be considered if polyhydramnios recurs and if the mother becomes symptomatic.

Procedure

Amnioreduction is typically performed in local anesthesia, using an ultrasound-guided 18-gauge (in certain cases 16) needle. Excess fluid may be evacuated using a 50-mL syringe or continuous suction at 100–125 mL/min. The procedure is continued until AFI of 15–20 cm or MVP of < 8 cm are achieved. The literature offers no clear guidelines about the recommended volume of fluid to be evacuated at one time, but a threshold of max. 2–2.5 Liters is typically advised. A course of steroids and tocolysis may be considered in fetuses under 34 weeks GA. There is no consensus regarding antibiotic prophylaxis [11]. However, it seems prudent to administer prophylactic antibiotics in case of complications during the intervention, the need for repeat puncture of the amniotic sac, or prolonged duration of the procedure.

Possible amnioreduction-related complications

The most common complications include prelabor rupture of the membranes within 48 hours after the procedure (1%), premature labor within 48 hours (4%), intraamniotic infection (< 1%), and placental abruption (< 1%) [11].

The literature offers no evidence that amnioreduction prolongs the duration of pregnancy by reducing the risk for spontaneous premature labor.

Delivery

Timing and mode of delivery should depend on the cause of polyhydramnios or other obstetric indications. In mild and moderate idiopathic polyhydramnios, vaginal delivery is recommended at term, but no later than between 39 + 0 and 40 + 6 weeks GA, whereas in severe polyhydramnios delivery may be considered after 37 weeks GA [1, 12]. During labor, it is vital to monitor fetal position as the excessive amount of fluid — and the associated higher fetal mobility — may promote fetal conversion to transverse lie or breech presentation. Additionally, spontaneous rupture of the membranes may cause sudden severe uterine decompression, resulting in placental separation or cord prolapse. Gradual transabdominal or vaginal amnioreduction may be considered as a prophylactic measure to lower the risk for these complications, on condition the fetal head is positioned adequately.

OLIGOHYDRAMNIOS

The amniotic fluid surrounds the fetus, cushioning it from trauma and providing a safe environment. The fluid is indispensable for fetal development. Oligohydramnios is defined as decreased volume of the amniotic fluid, while the absence of the fluid is known as anhydramnios. Oligohydramnios is diagnosed at AFI of ≤ 5cm or MVP of ≤ 2 cm. The most common pathologies of pregnancy concomitant with oligohydramnios are presented in Table 2 [13].

The prevalence of oligohydramnios has been estimated at 0.5–5.5% of all pregnancies. The diagnosis of oligohydramnios at any stage of pregnancy is a warning sign and may be indicative of a serious threat to fetal wellbeing [13–15]. The etiology and the effects of oligohydramnios on the course of pregnancy and the prognosis depend on the gestational age at which the symptoms of oligohydramnios have been detected on ultrasound. Oligohydramnios in the first trimester is an extremely rare, albeit reported, occurrence and is always associated with unfavorable prognosis for the fetus. In the second trimester, it is mostly caused by defects of the fetal urinary tract (51%) or preterm prelabor rupture of membranes (pPROM) (34%), and in the third trimester by prelabor rupture of membranes (PROM) and fetal growth restriction (FGR) (Tab. 3) [16].

Table 2. Pathologies of pregnancy concomitant with oligohydramnios [13]

Congenital fetal defects, especially of the urinary tract
Prelabor rupture of membranes (PROM)
Fetal growth restriction (FGR)
Twin-to-twin transfusion syndrome (TTTS) (donor)
Post-term pregnancy
Side effects after pharmacotherapy: • prostaglandin synthase inhibitors • angiotensin-converting enzyme inhibitors

Table 3. The most common causes for oligohydramnios, depending on gestational age [16]

I trimester	II trimester	III trimester
• iatrogenic after amniocentesis, CVS • fetal genetic defects, intrauterine fetal demise, amniotic sack rupture • idiopathic (rare), associated with poor fetal prognosis	• urinary tract defects **(obstructive uropathies — 51%)** • **pPROM — 34%** • chorioamniotic membrane separation — 7% • FGR — 5%	• **PROM** • **FGR** • placental separation • use of angiotensin-converting enzyme inhibitors or prostaglandin synthase inhibitors

CVS — chorion villous sampling; pPROM — preterm prelabor rupture of membranes; FGR — fetal growth restriction; PROM — prelabor rupture of membranes

Gestational age at diagnosis affects the fetal prognosis. The diagnosis of oligohydramnios established as early as the second trimester is associated with high rate of unfavorable fetal outcomes. The risk for fetal demise is additionally elevated by congenital defects, genetic malformations, pulmonary hypoplasia, severe prematurity, and intrauterine fetal infection.

In some cases of oligohydramnios (*e.g.* concomitant with early-onset fetal hypotrophy), genetic diagnostics [fetal karyotyping or — preferably — microarray-based comparative genomic hybridization (aCGH) testing] should be considered. However, due to the decreased volume of the amniotic fluid, amniocentesis is not always technically feasible (in such cases cordocentesis should be considered).

Diagnostic amnioinfusion may be considered in some cases of oligohydramnios. The procedure is recommended not only to diagnose the primary defects of the urinary tract, but it may also play a valuable auxiliary role in detecting other concomitant anatomical defects that cannot be diagnosed on ultrasound due to the absence of the amniotic fluid. Diagnostic amnioinfusion may help to differentiate between prelabor rupture of the membranes and urinary tract defects in the fetus, *e.g.* renal agenesis [17].

Continuous therapeutic amnioinfusion in case of pPROM or PROM does not seem to improve the prognosis or lower the risk for intrauterine infection or pulmonary hypoplasia [18–20]. Still, the literature offers casuistic reports about improved prognosis in cases of pPROM or FGR concomitant with oligohydramnios. According to those sources, continuous amnioinfusion (also through the shunt allowing permanent access to the amnion) alleviated cord compression and prolonged pregnancy [21, 22]. At present, the available evidence is not sufficient to support routine infusions, continuous and using the shunt, in such cases. Regardless, it is necessary to emphasize that the final recommendations and eligibility for the amnioinfusion should be issued by an experienced obstetrician-gynecologist or a perinatologist from a tertiary referral center. Reports are scarce due to restricted indications and a small number of such procedures performed globally. One should bear in mind that amnioinfusion may be associated with the risk for hemorrhage, amniotic fluid embolism, and the onset of uterine contractility.

Procedure

Amnioinfusion is typically performed in local anesthesia, using an ultrasound-guided 16- or 18-gauge needle. The fluid (*e.g.* warm Lactated Ringer's solution) is administered using a 50-mL syringe or a rapid infusion set. The procedure is continued until achieving fluid volume which allows for spontaneous and unrestricted fetal movement within the uterus and ultrasound assessment of the fetal anatomy. There is no consensus regarding antibiotic prophylaxis.

NON-IMMUNE HYDROPS FETALIS (NIHF)

Non-immune hydrops fetalis is a pathologic condition characterized by excessive fluid accumulation in at least two interstitial compartments including peritoneal cavity, pleural cavity, pericardium, and skin. The symptoms are frequently accompanied by polyhydramnios and placental edema. The overall prevalence of NIHF has been estimated at 3/10 000 births, although data remain conflicting. The number of NIHF cases diagnosed in the first and second trimester is significantly higher and has been estimated at 1:1600–1:2000 fetuses [23]. The underlying causes for non-immune hydrops fetalis include fetal cardiovascular defects (21.7%), idiopathic etiology (17.8%), genetic factors (13.4%), fetal hematological issues (10.4%), fetal infection (6.7%), fetal chest tumors (6.7%), complications of monochorionic twin pregnancy [twin-to-twin transfusion syndrome (TTTS), twin reversed arterial perfusion (TRAP)] (5.6%), urinary tract defects (2.3%), fetal metabolic diseases (1.1%), and — although rarely — fetal gastrointestinal abnormalities (0.5%) [24–26].

The risk for genetic abnormalities in fetuses with NIHF increases with concomitant structural anomalies or if hydrops fetalis is diagnosed in the first or early in the second trimester. The diagnosis of non-immune hydrops fetalis should be an indication for genetic testing [24]. Microarray-based comparative genomic hybridization remains the method of choice. It detects submicroscopic genomic changes — microdeletions and microduplications, and such genetic issues are found in as many as 7% of the fetuses diagnosed with structural abnormalities and normal karyotype [27, 28]. Importantly, that method does not detect triploidy, which may also present with generalized edema.

After the diagnosis of NIHF, the mother should be referred to a tertiary referral center. As numerous etiologies may lead to non-immune hydrops fetalis, the perinatal care plan should be tailored to the individual needs of the patient. Ultrasound diagnostics, including fetal growth evaluation, diagnosis and monitoring of the existing anomalies, as well as echocardiographic assessment of the anatomy of the fetal heart and circulatory efficiency, are of key importance. Structural anomalies of the fetal heart, vascular anomalies and fetal heart arrhythmias may account for 20% of all NIHF cases [24]. The frequency of follow-up tests needs to be individually adjusted to each patient and should depend on type of abnormality, fetal circulation, the risk for fetal anemia, and the choice of management.

The recommended laboratory tests from maternal blood include complete blood count (CBC), blood typing (AB0 and Rh), indirect Coombs, Kleihauer-Betke, venereal disease research laboratory (VDRL), antibodies against toxoplasmosis and B-19 parvovirus, CMV, anti-RO/SSA antibody, and G6PD test (depending on maternal ethnicity).

Table 4. The recommended range of tests for fetal non-immune hydrops fetalis (NIHF) (depending on the sample)

Maternal blood	Fetal blood	Amniotic fluid	Fetal investigations (*e.g.* pleural effusion, ascitic fluid)
• CBC • blood type (AB0 and Rh) • indirect Coombs • Kleihauer-Betke	• CBC with smear • direct Coombs, • blood type (AB0 and Rh)	• aCGH	• lymphocyte count • total protein • albumin
• VDRL test • antibody test against toxoplasmosis, B-19 parvovirus, cytomegalovirus	• TORCH panel	• PCR for CMV, • PCR for B-19 parvovirus/ /toxoplasmosis	• creatinine/electrolytes
• G6PD	• total protein and albumin		
• anti-RO/SSA antibody	• PCR for CMV • PCR for B-19 parvovirus/ /toxoplasmosis		

CBC — complete blood count; aCGH — microarray-based comparative genomic hybridization; VDRL — venereal disease research laboratory; PCR — polymerase chain reaction; CMV — cytomegalovirus

The recommended laboratory tests from the amniotic fluid include aCGH, polymerase chain reaction (PCR) for CMV, PCR for B-19 parvovirus/toxoplasmosis.

The recommended laboratory tests from fetal blood include CBC with smear, direct Coombs, blood typing (AB0 and Rh), the Toxoplasmosis, Other (Syphilis, Hepatitis B), Rubella, Cytomegalovirus, and Herpes simplex (TORCH) panel, total protein and albumin, PCR for CMV, PCR for B-19 parvovirus/toxoplasmosis.

The recommended laboratory tests from fetal investigations (pleural effusion, ascitic fluid) include lymphocyte count, total protein, albumin, creatinine/electrolytes.

Tests which might be considered for patients with NIHF are presented in Table 4.

Fetal therapy for NIHF

The scope of therapeutic interventions in fetuses with non-immune hydrops fetalis is broad and the choice of optimal therapy depends on the etiology of NIHF and symptom severity. The recommended management may include both, non-invasive and invasive procedures.

Repeated puncture or shunt placement:
— pleural effusion;
— lymphatic system defects (chylothorax);
— ascites.

Administration of the medication to the fetus (cordocentesis):
— hypoalbuminemia (albumins);
— fetal anemia (red cell concentrates).

Delivery

The decision about the timing and mode of delivery, if possible, should be made at a tertiary referral center by an interdisciplinary team, including at least a perinatologist and a neonatologist, ideally a cardiologist/neonatal cardiac surgeon and/or neonatal surgeon. Current obstetric guidelines for preterm delivery (prenatal steroid therapy, the use of magnesium sulfate for neuroprotection) should also be taken into consideration.

Absolute contraindications for the intrauterine procedure

— multiple structural defects;
— severe genetic abnormalities in the fetus;
— mirror (Ballantyne) syndrome in the mother;
— severe preeclampsia in the mother;
— symptoms of progressing intrauterine infection;
— lack of maternal compliance/consent.

Benefits of the intrauterine procedure

The benefits of fetal therapy depend on fetal condition and the principal cause of hydrops. Intrauterine procedures aim to eliminate the direct cause of the fetal defect or to lower the intensity of those symptoms which constituted a threat to fetal wellbeing. Nevertheless, the management of NIHF may in some cases be limited to the treatment of symptoms. The potential benefits should not be outweighed by the risk associated with the procedure.

Complications after the procedure

— pPROM;
— intrauterine infection;
— placental abruption;
— miscarriage, preterm labor;
— transient bleeding from the needle puncture site (cordocentesis);
— cord tamponade (cordocentesis);
— shunt dislocation;
— improper implantation of the shunt;
— intrauterine fetal demise.

FETAL HEMOLYTIC DISEASE

Despite routine antenatal immunoprophylaxis, which consists in administering anti-D immunoglobulin to all non-sensitized, Rh-negative women who present with no anti-D antibodies, alloimmunization to that antigen continues to be the main cause of fetal hemolytic disease.

In fact, all RBC (red blood cells) antigens may trigger alloimmunization. Therefore, other serological conflicts caused by incompatibility with other antigens (*e.g.* C, c and E) and other blood group systems (*e.g.* Kell, MNSs, Kidd, Duffy, Diego, Colton and AB0) should not be excluded. Rh incompatibility and the resulting fetal hemolytic disease constitute a significant issue for perinatal medicine. The prevalence of fetal hemolytic disease has been estimated at 0.2–0.3% of all gestations.

Rh incompatibility means that the maternal immune system produces alloantibodies against fetal antigens. The antibodies in question can cross the placental barrier (active transport), bind to RBC antigens, and cause hemolysis.

It has been estimated that the minimal volume of foreign antigen blood required to sensitize the mother is 0.2 milliliters. Fetomaternal hemorrhage, which leads to alloimmunization, usually occurs in all situations associated with damage to the villi and compromise to the placental barrier, *i.e.* during delivery, miscarriage (spontaneous or induced), surgery for ectopic pregnancy, intrauterine interventions, and during some cases of antenatal hemorrhage.

Over the years, the prognosis for fetuses with hemolytic disease due to Rh incompatibility has significantly improved after the implementation of non-invasive methods of monitoring for fetal anemia, as well as modern and safe methods of intrauterine intravascular blood transfusion. Currently, the survival rate among fetuses with hemolytic disease due to Rh incompatibility after a series of fetal intravascular transfusions has been estimated at 97% [29].

Diagnosis

In cases with low anti-D antibody titer (up to 1:16), expectant management with monthly monitoring of the titer is advised. Fetal ultrasound monitoring is necessary if the titer is elevated. Patients with obstetric history of severe hemolytic disease (intrauterine fetal demise, generalized edema, intrauterine treatment) and those with anti-Kell antibodies are a notable exception. In such cases, ultrasound monitoring should be considered even if the titer is lower (> 4). Ultrasound diagnostics should include Doppler testing of the alloimmunized patients to evaluate the middle cerebral artery peak systolic velocity (MCA PSV) of the fetus, starting from 18 weeks GA. In order for the measurement to be diagnostic, it is necessary to meet the following technical requirements: Doppler angle close to 0°, Doppler gate of 1–2 mm positioned near the Circle of Willis, and light pressure of the transducer on the fetal head. Multiple of median (MoM) of ≥ 1.5 is an indication for cordocentesis and intrauterine treatment [30]. The sensitivity of 86% and specificity of 71% have been confirmed for detecting severe and moderate anemia using MCA PSV in fetuses with no history of transfusions [31].

Fetal genotyping offers yet another non-invasive diagnostic method in cases with Rh incompatibility. It involves isolating cell-free fetal DNA from maternal serum and searching for RBC antigen coding genes, using the real-time polymerase chain reaction (RT-PCR) method. Currently, it is possible to detect the presence of not only the D antigen, but also the remaining antigens of the Rh system and the K antigen of the Kell system. The sensitivity of 99.3% and specificity of 98.4% have been confirmed for such tests in the first and second trimester of pregnancy [32].

Approximately half (54%) of the fetuses whose mothers present with a high antibody titer (over 1:16) will develop the hemolytic disease *in utero* or during infancy. In that group, 26% will develop severe prenatal anemia (fetal edema, intrauterine fetal demise, the need for fetal intrauterine transfusions), 24% will need phototherapy or secondary transfusions after the delivery, and 4% will develop moderate anemia which will require specialist neonatal care [33].

Fetal therapy

Severe fetal anemia — usually caused by Rh incompatibility and the subsequent fetal hemolytic disease — is most often treated with transfusing red cell concentrates into the umbilical cord vessels (cordocentesis) or, in some cases, into the intrahepatic course of the umbilical vein [34]. Fetuses with severe anemia, typically induced by alloimmunization with foreign red blood cell antigens, are eligible for intravascular intrauterine transfusions [35–37]. Fetal anemia due to other causes, *e.g.* parvovirus B19 infection, may also be an indication for a transfusion [36, 38–41]. The volume of the transfused blood depends on gestational age, which has a direct effect on the capacity of the fetal vascular bed. The degree of fetal anemia and the hematologic parameters of the transfused blood should also be taken into consideration. The procedure should be performed by an experienced team, which is able to select the suitable route of transfusion and volume of the RBC concentrate, or else fetal wellbeing and life might be threatened.

Procedure-related complications

The most serious complications after therapeutic cordocentesis (intrauterine transfusion) include [38, 42, 43]:

— transfusion-associated circulatory overload in the fetus after transfusing excess volume of blood;
— umbilical cord occlusion as a result of extravascular blood transfusion – to Wharton's jelly;

— reflex bradycardia;
— intraamniotic hemorrhage;
— intrauterine fetal demise.

Post-procedure monitoring

Intermittent monitoring of the fetal heart is obligatory during the procedure. Periodic monitoring of the fetal heart is advised immediately after the surgery and for a few hours afterwards.

Muscle relaxants and anesthetics may, in some cases, be administered into the fetal circulation pre- and perioperatively. These medicines not only abolish fetal movement but also cause reduced variability on cardiotocography (CTG), which should not affect therapeutic decisions at that time. Abnormal CTG readings are expected for 4–6 hours postoperatively so early cardiotocography is not recommended. CTG monitoring is recommended only if bradycardia, severe tachycardia, or uterine contractility are observed.

BRONCHOPULMONARY SEQUESTRATION (BPS)

Bronchopulmonary sequestration is characterized by the presence of a mass composed of non-functioning lung tissue, with no communication with the tracheobronchial tree. The tumor receives its arterial blood supply from the systemic circulation, most often directly from the descending thoracic aorta (73%), less often from the descending abdominal aorta, celiac artery, or splenic artery (21%). In extremely rare cases, the tumor may be supplied by the right coronary artery or the subclavian artery [44]. The prevalence of BPS has been estimated at 1:15 000 births [45]. On ultrasound, bronchopulmonary sequestration is visualized as hyperechogenic mass in fetal lung tissue, predominantly on the left side, supplied directly by the descending aorta, although other variants are also possible (Fig. 1 and 2). Bronchopulmonary sequestration is intralobar [microcystic congenital pulmonary airway malformation (CPAM)-like presentation] in 75% of the cases, while 25% of the cases are extralobar, with their own pleura and frequently with pleural effusion. The extralobar variant is more often found in fetuses with other concomitant anatomical defects. The use of color Doppler is of key importance in differential diagnosis as it usually allows to identify the source of the blood supply for the tumor. The congenital pulmonary airway malformation volume ratio (CVR) is applied to determine the prognosis. It is calculated using the following formula [46]:

CVR = height × anterior-posterior view × transverse view × 0.52 (constant)/fetal head circumference

Congenital pulmonary airway malformation volume ratio of > 1.6 is associated with a slightly higher risk for hydrops fetalis — as many as 58% of the cases, if the CVR ratio is high [47]. Bronchopulmonary sequestration is rarely concomitant with other chromosomal abnormalities — on its own it is not an indication for invasive diagnostic procedures. Additional structural defects (diaphragmatic hernia, cardiac and spinal defects) may be anticipated in 50% of the cases.

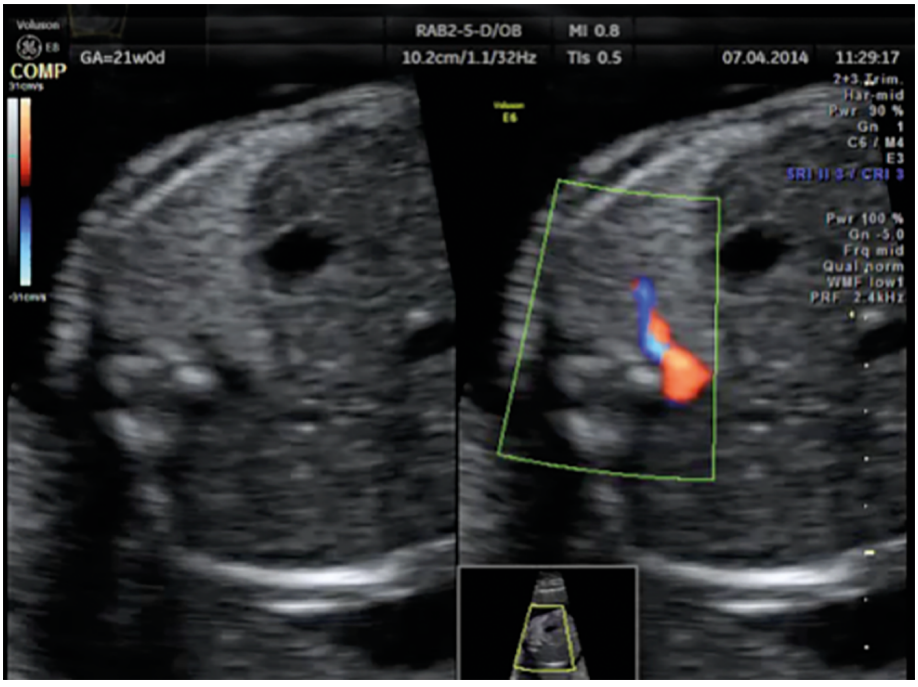

Figure 1. Fetal left lung sequestration and the feeding vessel on color Doppler imaging

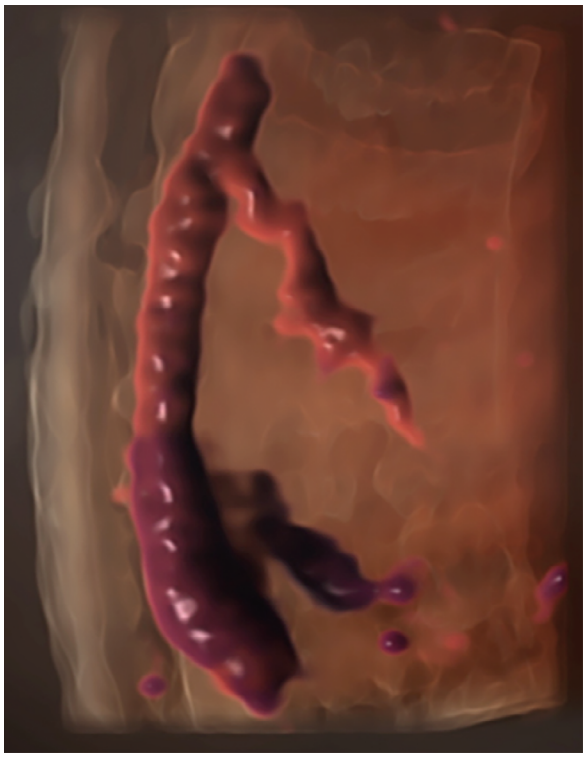

Figure 2. 3D rendering of pulmonary sequestration feeding vessel supplied by the systemic circulation

In BPS, ultrasound monitoring to evaluate tumor growth, pleural effusion and/or fetal edema is recommended every 4 weeks. In 75% of the cases, spontaneous regression and decreased lesion size are observed with progression of pregnancy [48, 49]. Typically, the greatest lesion size is noted between 26–28 weeks GA [50].

Laser coagulation of the tumor-feeding vessel under ultrasound guidance may be considered in the rare cases when BPS is complicated by generalized edema or massive pleural effusion. The procedure requires the operator to have experience with ultrasound-guided surgeries and to know the exact location of the feeding vessel [51]. Possible postoperative complications include preterm labor, PROM, infection, and intrauterine fetal demise.

Uncomplicated bronchopulmonary sequestration is not an indication for a cesarean delivery. In those patients, vaginal delivery is recommended after 38 weeks GA. The prognosis for the fetus is generally (95%) favorable. In cases of BPS complicated by generalized edema, cesarean section at a tertiary referral center is advised.

CONGENITAL PULMONARY AIRWAY MALFORMATION (CPAM)

The prevalence of echostructural abnormalities in fetal lungs presenting as CPAM has been estimated at 1:4000 gestations. Congenital pulmonary airway malformation is a multicystic hamartoma lesion composed of non-functioning lung tissue, predominantly unilateral (> 95%) and restricted to one pulmonary segment or lobe. The blood supply to the lesion comes from the pulmonary circulation. Typically, it is an isolated change, with negligible risk for repeat diagnosis in subsequent pregnancies. Concomitant abnormalities such as cardiac or renal defects as well as tracheoesophageal fistulas are observed in 10% of the cases. After 26 weeks GA, the fetus is at risk for developing polyhydramnios due to the lesion compressing on the fetal esophagus [52, 53].

Congenital pulmonary airway malformation lesions are usually detected during a routine ultrasound test between 18 and 24 weeks GA. Adzick et al. [54], devised an ultrasound classification of CPAM and differentiated between several types of lesions [54]:

- **macrocystic** — single or multiple cysts, at least 5 mm in diameter; intrauterine therapy is possible if symptoms of circulatory failure appear (Fig. 3);
- **microcystic** — solid cysts on ultrasound, less than 5mm in diameter; the prognosis for fetuses with the microcystic type depends on the degree of underdevelopment of the lung tissue and presence of hydrops fetalis (Fig. 4);
- **mixed** — when both CPAM types — microcystic and macrocystic — are detected in the fetus.

The most dynamic growth of CPAM is observed between 18 and 26 weeks GA. The macrocystic tumors are characterized by less dynamic growth as compared to the microcystic lesions. The lesion size decreases with pregnancy progression in approximately 15% of the cases. The CPAM volume ratio (CVR) is a sonographic volumetric index of the mass size, which allows to predict the evolution of the change and undertake adequate diagnostic-therapeutic measures. The index is based on the volume of the cystic mass versus fetal head circumference to adjust the obtained value for gestational age:

CVR = height × anterior-posterior diameter × transverse diameter × 0.52 (constant)/fetal head circumference

Congenital pulmonary airway malformation lesions are associated with elevated risk for developing non-immune hydrops fetalis at CVR above 1.6 [46]. Hydrops fetalis in CPAM is found in <10% of the cases. Typically, if hydrops did not present until 28 weeks GA, the risk of developing it later in pregnancy is extremely low.

Monitoring and delivery

If a CPAM lesion is suspected, ultrasound testing is advised at regular intervals (every 4 weeks at least) to monitor fetal growth, lesion size, and AFV (polyhydramnios may be the result of lesion compression on the fetal esophagus). Due to the altered echogenicity of normal lung tissue early in the third trimester, over 80% of the microcystic changes

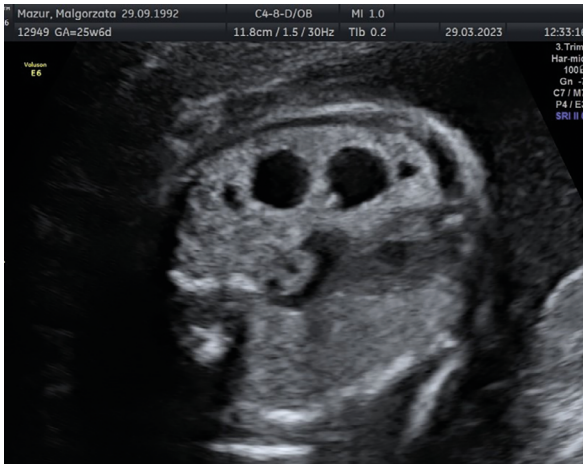

Figure 3. Macrocystic congenital pulmonary airway malformation (CPAM)

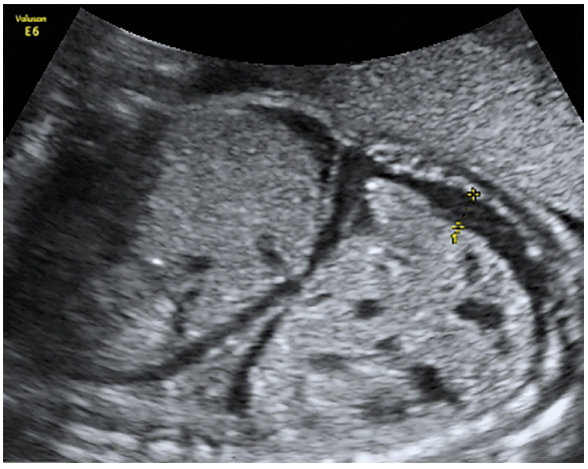

Figure 4. Microcystic congenital pulmonary airway malformation (CPAM)

become less pronounced on ultrasound, although in most cases it is not consistent with lesion regression, but rather technical impossibility to visualize the lesions. Typically, diagnostic imaging after the delivery is necessary [55].

After 38 weeks GA, vaginal delivery at a tertiary referral center — with intense neonatal care unit and neonatal surgery unit on the premises — is recommended. Earlier elective delivery should be considered if signs of fetal growth restriction or circulatory failure have been detected. Intrauterine therapy using thoraco-amniotic shunts may be used if the cystic lesions cause significant mediastinal shift and/or hydrops fetalis. Non-isolated nature of the change is usually an exclusion criterion for intrauterine therapy. The aim of the intrauterine intervention is continuous drainage of the cystic mass allowing to decrease the pressure on the systemic veins and the mediastinal shift, and in consequence to reverse the symptoms of circulatory failure [56, 57].

Risks associated with intrauterine procedure include:

— pain and discomfort at the puncture site;
— shunt dislocation and occlusion which requires reintervention;
— fetal hemorrhage which requires blood transfusion;
— miscarriage or fetal demise (risk 10/100);
— maternal infection (risk < 1/100);
— maternal hemorrhage from the uterine vessels which requires blood transfusion (risk <1/100).

A full course of steroids should be considered in cases with microcystic lesions leading to the development of hydrops fetalis, as some sources claim it decreases tumor volume and leads to the resolution of hydrops [58]. It seems prudent to plan for a steroid therapy in fetuses with severe hydrops and after 32 weeks GA, although the literature lacks consistent reports on the matter. Also, data about sclerotherapy for microcystic lesions and mixed CPAM are scarce [59].

Vaginal delivery is the method of choice after the intrauterine intervention. Immediately after delivery, the shunt needs to be closed or removed from the chest to prevent the development of pneumothorax.

CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

Diaphragmatic hernia is a non-homogenous anatomical defect consistent with varying degrees of herniation of the visceral organs into the thoracic cavity as a result of diaphragmatic discontinuity. Other anatomical abnormalities of the diaphragm include diaphragmatic eventration and complete diaphragmatic agenesis. The prevalence of the defect has been estimated at 1:4000 live births. Posterolateral defects on the left side of the diaphragm comprise most cases of diaphragmatic hernia. The defect is usually unilateral — left-sided in 80% and right-sided in 13% of the cases, with bilateral hernia reported in only 2% of the cases. Congenital diaphragmatic hernia is a non-homogenous anatomical defect, ranging from extremely large defects in the diaphragm, with 90–100% mortality rates, to slight defects of little clinical significance, with 90–100% survival rates among the affected infants [60]. The prognosis depends not only on the size of the defect but also the degree of pulmonary hypoplasia, which in turn depends on the affected side (left or right) and which organs herniated into the thoracic cavity [61]. Hypoplastic lungs in fetuses with CDH are characterized by impaired pulmonary vascular development — over-muscularization and decreased number of pulmonary vessels per lung unit. Also, decreased bronchiolar branching and thickening of the alveolar-capillary barrier are observed. In severe CDH, these abnormalities in the anatomy of the lungs will inhibit effective gas exchange immediately after the cord is cut and will inevitably lead to neonatal death.

In most cases, congenital diaphragmatic hernia is an isolated defect, but concomitant genetic or anatomical

abnormalities (heart or renal defects) have also been reported. Immediately upon diagnosis, it is necessary to exclude the genetic abnormality which is the primary cause of the diaphragmatic defect, especially in cases deemed eligible for an elective intrauterine procedure. The most common abnormalities include trisomy 18 or tetrasomy 12p (Pallister-Killian syndrome) [62]. However, other significantly less common genetic syndromes, with congenital diaphragmatic hernia among their symptoms, have also been reported. Therefore, at least karyotyping is a prudent course of action. It is essential to exclude other anatomical defects in the fetus, especially heart defects, which additionally worsen the prognosis.

Eligibility for the intrauterine procedure

In 1996, Metkus et al. [63], described a sonographic method of assessing CDH severity using the lung area-to-head circumference ratio (LHR), calculated as the lung area opposite the CDH divided by fetal head circumference. A direct correlation has been found between the LHR index and fetal survival, with 0% survival for LHR < 0.6, 61% survival for LHR 0.6–1.35, and 100% survival for LHR > 1.35 [63]. However, the LHR index is not without limitations, chief among them its variability at various stages of the pregnancy. That is why it was necessary to select a parameter which would not depend on the gestational age to such an extent. The observed-to-expected (o/e) LHR, which indirectly evaluates the degree of organ herniation into the chest cavity by measuring the space occupied by the lung (greater protrusions of the fetal organs into the chest cavity corresponds to greater diaphragmatic defect and lower lung volume). The o/e LHR parameter and liver herniation to the fetal chest have been demonstrated to be the most reliable tools of assessing CDH severity and fetal prognosis [64]. The o/e LHR of < 25% is indicative of severe congenital diaphragmatic hernia and constitutes an indication for an intrauterine procedure [65]. A fetus with CDH will be deemed eligible for intrauterine intervention if the following criteria are met: isolated fetal defect, normal fetal karyotype, o/e LHR of < 25%, gestational age of 25–27 weeks, maternal consent.

Fetoscopic endoluminal tracheal occlusion (FETO)

Fetoscopic endoluminal tracheal occlusion is typically performed under epidural anesthesia. After having prepared the surgical field, fetal (presentation, position, location of the mouth) and placental location is determined under ultrasound guidance. The fetus needs to be immobile and anesthetized, which is achieved by intramuscular (lower limb) or intravenous (umbilical vein) medicine administration.

A fetoscope is inserted into the fetal trachea, below the vocal cords, and — with the use of a catheter — a detachable balloon is passed, inflated, and detached to achieve water-tight occlusion (Fig. 5). The balloon is typically placed

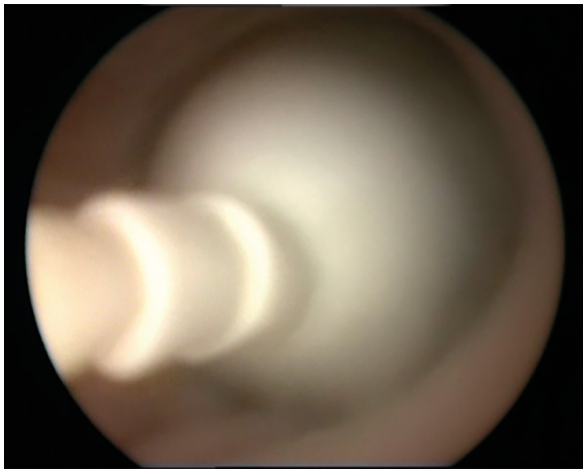

Figure 5. Balloon inside the trachea of a fetus with congenital diaphragmatic hernia (CDH) [fetoscopic endoluminal tracheal occlusion (FETO)]

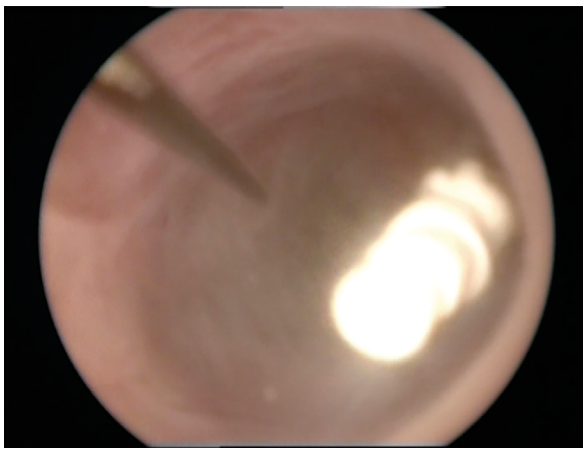

Figure 6. Balloon puncture inside the fetal trachea (visible needle in the upper-left corner)

inside the fetal trachea at 25–27 weeks GA, where it remains until 33–34 weeks. Next, it is punctured with a needle, usually during a second fetoscopic procedure (Fig. 6).

The findings of the randomized TOTAL TRIAL confirmed the efficiency of the FETO procedure in severe congenital diaphragmatic hernia and improved survival, from 15% (no FETO) to 40% (post FETO) [66]. The potential risks associated with the FETO procedure include prelabor rupture of membranes, preterm labor, and placental abruption.

Monitoring and delivery

Fetuses with CDH are at a higher risk for developing polyhydramnios due to the disturbed passage through the fetal gastrointestinal tract. The FETO procedure does not increase the risk for polyhydramnios and, what is more, a timely amnioreduction lowers the risk for preterm labor which might be caused by excess amniotic fluid. Regular

ultrasound monitoring, *i.e.* every 2–4 weeks, is advised. After the FETO procedure, vaginal delivery at the highest level of care center is recommended as CDH is not an indication for cesarean delivery. As severe CDH is associated with unfavorable prognosis, the affected fetuses, especially after the FETO procedure, require multidisciplinary care. Also, transportation of the mother after an intrauterine procedure and the fetus after the delivery should be avoided. The center which provided care to the woman during pregnancy and whose team of perinatologists, neonatologists, and surgeons consulted on the case and may schedule post-delivery procedures on site (intensive care unit [ICU], extracorporeal membrane oxygenation [ECMO], surgery), is the optimal place for delivery.

Emergency balloon puncture

In the event of preterm labor, before elective balloon removal, there are several ways of reversing the tracheal occlusion:

1. An attempt at fetoscopy after membrane rupture — after careful evaluation of the technical conditions and in the absence of regular uterine contractility, it is usually possible to perform amnioinfusion and attempt to remove the balloon using fetoscopy.
2. Balloon rupture through neonatal neck — immediately after delivery, before the cord is cut, a needle is inserted 1–2 cm above the upper sternal region, midline (the procedure may but need not be performed under ultrasound guidance).
3. Balloon rupture through maternal abdomen — it is possible to puncture the balloon by guiding the needle through the maternal abdomen if fetal position allows it. The accessibility depends on fetal presentation and location of the placenta.
4. The EXIT procedure — after neonatal head is delivered and the child is intubated, the balloon is punctured, preferably using a bronchoscope, and the collapsed balloon is removed with small forceps.

Research on developing an improved model of a balloon, which will deflate *in utero* after applying a magnetic field or other triggers, continues and hopefully it will limit the FETO procedure to a single intervention.

SEVERE VENTRICULOMEGALY

Enlargement of the cerebral ventricles of the central nervous system — ventriculomegaly (VM) — is not a separate disease entity in a fetus, but merely a pathological symptom resulting from various causes, chief among them:

— chromosomal abnormalities in the fetus;
— defects of the central nervous system in the fetus;
— intracranial bleeding;
— congenital infection.

Oftentimes, the exact etiology of the condition remains elusive and ventriculomegaly of an idiopathic origin is diagnosed in those cases. In extremely severe cases, VM is associated with elevated risk for perinatal death or unfavorable postnatal outcomes, as well as neurologic defects in the infant.

Enlargement of the lateral cerebral ventricles results in excessive ventricular volume, typically caused by increased pressure of the cerebral spinal fluid secondary to abnormal circulation or abnormal absorption of the CSF. That, in turn, is the source of pressure on the cerebral tissue, leading to irreversible neurological consequences.

Hydrocephalus is defined as increased intracranial pressure in the central nervous system. Antenatal assessment of the intracranial pressure is not feasible, although in extreme cases the effects of the high pressure in the ventricular system may manifest as significantly enlarged head circumference. In the early stage of hydrocephalus, edema, and leukomalacia of the white matter as well as axonal swelling are observed, what later leads to demyelination changes.

Prevalence

The prevalence of mild or moderate ventricular enlargement in the fetal brain has been estimated at 1%, while severe enlargement is observed in approximately 1:1000 of the newborns [67]. The width of the lateral ventricles in the second and third trimester does not usually exceed 10mm, so ventricular thickness of > 10 mm at any stage of pregnancy is defined as ventriculomegaly [68, 69].

Depending on symptom intensity, the following defects have been differentiated:

— **ventriculomegaly**
  Enlargement of the lateral ventricles of the fetal brain with normal biparietal diameter and/or normal circumference of the fetal head. Depending on ventricular enlargement, three stages of ventriculomegaly have been distinguished [70]:
  - mild: 10–12 mm,
  - moderate: 13–15 mm,
  - severe: 15–20 mm;

— **hydrocephalus**
  Hydrocephalus is defined as severe enlargement of the lateral ventricles of the fetal brain and significant enlargement of the biparietal diameter and/or the circumference (at least three standard deviations) of the fetal head. Progressive enlargement of the width and volume of the fetal lateral ventricles during pregnancy is a characteristic symptom of hydrocephalus. The ventricular width is over 20mm and the biparietal diameter of the fetal head (or head circumference) is above 3 standard deviations higher than expected for gestational age. Placement of a ventriculo-amniotic shunt, which allows for continuous evacuation of the excess cerebrospinal

fluid, is one of very few intrauterine therapeutic possibilities in those patients. Still, the literature offers no unambiguous results from large sample size studies to confirm improved neurological prognosis after such interventions. The main outcome and goal of intrauterine therapy in those patients is to decrease the fetal head circumference before delivery by lowering the intracranial pressure. Lowered intracranial pressure may potentially improve the perfusion of the central nervous system (CNS), which in turn may stimulate the reparatory processes in the CNS structures. Nevertheless, the placement of a ventriculo-amniotic shunt does not necessarily lower the risk for neurological damage to the fetus. The primary goal of lowering the pressure in the central nervous system is to slow down the potentially irreversible and destructive changes within the fetal cortex, and to decrease the fetal head circumference before delivery.

Eligibility criteria for the intrauterine procedure

The process of eligibility for invasive diagnostics and intrauterine therapy includes:

— optimal timing for the placement of the ventriculo-amniotic shunt — 23–32 weeks GA;
— fetal karyotyping or, preferably, aCGH testing;
— PCR testing of the amniotic fluid for the following infections:
  - toxoplasmosis,
  - cytomegaly;
— in some cases, the diagnostics of the cerebrospinal fluid obtained during puncture of the enlarged lateral ventricle in the fetal brain (cephalocentesis).

Postnatal management includes

— detailed assessment of the fetal anatomy to exclude concomitant structural anomalies – ultrasound, neurosonography, magnetic resonance imaging;
— monitoring of the lateral ventricular width to determine the dynamics of hydrocephalus progression;
— echocardiography to exclude fetal heart defects;
— maternal serology to detect infection (TORCH);
— if possible and advisable, neurosurgical consultation — to provide information about the type of defect, therapeutic options, and prognosis.

The following criteria need to be met for the fetus to be deemed eligible for intrauterine therapy — implantation of a ventriculo-amniotic shunt

1. Isolated hydrocephalus (lateral ventricle width of ≥ 20 mm and abnormal head circumference) confirmed on ultrasound, neurosonography and/or magnetic resonance imaging (MRI).
2. Dynamic enlargement of the lateral ventricles on subsequent ultrasound tests.
3. Normal karyotype: detection of chromosomal aberrations or presentation with other anatomical defects is indicative of extremely unfavorable prognosis.
4. No evidence of an infection as the underlying cause of the defect.

Prenatal management in the diagnostic-therapeutic process for severe fetal ventriculomegaly/hydrocephalus is presented in Figure 7.

Post-procedure management

During the first few days after the intrauterine intervention, it is necessary to perform an ultrasound test to evaluate the following:

— location of the shunt — normal; possible dislocation into the amniotic sack or into the lateral ventricle of the fetal brain;
— width of the lateral ventricles of the fetal brain;
— minimum and maximum cortical thickness;
— fetal wellbeing.

Delivery after the intrauterine procedure

1. Typically, no indications for earlier elective delivery.
2. Vaginal delivery is possible if fetal head circumference (HC) of < 40cm has been confirmed on ultrasound.
3. Mode and timing of the delivery depend on the recommendation of the obstetric team.

GASTROSCHISIS

Gastroschisis (GS) is a congenital abdominal wall defect, typically located on the right side of the umbilical ring, with the intestine — or other organs, albeit rarely — protruding outside the abdominal cavity. It is a full-thickness defect of the anterior wall of the fetal abdominal cavity, including the peritoneum [71]. The prevalence of gastroschisis has been estimated at 5 in 10000 live births [72, 73]. Typically, it is an isolated defect, and the prevalence of chromosomal abnormalities in fetuses with isolated gastroschisis is similar to that of the general population. Therefore, detection of an isolated defect is not an absolute indication for invasive diagnostics [71, 74–76].

The exact etiology of the defect remains to be elucidated but several theories have been proposed to explain both, the mechanism of its formation and of the secondary damage to the fetal intestine caused by contact with the amniotic fluid. The presence of concomitant intestinal defects (atresia, necrosis, perforation, and torsion) is indicative of a complex gastroschisis (cGS), as compared to simple gastroschisis without any other intestinal abnormalities (sGS). Notably, concomitant defects are more clinically relevant than the pathomechanism of the disease [77].

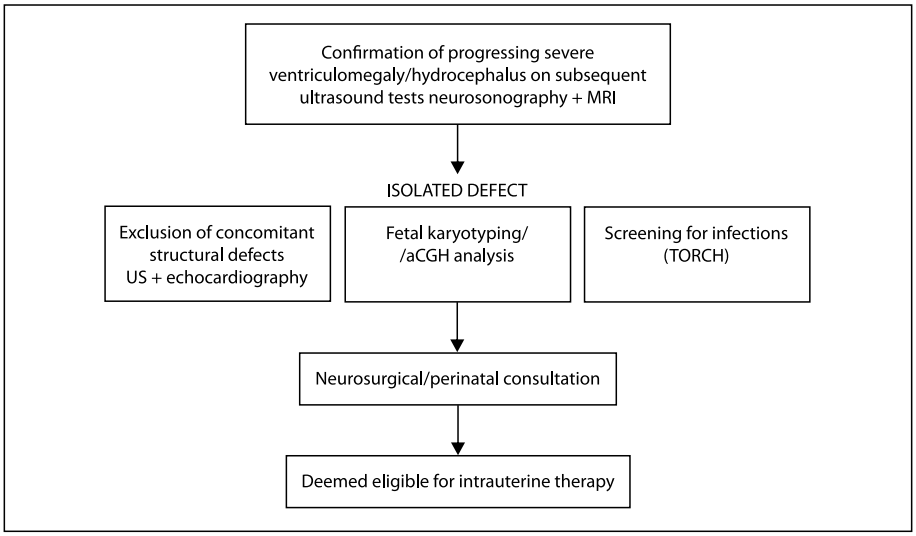

Figure 7. Eligibility stages for intrauterine therapy; MRI — magnetic resonance imaging; aCGH — microarray-based comparative genomic hybridization; TORCH — Toxoplasmosis, Other (Syphilis, Hepatitis B), Rubella, Cytomegalovirus, and Herpes simplex

Overall, cGS is associated with less favorable outcomes [78]. Moreover, progressive intestinal damage — caused by mechanical and chemical stimuli (ischemia, compression from the mesenteric lymph vessels at the site of the defect, and irritants in the amniotic fluid) — is responsible for higher mortality and morbidity also among neonates with sGS [79–81]. Simple gastroschisis in a fetus is associated with favorable prognosis. The neonatal survival rate for fetuses with gastroschisis has been estimated at > 90%, but the rates differ significantly for simple as compared to complex gastroschisis [77, 78, 82–85]. Every single stage of the diagnostic-therapeutic management: from the diagnosis, to proper monitoring, choice of center, time and mode of delivery, duration and type of surgical correction of the defect/surgical intervention, and long-term care, matters as far as improvement of the therapy outcome is concerned [86, 87].

Diagnosis

Prenatal diagnosis of gastroschisis is achieved in 90% of the affected fetuses, in some cases as early as the first trimester. Color Doppler sonography may be used to differentiate between the umbilical loops and the intestinal loops. In the second trimester, it is usually possible to visualize the intestinal defect located on the right side of the umbilical ring and the intestinal loops floating freely in the amniotic fluid. As for differential diagnosis, it is crucial to differentiate between GS and the omphalocele as the diagnostic management of the two conditions varies considerably.

Fetal therapy in gastroschisis

Over the years, amnioexchange has been used in the attempt to lower the concentration of the irritants in the amniotic fluid, which contribute to the inflammatory process. However, randomized studies found that amnioexchange has no definite benefits for fetuses with simple gastroschisis. Serial transabdominal amnioinfusions have also been found to be ineffective in improving the prognosis for the survival or the intestinal and pulmonary function. Nevertheless, amnioinfusion may be propitious for GS fetuses with oligohydramnios [88–91].

The advancements in the field of fetal therapy promote the search for intrauterine therapeutic interventions for complex gastroschisis, but the benefits need to be counterbalanced against the anticipated outcomes and the risk for complications. In theory, antenatal therapy for cGS might prevent secondary damage to the fetal intestine resulting from contact with the irritants in the amniotic fluid or mesenteric ischemia, and in consequence improve the perinatal, neonatal, and long-term outcomes with regard to intrauterine fetal demise, preterm labor, mortality, sepsis, duration of parenteral nutrition and hospitalization, liver failure, number of intestinal complications (short bowel syndrome, necrotizing enterocolitis, functional gastrointestinal disorders), as well as improve the quality of patient life. At present, studies on animal models are being conducted to demonstrate that fetoscopic or open fetal surgery (OFS) enlargement of the defect, with simultaneous covering of the exposed bowel using an artificial graft, might prevent secondary damage to the intestine due to mesenteric ischemia or contact with the irritants in the amniotic fluid. Studies on using transamniotic stem cell therapy to restore bowel function, promote wound healing, and minimize inflammation by stimulating tissue regeneration and direct as well as indirect anti-inflammatory treatment, are also in progress [92–94]. Experimental studies on animal models have demonstrated a possibility of closing

the defect *in utero* using OFS and fetoscopic methods [94]. A report about the first successful fetoscopic repair in a fetus with gastroschisis has been published, but further observational and preferably randomized studies are necessary to evaluate the clinical efficacy of fetal surgery for GS [95]. Attempts have been made to use the Ex Utero Intrapartum Treatment — like (EXIT-like) procedure which involves complete reintroduction of the bowel loops and primary closure of the evisceration during an elective cesarean section before the cord is cut and the first breath is drawn, which prevents significant bowel distention caused by neonatal breathing [93, 96].

All antenatal interventions are associated with an inherent risk for fetal complications and that is why eligibility determination process is crucial, especially if the defect is associated with high survival rate. Fetal therapy is justifiable if significant benefits are to be gained; the primary aim of antenatal therapy for gastroschisis is to prevent secondary bowel injury resulting from contact with the irritants in the amniotic fluid or mesenteric ischemia [94].

Monitoring and delivery

Monitoring of the fetal growth is typically performed at 24 weeks GA and repeated every 3–4 weeks [97]. Most authors recommend more frequent monitoring from 32 weeks GA onwards (every 2 weeks) to evaluate fetal growth, AFI index, and Doppler test. If abnormal fetal growth is confirmed, additional CTG (once a week) is advised [97, 98]. In fetuses with growth restriction or significant bowel distension before 32 weeks GA, monitoring is typically initiated earlier because FGR in fetuses with abdominal defects may be associated with elevated risk for complications, including fetal demise [99, 100].

Timing and mode of delivery remain the topic of much heated debate. The literature lacks conclusive evidence relating to the optimal mode and gestational age at delivery. In the absence of unambiguous data about the effect of continuous exposure of the fetal bowel to the amniotic fluid and the consequences of preterm labor, there is no consensus about the benefits of preterm as compared to term delivery for fetuses with gastroschisis [101, 102]. Nevertheless, delivery at ≥ 38 weeks GA has been reported as more beneficial by a significant number of sources, except for cases associated with a threat to fetal wellbeing, abnormal fetal growth, or significant dilation of the bowel loops.

Considering the above, the choice of the mode of delivery and timing should remain at the discretion of the center providing care to the mother. The decisions concerning gestational age and mode of delivery are made based on the following factors: stage of pregnancy, results of ultrasound tests (fetal growth, AFI, Doppler test, fetal bowel presentation), and CTG. Pre-delivery consultation with a team of specialists, including maternal-fetal medicine expert, neonatologist, neonatal surgeon, and the mother is advised to discuss the details of perinatal management.

Delivery at a tertiary referral center, which is equipped to treat the neonate surgically immediately upon birth, is always advised as it eliminates the necessity to transport the infant with a severe congenital defect. Much evidence indicates that a delivery at a high level of care center is associated with better neonatal outcome as compared to neonates who required transportation [86, 87].

OBSTRUCTIVE UROPATHY

Obstructive uropathy is an anatomical fetal defect which is defined as physiological blockage that inhibits flow of urine from the fetal kidneys to the ureters, bladder, urethra, and the amniotic sack. The prevalence of hydronephrosis due to obstructive uropathy has been estimated at 5–50/1000 fetuses.

Depending on the location of the obstruction, obstructive uropathy results in unilateral or bilateral dilation of one, several or all of the following elements: pelvicalyceal system, ureter, bladder, proximal part of the urethra. Uropathy is classified into lower urinary tract obstruction (LUTO) or upper urinary tract obstruction (UUTO). The prevalence of LUTO has been estimated at 1/2000–4000 fetuses [103–105]. The most common causes of obstructive uropathy include uteropelvic junction obstruction, urethral valve/agenesis, ureterocele, duplex pelvicalyceal systems, cloaca, compression from the neighboring pathological structures, renal tumors/cysts [103, 106].

Diagnosis

Obstructive uropathy is most often diagnosed in the second or third trimester if the presence of hydronephrosis, dilation of at least one ureter, or significantly distended fetal bladder (vesical wall thickness of up to > 2.5 mm) are observed. Amniotic fluid index may be normal or significantly decreased, depending on the type of the defect.

Definitions

1. Hydronephrosis — renal pelvic dilation in the AP plane of > (8)10 mm and/or calyceal dilation of > 2.5 mm and/or dilated/hyperechogenic renal cortex.
2. Ureteral dilation — the ureter is filled with fluid, in advanced cases with haustral folds (megaureter) [106].
3. Distended bladder — bladder sagittal length (in millimeters) above the following value: (Gestational week + 12) [107].

It is necessary to differentiate between obstructive uropathy and other causes of urinary retention, *e.g.* vesicoureteral reflux (typically presenting without bladder wall

distention), or genetic abnormalities, *e.g.* the megacystis, microcolon, intestinal hypoperistalsis (MMIH) syndrome [103, 108, 109].

Indications for invasive diagnostics/ /concomitant genetic abnormalities

— in isolated, typical obstructive uropathies, the risk for chromosomal abnormalities has been estimated at 3–8%;
— in case of concomitant defects and early diagnosis of a distended bladder, the risk for genetic abnormalities is 10–20%;
— the risk for various syndromes [*e.g.*, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities (VACTERL), campomelic dysplasia] is 5–15%;
— invasive diagnostic procedures — although sometimes challenging, *e.g.*, in anhydramnios — are always recommended for patients undergoing elective intrauterine interventions [103, 106, 110–113].

Prenatal management

— depends on the type of the defect (unilateral or bilateral), AFV, gestational age, choice of intrauterine therapy;
— in unilateral uropathy with normal AFV, expectant management with regular ultrasound monitoring (every 4 weeks) is recommended to assess the progression of the defect, function of the contralateral kidney, AFV, and function of other organs at risk for compression from the obstructed structures [114];
— in LUTO with anhydramnios — invasive diagnostics: genetic (ideally aCGH), evaluation of the prognostic parameters from fetal urine sampling; consultation with the mother about the management (pediatric urologist, neonatologist, psychologist); continuation of the expectant management (prenatal hospice) or diagnostic amnioinfusion, or eligibility determination process for intrauterine intervention.

Fetal interventions

— diagnostic-therapeutic amnioinfusion;
— vesicocentesis with prognostic evaluation of the fetal urine;
— serial amnioinfusions (in selected cases);
— vesicoamniotic shunt [104, 111, 113, 115, 116];
— urethroplasty with a balloon catheter in the posterior urethral valve (PUV) (in selected cases) [117];
— cystoscopy (in selected cases) — PUV ablation [118].
— the literature offers a handful of case reports about using nephroamniotic shunting in some patients, including cases complicated by shunt dislocation to the pleural cavity and iatrogenic pleural effusion [119]. In the absence of conclusive evidence about the benefits and risks associated with the procedure, the use of such management in clinical practice is limited. In light of the above, nephroamniotic shunting is not recommended at present.

Eligibility for the procedure [103, 104, 113, 115, 116, 118, 120]

— early (first trimester, early second trimester) LUTO with rapidly progressing destruction of the upper levels of the urinary tract with anhydramnios;
— bilateral obstruction with progressing oligohydramnios;
— significant bilateral vesicoureteral reflux (pseudouropathy) with progressing destruction of the ureters and/or hydronephrosis;
— unilateral, high-intensity obstruction which negatively affects the function of other organs (*e.g.*, circulatory system);
— normal biochemical parameters of fetal urine sampling (Na < 100 mEq/mL, Cl < 90 mEq/mL, osmotic concentration < 210 mOsm/L, Ca < 2 mmol/L, B2 microglobulin < 2 mg/L);
— no other significant concomitant anomalies and other genetic defects in the fetus.

Exclusion criteria

— unilateral uropathy with preserved function in the non-affected, normal AFV and no detrimental effect on the other organs;
— severe subsequent bilateral hydronephrosis with cortical damage (obstructive dysplasia) and/or abnormal biochemical parameters of urine in the subsequent tests (the abovementioned markers above the normal range);
— severe concomitant defects and/or genetic abnormalities in the fetus;
— general infections;
— lack of maternal consent for treatment.

Benefits of the intrauterine procedure

— preserved renal function (complete/partial);
— no/low risk for pulmonary hypoplasia;
— no/low risk for fetal deformations due to anhydramnios, prune-belly syndrome.

Complications after the procedure

— PROM, infection;
— preterm labor;
— 'urinary ascites' due to iatrogenic damage to the vesical wall/distended ureters;
— dislocation of the vesicoureteral shunt (to the amnion, bladder, peritoneum, through the uterine muscle);
— organ damage (mostly bowel, vascular), fetal demise.

Monitoring and delivery

Due to the possibility of dynamic changes in the fetal urinary tract as well as the amniotic fluid volume, monitoring every 3–4 weeks is recommended. More frequent monitoring is advised after fetal therapy interventions — immediately after an invasive procedure. The decision about the timing and mode of delivery is based on several factors, including gestational age and ultrasound test results (fetal growth, presentation of the urinary tract, AFI, fetal Doppler). Surgery for obstructive uropathy is not an absolute indication for a cesarean delivery. Nevertheless, the final decision about the mode of delivery remains at the discretion of the obstetric team. Apart from the basic obstetric criteria, the decision also depends on the prognosis, fetal abdominal circumference (AC/HC), and fetal wellbeing.

MYELOMENINGOCELE

Myelomeningocele (MMC) is a fetal dysraphism of the spinal cord and spinal canal defined as incomplete fusion of the spine and the structures around the spinal cord [121]. Low folate consumption, antiepileptic drugs, diabetes, environmental (elevated temperature during neurulation) and genetic factors promote the development of MMC [122]. Normal progression of MMC is associated with an intrauterine development of Chiari II malformation, presenting as fetal VM, progressive hindbrain herniation, and loss of motor function in the lower extremities, as well as bladder, bowel, and sphincter dysfunction [123].

The defect may have two anatomical presentations:

— open — with hernia sack (meningocele or myelomeningocele) or without hernia sack (myeloschisis);
— closed — the defect in the spinal cord is covered by skin.

The prevalence of the defect has been estimated at 1:2000 births. The survival rate for the first year of neonatal life is 90%, with 75–80% of the affected individuals reaching adulthood [124, 125].

The diagnosis of a bifid spine involves ultrasound imagining of the dysraphism of the vertebral arches, soft tissues, and skin, most often with hernia sack. At present, myelomeningocele is mostly diagnosed during the ultrasound test between 18–22 weeks GA, but in some cases it is possible to visualize the defect as early as during the first trimester ultrasound, not only by evaluating spinal anatomy, but also indirectly by evaluating the intracranial translucency (IT) — an ultrasound assessment of the fourth ventricle and posterior cranial fossa [126, 127]. Second trimester antenatal scan assesses the fetal spine using the sagittal, transverse, and frontal view. It is essential to establish the upper level of the spinal defect, which is defined as the uppermost vertebra with defectively fused ossification centers. Despite the experience of the expert technicians, as well as highly advanced equipment which is currently used for ultrasound testing, the diagnosis of spinal dysraphism may be challenging or altogether impossible. When in doubt or in cases with complex anatomical defects, MRI imaging is recommended. Ultrasound is used to visualize the abnormalities which are characteristic for MMC, including the spine, the central nervous system, and the lower extremities of the fetus (Tab. 5).

Table 5. Three stages of myelomeningocele (MMC) evaluation on ultrasound

	Parameters assessed on ultrasound
Spine	Upper-level defect/spinal dysraphism, signs of tethered spinal cord, hernia sack, placode location, spinal deformity (scoliosis, kyphosis)
Central nervous system (CNS)	Ventriculomegaly (mild, moderate, severe), microcephaly, colpocephaly, banana sign, lemon sign, degree of hindbrain herniation
Lower extremities	Talipes, abnormal motor function

Indications for invasive diagnostics/ /concomitant genetic defects

Intrauterine intervention may be considered in fetuses with an isolated defect, with normal fetal karyotype as the necessary eligibility criterion. It is associated with the fact that approximately 20% of neural tube defects have a genetic component. The most common chromosomal abnormalities as far as spinal dysraphism is concerned include trisomy 18 and 13, and triploidy, but also single-gene abnormalities.

Prenatal management

If MMC is confirmed, non-directive counselling about the possibilities of pre- and postnatal management and referral to a high level of care center which specializes in fetal diagnostics and therapy are advised. Until the patient is transferred to that center, most associations — including the Fetal Medicine Foundation (FMF) — recommend follow-up visits every 4 weeks. Progressive VM is a typical development in spina bifida and is found in 44% of the fetuses before 24 weeks GA, but in 94% of the same fetuses after 24 weeks GA [128, 129]. The 2003–2010 randomized 'Management of Myelomeningocele Study' study (MOMS) analyzed the outcomes of patients who underwent open fetal surgery as compared to a postnatal repair. Randomization was stopped due to ethical concerns. Antenatal repair turned out to be associated with significantly better neurological prognosis for the newborn (unassisted walking: 42% vs 21%), and lower number of ventriculoperitoneal shunts (40% vs 82%) [130, 131].

Table 6. Management of Myelomeningocele Study (MOMS) eligibility criteria for open fetal surgery for myelomeningocele (MMC)

Inclusion criteria	Exclusion criteria
• Gestational age 20 + 0–25 + 6 weeks • Maternal age ≥ 18 years • Ventricular width of the anterior horns of the lateral ventricle < 18 mm • Hindbrain herniation: CM II > 0° • Singleton pregnancy • Normal fetal karyotype • Preserved mobility of the fetal lower extremities • MMC with upper-level defect at ≥ S1	• Fetal defects concomitant to MMC • Type 1 diabetes • Kyphosis > 30° • Cervical incompetence CL < 20 mm • Placenta previa • BMI ≥ 40 kg/m^2 • Rh D alloimmunization and other Rh alloantibodies • Infections: TORCH, HIV, HCV, HBV, active SARS-COV-2 viremia • Uterine anomalies (Müllerian ducts anomalies) • Contraindications to anesthesia • Lack of support from husband/partner • Hypertension, preeclampsia or eclampsia in the current or previous pregnancy • Epilepsy • Extremely low social-economic status • Lack of consent to long-term hospitalization during the postoperative period • Inadequate patient comprehension of the management • History of > 2 cesarean sections • Uterine myomas • History of pelvic laparotomy with purulent peritonitis

CM — cytomegalovirus; CL — cervical length ; BMI — body mass index; TORCH — Toxoplasmosis, Other (Syphilis, Hepatitis B), Rubella, Cytomegalovirus (CMV), and Herpes simplex

In light of the above, it was concluded that surgical intervention in a fetus with spinal dysraphism *in utero* may improve the neonatal outcome and lower the number of complications associated with the CNS defects and the need for ventriculoperitoneal shunting.

Open fetal surgery

Open fetal surgery (OFS) involves incision of the uterine muscle and positioning the fetus so that the repair of fetal MMC may be performed. The procedure has a neurosurgical status since complete untethering of the spinal cord and anatomic reconstruction may be achieved [132]. Management of Myelomeningocele Study eligibility criteria for OFS are presented in Table 6 [130].

In 2017, the Perinatal Center in Bytom, Poland, reported the following results: better psycho-motor function, decreased risk for postnatal implantation of the ventriculoperitoneal shunts (up to 27.8% in the OFS group vs 80% in the postnatal repair group), as well as lower risk for progression of hindbrain herniation (11% vs 70%) [133]. Intrauterine repair not only mechanically shields the spinal cord from the detrimental effects of the amniotic fluid, but it also reduces inflammatory infiltration within the dura matter and the skin [134]. Another benefit of the intrauterine repair is improved continence and the so-called 'social continence' at 3 years of age, which was achieved in 81% of OFS patients vs 70% in the postnatal repair group [135].

Fetoscopic method

The fetoscopic approach offers an alternative to the laparotomic repair of the spinal dysraphism. It uses a minimally-invasive access to the amniotic cavity, *i.e.*, the entire procedure is performed with tools introduced through the trocars. Therefore, difficulty with trocar placement in the amniotic cavity, for example in very obese patients, is the main contraindication for fetoscopic surgery. One of the trocars is the optic trocar, the remaining ones are used to insert the miniatured tools. After the trocars are inserted into the amniotic cavity, it is insufflated with heated and humidified CO_2. Despite being more technically challenging and time-consuming as compared to the open surgery, the fetoscopic repair is infinitely less invasive for the expectant mother, allowing for shorter convalescence and hospitalization, and decreasing the risk for thromboembolic complications [136]. Eligibility criteria for a fetoscopic repair are presented in Table 7. Benefits of the fetoscopic intervention for MMC as well as preoperative management are presented in Table 8.

Hybrid method

Intrauterine surgery for MMC using the hybrid (Belfort) method offers an interesting alternative to the two techniques for spina bifida repair which had been used so far — open fetal surgery and fully percutaneous fetoscopic repair. It is known as 'the hybrid method' as it combines the elements of the abovementioned surgical techniques. It is also called the 'open fetoscopy' method. The abdominal cavity is opened to exteriorize the uterus (that part of the surgery is identical to the classic OFS), and then the trocars are inserted into the uterus directly through the uterine wall — initiating the fetoscopic phase of the surgery [137].

Clinical observations seem to indicate that this surgical method is beneficial, both in terms of technical aspects as well as complications and patient safety [138]. The main technical limitation of the fully percutaneous fetoscopic method is placental location on the anterior wall, which often inhibits safe placement of the trocars into the uterine cavity and constitutes an exclusion criterion for the procedure. The Belfort technique circumvents that problem as the trocars can be inserted at any place, once the

Table 7. Eligibility criteria for fetoscopic myelomeningocele (MMC) repair

Inclusion criteria	Exclusion criteria
• isolated open spinal dysraphism at Th 1–S 1 • gestational age 24–28 weeks • ventriculomegaly < 18 mm • normal fetal karyotype • cerebral manifestations of spinal dysraphism (hindbrain herniation to the spinal canal)	• cervical length on ultrasound < 20 mm • active HIV, HBV and HCV infection • multiple gestation • placental previa • complete paralysis of the fetal lower extremities • fetal kyphosis > 30° • maternal BMI > 35 kg/m^2 • maternal diseases which increase the risk for complications (uncontrolled diabetes, poorly controlled hypertension, or others)

BMI — body mass index

Table 8. Benefits of the intrauterine fetoscopic intervention for myelomeningocele (MMC) as compared to open fetal surgery and postoperative management

Benefits of intrauterine fetoscopic repair for MMC	• shorter maternal convalescence after surgery as compared to other methods (shorter hospitalization) • lower risk for uterine dehiscence /rupture as compared to the open surgery method • chance for a vaginal delivery
Postoperative management	• hospitalization for 7 days postoperatively • out-patient check-up every 2–4 weeks • follow-up ultrasound testing every 2–4 weeks (assessment of the cerebral manifestations, limb mobility, amniotic fluid volume, fetal growth) • monitoring of the inflammatory markers once a week for the first postoperative month

uterus has been exteriorized, which allows to by-pass the placenta. Another advantage over the open method is that the hybrid method does not require the uterine wall to be excised as the minimally invasive fetoscopic technique is applied once the uterus is exteriorized. Importantly, in the original Belfort technique two trocars are inserted into the uterus and not three, as is usually the case in the fully percutaneous method. Another benefit of this technique is the use of additional supporting sutures, which are placed at the designated trocar sites, thus lowering the risk for amniotic membrane dissection — similar sutures are used by some of the centers offering the fully percutaneous repair. Additionally, it is possible to suture the muscular layer of the uterine wall at the trocar site. Both these elements of the procedure significantly lower the risk for PROM, which is one of the complications after intrauterine interventions [139]. Unlike in case of the open surgery, another advantage of both, intrauterine surgery and fully percutaneous fetoscopic intervention is the possibility of a vaginal delivery. Undoubtedly, this surgical method should be considered in the eligibility determination process for an intrauterine intervention in fetuses with spinal dysraphism.

Benefits of the intrauterine surgery for MMC

According to the available sources, despite significant differences between various surgical techniques, the benefits of intrauterine surgery for MMC in fetuses at 12 months of follow-up are similar [136]:

— minimization of the detrimental effect of the amniotic fluid on the exposed neural tissue;
— lower risk for the necessity of ventriculoperitoneal shunting in the neonate (from 82% to 43%);
— higher chance for unassisted walking (by approximately 50%);
— lower risk for hindbrain herniation (> 90%).

The current trend to modify the surgical techniques is the consequence of the attempts to recreate the stages of a postnatal repair, resulting in better neonatal outcomes. Maternal complications — mostly associated with scar dehiscence — and the possibility of vaginal delivery remain the main differences between the procedures. Reports about the decreasing risk for preterm labor and PROM, especially in case of the hybrid method, are optimistic. Nevertheless, further observational studies, preferably randomized, are necessary to conclusively determine the superiority of one method over the other. The final decision about the surgical method should remain at the discretion of the fetal therapy team. That is why it is vital for the centers which offer different surgical techniques to cooperate, to jointly participate in the eligibility determination process, and even refer the patient to the center which has more experience in the selected method.

Delivery

Fetal MMC is not an indication for cesarean section, although such mode of delivery should be considered in cases with large open defects which include several vertebrae and/or large hernia sack, and/or hydrocephalus, which might be an obstetric challenge. As far as patients undergoing OFS are concerned, cesarean section is advised due to the insufficient amount of time for the hysterotomy site to heal. Vaginal delivery remains an option in case of fetoscopic (0% uterine rupture) and hybrid procedures [136].

Complications

Intrauterine surgery, like all surgical interventions, is associated with the risk for complications, with preterm labor as the most common complication. According to MOMS, preterm labor was observed in 79% of the fetuses from the OFS group, out of those 13% were delivered before 30 weeks GA and 21% reached > 36 weeks GA at delivery [130]. According to the Bytom Clinic data, hysterotomy using a diode laser and uterine muscle suture, combined with the tocolysis protocol and the perioperative exchange of the amniotic fluid, resulted in complete reduction of deliveries at < 30 weeks GA and high rate (36%) of deliveries at > 36 weeks GA [140]. Complications after intrauterine interventions due to fetal MMC, regardless of the surgical techniques, are as follows:

— placental abruption;
— prelabor rupture of the membranes;
— hemorrhage;
— preterm labor;
— intrauterine infection;
— fetal demise.

SACROCOCCYGEAL TERATOMA (SCT)

Sacrococcygeal teratoma (SCT) is a neoplasm which originates from the cells from one, two, or three germ layers: ectoderm, mesoderm, and endoderm. Typically, the tumor is located along the midline of the body, with the sacral region (SCT), neck, and the oropharyngeal cavity (where it is known as the 'epignathus') among the most common locations. Less frequent locations include the brain, pericardium, mediastinum, abdomen, and testicles. The tumor is a rare finding in multiple gestations. SCT is the most frequent tumor in the fetus and the neonate, with the prevalence ranging from 1 in 23 000 to 1 in 40 000 live births. The odds of SCT development are 4-fold higher in female fetuses. Intrauterine fetal demise due to SCT significantly lowers the prevalence of the defect in live birth. Most gestations with SCT require careful obstetric monitoring but are otherwise uncomplicated. Fetal anemia or fetal circulatory failure due to rich tumor vascularization may develop in some cases. Expectant management will typically lead to polyhydramnios, generalized edema with the mirror syndrome in the mother, and even intrauterine fetal death. Polyhydramnios may be the cause of preterm labor. Middle cerebral artery peak systolic velocity may be used as a non-invasive method of screening for fetal anemia.

The diagnosis is usually made in the second or third trimester of pregnancy, if on ultrasound the tumor presents as a mass with mixed echogenicity, partially cystic and partially solid parts, calcifications, and variable perfusion. Approximately 15% of the cases are cystic, the remaining 85% are solid and mixed lesions.

According to the American Academy of Pediatrics Surgical Section (AAPSS) classification, four types of sacrococcygeal teratomas may be distinguished:

— type I — the lesion is almost completely extrapelvic, with only a small part inside the fetal body (47%);
— type II — the lesion is predominantly extrapelvic, with a significant part of the tumor located inside the body (34%);
— type III — most of the lesion is intrapelvic, with only a part of the tumor growing outside the body (9%);
— type IV — the lesion is completely intrapelvic (10%).

An overwhelming majority (80%) of SCT cases are type I and II. Type IV presents the greatest diagnostic challenge, which impedes early diagnosis, and the prognosis is typically unfavorable. The lesions develop inside the uterus, compressing the neighboring organs and leading to ureter or bladder obstruction, and hydronephrosis. MRI testing is advised in such cases.

Approximately 15% of SCT patients present with concomitant congenital defects such as rectal atresia, sacral bone defects, bicornuate vagina and/or uterus, spinal dysraphism, myelomeningocele. Teratomas are mostly sporadic, although the literature offers reports of familial cases, *e.g.*, Currarino syndrome (anorectal anomalies, sacral tumors, sacral bone deformities). Only a handful of SCT cases with concurrent chromosomal aberrations have been reported. Currently, there are no indications for fetal karyotyping in fetuses with SCT, although karyotyping may be used as an eligibility criterion for an intrauterine intervention.

It is essential to diagnose SCT antenatally. In a study of 97 SCT cases in Japan, between 2000 and 2009, the perinatal mortality rate was 26%. Out of those, about 21% were born before 32 weeks GA and the mortality rate in that subgroup was 44%. Fetal demise is mainly observed in cases with a rapidly growing, solid, and highly vascularized tumor, as that quickly leads to circulatory failure in the fetuses with non-immune hydrops fetalis. It is the consequence of the so-called 'vascular steal' phenomenon by the tumor, which mirrors the features of a large arteriovenous malformation. Small tumors (< 10cm) constitute a small risk for the fetus and do not require high-intensity ultrasound monitoring (every 2–3 weeks). Larger and more vascularized tumors should be monitored more frequently (every 7–14 days). Ultrasound testing is used to assess tumor size, AFV, echocardiographic and Doppler evaluation of the circulatory system function, and tumor vascularization.

The tumor may also cause damage to the pelvic structures, with some defects developing *in utero* and others due to surgical resection. Vesical rupture *in utero* and urinary tract occlusion have been reported. Also, problems with the rectal and the urinary tract function may be more

prevalent if a sizable portion of the tumor is located within the fetal pelvis.

Early prognostic classification of fetuses with SCT establishes the tumor volume to fetal weight ratio (TFR). Fetuses with TFR of ≤ 0.12 calculated before 24 weeks GA have more favorable prognosis. TFR of > 0.12 is associated with higher incidence of fetal edema (80%) and mortality rate (60%). In one study, TFR of < 0.12 was linked with a 100% survival rate [141]. Other multicenter case reviews confirmed the correlation between TFR of > 0.12 and poor prognosis. Apart from the TFR index, a series of analyzed cases demonstrated that cystic teratomas were associated with better perinatal outcomes as compared to solid lesions [142].

Fetal therapy

After the fetus is diagnosed with SCT, the mother should be referred to a high level of care center which specializes in intrauterine therapy for full-scale diagnostics and eligibility determination process for *in utero* repair. Ideally, the diagnostic process should be conducted at a center which is equipped to perform the intrauterine intervention. The diagnostic process includes 2D and 3D ultrasound, Doppler, and MRI - if necessary. Doppler test and echocardiography are advised to evaluate fetal circulatory efficiency.

Intrauterine interventions in fetuses with SCT

First attempts at fetal therapy involved tumor resection using either laparotomy or open hysterotomy. At present, minimally invasive techniques are more often advised, including:

— interstitial tumor ablation using laser or radiofrequency;
— vascular laser coagulation of the tumor vessels;
— sclerotherapy of tumor vasculature.

The survival rate was 55% (6/11) for open fetal surgical resection as compared to 30% (6/20) for minimally invasive procedures, including electrosurgery, radiofrequency, and laser ablation. Notably, even though the survival rates were relatively low in both groups (OFS and minimally invasive procedures), the surgery was performed in fetuses with non-immune hydrops fetalis, which is associated with extremely high mortality rates even without intrauterine intervention. Mean gestational age at delivery was < 30 weeks in both groups, which emphasizes the risk for preterm labor after surgical intervention and the need for intensive neonatal care after birth.

In another study, laser interstitial tumor ablation (whose objective is to directly ablate the tumor) and vascular laser coagulation (whose objective is to target the tumor's feeding vessel) were compared. Vascular laser coagulation was performed in 11 fetuses and the survival rate was 63.6%. This outcome was more beneficial as compared to the 40.9% survival rate in 22 fetuses who underwent laser interstitial tumor ablation. The authors hypothesized that sudden tumor necrosis and later risk for hemorrhage contributed to the lower survival rate in case of laser interstitial tumor ablation [143–145]. Intrauterine interventions also include amnioreduction, treatment of fetal anemia, and percutaneous shunting of a secondary obstruction in the fetal urinary tract [146] but clinical experience remains limited.

Eligibility determination process for intrauterine intervention

The process of eligibility determination for intrauterine interventions should take place at a high level of care centers, with considerable experience in fetal therapy. At present, non-immune hydrops fetalis and other symptoms of circulatory failure (*e.g.*, cardiomegaly) are among the most significant eligibility criteria for *in utero* interventions. Ideally, the procedure should be performed between 23 and 30 weeks GA. In case of polyhydramnios or fetal anemia, amnioreduction and intrauterine transfusion are also advised.

The main exclusion criteria for fetal therapy are as follows:

— tumor volume: lesion size of up to 10cm is an indication for expectant management;
— type of change: expectant management is typically recommended for cystic and fluid-filled lesions.

In cases with fetal heart failure after 30 weeks GA, elective cesarean section (after a full-course steroid therapy) and subsequent neonatal surgery might be a better solution and help to avoid intrauterine fetal demise. The survival rate for such a course of action is almost 50%.

Postoperative complications

The most common complications associated with fetal therapy for SCT include preterm labor, tumor rupture and hemorrhage (also during the neonatal period), fetal cardiac arrest, tumor recurrence.

Delivery

In the absence of concomitant abnormalities, without the risk of obstructed labor and with the largest tumor volume of < 10 cm, vaginal delivery may be considered. In the remaining cases, elective cesarean section is recommended, especially after fetal therapy interventions.

MONOCHORIONIC PREGNANCY COMPLICATIONS

Twin-to-twin transfusion syndrome

Twin-to-twin transfusion syndrome is a common complication in a monochorionic pregnancy when at least two fetuses share a placenta. Twin-to-twin transfusion syndrome is a hemodynamic volume imbalance across the vascular

Table 9. The Quintero Staging System for twin-to-twin transfusion syndrome (TTTS)

Stage	I	II	III	IV	V
Oligohydramnios/polyhydramnios	+	+	+	+	+
Donor bladder is no longer visible	–	+	±	±	±
Hemodynamic disturbance (AREDF in the umbilical artery, umbilical venous pulsatility, absent flow or negative a-wave in ductus venosus)	–	–	+	+	+
Generalized edema in at least one fetus	–	–	–	+	+
Intrauterine fetal demise of at least one fetus	–	–	–	–	+

AREDF — absent or reversed end-diastolic flow

anastomoses between the fetuses: more blood flows through the vascular anastomoses from the 'donor' twin (donor) to the 'recipient' twin (recipient) [147]. The prevalence of TTTS has been estimated at 5–15% of all monochorionic twin pregnancies [148, 149].

Diagnosis of TTTS

Oligohydramnios in the donor and polyhydramnios in the recipient, with a shared chorion for at least two fetuses, is the basis for the diagnosis of TTTS, if the following conditions are met:

— oligohydramnios: MVP or deepest vertical pocket (DVP) of ≤ 2 cm;
— polyhydramnios: MVP of ≥ 8 cm regardless of GA [147] or ≥ 8 cm until 20 weeks GA, ≥ 10 cm afterwards [150].

The Quintero Staging System — which is used to evaluate the severity of TTTS — is presented in Table 9 [151].

Fundamentals of TTTS management:

— isolated TTTS is not an indication for invasive diagnostics to test for genetic abnormalities;
— patient should be referred to high-level of care center for antenatal therapy;
— elective cesarean section is the recommended mode of delivery for TTTS with expectant management [152];
— TTTS is associated with elevated risk for ischemic and thrombotic complications for the twins (especially the recipient), which might result in deformity or limb deficiency — that complication has also been reported in pregnancies without laser therapy [153–155].

Fetal therapy

Fetoscopic laser ablation of the placental anastomoses remains the standard of care for TTTS. The diagnosis poses little, if any, challenge for an experienced sonographer and is the main eligibility criterion for intrauterine therapy. Still, the eligibility determination process may be contestable in ambiguous cases, especially in stage I TTTS (Quintero) with no clinical manifestations (polyhydramnios, short cervix) and in fetuses at < 16 and > 26 weeks GA [156–159].

Table 10. Management in twin-to-twin transfusion syndrome (TTTS) versus gestational age

< 16 weeks	16–26 weeks	> 26 weeks
Expectant management	Fetoscopy	Amnioreduction Steroid therapy Neuroprotection delivery

Exclusion criteria for laser therapy: premature rupture of membranes, uterine contractility, coagulation disorders, technical obstacles, blood-stained amniotic fluid (relative contraindication), chorioamniotic separation or septostomy after amniocentesis or amnioreduction (relative contraindication).

Risk factors: proximate cord insertion, chorioamniotic separation, GA < 16 and > 26 weeks [158, 160, 161]

Types of intrauterine procedure

The recommended management — depending on gestational age — is presented in Table 10.

Benefits of intrauterine intervention [149, 156, 162, 163]

Technically successful laser ablation of the fetal anastomoses improves survival and neonatal outcomes but does not guarantee that both fetuses will be saved. The survival rates and risk for CNS damage for different types of management are presented in Table 11.

Complications after the procedure

The most common complications after laser therapy in TTTS include: rupture of the membranes, vaginal bleeding or into the abdominal cavity, uterine contractility, intrauterine infection, pulmonary edema, amniotic fluid embolism, and amniotic fluid leakage into the maternal peritoneal cavity [164, 165].

Post-procedure management

1. Weekly follow-up for the first 2 weeks postoperatively — afterwards at the discretion of the physician (every

Table 11. Survival rate and risk for central nervous system (CNS) damage versus choice of treatment

	Expectant management	Amnioreduction	Fetoscopy
Survival of at least one fetus	< 10%	30–83%	76–90%
Survival of both fetuses	< 10%	20–80%	36–70%
CNS damage	50%	14%	6%

1–2 weeks): biometric parameters; MVP; blood flow in the umbilical vessels, middle cerebral artery, ductus venosus; evaluation of the brain, heart, and limbs.

2. If one twin died after the procedure: neurosonography or MRI 4–6 weeks after the intervention [166].

Recommended mode of delivery after intrauterine intervention

Fetoscopic procedure is not an absolute indication for a cesarean section. If ultrasound manifestations of TTTS or twin anemia-polycythemia sequence (TAPS) persist, delivery after 34 weeks GA should be considered [149, 166]. The final decision about the mode of delivery remains at the discretion of an experienced obstetric team.

Selective fetal growth restriction (sFGR) in monochorionic twin pregnancy

Selective fetal growth restriction is characterized by significantly restricted growth of one fetus. Selective fetal growth restriction is believed to be caused by unequal sharing of the placenta and the resulting insufficient transfer of oxygen to the smaller fetus. The prevalence of sFGR has been estimated at 10–15% of all monochorionic twin gestations [167].

Diagnosis

The so-called 'Delphi definition' for sFGR is used in the diagnostic process: detection of one solitary parameter or at least two out of four contributory parameters (Tab. 12) [168].

According to the Fetal Medicine Foundation guidelines, all three of the following criteria need to be met for the sFGR to be diagnosed:

— EFW < 5th centile;
— EFW discordance between the fetuses of ≥ 25%;
— decreased AFV in the smaller twin but normal AFI in the other twin [169].

Selective fetal growth restriction severity

According to the criteria published by Gratacós et al. [170], the umbilical artery Doppler flow in the smaller twin may be used to assess the severity of sFGR :

— type I: normal umbilical artery (UA) Doppler;
— type II: absent or reversed end-diastolic flow in the UA;
— type III: intermittent absent-reversed end-diastolic flow in the UA.

Table 12. Diagnostic criteria for selective fetal growth restriction (sFGR)

Hypotrophic features	Monochorionic pregnancy
Solitary	EFW of 1 of the fetuses < 3rd centile
Contributory	EFW of 1 of the fetuses < 10th centile
	AC of 1 of the fetuses < 10th centile
	EFW discordance ≥ 25%
	PI in the umbilical artery of the smaller fetus > 95th centile

EFW — estimated fetal weight; AC — abdominal circumference; PI — pulsatily index

Fetal therapy

The diagnosis of sFGR with high risk for intrauterine fetal demise (type II but also type III, according to some authors) — is the main eligibility criterion for laser ablation of fetal anastomoses and separation of the fetal venous circulations [171]. In some centers, umbilical cord occlusion of the hypoxic twin is recommended. The procedure is performed to minimize the risk for intrauterine fetal demise of the eutrophic twin. The intervention is contraindicated in the following cases: PROM, uterine contractility, coagulation disorders, technical obstacles (little chance for a successful procedure), blood-stained amniotic fluid after amniocentesis or amnioreduction (relative contraindication).

Higher risk for complications is associated with the following parameters

— proximal cord insertion;
— chorioamniotic separation;
— GA < 16 and > 26 weeks.

Results of the intrauterine intervention are presented in Table 13.

Intrauterine interventions have negligible effect on the prognosis: the mortality rate after the procedure is similar to that observed in expectant management, or higher according to some sources (cord occlusion, post-procedure complications), and the prevalence of damage to the CNS is comparable, slightly less frequent in the normal-weight

Table 13. Results of intrauterine management of selective fetal growth restriction (sFGR)

	Expectant management	Cord occlusion	Ablation of placental anastomoses
Intrauterine fetal demise	4.6–32.7%	53.4–58%	44.3–46.8%

twin and more frequent in the hypotrophic twin. According to most sources, the prognosis for the larger twin improves after cord occlusion in the hypotrophic twin.

Complications after the procedure

The most common complications after laser ablation for sFGR include rupture of the membranes, bleeding from the genital tract or into the abdominal cavity, uterine contractility, intrauterine infection, amniotic fluid leakage into the maternal peritoneum [164, 167].

Post-procedure management

1. Weekly follow-up for the first 2 weeks postoperatively — afterwards at the discretion of the physician (every 1–2 weeks): biometric parameters, MVP, blood flow in the umbilical vessels, middle cerebral artery, ductus venosus, evaluation of the brain, heart, and limbs.
2. If one twin died after the procedure: neurosonography 4–6 weeks after the intervention [165].

Delivery

Fetoscopic intervention is not an absolute indication for a cesarean section. Nevertheless, the mode of delivery depends on the number of live fetuses, their presentation, EFW, potential threat to fetal wellbeing, and fetal hypoxia. If type I hypotrophy is found in the second twin, and in the absence of hypoxia in that twin, vaginal delivery remains an option for pregnancies which do not require laser ablation. Hypotrophy in the first twin, non-cephalic presentation of the first twin and symptoms of fetal hypoxia are indications for a cesarean delivery. The final decision should remain at the discretion of the obstetric team.

Twin reversed arterial perfusion (TRAP)

Twin reversed arterial perfusion develops in a monochorionic pregnancy as a result of abnormal arterioarterial anastomoses in the placenta, with all the blood flowing directly from one fetus to the other. Reversed blood flow in the aorta and a single umbilical artery are typically observed. The body structures of the recipient located above the chest cavity (mainly the head and the upper extremities) will atrophy in the initial stages of the embryonic development due to lack of normal perfusion and tissue nutrition. As the blood flowing through the arterioarterial anastomoses bypasses the placental circulation, it is deoxygenated and lacks nutrients, but it is rich in metabolites of the donor twin.

The donor twin is also known as the 'pump twin,' while the recipient is also known as the 'acardiac' or 'parasitic' twin. As far as the latter twin is concerned, although the term 'acardiac' is more commonly found in the literature, it is not entirely correct as sporadic heart activity may be observed in the theoretically acardiac fetus. The term 'parasitic' is more accurate from the pathophysiological point of view. It is also useful during counselling, when umbilical cord laser ablation of the 'parasitic' fetus is advised. From the psychological as well as medical and legal point of view, this procedure is dissimilar to embryo reduction.

Twin reversed arterial perfusion may only develop in monochorionic pregnancies, monoamniotic as well as diamniotic. At present, the prevalence of TRAP is estimated at 2.6% of monochorionic pregnancies, *i.e.* from 1:9500 to 1:11000 of all gestations, depending on the number of pregnancies achieved using ART and kinds of techniques used in a given population [172].

Approximately 50% of the pump twins die due to congestive heart failure or extreme prematurity due to rapidly progressing polyhydramnios. TRAP has been also reported in a triplet monochorionic pregnancy or even a quadruplet pregnancy.

Diagnosis

The diagnosis of TRAP is typically made between 11–14 weeks GA. The parasitic twin is severely malformed, in most cases the head and the upper limbs are not developed. The lower limbs are developed and mobile. Blood flow in the fetal aorta and the umbilical artery is reversed. Sporadically, at the initial stages of pregnancy, the fetal heart, residual cranial structures, and even upper limbs may be identified.

Indications for invasive diagnostics

The literature offers reports about an elevated risk for chromosomal aberrations in the TRAP syndrome. During the procedure, amniotic fluid is routinely sampled for fetal karyotyping or chromosomal microarray analysis (aCGH).

Fetal therapy

Several methods of vessel occlusion to stop the blood flow to the parasitic twin have been described but their value nowadays is mostly historic. At present, the microinvasive laser coagulation of the intraabdominal vessels of the parasitic twin is the method of choice for TRAP, in cases with timely diagnosis. At late diagnosis, *i.e.*, when the

abovementioned method would be unsuccessful, laser occlusion of the umbilical vessels of the parasitic twin remains an option. Approximately 45% of the pump twins survive the expectant management. Postoperative survival rate is 80% for interventions performed after 16 weeks GA. Delayed intervention until 16–18 weeks GA is associated with 60% risk for spontaneous fetal demise in the acardiac twin, and with hemorrhaging to the CNS or fetal death of the pump twin in 60% of the cases. It is recommended to schedule the procedure immediately after the diagnosis of TRAP is confirmed [173].

Eligibility determination process

— TRAP;
— GA at intervention: 12–14 weeks;
— at late presentation or diagnosis (> 23 weeks GA) — individual eligibility process at a high-level care center is advised [173, 174].

Exclusion criteria

late diagnosis, advanced gestational age with low-intensity hemodynamic changes and polyhydramnios.

Types of intrauterine interventions

Microinvasive laser coagulation of the intraabdominal vessels of the parasitic twin involves an ultrasound-guided introduction of a 18G-needle and 400 µm in outer diameter optical fiber (or 17G needle and 600 µm optical fiber) into the parasitic twin and coagulation of the umbilical artery in the pelvis, the iliac arteries, and distal parts of the aorta [175].

At late diagnosis — depending on the clinical situation and experience of the center — fetoscopic laser occlusion of the parasitic twin umbilical cord vessels or bipolar diathermy coagulation may be used. In a monochorionic monoamniotic gestation, it is prudent to consider cord resection of the parasitic twin to avoid cord entanglement later on, which might lead to the demise of the pump twin [176, 177].

A significantly improved chance for the birth of a healthy child is the main benefit of the intrauterine intervention. Complications include ineffective coagulation of the blood vessels (recurrent perfusion), risk for neurologic complications, and death of the pump twin due to hemorrhage.

Monitoring

If the intrauterine intervention proved to be effective, ultrasound monitoring of the remaining fetus is recommended on postoperative days: 2, 7, and 14, followed by a check-up visit every two weeks. During the first and second postoperative ultrasound, particular attention should be paid to developmental abnormalities in the CNS of the healthy fetus. In case of late diagnosis/expectant management, the frequency of check-up visits should be individually assigned to each patient at the fetal therapy center.

Delivery

The mode of delivery depends on the obstetric status. If the intrauterine intervention was successful, there are no indications for a cesarean section.

Twin anemia-polycythemia sequence

Twin anemia-polycythemia sequence is a rare complication of a twin or multifetal monochorionic pregnancy. It is a form of acute feto-fetal hemorrhage (described in 2007 by Lopriore et al.) resulting from blood flow from one fetus (donor) to the other (recipient) through extremely small arteriovenous anastomoses (< 1 mm in diameter). The absence of the polyhydramnios-oligohydramnios sequence differentiates TAPS from TTTS [178, 179].

Twin anemia-polycythemia sequence may develop spontaneously or as a complication after laser photocoagulation of the fetal anastomoses for TTTS. Due to low prevalence, the findings of statistical analyses for TAPS remain disputable and estimative. The prevalence ranges from 1.6% to 5% of all monochorionic diamniotic gestations for spontaneous TAPS and 16% after fetoscopic laser therapy for TTTS. It is important to differentiate between TAPS and Acute Feto-Fetal Hemorrhage (AFFH), which may develop after labor.

Diagnosis

Antenatal diagnosis of TAPS is based on the measurements of the middle cerebral artery peak systolic velocity (MCA-PSV): > 1.5 MoM in the donor and < 1.0 MoM in the recipient. Postnatal diagnostics involves detection of a significant intertwin difference in hemoglobin (Hb) concentration in the neonatal blood (> 8 g/dL), and one of the two symptoms: reticulocyte index of > 1.7 or the presence of small anastomoses on the surface of the placenta (Fig. 8). Prolonged erythroblastosis in the donor, which is indicative of chronic anemia, has also been described [180]. Stages of TAPS are presented in Table 14.

Fetal therapy

Causative management

The causative management uses laser photocoagulation of the anastomoses, like in case of TTTS. The absence of polyhydramnios in one of the amniotic sacks, lower amniotic fluid clarity and non-smooth surface of the fetal placenta impede identification of the anastomoses, which are small and often peripheral, making the procedure moderately challenging. Still, the method grows in popularity because it is a causative management, but also because longer duration of pregnancy was achieved in patients undergoing laser coagulation of the anastomoses,

even if it is associated with an elevated risk for PPROM. Postnatally, intertwin hemoglobin difference is less pronounced, the Hb levels return to the normal values more swiftly, and the discrepancy in fetal weight is less significant, mainly as a result of improved intrauterine growth in the donor [181].

Symptomatic management

Intrauterine transfusion to the anemic donor is used as a form of symptomatic treatment in cases when technical obstacles impede the laser intervention. Despite considerable experience of the operators in intrauterine transfusions directly to the umbilical vein, some authors suggest using the intraperitoneal transfusion which — by slowing down the absorption of the red blood cells — is supposed to prevent their immediate transfer to the circulation of the recipient twin. That technique is considered to be a temporary solution. Also, it has been suggested to conjoin intrauterine fetal transfusion in the donor with partial exchange transfusion in the recipient to lower its polycythemia. In selected cases, blood obtained from the recipient twin may be transferred to the donor twin instead of blood from another donor. The method is not without limitations, chief among them the need for a double cordocentesis, both in the donor and the recipient, increasing the intervention-related risk. If possible, it is advised to secure allogeneic Rh-matched RBC concentrate, same as for intrauterine transfusions, as it is safer for the mother.

Despite the still existing anastomoses, TAPS recurrence rate after the transfusions is low and the need for repeat transfusions decreases after blood transfusions. Also, the mechanism of anastomotic thrombosis, disabling the existing vascular connections, has also been suggested [181].

Figure 8. Small anastomoses on the surface of the placenta

Management of iatrogenic TAPS

In case of iatrogenic TAPS — after laser therapy for TTTS — yet another procedure is not always effective and if the small anastomoses had not been identified during the first surgery, it might be challenging to identify them during the subsequent intervention. The Solomon technique is recommended during the first laser surgery for TTTS to avoid such cases [181].

Eligibility process

In light of the fact that the survival rates are similar for expectant as well as active management (94% — laser therapy; 84% — expectant management and transfusion), expectant management is advised, while active management is recommended only in severe TAPS. In such cases, higher prevalence of cardiomyopathy and hypertension have been reported in the recipients. Also, elevated creatinine levels in the donors are indicative of transient renal dysfunction [182].

Data on damage to the central nervous system in fetuses with TAPS remain conflicting — intellectual disability and spastic paraplegia have been reported. Inconsistent observational study samples as far as the causal factor for TAPS is concerned, especially cases after earlier laser therapy for TTTS, are believed to be responsible for those inconsistencies. Small sample size of the studies has also been mentioned. Nevertheless, neurological deficits have been observed both, in donors and recipients, although less often in spontaneous TAPS [181, 183–185].

Table 14. Twin anemia-polycythemia sequence (TAPS) stages

Stage	Antenatal	Postnatal difference in Hb concentration
1	Donor MCA-PSV > 1.5 MoM recipient MCA-PSV < 1.0 MoM	> 8 g/dL
2	Donor MCA-PSV > 1.7 MoM recipient MCA-PSV < 0.8 MoM	> 11 g/dL
3	As in stage 1 or 2 + critical cardiac compromise	> 14 g/dL
4	Hydrops in the donor	> 17 g/dL
5	Fetal demise of one or both twins preceded by TAPS	> 20 g/dL

MCA-PSV — middle cerebral artery peak systolic velocity; MoM — multiple of median

Complications

It is necessary to be vigilant about possible complications in pregnant women with TAPS who present with pulmonary embolism or the mirror syndrome [186]. Due to the severity of the pathology and variety of therapies, care over patients with TAPS requires considerable experience and should be offered at a tertiary referral center. In the absence of definite guidelines, the therapy needs to be tailored to the individual needs of the patient, depending on the experience of the perinatologist team and the clinical situation.

Monitoring and check-up visits

Check-up visits at least every 2 weeks with normal fetal parameters, and at least once a week when signs of deteriorating fetal wellbeing appear, are necessary for timely detection of pathological findings in a monochorionic twin pregnancy [186, 187].

Delivery

The literature offers guidelines on the mode and timing of delivery for uncomplicated monochorionic pregnancies but lacks clear recommendations for gestations complicated with TAPS. Therefore, it is safe to assume that vaginal delivery, as per the monochorionic delivery protocol, is possible if the obstetric team can monitor for acute feto-fetal hemorrhage during labor. The decision about timing should remain at the discretion of an experienced team of perinatologists [186, 187].

Article information and declarations

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Conflict of interest

All authors declare no conflict of interest.

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