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Fetal Surgery Centres in Europe

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Summary

This literature review will describe four common and relevant birth defects. Their pathogenetic mechanism, diagnosis and most importantly also relevant treatment options will be discussed. Spina bifida, twin-to-twin transfusion syndrome, congenital diaphragmatic hernia and lower urinary tract obstruction are all currently treatable by a prenatal approach in fetal surgery centres. Fetoscopic closure of the defect in spina bifida, laser coagulation of the placental anastomoses in twin-to-twin transfusion syndrome, fetal endoscopic tracheal occlusion in congenital diaphragmatic hernia or the placement of a vesicoamniotic shunt in lower urinary obstruction are all procedures that are nowadays performed in several fetal surgery centres in Europe. During the last decades, a prenatal approach to the management of these four birth defects has been established and replaced several other approaches, frequently also the termination of the pregnancy.

This development from a postnatal management to a prenatal one offers new perspectives to not only the survival of many of those affected pregnancies, but also the improvement regarding the child's quality of life later on. Therefore, practicing obstetricians, pediatricians, or perinatologists that encounter patients whose pregnancy might be complicated by one of the mentioned birth defects should be aware of the treatment options that exist and to which fetal surgery centres to potentially refer the expecting mother.

Keywords: fetal surgery, spina bifida, myelomeningocele, twin-to-twin transfusion syndrome, congenital diaphragmatic hernia, lower urinary tract obstruction

Introduction

As technological advancement improves not only treatment options but also diagnostic measures, the medical field has been undergoing significant changes in the last few decades. These changes have also been noted in the field of obstetrics and perinatology, respectively. Fetal surgery has now been performed for over 50 years and is still changing by the day. A lot has changed since the first ever fetal therapy, which was the use of intrauterine blood transfusion in cases of Rh incompatibility by Liley in the year 1961. Plenty of milestones have since changed the scope of possibilities and techniques in the field of fetal therapy surgery. One example is the MOMS trial, which has significantly changed the management of spina bifida. (1)

Many congenital birth defects, which would have been a predictor of mortality or severe morbidity in the child's later life, or which would have led the parents to decide for a termination of the pregnancy in the past, can now be treated prenatally. Not only can the fetus' life be saved, but also the child's quality of life can be tremendously improved.
As practicing obstetricians, pediatricians, pediatric surgeons or perinatologists it is important to be aware of the surgical therapeutic options that exist for common congenital anomalies.
In this review, the focus will be set on four of those anomalies, which are spina bifida, twin-to-twin transfusion syndrome, congenital diaphragmatic hernia, and lower urinary tract obstruction. The goal will be to give an overview of the conditions, the indications for the surgical treatment, how this treatment will look like and what the outcome of said treatment would be. Most importantly, the main objective will be to give an overview of some of the major fetal surgery centres in Europe and where each of the four conditions can be treated most effectively, respectively.

Literature selection strategy

For this literature review, the PubMed database was searched. The search regarding publishing years of the used literature was unlimited. Keywords that were used were: fetal surgery, spina bifida, twin-to-twin transfusion syndrome, congenital diaphragmatic hernia, lower urinary tract obstruction.
Information was also sought from websites of the fetal surgery centres in Zürich, Mannheim, Leuven and Warsaw, as well as from Stanford Medicine.

Clinical description of the birth defects, disease mechanisms and pathology, treatment methods

Spina bifida

Spina bifida is one of the most common severe congenital birth defects, affecting about one in 1000 live births. (2) It can be assumed that the actual number of affected pregnancies is much higher than that, since around 25% to 40% of those pregnancies result in abortion. (3) Spina bifida is often used synonymously with the term myelomeningocele, which is the most severe, and open, form of spina bifida. In this birth defect, the neural tube does not close up completely during pregnancy, leaving the vertebral column open and exposing the spinal cord on the back of the fetus. This

exposure of neural tissue leads to both motor and sensory impairments, as well as cognitive impairments in the child later on. (2)

This process is often explained by the so-called two-hit-theory. This theory was first introduced in the year 1990 by Heffez et al and suspected two major processes affecting the exposed spinal cord to cause later neurological deficits. (4)

The first process, also called the first hit, is the failure of the neurulation process, causing the neural tube not to close up completely. This leads to the subsequent malformation of the spinal cord, leaving it exposed and protruded. That exposure of the spinal cord and the meninges causes the second hit: the inflammation of the neural tissues caused by the amniotic fluid they are exposed to. The second hit also describes the mechanical forces which are applied to the spinal cord. (5)

Myelomeningocele is almost always connected with malformations such as the type II Chiari malformation, which is the downward protrusion of the cerebellar vermis and tonsils through the foramen magnum and therefore into the vertebral canal. This malformation causes a subsequent hydrocephalus in the fetus in 90% of the time, resulting from cerebrospinal fluid flow obstruction. (6)

Myelomeningocele may manifest with lower limb paralysis, as well as sensory impairments and urinary or fecal incontinence. There are several other malformations of orthopedic nature as well, such as club foot or hip dislocation for example, that often are exhibited in the fetus. Some, though rather rare, cognitive impairments resulting from open spina bifida include decreased IQ or attention deficits. (2)

Diagnosis is usually established during a routine ultrasound screening in the second trimester of the pregnancy. (2) The so-called “lemon sign” shows the myelomeningocele by crenated frontal bones, while the “banana sign” shows the cerebellum of the fetus in an unusual convex shape. Both of these signs are indicative of a myelomeningocele, as well as a relatively small biparietal diameter or ventriculomegaly. (2) AFP measurements from the mother`s blood and/or the amniotic fluid early on in the pregnancy as a screening method are not performed that frequently anymore, but are sometimes still done in obese mothers, as obesity is a known risk factor for myelomeningocele. (2)

While there is both the option to terminate the pregnancy once myelomeningocele is diagnosed, or to treat the birth defect postnatally, the two-hit theory suggests that the mentioned impairments in the child’s life can be partially prevented, or at least improved, by closing the opening in the back of the fetus and covering meninges and spinal cord, hence protecting them from further neurodegeneration. (7)

Several centres in Europe offer fetal surgery in order to close the open spina bifida. Most centres use similar inclusion criteria for the surgery, some of which are if the affected pregnancy is a singleton pregnancy, a normal karyotype is present in the fetus, the mother is over 18 years old and bilateral leg movement can be observed in utero. (5) The Silesian Centre of Perinatology, Gynecology and Fetal Surgery in Bytom, Poland offers a surgical repair of myelomeningocele in an open manner for almost two decades now. (5)
While spina bifida is usually operated on between 20 to 25 weeks of gestation in Bytom, another large fetal surgery centre located in Switzerland, operates from 23 to 26 weeks. The Universitäts-Kinderspital Zürich offers an open surgical management as well.
The open surgery starts with a hysterotomy and a following adjustment of the fetal position and the myelomeningocele. The lesion is then carefully dissected and covered with several layers of fetal tissue, including a layer of muscle. Finally, the fetal skin is closed, followed by the uterus. The fetal neural tissues are now covered and protected from further damage, while damage that has already occurred cannot be reversed by this or any other operation. (8)
Contrary to the two centres just mentioned, the German Centre for Fetal Surgery and Minimally Invasive Therapy (DZFT) in Mannheim, Germany, offers a fetoscopic approach between weeks 21 and 26. (9)
Professor Thomas Kohl pioneered in Europe by introducing the first minimally invasive surgery in order to manage open spina bifida in the year 2006. (10) Access is established in a percutaneous manner with three ports. Some of the amniotic fluid is removed, after which the amniotic cavity is filled with CO_2 for better visual presentation. This technique is also commonly referred to as PACI – Partial Amniotic Carbon Dioxide Insufflation. The placode is then dissected and covered with a patch of collagen. (10)
The year 2011 has been a significant one in the field of fetal surgery for spina bifida. That specific year, the MOMS study has been published, which compared the results of prenatal versus postnatal management of myelomeningocele. The prenatal treatment comes with certain risks, such as premature rupture of the membrane leading to preterm delivery, placental abruption, oligohydramnios, or uterine dehiscence in the next pregnancy. (11) While there are always risks for complications, the MOMS trial also showed that “prenatal surgery for myelomeningocele that was performed before 26 weeks of gestation decreased the risk of death or need for shunting by the age of 12 months and also improved scores on a composite measure of mental and motor function, with adjustment for lesion level, at 30 months of age” (11) Secondary outcomes have also been

noted, which include an improved motor function and a decrease in the severity of the type II Chiari malformation.(11)

While the MOMS trial therefore showed a benefit of the prenatal surgical approach, there has been a discussion whether the open or the fetoscopic approach should be performed. The fetoscopic method showed higher rates of preterm rupture of the membranes as well as higher rates of leakage, for example. (12) These risks and possible complications should be avoided in the future by optimizing the fetoscopic approach further in order for this method to be significantly beneficial compared to the open approach. (12) Overall, the two methods yield somewhat similar outcomes, though it should be noted that following the fetoscopic approach, vaginal delivery is still possible and therefore eliminates the possible risk of uterine scar dehiscence in a further pregnancy. (13)

One surgical technique that should be noted when discussing the fetal therapy of spina bifida and myelomeningocele is the open fetoscopic approach developed by Michael Belfort and William Whitehead. This technique includes a laparotomy, externalizing the uterus. After that, ports are inserted directly into the uterus and the following part of the surgery is carried out in a fetoscopic manner. (14) Therefore, this approach demonstrates a mix between the open and fetoscopic technique. The results of this specific procedure are significant, since it shows decreased rates of preterm premature rupture of membranes and the risk of damaging the placenta, for example. (15)

Further developments regarding future studies and implementations of this technique should therefore be closely observed.

Twin-to-twin transfusion syndrome

About 10% to 15% of monochorionic twin pregnancies are complicated by the so-called twin-to-twin transfusion syndrome. Without treatment, this birth defect causes the death of the fetus in around 90%, commonly due to premature birth. (16,17) Usually, the placenta is shared equally in monochorionic twin pregnancies, the vessels of each fetus claiming one half of it, respectfully. The so-called vascular equator represents the line where the vessels of each fetus meet on the placenta. (18) The main pathogenetic process is the presence of an arteriovenous anastomosis on the shared placenta of the twins, which leads to a unidirectional blood flow from one twin to another. Purely arterial or venous anastomoses on the other hand have been shown to actually be preventive of the development of a twin-to-twin transfusion syndrome since they enable bidirectional blood flow. (18)

The unidirectional flow of not only blood but also vasoactive substances leads to a significant volume disbalance between the two fetuses. (19)

When talking about this particular birth defect, one fetus is usually referred to as the "donor", while the other is the "recipient". The recipient twin exhibits signs of an increased preload, such as an increased bladder filling and an increased venous umbilical blood flow. (18) This increase in preload subsequently gives rise to the development of polyhydramnios but also hypertension by the release of endothelin. The changes in homeostasis in the twins generates cardiac consequences as well, such as valvular regurgitation or cardiac hypertrophy in the recipient twin. (18)

The donor twin on the other hand exhibits signs of hypovolemia. (17) Contrary to its twin, the bladder filling is significantly decreased which leads to oligohydramnios. The hypovolemia of the donor twin causes the activation of the renin-angiotensin system, which affects the recipient twin by intensifying its hypertension additionally. (18)

The diagnosis is done via ultrasound, by identifying the polyhydramnios in the recipient twin and oligohydramnios in the donor twin. The condition is usually developing between 16 to 26 weeks of gestation. (20) For polyhydramnios, the deepest vertical pocket of amniotic fluid should be over 8 cm up to 20 weeks and over 10 cm after 20 weeks. When oligohydramnios is diagnosed, the deepest vertical pocket has to be measured under 2 cm. (20)

Twin-to-twin transfusion syndrome is classified into five stages, which was first introduced by Quintero et al in 1999. (21) In stage I, bladder filling can still be seen in the donor twin on ultrasound, while in stage II, it is absent. During stage III, abnormal blood flow is observed in the umbilical cords or on the vessels of the hearts of the fetuses, which affects the cardiac function. Stage IV describes presence of hydrops fetalis and stage V is diagnosed in case of the demise of one or both twins. (21)

Table 1. Staging of twin-to-twin transfusion findings according to Quintero et al. (1999)

Stage	**Ultrasound findings**
Stage I	Normal bladder filling in donor twin
Stage II	Absent bladder filling in donor twin
Stage III	Abnormal blood flow in umbilical cords/ heart vessels
Stage IV	Hydrops fetalis
Stage V	Demise of one or both twins

It has often been assumed that the treatment should differ according to the stage that has been diagnosed. For example, stage I has often not been an indication for fetal surgery and instead, close monitoring or amnioreduction have been the management of choice. Other data suggests that the stage of the condition should not influence the treatment, and that laser surgery could be beneficial for stage I as well. (22)

The UZ Leuven in Belgium under Professor Jan Deprest conducts selective fetoscopic laser coagulation of the anastomoses on the chorionic plate of the placenta which are connecting the two vasculatures of the twins. (22) Sequential lasering should be performed, meaning that arteriovenous anastomoses from donor to recipient should be coagulated first, followed by venoarterial anastomoses from recipient to donor. This technique showed increased survival rates. (20)

A line is drawn with the laser across the placenta, to completely seal off any connected vessels. This creation of the line is the functional dichorionization of the placenta, also called the Solomon technique. Following the laser, an amnioreduction is performed before the incision is closed again. (20) The surgery is usually conducted from 16 to 26 weeks of gestation, while procedures done before 17 weeks result in higher rates of preterm premature rupture of membranes (PPROM) and procedures done after 26 weeks are technically more difficult. (18)

The German Centre for Fetal Surgery and Minimally Invasive Therapy (DZFT) in Mannheim, Germany, uses laser coagulation as well. They operate between 16 and 28 weeks, while the exact timing of the intervention depends on the stage of the condition. This centre advertises the fact that procedures are performed even under difficult conditions, such as an obese mother or an anterior position of the placenta. (23)

There are other options for treatment such as serial amnioreduction, which carries a higher risk of mortality and morbidity such as neurological pathologies in the fetus and is therefore no longer the standard treatment. Another option is the selective fetal reduction by the obstruction of its umbilical cord, or the complete termination of the pregnancy. These options are usually chosen if the survival of one or both twins is unlikely in the first place or if other options were not feasible. (20)

Endoscopic laser coagulation does not come without risks as well. Preterm premature rupture of membranes (PPROM) is one possible complication of the procedure, caused by fluid located between the amnion and the chorion. If the surgery is performed under 17 weeks, the risk of PPROM is the highest.

Another risk is the shortening of the cervix, which also leads to prematurity. A cervical length under 28 mm is said to be contributing to an increased risk of premature birth. Administration of betamethasone is therefore recommended after the surgery to reduce the risk of prematurity. (18)

There are some maternal complications that should be considered and looked out for as well, including pulmonary edema, placental abruption or intraperitoneal liquid such as blood or amniotic fluid for example. (18) The surgery has yet no impact on any future pregnancies or the mother's overall fertility. (20)

Laser ablation is the sole treatment option that cures the disease since it stops the pathogenetic process. Laser is therefore the only possibility, that both twins might survive the pregnancy. In fact, 65% of the pregnancies treated with laser coagulation resulted in the survival of both fetuses and the probability to survive for a single fetus is up to 88%. It is recommended to monitor the pregnancy closely after the intervention, including ultrasound controls in a weekly or two-week interval, depending on the stability of the mother. (18)

Congenital diaphragmatic hernia

Congenital diaphragmatic hernia is a birth defect affecting around one to five newborns in 10.000. The exact etiology of the condition is still not entirely known, though it is often associated with syndromes such as Pallister-Killian or Cornelia de Lange, as well as several chromosomal anomalies as well. (24)

Therefore, a partially genetic etiology can be assumed, although teratogenic agents and nutritional factors seem to play a role in some cases as well. (25)

The pathogenetic process begins early in pregnancy, and includes the failed formation of the pleuroperitoneal membranes, which are an essential part of the diaphragm. This causes the formation of a hernia in the diaphragm, which in turn results in abdominal viscera being pushed up through the opening. (25)

The herniation is found on the left side of the diaphragm in most cases, in a posterolateral position in 70% to 75% of the cases. In this most common left-sided location, the viscera that are pushed into the thoracic cavity are possibly made up of stomach, spleen, small and large bowel, or parts of the liver for example. (24)

Two major consequences of the hernia are the hypoplasia of the lungs and pulmonary hypertension. (26) Pulmonary hypoplasia is usually more severe on the ipsilateral side in relation to the hernia, but the process is affecting both sides of the lung. Pulmonary

hypertension is caused by increased thickening of the arterial walls of pulmonary vessels. (25)

One of the first symptoms presenting in the newborn is respiratory distress, which can be noticed by low APGAR scores, as well as low oxygen levels and the protrusion of the newborns chest in effort to breathe. Upon auscultation, breathing sounds are decreased. (24) In cases of hernias of small size, the clinical presentation might be delayed and only shows through feeding difficulties later in life, for example. (25)

The diagnosis of a congenital diaphragmatic hernia is usually established prenatally. In fact, in 68% of the time, the defect is noticed before birth. Important to note in this context is that survival rates are generally lower if the defect is diagnosed earlier. Hernias that are diagnosed postnatally are usually smaller and therefore account for a lower mortality rate. (26) The prenatal diagnosis is established by ultrasound, which might show the pulmonary hypoplasia or abdominal organs located in the thoracic cavity. To assess the size of the lung, the lung-to-head-ratio can be used, which can also be used to predict mortality if the score is under one. Another method frequently used, is the lung/thorax transverse area ratio. (24) During diagnosis and prognosis, it is also quite important to differentiate between the so-called liver-up and liver-down positions, since the former accounts for higher mortality rates or the need of ECMO support later on. (24)

Finally, the exact positioning of the congenital diaphragmatic hernia should be made sure of. The posterolateral position is referred to as a “Bochdalek hernia”, and as already mentioned, usually finds itself on the left side of the diaphragm. If the hernia is located in a more anteriomedial position, we speak of a “Morgagni hernia”, which accounts for 20% to 25% of cases. (25)

Prenatal surgical treatment consists of the occlusion of the fetal trachea by an inflatable balloon during endoscopy. This is recommended for moderate to severe cases, while monitoring might be sufficient in milder stages. (25) In moderate cases, a placement of the balloon is recommended between 30 to 32 weeks of gestation. Severe cases warrant for an earlier placement, usually between 27 to 29 weeks of gestation. (26) Fetal endoscopic trachea occlusion (FETO) includes the anesthesia of the mother, the placement of a canula through the abdominal wall and uterus of the mother and directing it into the mouth of the fetus. Then, a catheter with a deflated balloon enters the fetal trachea up until the carina where the balloon is then inflated with 0.6ml of saline solution and left until its removal in the 34th week. (26)

The UZ Leuven in Belgium under Professor Jan Deprest operates on congenital diaphragmatic hernia with the described method of fetal endoscopic tracheal occlusion (FETO). (27) In fact, Jan Deprest was one of the leading researchers of the so-called TOTAL (Tracheal Occlusion to Accelerate Lung Growth) study, which was a randomized clinical trial that studied moderate and severe congenital diaphragmatic hernias and the survival rates in respect to either conservative or FETO management. (28) The results of this study are of great significance, as they found that the survival rate of newborns with severe congenital diaphragmatic hernia increased from only 15% with conservative expectant care to 40% with FETO surgery. Possible adverse events of FETO were also discussed, which were mainly PPROM and preterm delivery. (28)
The beneficial effect of FETO is demonstrated quite shortly after the placement of the balloon, as changes in ultrasound of the lung can already be seen only 48 hours after the procedure. (26)

Lower urinary tract obstruction

Lower urinary tract obstruction is not just one condition, but it is rather a collection of birth defects leading to an obstruction of urinary outflow of the fetus into the amniotic sac. This blockage of the urethra is most often caused by posterior urethral valves in male fetuses. As this is the most common cause, the majority of affected fetuses are male. (29) Prune belly syndrome is another cause which is also most commonly found only in male fetuses. (30) Other possible etiologies of lower urinary tract obstruction that can also possibly affect females are urethral stenosis, urethral atresia, or cloacal dysgenesis for example. (29) Lower urinary tract obstruction affects about 2 to 3 newborns in 10.000 births, though like with most birth defects, the true incidence is suspected to be higher, as many affected pregnancies are terminated early on or there might be cases of intrauterine fetal demise (IUFD). (30,31)
The obstruction of the urethra and the resulting decreased outflow of urine into the amniotic fluid leads to hypertrophy of both bladder neck and wall, as well as megacystis. (29,30) The kidney is also usually damaged in the form of hydronephrosis or hydroureteronephrosis, and dysplastic changes in more advanced cases. (29) The result of the obstruction of urine flow in more severely affected fetuses is oligohydramnios, which again leads to pulmonary hypoplasia in the fetus caused by the restricted thoracic cavity size. (29,32) Pulmonary hypoplasia, as in other birth defects, is an almost definite cause of neonatal death. (32)

In most cases, the diagnosis is established via prenatal ultrasound, usually during a routine examination in the second trimester. If the case of lower urinary tract obstruction is more severe, it might be diagnosed during the first trimester as well. (29) The so-called "keyhole sign" is usually the main clue in the ultrasound examination. The keyhole sign is formed by the enlarged bladder occurring together with a dilatation of the posterior urethra. The bladder wall is thickened, sometimes measuring more than 2 to 3 mm. (29) Other sonographic findings such as caliectasis and hydronephrosis are also common, though they might be absent in about half of the cases. (29,31) This means, the absence of either of the named sonographic findings does not exclude the diagnosis of lower urinary tract obstruction. The diagnostic measures should also include other examinations, such as a fetal echocardiogram and genetic work-up, to detect possible other underlying malformations. (29) Vesicocentesis of the fetal bladder is usually performed as well, to assess the fetal urine both in a genetic and kidney function aspect. Several parameters should be evaluated to determine the fetal renal function, such as sodium, chloride, calcium, beta-2-microglobulin and osmolarity. The results of these evaluations act as prognostic criteria. (29) The results of the urine biochemistry is considered favorable, if sodium is measured lower than 100 mEq/l, chloride lower than 90 mEq/l, calcium less than 2 mmol/l, beta-2-microglobulin under 2 mg/l and osmolarity less than 210 mEq/l. (29,33)

Table 2. Favorable fetal urine biochemistry

Urine biochemistry parameters	**Results considered favorable**
Sodium	< 100 mEq/l
Chloride	< 90 mEq/l
Calcium	< 2 mmol/l
Beta-2-microglobulin	< 2 mEq/l
Osmolarity	< 210 mEq/l

Another way to assess the severity and probability of survival is the staging system introduced by Ruano et al. (33) This staging system includes the evaluation of three parameters: the amount of amniotic fluid, ultrasound markers and the renal function of the fetus. The staging system includes four stages, where stage I has the most favorable diagnosis. (33) Stage I includes amniotic fluid index measurement within normal range as well as no renal abnormalities. The results of the urinary biochemistry should be favorable. (33) Stage II is diagnosed when oligohydramnios is present and there is

significant bilateral hydronephrosis, and the urinary biochemistry is still favorable. It is considered to be a moderate lower urinary tract obstruction. (33) If oligo- or even anhydramnios are present, as well as hyperechogenic kidneys on ultrasound, including renal parenchymal changes such as cysts, the lower urinary tract obstruction is considered stage III and therefore as severe. The results of the urine sampling are unfavorable at this point. (33) The last and final stage IV includes renal dysplasia and hyperechogenicity with anhydramnios and resulting anuria, with unfavorable results of the urine biochemistry. (33)

Table 3. Stages of lower urinary tract obstruction according to Ruano et al (2017)

Stage	**Amniotic fluid**	**Renal findings on ultrasound**	**Urinary biochemistry results**
Stage I	Normal	Normal	Favorable
Stage II	Oligohydramnios	Bilateral hydronephrosis	Favorable
Stage III	Oligo- or Anhydramnios	Hyperechogenic kidneys; Renal parenchymal changes (e.g., cysts)	Unfavorable
Stage IV	Anhydramnios with anuria	Renal dysplasia with hyperechogenicity	Unfavorable

Ruano also proposes different treatment methods, according to the stage of the condition. Stage I, as it is still mild, should merely be monitored by ultrasound in a weekly manner and does not yet require any further intervention. (33) Stage II though should be managed in in a more proactive way in order to prevent pulmonary hypoplasia from developing. (29) The proposed treatment method here is either fetal cystoscopy or vesicoamniotic shunting. (29) It should be noted here, that in the case of posterior urethral valves as an etiology, cystoscopy is usually the preferred method of intervention since it can diagnose and treat the condition simultaneously by using laser. (30,33) Stage III should be managed by using a vesicoamniotic shunt (VAS). (33) VAS placement is performed under sonographic control and an amnioinfusion is usually done beforehand. While local anesthesia may be used for the mother, fentanyl and pancuronium are used for fetal pain control, either by injection in the umbilical vein or in an arm muscle. (31) A catheter is

then inserted into the fetal bladder, that leads to the amniotic cavity. This allows the fetal urine to pass into the amniotic fluid without further obstruction. (30) Following the shunt placement, routine sonographic examinations should be performed, to assess the correct position and successful drainage of the bladder. Cystoscopy should not be considered in stage III, as the fetal bladder is too small in size. (33) Some inclusion criteria for a vesicoamniotic shunt placement are a normal fetal karyotype, oligo- or anhydramnios or a successful bladder filling after vesicocentesis for example. (34)

In stage IV lower urinary tract obstruction, the progression of the condition is already that severe that neither shunt placement nor cystoscopy are of use anymore. (29) In these advanced cases, amnioinfusions and/or palliative measures are the only management options that can be considered. (29,33)

As with any other fetal intervention, there are certain risks that come with the procedures. Vesicoamniotic shunt placement compared to cystoscopy and their outcomes were studied during the PLUTO trial. (35)

The most common complications during vesicoamniotic shunt placement were preterm premature rupture of membranes, the dislodgement of the shunt or its obstruction, for example. (29) It is for these possible outcomes, that the mother should be monitored for 24 hours following the procedure and sonographic controls should be performed in a one-to-two-week rhythm. (29)

Cystoscopy, similarly, also carries the risk of preterm premature rupture of membranes and prematurity in general. (29) It should though be noted that cystoscopy was found to be the intervention that improved long-term renal function of the neonate as well as its 6-month survival rate the most. (35)

The German Centre for Fetal Surgery and Minimally Invasive Therapy (DZFT) in Mannheim, Germany is specialized in VAS placement between 14 and 30 weeks of gestation. Contrary to many other fetal surgery centres, the centre in Mannheim does not use a two tailed pigtail catheter, but one where the risk of PPROM is significantly lower. Additionally, a catheter with a relatively wide diameter is used, so blockage rates are lowered as well. (36)

The vesicoamniotic shunt is most commonly inserted after 17 weeks of gestation, due to the extensive testing performed before the procedure. (37) Recent findings by Professor Thomas Kohl of the DZFT in Mannheim have though shown that a VAS placement before the completion of 16 weeks may yield improved survival rates, so further future developments in this regard should be observed closely. (37)

Conclusions and suggestions

Spina bifida

Spina bifida, and its severe form myelomeningocele, accounts for quite a large portion of birth defects. Its mechanism of pathology is explained by the failed closure of the neural tube in early weeks of gestation. The so-called two hit mechanism explains the consequential possible sensory and motor impairments in the child's life later on. The first hit describes the unsuccessful closing of the neural tube which leaves the neural tissue exposed, while the second hit describes the destruction of that tissue by chemical and mechanical factors of the amniotic fluid and the uterine wall. The diagnosis is usually established with ultrasound by identifying both the "banana sign" and the "lemon sign". Consequences of spina bifida and/ or myelomeningocele are commonly pathologies like the type II Chiari malformations or lower limb paralysis in the course of the child's life. While there is the option to terminate the pregnancy or treat the newborn after its born, these and other defects can be partially prevented, or at least stopped from progressing by intervening prenatally.

There are several options how the fetus can be treated surgically in the womb. The procedure can either be performed in an open, or in a fetoscopic manner.

One centre in Europe that offers an open approach to the repair of spina bifida is the Silesian Centre of Perinatology, Gynecology and Fetal Surgery in Bytom, Poland.

The surgery here is usually performed between weeks 20 to 25 of gestation, and inclusion criteria include the maternal age over 18 years, bilateral leg movement of the fetus that can be observed in utero, a healthy karyotype and the pregnancy being a singleton pregnancy.

Another hospital that offers an open repair of myelomeningocele is the Universitäts-Kinderspital Zürich in Switzerland in the range from 23 to 26 weeks of gestation.

The open approach is performed via hysterotomy and the covering of the defect with multiple layers of fetal tissue.

A minimally invasive approach by fetoscopy is offered in the German Centre for Fetal Surgery and Minimally Invasive Therapy (DZFT) in Mannheim, Germany. The procedure is usually performed in the span of 21 to 26 weeks of gestation. This centre uses the so-called PACI (Partial Amniotic Carbon Dioxide Insufflation) technique, which describes the removal of amniotic fluid and its replacement with CO_2 for the duration of the operation. The exposed neural tissue is covered by a patch of collagen and therefore protected of further damage.

Outcomes of the MOMS trial showed a clear benefit of the prenatal treatment compared to postnatal management of spina bifida and myelomeningocele. A prenatal repair of the birth defect resulted in improved rates of survival, but also decreased rates of motor function or the development of type II Chiari malformation for example.
A prenatal management either with an open or fetoscopic manner should therefore be considered and recommended during consultations with the mother if inclusion criteria are met. Fetoscopic operations carry certain risks such as premature rupture of membranes for example, though it also allows vaginal birth following the procedure. The decision about which procedure, open or fetoscopic, and as a consequence also which centre are best suited for each mother should therefore be made according to the individual situation.

Table 4. European centres and treatment options for spina bifida

Centre	**Procedure offered**	**Gestational weeks**
Silesian Centre of Perinatology, Gynecology and Fetal Surgery (Poland)	Open spina bifida repair via hysterotomy	20th to 25th week
Universitäts-Kinderspital Zürich (Switzerland)	Open spina bifida repair via hysterotomy	23rd to 26th week
German Centre for Fetal Surgery and Minimally Invasive Therapy (DZFT) (Germany)	Fetoscopic spina bifida repair with PACI technique	21st to 26th week

Twin-to-twin transfusion syndrome

Twin to twin transfusion syndrome affects about 10% to 15% of monochorionic pregnancies and develops due to an arteriovenous anastomosis in the shared placenta of the twins, leading to a unidirectional blood flow from one “donor” twin to the other “recipient” twin. This unidirectional blood flow accounts for an increased preload in the recipient twin, while the donor twin exhibits signs of hypovolemia and its consequences. The condition is commonly lethal if not treated, therefore it should be looked out for during screening ultrasound examinations, especially during and after the 16th to 26th week, as this is the time span where the birth defect usually develops. During the ultrasound examination, signs of poly- and oligohydramnios in the respective twins are indicative of the presence of twin-to-twin transfusion syndrome. As the condition is

diagnosed, the condition should be staged according to its stages from I to V, as treatment options can differ according to the present stage.

The management option to obstruct one of the umbilical cord or to terminate the pregnancy should for example be recommended if the survival of one or even both twins is unlikely, so at a stage of the disease that is already quite advanced.

One fetal surgery centre that offers fetoscopic management of twin-to-twin transfusion syndrome is the UZ Leuven in Belgium under Professor Jan Deprest. The centre conducts the operation usually between 16 to 26 weeks of gestation.

The German Centre for Fetal Surgery and Minimally Invasive Therapy (DZFT) in Mannheim, Germany offers fetoscopic treatment of the condition as well, though the procedures are performed even until the 28th week of gestation.

Both centres use sequential lasering as a technique, which ensures the functional dichorionization of the shared placenta and therefore stops the unidirectional blood flow between the twins. The choice of which centre to send the expecting mothers to depends on the gestational age of the pregnancy, as Leuven offers laser ablation only until the 26th week for example. Other factors, such as maternal obesity or an anterior position of the placenta should also be taken into consideration, since the DZFT in Mannheim advertises to treat even under certain difficult conditions like these.

The procedure generally always carries certain risks such as preterm premature rupture of membranes, pulmonary edema of the mother or placental abruption. To reduce the risk of shortening of the cervix, which might also occur, betamethasone should be administered after the procedure. Overall, the procedure results of the survival of both twins in 65%, and the survival of one twin in 88% of the cases.

In all cases, the pregnancy should be closely monitored in check-up appointments in a span of at least every two weeks in order to screen for certain complications.

Table 5. European centres and treatment options for twin-to-twin transfusion syndrome

Centre	**Procedure offered**	**Gestational weeks**
UZ Leuven (Belgium)	Fetoscopic approach with sequential lasering	16th to 26th week
German Centre for Fetal Surgery and Minimally Invasive Therapy (DZFT) (Germany)	Fetoscopic approach with sequential lasering	16th to 28th week

Congenital diaphragmatic hernia

A congenital diaphragmatic hernia develops due to a defect in the formation of pleuroperitoneal membranes during gestation, leading to a hole in the later diaphragm. This hole allows visceral organs like stomach, liver, spleen or intestine for example to be pushed up into the thoracic cavity. Most of the hernias are to be found on the left side of the diaphragm, usually in a posterolateral position. This position is referred to as a "Bochdalek" hernia. In case of an anteromedial position of the hernia, it is referred to as a "Morgagni" hernia.

Consequences of the hernia and visceral organs finding their way into the thoracic cavity are conditions like pulmonary hypoplasia or pulmonary hypertension in the fetus. These can be noted by the presence of respiratory distress in the fetus, as well as low APGAR scores resulting from it. The diagnosis is usually established via an ultrasound examination, during which the exact position of the hernia should be made sure of, as well as the differentiation between a so-called liver-up or liver-down position. A liver-up position accounts for a higher mortality rate, therefore the detection of such position is of high significance. During diagnosis, measurements such as the lung-to-head ratio and the lung/thorax transverse area ratio should be taken additionally, as these determine prognosis to a certain extent as well.

Mild stages of the condition might only need to be monitored closely, while moderate and severe stages require prenatal surgical treatment. This treatment consists of fetal endoscopic tracheal occlusion (FETO) by an inflatable balloon, which is inserted by placing a canula through the abdominal wall of the mother and a subsequent placement of a catheter through the mouth of the fetus. In moderate cases of congenital diaphragmatic hernias, the placement usually takes place between the 30^{th} to 32^{nd} weeks, while severe cases require an earlier placement, commonly between the 27^{th} to 29^{th} week. The balloon is then left in place until its removal in the 34^{th} week.

One fetal surgery centre in Europe that offers such fetal endoscopic tracheal occlusion (FETO) treatment is the UZ Leuven in Belgium. Professor Jan Deprest was one of the participating researchers of the so-called TOTAL trial, which studied the survival rates of fetal endoscopic tracheal occlusion (FETO) management compared to conservative management options. The study showed a great benefit of the fetal endoscopic tracheal occlusion (FETO) management, as survival rates of newborns with severe congenital diaphragmatic hernias increased from 15% to 40% after the placement of the balloon.

Mothers should yet be informed, that the procedure may come with risks such as preterm premature rupture of membranes and prematurity as a consequence, for example.

Table 6. European centre and treatment option for congenital diaphragmatic hernia

Centre	Procedure offered	Gestational weeks
UZ Leuven (Belgium)	Fetal endoscopic tracheal occlusion (FETO)	Moderate: 30th to 32nd week Severe: 27th to 29th week Removal: 34th week

Lower urinary tract obstruction

Lower urinary tract obstruction describes a collection of conditions that prevent the outflow of fetal urine into the amniotic fluid. Common conditions that cause lower urinary tract obstructions in fetuses are posterior urethral valves or prune belly syndrome in males. Conditions that could lead to lower urinary tract obstruction in female fetuses as well are urethral stenosis or urethral atresia for example. The result of the obstruction of the urine flow is a distended fetal bladder and oligohydramnios. Renal changes and pulmonary hypoplasia are both severe consequences that follow, that might often even be lethal to the fetus.

Therefore, an early and accurate diagnosis and staging of the condition is essential to the survival of the fetus. As most other birth defects, a diagnosis can be partly established by routine ultrasound examinations. The keyhole-sign on ultrasound is one of the main indications for the presence of a lower urinary tract obstruction. But also changes like hydronephrosis, oligohydramnios and pulmonary hypoplasia are important findings that should raise concerns for the presence of this birth defect.

If a lower urinary tract obstruction is diagnosed, it is essential to also perform vesicocentesis to measure sodium, chloride, calcium, beta-2-microglobulin and osmolarity. This should be done in order to assess the renal function of the fetus. Results of the biochemistry can either be favorable or unfavorable for the prognosis.

For a favorable prognosis, sodium should be measured lower than 100 mEq/l, chloride lower than 90 mEg/l, calcium less than 2 mmol/l, beta-2-microglobulin under 2 mg/l and osmolarity less than 210 mEq/l.

According to the ultrasound findings combined with the results of the biochemistry, the condition should be staged. The treatment option should then be chosen according to the stage of the lower urinary tract obstruction.

Table 7. Management of fetal lower urinary tract obstruction according to Ruano et al (2017)

Stage	**Management**
Stage I	Monitoring by weekly ultrasound
Stage II	Cystoscopy (posterior urethral valves) or vesicoamniotic shunt (VAS) placement
Stage III	Vesicoamniotic shunt (VAS) placement
Stage IV	Amnioinfusions and/or palliative care

As a vesicoamniotic shunt placement increases the risk for certain complications such as the obstruction or dislodgement of the shunt, as well as preterm premature rupture of membranes, weekly ultrasound screenings should be performed. Additionally, the mother should be observed for the first 24 hours after the shunt placement.
Cystoscopy also increases the risk for prematurity, though the 6-month survival rate is highest here, as shown in the PLUTO trial.
The decision what procedure and which centre to recommend therefore depends on the stage of the condition and the gestational age of the pregnancy.
The German Centre for Fetal Surgery and Minimally Invasive Therapy (DZFT) in Mannheim, Germany offers surgical vesicoamniotic shunt (VAS) placement between the 14th to 30th weeks of gestation. The centre uses catheters with lower rates of obstruction and preterm premature rupture of membranes, therefore a treatment in this institution decreases the risk of complications, if shunt placement is indicated.

Table 8. European centre and treatment option for fetal lower urinary tract obstruction

Centre	**Procedure offered**	**Gestational weeks**
German Centre for Fetal Surgery and Minimally Invasive Therapy (DZFT) (Germany)	Vesicoamniotic shunt (VAS) placement	14^{th} to 30^{th} week

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