# Fetal Interventions: A Closer Look at Fetoscopic Laser Surgery
## A Literature Review

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# Resumo

Nas últimas décadas, a evolução da técnica imagiológica permitiu o diagnóstico pré-natal de um maior número de malformações congénitas. Simultaneamente com os avanços da técnica cirúrgica e dos próprios instrumentos utilizados, o tratamento fetal destas patologias surge como uma alternativa às opções terapêuticas pós-natais, de modo a melhorar o prognóstico neonatal e otimizar a transição do feto à vida extrauterina. Deste modo, a cirurgia fetal torna-se uma realidade, abrangendo procedimentos por via aberta e intervenções minimamente invasivas, como a fetoscopia. A cirurgia fetoscópica, ou cirurgia endoscópica fetal, consiste na utilização de técnicas de endoscopia para a correção de anomalias estruturais e/ou funcionais do feto, com o auxílio de monitorização ecográfica contínua. A fetoscopia é uma intervenção realizada maioritariamente por abordagem percutânea, permitindo a visualização direta do feto e estruturas adjacentes. Atualmente, a cirurgia fetal mais frequentemente realizada tem como indicação a síndrome de transfusão feto-fetal, complicação da gravidez gemelar monocoriónica, recorrendo à fetoscopia com coagulação a laser. A cirurgia fetal a laser pode também ser uma opção terapêutica noutras complicações das gestações gemelares monocoriónicas, como na sequência anemia-policitemia gemelar e na sequência de perfusão arterial reversa gemelar. Além destas patologias, o tratamento fetoscópico a laser foi também descrito na síndrome da banda amniótica, uropatia obstrutiva, síndrome de obstrução congénita das vias aéreas superiores, corioangioma e teratoma sacrococcígeo.

Esta revisão bibliográfica pretende explorar os diferentes tipos de cirurgia fetal, focando-se na descrição da técnica da cirurgia fetoscópica a laser, bem como nas suas indicações e diferentes prognósticos após a intervenção fetal.

# Palavras-chave

cirurgia fetal;intervenção intrauterina;fetoscopia;cirurgia fetoscópica a laser;procedimento minimamente invasivo

# Resumo Alargado

## Intervenções Fetais: O Papel da Cirurgia Fetoscópica a Laser

Atualmente, a cirurgia pós-natal é a primeira linha terapêutica no tratamento de malformações congénitas. No entanto, um número crescente de patologias pode beneficiar do tratamento *in utero*. A melhoria da precisão e disponibilidade do diagnóstico pré-natal bem como a evolução das técnicas imagiológicas e cirúrgicas e os avanços ao nível dos próprios instrumentos utilizados, permitiu a expansão do campo da medicina materno-fetal e, mais concretamente, da cirurgia fetal.

O tratamento intrauterino de anomalias congénitas surge então como uma alternativa às opções terapêuticas pós-natais, de modo a melhorar o prognóstico neonatal e otimizar a transição do feto à vida extrauterina. Deste modo, a cirurgia fetal tornou-se uma realidade, incluindo procedimentos por via aberta e intervenções minimamente invasivas. O procedimento intraparto extra-uterino (EXIT) é por vezes considerado um tipo isolado de intervenção, enquanto que alguns autores o incluem na categoria da cirurgia aberta.

Nas últimas décadas, a investigação médica tem se focado no desenvolvimento de técnicas minimamente invasivas numa tentativa de minimizar a incidência da rutura prematura pré-termo de membranas (RPPM), considerada o calcanhar de Aquiles da cirurgia fetal. Os procedimentos minimamente invasivos incluem a cirurgia fetoscópica e intervenções percutâneas guiadas por ecografia. A cirurgia fetoscópica, ou cirurgia endoscópica fetal, consiste na utilização de técnicas de endoscopia para a correção de anomalias estruturais e/ou funcionais do feto, com o auxílio de monitorização ecográfica contínua. A fetoscopia é uma intervenção realizada maioritariamente percutaneamente, permitindo a visualização direta do feto e das estruturas adjacentes. A cirurgia fetoscópica abrange ainda uma grande variedade de procedimentos, destacando-se a fetoscopia com coagulação a laser para o tratamento da síndrome de transfusão feto-fetal (STFF), por ser a cirurgia fetal mais frequentemente realizada.

A STFF é uma complicação das gestações gemelares monocoriónicas, resultando numa taxa de mortalidade perinatal de cerca de 90%, se não tratada. Nesta síndrome, a distribuição desigual de anastomoses vasculares placentárias provoca um fluxo sanguíneo unidirecional de um feto para o outro, causando instabilidade hemodinâmica. Deste modo, instala-se uma discordância de líquido amniótico entre os fetos, resultando num gémeo recetor que apresenta poliúria, polihidrâmnios e hidrópsia e num gémeo dador

hipovolémico, oligúrico e com oligohidrâmnios. Atualmente, a fetoscopia com coagulação a laser é o tratamento *standard* desta síndrome, tendo o procedimento sofrido várias alterações desde a sua introdução em 1988. A cirurgia consiste na identificação e ablação das anastomoses por fetoscopia a laser, com contínua monitorização ecográfica. Previamente à terapia a laser, a amniocentese seriada era o tratamento de escolha. Para comparar esta abordagem terapêutica com a fetoscopia a laser, foi desenvolvido um ensaio clínico randomizado que provou a eficácia da coagulação a laser na STFF. Mais tarde, foi desenvolvida a fotocoagulação a laser seletiva em que apenas são coaguladas as anastomoses comunicantes entre os dois fetos, em contraste com a técnica anterior não-seletiva em que todos os vasos da membrana inter-fetal eram coagulados. Com o objetivo de reduzir a incidência de anastomoses residuais e, assim, diminuir o risco de sequência anemia-policitemia gemelar e STFF recorrente, foi desenvolvida a técnica de Solomon. Esta abordagem consiste na coagulação de todo o equador vascular, incluindo anastomoses que possam não ser visíveis fetoscopicamente, reduzindo a probabilidade de anastomoses residuais. A eficácia desta técnica foi posteriormente comprovada num ensaio clínico randomizado.

No entanto, a cirurgia fetal a laser pode também ser uma opção terapêutica noutras complicações das gestações gemelares monocoriónicas, como na sequência anemia-policitemia gemelar e na sequência de perfusão arterial reversa gemelar. Além destas patologias, a terapia laser foi também descrita no tratamento de condições como a síndrome da banda amniótica, uropatia obstrutiva, síndrome de obstrução congénita das vias aéreas superiores, corioangioma e teratoma sacrococcígeo.

Apesar dos avanços significativos na área da medicina fetal, existem ainda limitações e obstáculos que encaminham futuros estudos e ensaios clínicos. A RPPM representa o principal desafio, sendo que novas técnicas cirúrgicas, novos instrumentos fetoscópicos, e métodos de vedação membranar inovadores encontram-se já a ser investigados de modo a otimizar os *outcomes* após as intervenções fetais. Relativamente à cirurgia fetoscópica a laser para o tratamento da STFF, os aspetos a desenvolver focam-se na melhoria do prognóstico neurológico neonatal e do neurodesenvolvimento infantil.

# Abstract

Over the past decades, due to the advances in imaging methods, prenatal diagnosis of congenital malformations has become widely available. Simultaneously with the improvement of surgical techniques and the development of instrumentation technology, fetal treatment of these pathologies became possible, arising as an alternative to the standard postnatal therapy, aiming to improve fetal outcomes and optimize the transition into neonatal life. Thus, fetal surgery emerges, comprising open interventions and minimally invasive procedures, such as fetoscopy. Fetoscopic surgery, or fetal endoscopic surgery, is a technique that uses endoscopic technology to correct structural and/or functional fetal anomalies *in utero*, under continuous ultrasound guidance. Fetoscopy is mainly performed percutaneously and allows direct visualization of the fetus and adjacent structures. Nowadays, fetal surgery is most commonly indicated in the treatment of twin-to-twin transfusion syndrome, a complication of monochorionic twin pregnancies, using laser coagulation. However, fetoscopic laser surgery can also be performed for the management of other conditions affecting monochorionic pregnancies, such as twin anemia polycythemia sequence and twin reversed arterial perfusion sequence, as well as several other pathologies including amniotic band syndrome, lower urinary tract obstruction, congenital high airway obstruction syndrome, chorioangiomas, and sacrococcygeal teratomas.

The aim of this literature review is to provide a brief overview of the most common fetal interventions and to describe fetoscopic laser surgery, covering its indications, techniques, and outcomes following fetal treatment.

# Keywords

Fetal surgery;intrauterine intervention;fetoscopy;fetoscopic laser surgery;minimally invasive procedure

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| | |
|---|---|
| ABS | Amniotic Band Syndrome |
| CDH | Congenital Diaphragmatic Hernia |
| CHAOS | Congenital High Airway Obstruction Syndrome |
| EXIT | Ex-utero Intrapartum Treatment |
| FETI | Fetal Endoscopic Tracheal Intubation |
| FETO | Fetoscopic Endoluminal Tracheal Occlusion |
| FHR | Fetal Heart Rate |
| FTP | Fetal Treatment Program |
| IFMSS | International Fetal Medicine and Surgery Society |
| LUTO | Lower Urinary Tract Obstruction |
| MCA-PSV | Middle Cerebral Artery Peak Systolic Velocity |
| MMC | Myelomeningocele |
| MOMS | Management of Myelomeningocele Study |
| MRI | Magnetic Resonance Imaging |
| PPROM | Preterm Prelabor Rupture of Membranes |
| RCT | Randomized Controlled Trial |
| TAPS | Twin Anemia Polycythemia Sequence |
| TOPS | Twin Polyhydramnios-Oligohydramnios Sequence |
| TOTAL | Tracheal Occlusion to Accelerate Lung Growth |
| TRAP | Twin Reversed Arterial Perfusion |
| TTTS | Twin-to-Twin Transfusion Syndrome |
| UCSF | University of California San Francisco |

# 1. Introduction

In 2020, congenital malformations were the leading cause of all infant deaths in the United States, accounting for 21% of these deaths. (1) Despite the standard treatment for most birth defects remaining a planned delivery followed by postnatal therapy, a growing number of fetal anomalies may benefit from prenatal surgical intervention. (2) Therefore, fetal therapy emerged with the goal to provide high-quality management of high-risk pregnancies as well as good fetal and neonatal outcomes. (2,3)

Over the past decades, fetal surgery evolved drastically from an ideal to practice, due to the improvements in prenatal diagnosis accuracy and availability. (4,5) Together with research using animal models, prenatal ultrasound allowed for the detection and better understanding of the pathophysiology of several fetal conditions. (5) The advances in imaging methods, the development of modern instrumentation, and the progress of surgical techniques led the field of maternal-fetal medicine to grow into a medical subspecialty being able to offer prenatal diagnosis and management to a new class of patients – the fetus. (4,6,7) The aims of maternal-fetal interventions range from the reduction of irreversible organ damage to complete prenatal cure. (8)

From attempts in animal models to subsequent clinical studies and randomized controlled trials (RCTs), the treatment for each condition suffered several modifications until successful therapeutic approaches were established. (3,4,9) The positive outcomes from RCTs were essential to support fetal interventions, ensuring the feasibility, safety, and benefits of the studied procedures, but also to report the limitations of each intervention and to establish eligibility criteria. (9) Moreover, a detailed and cautious consideration of the risks and benefits, for both fetus and mother, is essential. (10,11)

It is vital to comprehend the range of fetal interventions, the differences between each type as well as their advantages and weaknesses, so that potential indications can be explored. Fetal surgery comprises two main types of procedures – open surgeries and minimally invasive interventions. (7,8,12) While some authors consider ex-utero intrapartum treatment (EXIT) procedures an open intervention, some classify them as a distinct fetal procedure. (8,11,13) Whereas a hysterotomy is required in open surgery, in minimally invasive interventions a needle or trocar is inserted intrauterinelly under ultrasound guidance. (3,12) In addition, minimally invasive interventions can be divided into fetoscopic surgery, including a wide range of techniques from laser therapy to tracheal balloon placement, and ultrasound-guided procedures. (7,8,14)

In the last decades, technological advances in endoscopic techniques propelled the progression from open fetal surgery to fetoscopy, aiming to decrease the maternal morbidity associated with open interventions, mainly related to preterm premature rupture of membranes (PPROM). (12,15) Currently, minimally invasive interventions are the most common type of fetal surgery, however, PPROM remains a challenge in these procedures. (8,15)

Nowadays, fetoscopic laser surgery for severe twin-to-twin transfusion syndrome (TTTS), a complication of monochorionic twin pregnancies, is the most frequently performed fetal surgery. (16,17) Nevertheless, there are other potential indications for fetoscopic laser interventions, such as amniotic band syndrome (ABS), lower urinary tract obstruction (LUTO), congenital high airway obstruction syndrome (CHAOS), chorioangiomas, and sacrococcygeal teratomas. (3,12,18–20) Laser photocoagulation can also be used for further fetal pathologies complicating monochorionic gestations, such as twin anemia polycythemia sequence (TAPS) and twin reversed arterial perfusion (TRAP) sequence. (21–23)

## 1.1. Objectives

Fetal surgery is a relatively recent area of maternal-fetal medicine, and one that is in constant evolution, therefore this literature review aims to clarify the types of fetal intervention, comparing the risks and benefits between them; to provide a better understanding of the indications, the evolution of techniques, the current technique and its modifications, and pregnancy and neonatal outcomes of fetoscopic laser surgery, currently the most commonly performed fetal procedure; and to explore future indications that may benefit from fetoscopic laser therapy.

# 2. Brief historical review and ethical concerns

Despite the majority of fetal anomalies having indication to be treated postnatally after planned delivery, there are some rare conditions in which treatment is needed before delivery, either to save the fetus's life or to prevent irreversible organ damage. (2,24) However, it is important to notice that the interventions are invasive and carry significant risks for both the fetus and mother, hence the importance of a conscious assessment of the risks and benefits before each procedure. (24)

In this brief review of the history of maternal-fetal medicine, the main focus will be on the events and landmarks that propelled the field.

The first fetal intervention was performed in 1963 by William Liley, in New Zealand. The procedure consisted of a percutaneous intrauterine transfusion for hemolytic disease of the fetus and newborn. (25) Still in the 1960s, different surgical techniques for fetal transfusions arose, namely by open hysterotomy. (26) However, open transfusion carried high morbidity and mortality, reason why it was rapidly left aside. Despite the urge to innovate, the knowledge of anesthesia and imaging techniques at the time was not enough to ensure positive outcomes. (7)

In the 1970s, the developments in ultrasound imaging boosted prenatal diagnosis, increasing the knowledge around fetal pathophysiology. (2,7) More than 80% of the most prevalent congenital birth defects develop in the first trimester of pregnancy, hence the importance of the first-trimester ultrasound. Furthermore, the improvements in ultrasound quality and pixilation, together with the possibility of dynamic flow evaluation and multi-dimensional structures reconstruction, increased the diagnostic sensitivity for anatomical anomalies. The use of transvaginal sonography also played an important role in increasing the precision of diagnosis. Later, 3D/4D imaging came to ameliorate the diagnosis and 3D ultrasound is now commonly used in the identification of congenital malformations as well as in surgical planning and in guiding both open and fetoscopic interventions. (2) The widespread use of ultrasound for prenatal diagnosis led to the next step in innovation in maternal-fetal medicine – the path of fetal therapy. (7)

In 1982, Harrison and his team at the University of California San Francisco (UCSF) Fetal Treatment Program (FTP), successfully performed the first therapeutic fetal intervention – a fetal vesico-amniotic shunt repair for hydronephrosis due to LUTO. The FTP was extremely relevant in the evolution of fetal therapy, allowing for multidisciplinary collaboration between specialists in maternal-fetal medicine, obstetricians, neonatologists, pediatricians, pediatric surgeons, and radiologists, which enabled innovation and high-quality patient care. (7, 24) Later in 1982, these experts organized an international meeting to discuss the future of maternal-fetal medicine. At the meeting, the guidelines that remain the ethical basis for the current practice were drafted. The multidisciplinary group gathered again a year later officially creating the International Fetal Medicine and Surgery Society (IFMSS). (7)

In 1986, UCSF accomplished the first successful open repair for congenital diaphragmatic hernia (CDH) and in 1994 the team conducted a trial for the treatment of CDH by open surgery. However, USCF wasn't the only center focused on innovation. (7) In 1988, in Salt Lake City, DeLia completed the first fetoscopic laser photocoagulation procedure for TTTS. (27) In many leading centers the enthusiasm around fetoscopy continued to grow and several fetoscopic techniques were developed. The first fetoscopic surgeries were mainly dedicated to the umbilical cord and placenta in monochorionic twin pregnancies. (7,24)

Fetoscopy emerged as an alternative to open surgery as an attempt to reduce iatrogenic PPROM, by minimizing uterine and membrane trauma. (24) Despite this being its main goal, fetoscopic surgery was also aimed at minimizing the maternal morbidity associated with the laparotomy incision. (2) The advances in endoscopic technology, which led to smaller and less invasive devices, played an important role in this transition. (7)

In 1998, the European Commission founded the Eurofetus project which was a milestone in the history of fetal medicine. (7) Beginning in 1999, the Eurofetus trial was the first European multicenter RCT in the field of maternal-fetal medicine. (28) Its goal was to compare fetoscopic laser ablation to amnioreduction for severe TTTS and the recruitment was terminated earlier, due to the significantly better outcomes of laser coagulation. (7,24,28) The acknowledged success of the trial diminished the concerns regarding the safety of endoscopic fetal surgery and proved the viability of fetoscopic techniques, being a crucial step for the wide scientific acceptance of fetoscopy. (24) In 2001, Eurofetus supported another multicenter RCT to evaluate the fetoscopic endoluminal tracheal occlusion (FETO) procedure in the treatment of severe CDH. (7,24) The trial demonstrated improved survival benefits and decreased maternal morbidity of FETO compared to the standard postnatal therapy. As the FETO trial was in progress, so was the Management of Myelomeningocele Study (MOMS) trial. The MOMS trial represented another key point in the evolution of maternal-fetal medicine. Beginning in 2002, its goal was to compare prenatal open surgery for myelomeningocele (MMC) with the standard postnatal repair. The North American RCT was stopped early due to the efficacy of prenatal surgery. (2,7) The trial reported improved postnatal neurological outcomes but it was associated with increased maternal complications related to the open surgery. (7,29) While the MOMS trial was studying MMC open repair, fetoscopic approaches started to appear attempting to decrease maternal morbidity. (30,31) In 2021, the results of a study comparing open fetal MMC surgery with fetoscopic repair were published, concluding that the perinatal mortality and postoperative complications were similar in both procedures, however, the fetoscopic approach allowed for vaginal deliveries, eliminating the risk of uterine dehiscence. (32) Following the success of the MOMS trial, and to confirm the results from the FETO trial, the Tracheal Occlusion to Accelerate Lung Growth (TOTAL) trials were created and consisted of two multicenter international RCTs to assess the survival benefit of the FETO procedure for moderate and severe left diaphragmatic hernia. (7,33,34) The trial for severe CDH showed significantly higher survival to discharge and survival to 6 months of the patients undergoing FETO, in comparison to the expectant care group. (33)

The path of fetal therapy has now over 50 years of history and continues to develop. Nowadays, the current management of pregnancy enables the early detection of fetal malformations allowing these cases to be referred to maternal-fetal centers for more precise diagnosis and treatment if required. (2,24) However, despite the advances in technology and surgical techniques, and the transition from open to minimally invasive surgery, preterm birth is still a major complication. Even though fetoscopy diminished the PPROM in comparison to open procedures, it is still considered the "*Achilles' heel of fetal surgery*". (24)

Despite the main goal of fetal interventions being the improvement of neonatal and future outcomes, it is essential not to disregard the health and needs of the mother. It is vital to bear in mind that the woman will also be submitted surgically and pharmacologically and that her understanding of the procedures and evaluation of risks and benefits for the fetus, neonate and herself must be discussed, respecting patient autonomy. Therefore, the pregnant woman informed consent is necessary to perform the interventions and her decision to decline treatment must be accepted and respected, even if after birth it could be overridden. This emphasizes the need of delivering accurate and useful information for a better decision-making process. Alternative management options should always be presented, including pregnancy termination and adequate referral services. Another factor of the decision-making process that should be taken into account is the distinction between standard or evidence-based interventions, and innovative or research procedures. The risk to the fetus and mother when submitting to innovative therapies needs to be carefully considered to protect both patients hence the importance of systematic formal research. (10)

Ultimately, the developments inherent to the enterprise of fetal therapy, lead to new challenges concerning high-quality care and the complex balance around the pursuit of innovation while maintaining responsible and ethical research. (7)

# 3. The surgical technique

As previously stated, fetal surgery can be divided into minimally invasive procedures, open interventions, and EXIT procedures. (7,8,35) Nowadays, minimally invasive interventions are the most common fetal surgery, comprising fetoscopic and ultrasound-guided surgeries. (8) Maternal-fetal surgery is usually performed in the second trimester of pregnancy, as it is considered a safe period for these interventions. (36)

## 3.1. Anesthesia and general considerations

Anesthetic techniques in fetal surgery have evolved during the last decades to guarantee the safety and viability of maternal-fetal interventions. (8,35)

All drugs are able to enter fetal circulation through the placental barrier, although to different extents. Volatile anesthetics, opioids, benzodiazepines, and atropine are some examples of drugs that easily transfer from maternal circulation to the fetus. (8)

Anesthesia and analgesia in maternal-fetal surgical procedures improve the surgery outcomes by inhibiting the fetal autonomic response to stress, minimizing fetal movement, and achieving uterine relaxation. Fetal analgesia prevents neuroendocrine and hemodynamic alterations, which can be activated from 18 to 20 weeks of gestation even if pain perception only develops later. (35) Moreover, if fetal physiological stress response is not inhibited, short- and long-term consequences in neurodevelopment can arise. Administration of fetal analgesia can be maternal or directly to the fetus, either intramuscularly or intravenously through the umbilical vein. (8) When provided fetally, analgesia is administered under ultrasound or endoscopic guidance. (3) Muscle relaxants can also be administered to decrease fetal movement. (8,35) The dosage of drugs given to the fetus is adjusted to the estimated fetal weight given by the latest ultrasound, considering anatomical defects that may alter its value. It is important to bear in mind that the umbilical cord and placenta are not sensory innervated, so fetal analgesia during interventions involving these structures is not necessary. (8) If needed, maternal opioid analgesia can be provided to diminish fetal movements. However, for the remaining procedures, direct fetal analgesia with opioids and muscle relaxants is given. Atropine is also often administered to decrease the risk of fetal bradycardia. (8,35)

Preoperatively, for both open and closed fetal surgery, pretransfusion tests should be performed and adequate blood products provided for transfusion. Uterotonics should also be available to avoid uterine atony, in the event of an emergent cesarean delivery. (8) In the preoperative period, prophylactic antibiotics and aspiration prophylaxis should be given. (3,8) Intraoperative monitoring of maternal and fetal hemodynamics is vital for minimizing the risk of possible complications. Fetal monitoring comprises the periodic assessment of fetal heart rate (FHR) by Doppler ultrasound and of fetal cardiac function. (8) Postoperative management is the standard postoperative care following a cesarean delivery with additional fetal monitoring, and, after open surgery, tocolysis. In minimally invasive interventions with preoperative tocolysis, the continuation of tocolytic agents administration is usually not necessary. The pregnant woman should also be monitored and special attention must be paid to signs of pulmonary edema. Regarding pain control, oral analgesics are the most commonly provided after minimally invasive procedures, while in the postoperative period of open surgery, epidural analgesia is preferred. A risk factor for preterm delivery is inadequate analgesia in the postoperative period. (8,35)

## 3.2. Open fetal surgery

Open maternal-fetal surgery is the most invasive type of fetal intervention and it is used in the treatment of several fetal pathologies, such as MMC, congenital pulmonary airway malformations, and sacrococcygeal teratoma. (3,4,37)

Open surgery offers excellent fetal exposure. (5) For proper technique of open fetal procedures, the woman is placed in supine position with left uterine displacement. (2,8) Maternal general anesthesia is administered and the achievement of profound uterine relaxation is essential before and throughout the procedure, until closure. Vasopressors can also be provided to ensure the maintenance of uteroplacental blood flow. Tocolytic agents may be administrated. Preoperatively, an epidural catheter should be inserted for postoperative analgesia. (8) The placenta and fetal position are then located through ultrasonography, and a laparotomy is performed to expose the uterus. (2,3,8) The amniotic membranes are fixed to the uterine wall by uterine staplers with absorbable sutures, allowing access to the uterine cavity, ensuring hemostasis, and preventing membrane separation. (2,8) The fetus is then positioned for the specific procedure and adequately monitored. (2) Maintenance of uterine volume is achieved by a continuous infusion of warmed saline solution. (2,8) At that stage, fetal analgesia is administered under ultrasound guidance. (4,8) Despite maternal general anesthesia allowing drug transfer to the fetal circulation, direct fetal analgesia is still required for adequate fetal immobilization and profound uterine relaxation. (8,35) Following the repair and closure of the uterus in multiple layers, warmed saline needs to remain being infused intrauterinelly to replace the loss of amniotic fluid. (2,8) Prophylactic antiemetic agents should be provided and the epidural catheter can be initiated. (8) Constant uterine monitoring should be established for 48 to 72 hours and tocolytics need to be administered. (2) The hospital stay after open maternal-fetal surgery is usually one week, nevertheless, close surveillance is required throughout the remaining gestation. (4) The fetus is delivered by a planned cesarean section at 36 weeks, but the average gestational age at delivery is 34 weeks due to preterm labor. (2) In this case, it is important not to disregard the risks associated with prematurity. (3) Moreover, a subsequent pregnancy is not recommended until two years after maternal-fetal open surgery and future deliveries will necessarily have to undergo a cesarean section. (3,4)

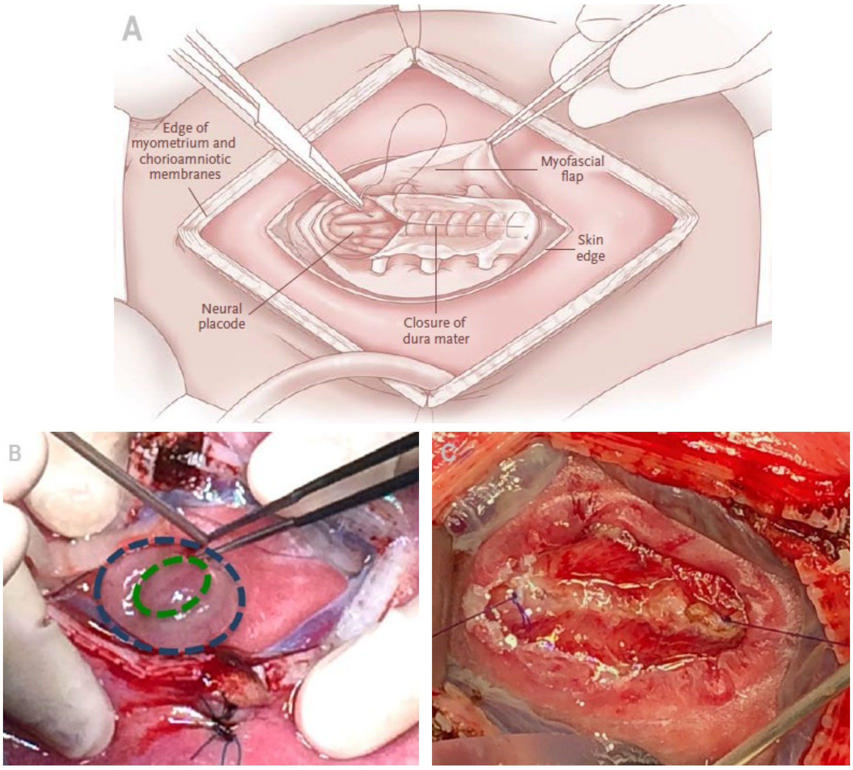


Fig. I - Prenatal repair of myelomeningocele. A. Illustrative representation of technique of open fetal surgery for MMC. B. Exposition of MMC in a fetus at 25 weeks through a hysterotomy. C. Multilayer closure. Adapted from Adzick et al., 2011; Danzer et al., 2020

The most common complications after open fetal surgery are premature rupture of membranes and preterm labor, nevertheless, chorioamniotic membrane separation, amniotic fluid leakage, uterine rupture, and risk of placenta accreta in further pregnancies can present. Maternal nonobstetric complications such as tocolytic-induced pulmonary edema and infections may also occur. Regarding the fetus, fetal bradycardia is the most frequently associated risk. (2,3,8)

## 3.3. Fetoscopic fetal surgery

As formerly discussed, the advances in imaging methods, endoscopic instruments, and surgical techniques led to the progression from open fetal surgery to fetoscopy. (12,24)

Fetoscopic surgery is a minimally invasive procedure, which combines surgical manipulation of the fetus with endoscopic and ultrasound imaging. (4,12) The dual-visualization technique for real-time imaging of the fetus, creates a direct fetoscopic image and a cross-sectional picture, displayed on two different screens. (4) Similarly to open fetal surgery, fetoscopic surgery can be aimed at the fetus itself, but also at the placenta, membranes, and umbilical cord. (4,38) However, the surgical field is far more restricted. (5) Fetoscopy can be performed percutaneously or with uterine exposure, through a mini-laparotomy or a laparotomy-assisted technique. (4,38) The percutaneous approach is the most commonly used and it avoids complications related to the laparotomy incision, thus being associated with better maternal postoperative recovery. The exposure techniques are reserved for cases of complete anterior placenta. (3,38,39)

In fetoscopic surgery, the access to the amniotic cavity is granted through ports, or cannulas, in the uterus and fetal membranes, in which the fetoscope and other instruments are inserted. (2,4,38) The ports are usually placed percutaneously, but when the uterus is exposed, they can be inserted directly. (15) There are two main types of cannulas: plastic cannulas, flexible and disposable, and metallic cannulas, rigid and reusable. The more frequently used cannulas in fetoscopy are thin-walled plastic cannulas, which have a length of 13 cm, a leakproof port house, and commonly an adjustable diameter with a range between 4 and 15 Fr. (3,38) According to the specific procedure, adequate endoscopes, sheaths, cannulas, and several instruments need to be selected. Endoscopes have diameters of 1.0 to 3.8 mm and a working length of 20 to 30 cm. In fetoscopic surgery, rod lens and fiber-optic endoscopes are the most commonly used. Endoscopes to be used before 12 weeks of gestation are referred to as embryoscopes, whilst those used after 12 weeks are named fetoscopes. Embryoscopes are smaller in diameter and length. Endoscopes are protected by a sheath that also serves as a guide. The sheath can have side ports, connections, or operative canals to hold other instruments. (38)

While open surgery is performed under maternal general anesthesia, minimally invasive surgeries are usually performed under local anesthesia. Prophylactic preoperative tocolysis can be provided and direct fetal analgesia is administrated. (8)

The majority of fetoscopic surgeries are single-port interventions. (16) The area of interest is located with an ultrasound transducer and the primary port is positioned percutaneously. (3,38) Cannulas can be inserted through the abdominal and uterine walls using the Seldinger technique or the surgeon can select cannulas loaded with a pyramidal tip trocar for direct insertion. (38) The endoscope is then placed into the amniotic cavity and the procedure can be performed, under constant ultrasound guidance. To decrease damage to the uterine wall and membranes, trocars with balloon tips can be used. (2) After the procedure, uterine access sites and maternal abdominal incisions are closed. Postoperatively, both fetus and mother should be closely monitored; additional tocolytic agents are rarely needed. (2,8) The fetus can be delivered by vaginal delivery, not only in the current gestation but also in subsequent pregnancies. (4)

When comparing fetoscopic surgery complications with the ones from open surgery, fetoscopy shows a decrease in maternal morbidity regarding the duration of hospitalization, need for blood transfusion, and need for intensive care. (2) Regarding nonobstetric maternal complications, the overall complication rate is 6% for fetoscopic surgery as opposed to 21% for open fetal surgery. When analyzing pregnancy outcomes, the rate of miscarriage following fetoscopy is similar to the general rate of spontaneous miscarriage. Opposing to open surgery, uterine rupture and uterine dehiscence are not present after minimally invasive procedures. However, as previously discussed, preterm birth rates after fetal interventions are higher than the usual prevalence. Despite the long-term maternal outcomes rarely being described in the literature, fertility rates after fetoscopic surgery appear to be similar to the ones of the general population. (11)

Nevertheless, the open fetal surgery complication that propelled the advances in fetoscopic surgery has not yet been eliminated – PPROM is still a reality in approximately 30% of fetoscopic interventions. (15,16) As PPROM increases the risk of chorioamnionitis, lung hypoplasia, and preterm birth, it also has an impact on the potential benefit of the surgery. There are some known risk factors more commonly associated with fetal membrane intraoperative damage, and, consequently, techniques to prevent PPROM after fetoscopy are being developed. The main focus is to minimize membrane damage at the port site, protect amniotic epithelium, and prevent choroamniotic membrane separation. Solutions include alternative port insertion techniques, smaller diameters of endoscopes, membrane sealing techniques (i.e., membrane plugs, patches, glues), and amniotic insufflation. (15) Amniotic insufflation is a recent technique that consists of distending the amniotic cavity with heated and humidified carbon dioxide. By directly anchoring the fetal membranes to the uterine wall, amniotic insufflation aims to prevent membrane dehydration and thus decrease the risk of rupture and chorioamniotic separation. This technique also allows for increased intrauterine visibility and instrument manipulation. (3,15) However, once the integrity of the fetal membranes has been compromised, there are still no clinical solutions to seal the defects. (6)

Fetoscopic techniques are being polished and the adoption of fetoscopy, to improve outcomes of pathologies currently treated by open fetal surgery, is growing.

## 3.4. Ultrasound-guided procedures

Ultrasound-guided fetal interventions are minimally invasive needle procedures, performed percutaneously and guided by continuous ultrasound imaging. (3,40) This is the least invasive method of fetal intervention. (4)

Like fetoscopic interventions, ultrasound-guided surgeries are performed under local anesthesia. However, for less invasive interventions, such as amnioreduction, anesthesia can be avoided. (8) Direct fetal analgesia is usually provided, except in procedures involving the placenta and umbilical cord. (3,8) In shunt placement procedures, prophylactic tocolysis may be administered preoperatively. Postoperatively, both mother and fetus should be adequately monitored and additional tocolytic agents are rarely required. (8)

Ultrasound-guided procedures comprise a wide range of interventions. For instance, several congenital heart defects can be treated prenatally with this technique to prevent irreversible alterations in cardiovascular anatomy and physiology. Some possible fetal cardiac interventions are interatrial stent placement, balloon aortic valvuloplasty, balloon pulmonary valvuloplasty, and balloon atrioseptoplasty. (40) Percutaneous interventions, such as cordocentesis, for diagnosis or fetal treatment, namely intrauterine transfusions; and amnioreduction, for symptomatic polyhydramnios, are also ultrasound-guided procedures. (6,16) Some other procedures using ultrasound guidance are selective reduction and multifetal pregnancy reduction. (3,6)

However, the most common ultrasound-guided fetal interventions are shunting procedures. Thoraco-amniotic shunts are employed in the management of fetal pleural effusion, bronchopulmonary sequestration, and macrocystic congenital pulmonary airway malformations. Vesico-amniotic shunts are the standard treatment for LUTO. (3,6,16) LUTO is a group of rare congenital malformations that result in obstruction of the fetal urinary tract, affecting predominantly males. (3,12) Severe LUTO is associated with severe pulmonary hypoplasia and renal failure, leading to high perinatal morbidity and mortality. (3,5,12) Vesico-amniotic shunting can be used in the treatment of severe LUTO with preserved renal function. (3,12) Under ultrasound guidance, the shunt is fixed between the bladder and the abdominal wall to decompress the dilated urinary tract and to allow urine passage into the amniotic cavity. (5,6,12,16) The use of a double pigtail catheter is preferred to reduce the risk of dislodgment. (3,6,16,38)

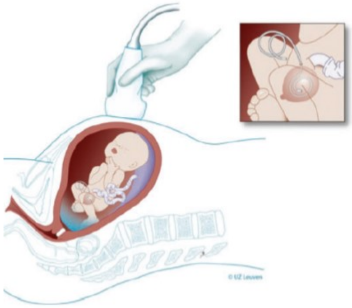

Fig. II - Schematic representation of vesico-amniotic shunting. Sampat & Losty, 2021

Fetal cystoscopy arose as an alternative treatment to intrauterine shunting for LUTO. The fetoscope is inserted in the fetal bladder, under ultrasound guidance, allowing direct visualization of the specific defect causing obstruction. (6,12) The most frequent causes of LUTO are urethral atresia and posterior urethral valves. (5) If the latter is present, the valves are ablated using laser therapy. (12) Despite the improved survival and renal function already reported, in comparison to expectant management, fetal cystoscopy remains an experimental procedure. Clinical trials and further investigation are still required to prove its safety and possible benefits. (6,12)

## 3.5. Ex-utero intrapartum treatment (EXIT) procedure

EXIT is a controlled specialized surgical delivery. (4,5,9) The EXIT procedure is designed to improve fetal outcomes and prevent hypoxia at delivery in cases of life-threatening neonatal airway obstruction. (13,41) It delivers a functioning airway so that the neonate can continue to be adequately oxygenated despite the loss of uteroplacental oxygenation after delivery. (4) The intervention is performed at the time of birth, ideally at or near term gestation, as a life-saving surgery. (4,8,13) The airway obstruction can be caused by teratomas, oropharyngeal or cervical lymphatic masses, branchial anomalies, severe micrognathia, subglottic stenosis or atresia, or tracheal or laryngeal atresia. (13,42)

The procedure is performed under maternal general anesthesia so that complete uterine relaxation is ensured. (4) It is vital to prevent uterine contractions and to maintain maternal normotension to guarantee adequate uteroplacental circulation. (5,9,13) While maintaining maternal-fetal circulation, a hysterotomy is performed and the fetus is partially extracted, only the head and neck are delivered. (5,8) Direct fetal analgesia is administrated intramuscularly and atropine may be provided. (8) An amnioinfusion of warmed saline solution is performed to maintain fetal normothermia and uterine volume. (13) Monitorization is implemented by fetal echocardiography, to monitor fetal cardiac function, and fetal pulse oximeter, which can warn about impaired placental perfusion.

(8,13,41) The airway is then assessed and secured. According to the severity of the obstruction, an endotracheal tube can be placed, or more invasive interventions can be performed such as a tracheostomy, resection of a mass, or insertion of catheters to provide extracorporeal membrane oxygenation. (5,8) Once the oxygen supply is granted, delivery can continue and the neonate can be further evaluated, stabilized, or resuscitated. (4,5,8,41) Following delivery and clamping of the umbilical cord, a rapid reversal of uterine relaxation is crucial to prevent maternal hemorrhage, hence intravenous oxytocin is administered to the mother. (5,8) Following the delivery of the placenta, uterine atony should be assessed and, if present, uterotonics are required. (8) The procedure is completed following the usual technique for cesarean sections. (13) The most frequent maternal complications associated with the EXIT procedure are uterine hemorrhage and atony, maternal hypotension, and fluid overload. (5,8,43) Further fetal definitive surgical treatment can be accomplished after delivery or in the neonatal period. (4)

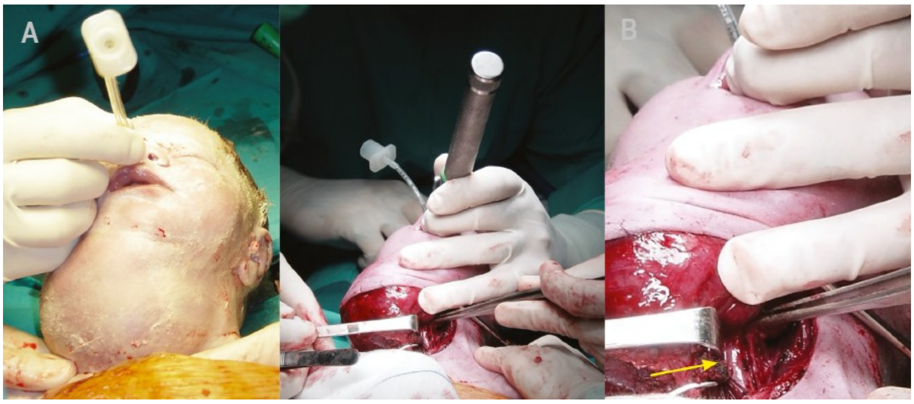


Fig. III - Neonate presenting cervical teratoma undergoing EXIT procedure. A. The airway is secured through endotracheal intubation. B. Tumor resection. Adapted from Varela et al., 2021

Fetal endoscopic tracheal intubation (FETI), arose as a potential alternative to EXIT procedures. In this technique, the patency of the fetal airway is granted *in utero* through a percutaneous fetoscopic tracheoscopy, under ultrasound guidance. The procedure is performed under maternal epidural anesthesia, instead of general anesthesia. The fetal airway is accessed fetoscopically, then the fetoscope is removed, and an endotracheal tube is inserted under ultrasound guidance. Previously to intubation, fetal analgesia and atropine are administered intravenously. FETI, first reported in 2015, aims to avoid the neonatal and maternal morbidity associated with EXIT procedure. Following the intervention, delivery is performed by cesarean section. (44) However, the procedure carries some risks - FETI is associated with fetal airway injury, which can cause hemorrhage or edema and, consequently, complicate neonatal intubation if a backup EXIT procedure is required. (43) A modification of the FETI procedure was later published reporting endoscopic intubation: the endotracheal tube is placed under continuous fetoscopic visualization in addition to ultrasound guidance. The technique is intended to diminish the risk of fetal airway injury associated with cannula insertion and to confirm directly the correct positioning of the endotracheal tube. (43) However, only a few cases of FETI have been reported and the EXIT procedure remains the standard of care for the management of fetal airway obstruction. (43,44)

# 4. Fetoscopic laser surgery for Twin-to-Twin Transfusion Syndrome (TTTS)

Nowadays, fetoscopic laser coagulation for severe TTTS is the most frequently performed fetal surgery. (16,17)

Monochorionic twin pregnancies represent 20% of twin pregnancies and 70% of monozygotic twin pregnancies. (24) These pregnancies are at increased risk of neonatal morbidity and mortality, having a perinatal mortality rate of approximately 11%. (14,24) The majority of complications are due to the presence of placental vascular anastomoses causing a chronic imbalance of blood flow, such as in the case of TTTS. (14) TTTS is a serious complication of monochorionic twin pregnancies, affecting 10 to 15% of these gestations. (45–47)

## 4.1. Pathophysiology, diagnosis, staging and prognosis of the disease

TTTS usually presents midgestation, between 16 and 26 weeks of gestation. (48) Placental injection studies have allowed for a better understanding of the pathophysiology of the disease. (49) In monochorionic pregnancies bidirectional (arterioarterial and venovenous), and unidirectional (arteriovenous) intertwin vascular anastomoses are usually present, connecting the two fetal umbilical circulations. (45,46,49) In TTTS, an unequal distribution of placental anastomoses on the chorionic plate, leads to unidirectional blood shifts from the donor twin to the recipient twin, causing hemodynamic instability. (46,49) Consequently, discordance in the amniotic fluid volume among the two fetuses forms, defined as twin polyhydramnios-oligohydramnios sequence (TOPS). (12,49) Additionally, the type, number, and diameter of the anastomoses seem to have a role in the risk of TTTS development. (45,48) Hormonal imbalance has also been associated with further disease development. (49)

TTTS causes anemia and hypovolemia in the donor twin, which can lead to anuria, oligohydramnios, and fetal growth impairment. In the recipient twin, hypervolemia and polycythemia may manifest as polyuria, polyhydramnios, fetal hydrops, and heart failure. (12,16)

TTTS can be diagnosed by prenatal ultrasound imaging. (24,48) A timely and accurate diagnosis, combined with immediate referral to maternal-fetal medicine centers, is vital for a good perinatal outcome. (45,48) The principal antenatal finding is the severe unbalance of amniotic fluid between the two fetuses, identified on ultrasound as polyuric polyhydramnios in the recipient, with deepest vertical pocket of ≥ 8.0 cm before 20 weeks of gestation and ≥ 10 cm after 26 weeks; and oliguric oligohydramnios in the donor twin with deepest vertical pocket ≤ 2.0 cm, according to Eurofetus criteria. (14,28,49) In monochorionic pregnancies, sonographic screening for TTTS should be routinely performed every two weeks from 16 weeks of gestation onwards. (45,48)

In 1999, Quintero published a classification system for TTTS to standardize the severity of the disease and its correlation with neonatal outcomes. (17,45) The Quintero staging system is based on ultrasound findings and it remains the most universally used staging criteria. (17,48) The staging system comprises five stages with increasing severity. In stage I, polyhydramnios in the recipient and oligohydramnios in the donor twin are present but the donor´s bladder is still visible, whereas stage II is associated with a collapsed bladder. Stage III is associated with signs of cardiovascular strain and Doppler anomalies in both fetuses, reflected by a positive "A" wave in the ductus venosus and a positive end-diastolic flow in the umbilical artery. Stage IV is defined by the presence of hydrops. Finally, stage V is characterized by the fetal demise of one or both twins. (16,45,49) However, despite being useful to describe the severity of the disease, this staging tool does not represent a chronological progression of the disease in all cases. (17,48) The Quintero system also fails in showing an accurate prediction of neonatal outcomes after fetoscopic laser surgery. (48)

If left untreated, TTTS has a poor prognosis, with a perinatal mortality rate of around 90%. (12,14,28) Despite the advances in the field of maternal-fetal medicine, the management of TTTS remains a challenge. (49) In TTTS, the risk of miscarriage and intrauterine fetal demise is significantly increased. (6,47) Furthermore, if the intrauterine demise of one twin occurs, the single survivor becomes at higher risk of severe hypovolemia and anemia, due to the acute blood transfusion from the surviving fetus into the co-twin. (49,50)

PPROM and preterm birth are the most frequent complications and the ones bearing more risk. (6,24,47) Therefore, preventing preterm birth is a major challenge in this syndrome, since prematurity is the most important risk factor for neonatal mortality and morbidity, especially regarding neurologic and neurodevelopmental outcomes. (45) Additionally, pregnancies complicated with TTTS are associated with fetal congenital heart defects due to the impaired cardiac development caused by severe hemodynamic imbalance. (48,49) TTTS is also related to hematological disorders and renal failure. (49) Nevertheless, due to its lifelong impact, poor neurological outcomes are the most significant complication of TTTS, with an incidence between 2 and 18%. (14,49) These neurological anomalies comprise severe cerebral injury and neurodevelopment impairments. (17) Cerebral lesions associated with TTTS can be detected by imaging methods, both by ultrasound and magnetic resonance imaging (MRI), and include cystic periventricular leukomalacia, intraventricular hemorrhage, posthemorrhagic ventricular dilatation, porencephalic or parenchymal cysts, and arterial ischemic stroke. (14,17,28,49) Regarding neurodevelopment impairments, cerebral palsy, severe developmental delay, fetal brain atrophy, blindness, and deafness were associated with TTTS. (17)

## 4.2. Advances in fetoscopic laser surgery

Fetoscopic laser surgery for TTTS consists of the identification and ablation of the placental anastomoses through fetoscopy. DeLia was the first to introduce fetoscopic laser surgery as a treatment for TTTS, in 1988. (51) Since then, the management of the disease has advanced and the procedure has undergone many changes, leading to a significant decrease in perinatal mortality and better neonatal and long-term outcomes, with survival rates of approximately 90% for at least one twin and 70% for both fetuses. (17,48,49,51)

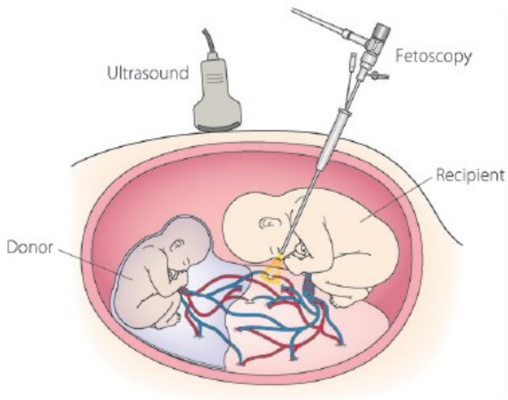


Fig. IV - Illustrative representation of a fetoscopic laser intervention for severe TTTS. Sago et al., 2018

Before the development of laser therapy for TTTS, fetal treatment was based on serial amnioreductions to decrease polyhydramnios and prevent preterm delivery. (49) In 2004, Eurofetus published the results of an RCT comparing endoscopic laser surgery with serial amnioreduction for severe TTTS before 26 weeks of gestation. (28) Amnioreduction is a widely available intervention consisting of the removal of large volumes of amniotic fluid. Serial amnioreductions were performed in TTTS to decrease polyhydramnios and hence prevent preterm birth; and to decrease placental surface pressure aiming to improve fetal hemodynamics. (28,49). The Eurofetus trial proved fetoscopic laser coagulation to be a more effective first-line treatment, in comparison to serial amnioreductions, and it established fetoscopic laser surgery as the best available treatment for TTTS. In this study, laser therapy was associated with higher survival rates of at least one twin, both in the neonatal period and during the first six months of life, for all Quintero stages, in comparison to amnioreduction. The incidence of PPROM and fetal death was similar in the laser and amnioreduction groups. However, the median gestation age at birth was higher in the laser group which is in agreement with its lower neonatal death rate. Regarding the neurologic outcomes, laser therapy was associated with better outcomes in the neonatal period. As previously stated, the recruitment for the study had to be interrupted, due to the significantly better outcomes of fetoscopic laser surgery. (28)

## 4.3. Current technique

Fetoscopic laser coagulation is now the standard treatment for stages II to IV severe TTTS at midgestation, between 16 and 26 weeks of gestation. (14,17,46) The mean gestational age at the time of laser surgery is approximately 21 weeks. (52)

Laser surgery is a causative treatment, opposite to amnioreduction, and a minimally invasive procedure. Maternal local or regional anesthesia is administered, as well as prophylactic tocolytics and antibiotics. (28,46,49) Maternal sedation may also be provided. (46) Fetoscopic laser surgery is mainly performed percutaneously, nevertheless, a laparotomy can be performed. (14,28) The visualization of the vascular equator of the placenta depends on placental location, amniotic fluid composition, and fetal position. (38) Proper visualization and an adequate angle of the laser fiber have to be ensured, thus the entry site on the maternal abdomen needs to be carefully chosen. (17,28,38) Under continuous ultrasound guidance, a cannula is inserted into the polyhydramniotic cavity of the recipient twin, either by the Seldinger technique or directly using trocars. (14,28) According to the fetal gestational age, adequate fetoscopes (1.3 mm or 2.0 mm) and cannulas (7-10 Fr) are selected. (14,17,46,47) In addition, rigid fetoscopes with straight sheaths are indicated in posterior placenta, whilst semi-rigid fetoscopes with curved sheaths are used in cases of anterior placenta. (17) The fetoscope is introduced in the recipient's sac and the anastomoses are identified. Then, a 400 µm or 600 µm diode laser fiber or an Nd:YAG laser (neodymium-doped yttrium aluminum garnet) is introduced through the operative channel of the fetoscopic sheath. (14,28) All visible vascular anastomoses are then ablated to interrupt the intertwin fetal transfusion process and thus restore hemodynamic balance. (14,28,46) The laser is fired with a no-touch technique at a distance of approximately 1 cm using an output of 20 to 70 W for one to three bursts of a few seconds each, depending on the diameter of the vessel. (14,28,38) The laser ablation should be performed frugally but making sure all the communicating vessels are removed, due to the risk of recurrence. (14,24,28) The optimal laser impact is obtained at an angle of 90 degrees. (38) Following laser intervention, drainage of excess amniotic fluid is performed. (14,28) A study reported "*coagulation of all vascular anastomoses that cross the vascular equator*", "*determination of site of insertion of fetoscope*", and "*ultrasound identification of placenta, fetuses, umbilical cord insertions and expected vascular equator*" as the most important fetoscopic laser coagulation substeps, by expert consensus. (51)

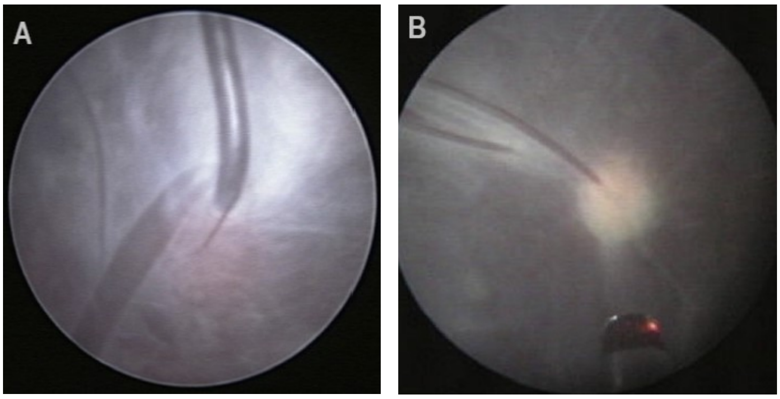


Fig. V - Fetoscopic image of placental anastomoses. A. Arteriovenous anastomoses on the placental surface during fetoscopy. B. Laser coagulation of the anastomoses. Adapted from Bamberg & Hecher, 2019

Postoperatively, the maternal hospital stay is usually from 24 to 48 hours following the procedure. (14,28,46) During this period, ultrasound assessment of twin viability, membrane integrity, deepest vertical pocket depth, bladder filling, anemia, and Doppler monitoring should be performed. (46) Due to the risk of cerebral injuries in survivors of TTTS, routine standardized imaging protocols need to be followed to adequately evaluate possible lesions. (49) The early detection of brain lesions is possible either by ultrasound or MRI. (24) A weekly follow-up ultrasound must be scheduled for at least a month after laser surgery. (14,28,46) Afterwards, patients are evaluated every two weeks. (14,46) Delivery is recommended at approximately 34 gestational weeks, in the absence of postoperative complications. (46) However, the mean gestational age at birth following fetoscopic laser surgery is 32 weeks. (52) Vaginal birth is preferred, either spontaneous or elective, except in the presence of abnormal fetal heart tracing and Doppler findings, severe weight discordance, absence of cephalic presentation of the first twin, and gestational age inferior to 32 weeks. (45)

## 4.4. Non-standard clinical indications

Early and late laser interventions have shown to be feasible and safe therapeutic options with improved neonatal outcomes. (48) Late TTTS, after 26 weeks of gestation, is present in 4 to 9% of all the syndrome cases. (45) Fetoscopic laser surgery after this gestational age is associated with intraoperative obstacles, such as amniotic fluid turbidity which makes the visualization of the anastomoses more difficult; and the presence of larger placental vessels causing further effort in coagulation. (17) Before 16 weeks of gestation, TTTS rarely complicates monochorionic pregnancies - the prevalence of early TTTS is approximately 2.5% of all cases. Early fetoscopic laser photocoagulation, performed at 16 weeks of gestation, was recently reported to be associated with significantly higher rates of PPROM, chorioamnionitis, and chorioamniotic separation, in comparison to standard laser surgery. (49,53) Nevertheless, twin survival rates did not seem to differ between both groups. (53)

Fetoscopic laser surgery is the standard-of-care treatment for stages II to IV severe TTTS. (45,46) Expectant management is offered for stage I in the absence of progressive polyhydramnios, maternal discomfort, preterm contractions, and cervical shortening. (3,48) In their presence, laser surgery is performed. (3) In 2021, the results of a multicenter RCT comparing fetoscopic laser surgery with expectant management in stage I TTTS were published. In women undergoing fetal therapy, percutaneous fetoscopic laser surgery of anastomotic vessels was performed. The patients of the expectant management group were evaluated on a weekly follow-up ultrasound. In case of progression to stage III or IV, presence of maternal complications related to polyhydramnios, significant cervical shortening, or TAPS, rescue fetoscopic coagulation was offered. The trial did not prove a clinically important difference in neonatal outcomes between expectant management and fetoscopic laser surgery, concluding that expectant management is a safe option for stage I TTTS without compromising the outcome of the cases that will progress and require surgical treatment. Nevertheless, in the presence of the complications already listed above, immediate fetoscopic laser surgery is indicated. (47)

## 4.5. Modified surgical techniques

The technique for fetoscopic laser surgery has suffered several modifications and developments over the last decades, especially regarding coagulation methods, leading to improved outcomes in the management of TTTS. (3,12,46)

Initially, laser photocoagulation was performed using a nonselective technique, in which all vessels crossing the intertwin membrane were ablated. (12,46,54) However, the nonselective laser ablation of placental anastomoses was associated with a higher risk of fetal demise. To reduce this outcome, Quintero and his team developed a selective laser photocoagulation technique aiming to only ablate anastomotic vessels at the vascular equator. The placental anastomoses are carefully identified fetoscopically and coagulated, sparing vessels not involved in the syndrome, but important for fetal survival. (54) This technique was later compared to the nonselective method, and it was reported to be more effective and have better outcomes, resulting in the replacement of the initial nonselective laser photocoagulation technique. (46,54)

Placental injection studies reveal the presence of residual anastomoses in approximately one-third of placentas, following fetoscopic laser surgery for TTTS. (12,14,49) Residual anastomoses can lead to postoperative TAPS or to recurrent TTTS, which are present in 13% and 14% of cases, respectively. (14,49) TAPS results from an unbalanced low-rate blood transfusion through small diameter and small caliber arteriovenous anastomoses, from the donor to the recipient twin. (23) The hemodynamic instability leads to anemia in the donor and polycythemia in the recipient, in the absence of amniotic fluid discordances. (23,49) In post-laser TAPS, the hemodynamic imbalance arises due to the residual anastomoses at the placental surface following laser surgery for TTTS. (23) Recurrent TTTS is defined as a persistent or recurrent TTTS, shown as a persisting or recurring amniotic fluid discordance after fetoscopic laser surgery. (14,55) TTTS recurrence also includes cases of syndrome reversal. (14) The diagnosis of recurrent TTTS is based on the same criteria used to define TTTS. (55)

To prevent the occurrence of residual anastomoses, a European multicenter RCT compared the Solomon technique with the standard selective fetoscopic laser coagulation in monochorionic twin pregnancies complicated by TTTS before 26 weeks of gestation. (14) The Solomon technique is a modified fetoscopic laser technique aiming to minimize the patency of residual vascular anastomoses after laser surgery. Using this technique, the whole vascular equator is coagulated, including deep anastomoses under the chorionic plate and small superficial anastomoses that might not be visualized fetoscopically. (14,46,51) After identification and ablation of all vascular anastomoses, a thin line is drawn with the laser from one edge of the placenta to the other edge, following the vascular equator, ablating the white areas between the already coagulated anastomoses. The goal of coagulating along this line is to entirely separate both parts of the chorionic plate of the placenta at the level of the vascular equator, creating a virtually dichorionic placenta, to reduce any remaining anastomoses and avoid later recurrences. (14) Solomonization differs from the nonselective photocoagulation above described, by following the vascular equator where the anastomoses are present, instead of ablating all the vessels crossing the intertwin membrane. (12,14) The Solomon technique was proven to significantly reduce the incidence of TAPS and recurrent TTTS, in comparison to the standard approach. Consequently, it was also reported a decrease in postoperative fetal morbidity in severe TTTS following this technique. A secondary analysis reported that despite the reduction of residual anastomoses by the Solomon technique, these still may occur hence the importance of the postoperative follow-up. (14)

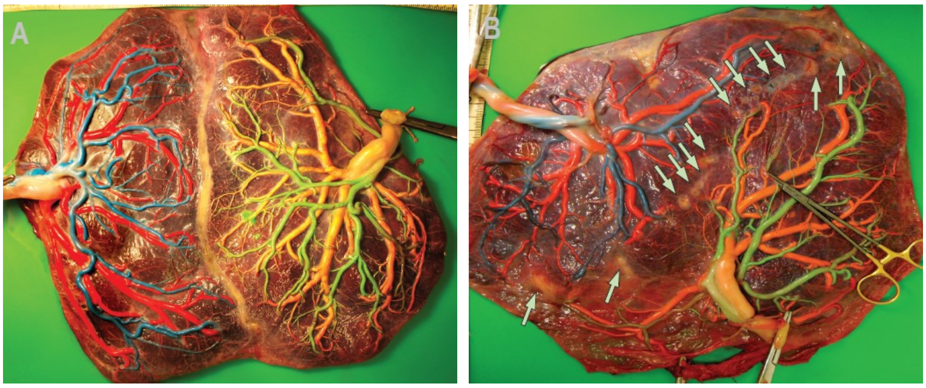


Fig. VI - TTTS placentas injected with colored dye following fetoscopic laser surgery (blue and green dye for the arteries and pink and yellow dye for the veins). A. TTTS placenta injected with colored dye, treated using the Solomon technique. The complete coagulation of the vascular equator is visible. B. TTTS placenta injected with colored dye, treated using the standard selective technique. The arrows indicate the single laser spots. Adapted from Slaghekke et al., 2014

Prior to this international trial, early studies using the Solomon technique had already reported significantly higher neonatal and 6-month survival rates and reduced risk of recurrent TTTS, TAPS, and amniotic fluid abnormalities, in comparison to the standard selective laser coagulation technique. (56,57)

More recently, a study evaluated the Solomon technique in comparison to the selective coagulation of anastomoses. The Solomon technique was associated with an overall improvement in twin and double survival as well as lower postoperative TAPS. However, the technique reported higher rate of PPROM in all gestation ages, especially at early gestational age (<24 weeks), and higher neonatal extraneurological morbidity – there was an increased risk of bronchopulmonary dysplasia in the Solomon group in comparison to the selective technique group. The study concluded that despite the increased risk of PPROM, the Solomon technique was confirmed to be a safe and beneficial technique regarding the overall outcome of TTTS. (46)

The main disadvantage of the Solomon technique is the increased extent of damage to the placenta, caused by laser ablation of healthy tissue. Therefore, a partial Solomon technique was developed, in which only the area surrounding the anastomoses is coagulated, instead of the coagulation of the entire vascular equator. In areas containing several anastomoses, a line is drawn connecting the already ablated anastomoses. However, in areas without vascular anastomoses, no further laser coagulation is performed. (51)

## 4.6. Alternative management options

Alternative approaches to the management of TTTS include serial amnioreduction and expectant management, as previously discussed. (3,28) Nevertheless, other therapeutical options arose over the decades, such as medical treatment, septostomy of the intertwin membrane, selective reduction, and pregnancy termination. (3,27,28) Medical management of the disease was used in combination with amnioreduction or laser coagulation, however, currently, medical therapy is not recommended as either routine adjunctive therapy or as first-line treatment for TTTS. Despite septostomy aiming to improve polyhydramnios and hemodynamics, studies reported no significant difference in neonatal survival, and the procedure was associated with intertwin membrane disruption and increased risk of umbilical cord entanglement and fetal demise. Therefore, septostomy was also left as a possible TTTS treatment. (27) Selective reduction is a procedure in which the transfusion process is interrupted by the intentional feticide of one twin. This intervention is reserved for severe cases of TTTS in which the death of one fetus is imminent or extremely likely. (27,28)

## 4.7. Pregnancy and neonatal outcomes

Fetoscopic laser surgery, despite being a minimally invasive procedure, is still an invasive intervention with inherent risks. (48)

PPROM is the major complication following fetoscopic laser surgery, occurring in about one-third of cases, most frequently in the first two weeks after surgery. (45–47,50,55) Cases of TTTS undergoing laser therapy, are also at further risk of preterm birth. (6,45,47) Extreme preterm birth is present in 10%, very preterm birth in 25%, and late preterm birth in 60% of cases. (6) PPROM and preterm birth are mainly related to short cervical length, early gestational age, chorioamniotic membrane separation, disruption of the intertwin membrane, dual survival, history of preterm birth, membrane damage at the entry site, and incomplete surgery. (6,45) However, it is important not to disregard that monochorionic twin pregnancies themselves are associated with a rate of preterm birth before 32 weeks of approximately 15%. (6) Miscarriage and intrauterine fetal demise are also significant risks of intrauterine surgery. (46,47,49) Besides PPROM and preterm birth, other obstetrical complications after laser surgery include chorioamnionitis, placental abruption, amniotic fluid embolism, pulmonary edema, intraperitoneal amniotic fluid leakage, and maternal mirror syndrome. (28,47,49) Important maternal nonobstetric complications are pulmonary edema and hemoperitoneum. (28,49) As previously discussed, TAPS and recurrent TTTS may also be present after fetoscopic laser treatment, carrying significant fetal and neonatal morbidity. (46,47,55)

Aiming to decrease the incidence of preterm birth following fetoscopic laser surgery in cases of TTTS, an RCT was created to investigate the use of a prophylactic cervical pessary. (58) Cervical pessaries are noninvasive devices, easy to use that can be removed at any time and different sizes and types are available. (58,59) In the trial, the use of a prophylactic cervical pessary is compared to expectant management in TTTS requiring laser therapy. The RCT is currently in the phase of analysis and results publication. However, a study from the same group had already found that the placement of a cervical pessary in these cases leads to a lower rate of preterm birth and improved neonatal morbidity, in comparison to expectant management. (58) The ProTWIN trial, a European RCT, showed that despite the prophylactic use of a cervical pessary not reducing the poor perinatal outcome in multiple pregnancies, in monochorionic pregnancies its use is associated with improved perinatal outcomes. (59)

Despite the significant improvement in survival following the introduction of fetal laser therapy and the subsequent modifications to the technique, the mortality rate in TTTS is still significant. (52) Furthermore, neurodevelopment impairment in survivors is present in 4 to 18% of neonates, following fetoscopic laser surgery, equally in the donor and recipient twin. (48,60) Earlier gestational age at delivery and low birth weight have been associated with an increased risk of severe brain injuries in survivors and neurodevelopmental impairment later in infancy. (49,60) Later gestational age at the time of laser intervention also increased the risk of neurologic morbidity, due to the increased fetal brain susceptibility to cerebral lesions later in pregnancy. (60)

As earlier described, prematurity is the most important risk factor for neonatal mortality and neurologic morbidity. (45) Nevertheless, preterm birth is also associated with extraneurologic neonatal morbidity, including renal failure, bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus, retinopathy of prematurity, ischemic limb injury, and severe neonatal sepsis. (14,46,47)

# 5. Fetoscopic laser surgery for other pathologies

Despite fetoscopic laser surgery being first performed as a treatment option for TTTS, there are other potential indications for fetoscopic laser interventions, such as ABS, LUTO, CHAOS, chorioangiomas, and sacrococcygeal teratomas. (3,12,18–20) Laser photocoagulation can also be a treatment option for other conditions complicating monochorionic pregnancies, such as TAPS and TRAP sequence. (21–23)

## 5.1. Twin Anemia Polycythemia Sequence (TAPS)

As previously described, TAPS results from an unbalanced blood flow due to the presence of small vascular anastomoses, causing hemodynamic instability. However, the slow intertwin transfusion rate seen in TAPS allows for hemodynamic compensatory mechanisms to occur. Therefore, the unbalance of amniotic fluid among both fetuses is prevented and TOPS is absent in this condition. (23)

TAPS antenatal diagnosis is based on Doppler findings by middle cerebral artery peak systolic velocity (MCA-PSV) measurement in both fetuses. In the presence of TAPS, a discordance in measurements occurs, with increased MCA-PSV (>1.5 MoM) in the donor, suggesting fetal anemia, and decreased MCA-PSV (twin (<1 MoM) in the recipient, an indicator of polycythemia. (23,46) The postnatal diagnosis is given by large hematologic discordances between twins and specific placental angioarchitecture. (23)

Fetoscopic laser surgery is a treatment option for TAPS. Nevertheless, laser therapy in TAPS appears to be more challenging than in TTTS, due to the small diameter and caliber of the arteriovenous anastomoses. Moreover, the absence of TOPS forms a wavering intertwin membrane, which complicates vascular equator visualization. The Solomon technique is preferred aiming to reduce the risk of residual anastomoses and TAPS recurrence. In several studies, laser coagulation improved perinatal outcomes by decreasing the incidence of respiratory distress syndrome and prolonging gestation. Nevertheless, further studies and RCTs are required to evaluate the feasibility, safety and potential benefits of fetoscopic laser surgery in the management of TAPS. (23)

## 5.2. Twin Reversed Arterial Perfusion (TRAP) Sequence

TRAP sequence can also complicate monochorionic twin pregnancies. (21,24,51) TRAP sequence is a rare condition, characterized by the presence of arterioarterial anastomoses and partial or complete lack of cardiac development in one twin (acardiac twin). The acardiac fetus is hemodynamically dependent on its morphologically normal co-twin (pump twin). Ultrasound prenatal diagnosis usually exhibits fetal biometric discordances, especially in the abdominal circumference; partial or complete absence of a morphologically normal heart in one fetus which may be associated with head, trunk and extremities malformations; presence of subcutaneous edema and fluid collections in the affected twin; and reverse flow in the umbilical cord and abdominal aorta to the upper body and head, which is a pathognomonic color Doppler finding. (21)

The treatment of TRAP relies on the interruption of the blood supply to the acardiac fetus, aiming to maximize the survival of the healthy twin, since the acardiac twin is non-viable. (21) Fetoscopic laser surgery for coagulation of placental anastomoses is a therapeutic option, by use of an Nd:YAG laser. (21,22) However, there are some intraoperative complications associated with the technique: edematous cords in acardiac fetuses presenting hydrops can make ablation difficult; and in cases of umbilical cord proximity, the pump twin's cord may be damaged. Moreover, laser therapy was associated with PPROM and chorioamnionitis in TRAP sequence cases. (21)

Despite the possibility of fetoscopic surgery in the management of TRAP sequence, currently, ultrasound-guided laser coagulation and radiofrequency ablation are the most commonly used techniques. However, in the presence of entangled umbilical cords, fetoscopic laser ablation of the acardiac twin cord is preferred. (21)

## 5.3. Amniotic Band Syndrome (ABS)

ABS is a rare congenital malformation. (3,61) In this condition, constricting fibrous amniotic bands cause the entrapment of fetal parts or of the umbilical cord, which may cause major deformities and amputations, as well as intrauterine fetal demise by strangulation of the cord. (3,18,61) The fibrous band forms a partial or full ring constriction around the affected area. (61) The pathophysiology of the syndrome is not fully understood but it seems to be associated with strands of the amniotic sac that entangle some parts of the fetus, resulting from amnion rupture. (3,61) Constriction bands mostly affect extremities, causing vascular obstruction, neurologic deficits, and lymphedema. Head and abdominal wall bands have also been described. (3,18,61)

Fetoscopic laser surgery for amniotic band release aims to release the bands before irreversible ischemia presents, allowing for the preservation of the limb structure and function. (3,18) The surgery also prevents the consequences of strangulation of the umbilical cord, when the latter is affected. (3) Due to the possible difficulty in band release deep within edematous tissue, adapted sheaths and laser energy are required. (38) In cases of inadequate visualization, amniotic insufflation may be considered. (3) Postoperatively, the extremities tend to have a grossly normal appearance, but vascular and lymphatic obstruction may persist, as well as histological changes. After delivery, a Z-plasty may be required to improve the aesthetic aspect. (18) Nevertheless, due to the known complications of fetoscopic laser interventions, surgery must be reserved for cases affecting the limbs with probable functional preservation or for the prevention of intrauterine demise caused by an entangled umbilical cord. (3)

Another fetoscopic approach to amniotic band release is the use of optical scissors, which consist of parrot-beaked scissors with an endoscope for direct visualization, for band sectioning. (18,38) This technique may reduce the damage caused by laser coagulation. (38)

## 5.4. Fetal Lower Urinary Tract Obstruction (LUTO)

As discussed earlier, vesico-amniotic shunts are the standard treatment for LUTO. (3,6,16) However, percutaneous fetal cystoscopy arose as an alternative treatment to intrauterine shunting. In this technique, the fetoscope is inserted in the fetal bladder, under ultrasound guidance, allowing direct visualization of the specific defect causing obstruction. (6,12) Then, laser coagulation is used to ablate the posterior urethral valves which are causing urinary tract obstruction. (12) This technique increases the visualization of the posterior urethra allowing for better differentiation between urethral atresia and posterior urethral valves. Cystoscopic laser ablation also prevents further interventions that may be necessary to correct shunt dislodgment. (18) In addition, laser surgery eliminates the need for amnioinfusion prior to the intervention and appears to allow a more physiological decompression of the dilated urinary tract. Despite the improved survival and renal function already reported, in comparison to expectant management, fetal cystoscopy remains an experimental procedure in the management of LUTO. (6,12,18)

## 5.5. Congenital High Airway Obstruction Syndrome (CHAOS)

CHAOS is a rare antenatal condition characterized by a noncontiguous fetal airway. (18,62) The obstruction may be caused by laryngeal atresia, tracheal atresia or stenosis, and tracheal cysts leading to lung hyperplasia with a distended tracheobronchial tree, followed by diaphragmatic flattening or eversion, ascites, progressive heart failure, fetal hydrops, and placentomegaly. (20,62,63) CHAOS is associated with an extremely high mortality and its incidence is largely unknown due to the associated high rates of intrauterine fetal demise. (62,63) The prognosis worsens in the presence of further malformations, such as in DiGeorge and Fraser syndromes. Besides the fetuses that develop spontaneous decompression of the obstruction, only the ones submitted to fetal intervention survive. (62) In fetuses which survive to delivery, failure to establish a functioning airway leads to death shortly after birth, so an EXIT procedure is usually performed. (62,63)

Fetal laser laryngotomy is a possible option for prenatal management of CHAOS, aiming to perforate the airway obstruction by laser photocoagulation. (20,62) Following fetal positioning to obtain optimal access to the fetal oral cavity, the fetoscope is inserted, under ultrasound guidance, and the cause of obstruction is identified. (20,63) The obstruction is then ablated creating a small opening to the trachea. (20,62,63) From different case reports, patients were discharged from NICU with tracheostomy on room air. (20,62) Laryngotracheal reconstruction and decannulation can later be performed. (20) In a recent study including 15 patients presenting CHAOS, three interventions were performed and the two patients that survived to birth were delivered via EXIT to tracheostomy. The procedures were associated with common fetoscopy-related complications, including PPROM, preterm birth, and placental abruption as well as with severe tracheobronchomalacia and neonatal death. (62)

Alternative management options for CHAOS include pregnancy termination, expectant management with comfort care measures following delivery, expectant management with an EXIT delivery, and multi-port fetoscopic decompression by balloon dilation with stent placement. (20,62)

## 5.6. Chorioangiomas

Chorioangiomas are usually asymptomatic benign tumors, incidentally found on ultrasound routine examination as solid circumscribed masses located near umbilical cord insertion. Increased values of alpha-fetoprotein can also be present. (3) However, large chorioangiomas (>4 cm) can function as an arteriovenous shunt, leading to high-output cardiac failure and fetal hydrops. Placental abruption, preterm delivery, polyhydramnios, fetal anemia and thrombocytopenia, intrauterine growth restriction, and maternal mirror syndrome are associated with this condition. (3,18)

Fetoscopic laser surgery is performed in selected cases, in the presence of fetal cardiac compromise and/or fetal hydrops. The goal of the intervention is to interrupt the vascular supply to the tumor and reverse fetal cardiac compromise, by ablation of the feeding vessel. (3,18) The surgery comprises risks that include severe hemorrhage and intrauterine fetal demise. In cases of successful laser coagulation, good perinatal outcomes are expected. (18)

Alternative treatments to photocoagulation for the treatment of chorioangiomas include amnioreduction, intrauterine transfusion, vascular embolization, and intratumoral injection of absolute alcohol. (18)

## 5.7. Sacrococcygeal teratomas

Fetal sacrococcygeal teratomas, despite being rare, are one of the most common congenital fetal tumors, affecting more frequently females. (3,19) Prenatal ultrasound diagnosis allows for its detection. Characterization of size, content, type and relation to the surrounding tissues can be performed with MRI. (19) The majority of sacrococcygeal teratomas are benign sacral masses, which can be solid, cystic or containing mixed cystic and solid components. These tumors tend to grow slowly and can be resected postnatally. (18,64) However, some sacrococcygeal teratomas are fast-growing and highly vascularized. These are usually large solid tumors in which the presence of arteriovenous fistulas leads to vascular steal. (3,18) In these cases, spontaneous rupture may occur as well as high-output cardiac failure and fetal hydrops, similarly to chorioangiomas. (3,18,19,64) In the presence of a sacrococcygeal teratoma, vigilant fetal monitoring is needed with periodic assessments of tumor size and growth rate, and of fetal cardiac function. (3)

Due to the low incidence of sacrococcygeal teratomas and the lack of guidelines or expert consensus to follow, intrauterine treatment is limited. (19,64) The management of this condition includes symptomatic treatment, fetal therapy, neonatal treatment, and pregnancy termination. (19) Fetal therapy might be considered in fetuses with large solid and hypervascularized tumors with a gestational age inferior to 28 weeks. The goal is to decrease the tumor vascularity and size, or to completely remove it, and prevent cardiovascular complications and intrauterine fetal demise. (3,18,19) Fetoscopic laser surgery for sacrococcygeal teratomas interrupts the vascular supply to the tumor by ablation of the feeding arteries. (18) Nevertheless, the inherent complications of laser therapy may occur. (19) Usually, a cesarean section is performed in tumors with large dimensions (>5 cm) to avoid fetal dystocia, tumor rupture, and severe hemorrhage. In fetuses with small sacrococcygeal teratomas (<5 cm) vaginal delivery can be performed. (19,64) Despite fetal treatment for sacrococcygeal teratomas still being experimental, considering the poor prognosis given by fetal hydrops and cardiac failure, minimally invasive procedures, such as fetoscopic laser ablation, are worthy of further investigation. (19,64)

Other therapeutical approaches include radiofrequency ablation, vascular embolization, intrauterine cyst aspiration (in tumors with a large cystic component), intratumoral injection of absolute alcohol, and open fetal surgery. (3,18,19,64) After 28 weeks of gestation, early delivery is recommended. (3)

# 6. Conclusions

Fetal surgery is already extending its applications to non-lethal and rare congenital anomalies and a growing number of fetal pathologies will certainly belong to the future indications of prenatal procedures. Previously, fetal treatment was focused on diminishing antenatal and neonatal mortality, while currently, the goal is gradually to change the progression of disease processes, decreasing postnatal morbidity through accurate prenatal diagnosis and treatment. However, it is vital to guarantee that experimental procedures follow adequate research protocols and the assessment of their safety and potential benefits need to be further evaluated through RCTs.

Several challenges remain ahead, namely PPROM, described as the *Achilles' heel* of fetal interventions, therefore, future efforts will certainly be made to optimize this outcome. New surgical techniques, improvements in operative technologies aiming to minimize membrane damage, and the development of effective membrane sealing techniques may help to reduce PPROM incidence following fetal surgery. As for fetoscopic laser surgery, despite its success and standardization to date in the treatment of severe TTTS, there is still room for improvement, not only concerning PPROM but also regarding the optimization of neurologic and neurodevelopmental outcomes.

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