MYELOMENINGOCELE, NEW INSIGHTS AND BETTER OUTCOME IN THE ERA OF FETAL SURGERY JOCHEM SPOOR

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Myelomeningocele, New Insights and Better Outcome in the Era of Fetal Surgery

Myelomeningocele, nieuwe inzichten en betere uitkomsten in het tijdperk van foetale chirurgie

Thesis

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Dankzij mijn naasten, allemaal.

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Introduction

Foto van een 11 weken oude baby met spina bifida aperta (1924, medische fotocollectie Narath-Lameris, Universiteitsmuseum te Utrecht; afgedrukt met toestemming)

Myelomeningocele

The neural tube is the embryonic precursor of the central nervous system. In the third week of gestation the neural tube closes. Failure to do so leads to open neural tube defects. Neural tube defects (NTD's) are amongst the most common severe congenital anomalies.[1,2,3] Myelomeningocele (MMC) or spina bifida is a complex open NTD of the spinal cord that is not covered by its usual layers of dura, spinal bone, muscle and skin. In the Netherlands NTD is present in approximately 1 in 2000 pregnancies.[4]

Chiari wrote a paper on the ectopia of cerebellar tissue in 1891, he described 4 different types.[5,6] Chiari type I is a deformation in which the cerebellar tonsils herniate into the spinal canal through the foramen magnum. In this type the brainstem and cerebellum are largely normally formed. In Chiari type II or Arnold Chiari Malformation (ACM) the brainstem and cerebellum descend through the foramen magnum and are malformed. Chiari type II is seen in most MMC patients and occurs only in patients with neural tube defects.

The cause of ACM is still a matter of debate but it is thought that during pregnancy, continuous leakage of cerebro spinal fluid (CSF) through the spinal defect leads to these and other brain changes. As a result, the descend of brain stem and cerebellum is thought to cause an obstruction for the CSF flow resulting in ventriculomegaly or hydrocephalus. A late complication in children with MMC is tethering of the spinal cord at the site of surgical repair known as a form of secondary tethered spinal cord syndrome (TSC).

Since failure of the neural tube to close already takes place in the third week of gestation, MMC is detectable by ultrasound of the fetus routinely performed during pregnancy. From 2007 on ultrasounds are routinely performed in the Netherlands after 20 weeks of gestation and since 2021 also after 13 weeks of gestation.

Like all NTD's, MMC has a multifactorial origin in which pathological gene variants together with environmental factors like maternal obesity, exposure to toxins and anti-epileptic drug use predispose to its development.[7,8,9,10,11]

Despite this multifactorial origin most NTD's like MMC seem to be linked to a malfunctioning folate pathway. In 1976 Smithells saw decreased levels of folate in the blood serum of women carrying a NTD pregnancy during the 1st trimester.[12] The MRC Vitamin Study Research group performed an international double-blind placebo-controlled randomized trial in over 1.800 women who had a NTD-pregnancy before and they saw a 72% reduction in NTD recurrence risk by peri-conceptional folic acid supplementation.[13]

Folate, as a co-enzym plays a key role in nucleotide formation and is essential for DNA repair and DNA construction. Folate is also essential in the methylation of DNA and thereby in epigenetic gene expression.

The clear role of folate on the formation of NTD's lead to the advice in many countries, like the Netherlands, for women planning to get pregnant to take a daily dose of folic acid of 0.4 mg, a high dose of 4 mg is recommended for future pregnancies in women who had a NTD-pregnancy before. Many pregnancies are however not planned and this lead to food fortification in large parts of the world.

Atta et al. showed a drop in the prevalence of MMC in countries where fortification was introduced and a higher prevalence in areas, like Asia and Europe where no fortification took place.[14]

MMC has a severe impact on patients' lives in many domains. Depending on the level of the defect, motor and sensory functions of parts the body are affected. Usually this results in paresis or paralysis of the lower limbs along with distorted sensory input and malfunction of bladder and bowel. Ventriculomegaly or hydrocephalus as mentioned above is highly present affecting cognitive function, MMC patients have a low to average IQ compared to peers. Sexual dysfunction is often present in MMC patients.[3,15,16]

MMC is a chronic condition that requires life-long multidisciplinary medical care, starting with closure of the defect before or shortly after birth. This closure of the defect consists of freeing the neural placode from its surroundings, creating a neural tube by meticulously stitching the lateral surfaces of the placode together: the "re-tubulation" and covering this spinal cord tissue with watertight layers of dura, muscle/fascia and skin.

Hydrocephalus needs a CSF-diverting treatment, mostly consisting of a ventricular peritoneal shunt. Usually multiple orthopedic and urological interventions follow later in life.

Historic perspective

Already in the early works of Hippocrates and Galenus descriptions of patients with MMC were found. Insights into the pathogenesis of this severe condition of the central nervous system started to develop in the early modern time with the rise of the study of human anatomy. Despite these insights, reports from doctors treating patients with MMC were almost exclusively on fatal infections. The dismal outcome of this treatment, mainly consisting of puncturing or underbinding the cele, was very demotivating and had non-treatment as a result. The introduction of *asepsis* and *antisepsis* by the end of the 19th century lead to an increase in the surgical treatment of MMC. Mortality remained high due mainly to hydrocephalus and urological complications leading to kidney failure.[17,18]

In the first half of the 20st century understanding of the physiology and the pathophysiology of the circulation of CSF, lead to treatment of hydrocephalus in MMC patients. This consisted mostly of lumbar punctions, ventricular punctions and opening of the corpus callosum.[19] It wasn't until the second half of the former century that for the treatment of hydrocephalus more and more advanced methods to divert the CSF to the heart, abdomen or pleural space were introduced. These methods consisted of implanting devices such as ventriculo-atrial or ventriculo-peritoneal shunts to drain the CSF to another cavity of the body. Together with advances in the urological treatment this lead to an increase in the survival of MMC patients. Physicians no longer postponed treatment till patients were 2 years old, an approach based on the conviction that only the strongest would survive that long.[20]

The British pediatrician Lorber and pediatric surgeon Zachary played an important role. Based on their experience with over 500 MMC patients they concluded that the conservative approach of not treating these patients was no longer acceptable.[21]

This more active treatment lead to an increase in survival, and consequently an increase in morbidity. This morbidity made Lorber himself not at all satisfied with the results. Treating the severe cases of MMC lead to profoundly affected patients; many of whom survived indeed but their quality of life was at least questionable.

This made Lorber establish criteria known as "the Lorber criteria" to help in deciding whether or not to treat. Severe paresis, large head circumference, kyphosis and severe additional congenital defects were reasons to withhold treatment, as they would predict a life of severe handicaps and chronic healthcare dependency.[22]

In the seventies and eighties the use of these criteria became common practice but they also remained subject of intense debate, amongst others by Lorber's colleague Zachary

and here in Rotterdam by neurosurgeon de Lange.[18] Points of concern were the relatively poor predictive value of the criteria. In many patients, treatment was withheld because their condition was deemed too severe, in the expectation that this poor condition would imply a very short life expectancy. However, many remained alive in a condition with more extensive handicaps then when treated. De Lange and Zachary also believed that having handicaps does not necessarily imply a poor quality of life.[23]

In the 1980's in the United States of America, a baby with severe MMC and hydrocephalus known to the public as "Baby Jane Doe" created a broad discussion. Her MMC, hydrocephalus and microcephaly were so severe that the treating physicians foresaw a life of severe handicaps, small mental capacities and suffering. Extensive consultations by these physicians, nurses, social workers and religious counselors made her parents decide to decline surgical treatment and opt for antibiotic treatment only, in hopes of protecting their daughter from extensive suffering. The Baby Jane Doe case lead to multiple lawsuits and went through multiple courts in the state of New York. The main lawsuit was called *Weber* in which the key question was whether parents are allowed to withhold possible life prolonging treatment. The case made it all the way to the Supreme Court, where however the justices declined to hear the case and thereby the ruling of the New York State's Court of Appeals stood: the parents of the baby had the right to deny life-prolonging surgery. By ruling purely based on procedural grounds, the Supreme Court gave no insights into this important question. Another lawsuit concerning Baby Jane Doe was started by a man named Washburn, a so called *right to life lawyer* who had no relationship to the baby and only found out about her situation through an anonymous tip. The courts made it clear that there was no place for such a non-party to try to overrule the parents' decision.[24]

Vitalism states that every life is worth living, the American Spina Bifida Association wrote a letter concerning the Baby Jane Doe case in which they questioned whether the future of patients with MMC can be adequately predicted at birth, by that they believed that urgent surgery after birth was indicated. In her paper, Steinbock sees this point of view as a form of *epistemological vitalism*; every life must be preserved, not so much because every life is worth living but we cannot know which lives will and which lives will not be worth living.[24]

Present situation

In the past decades the severity of MMC but probably also the difficulty in predicting the outcome of children with MMC lead to two different developments.

On the one hand, in "western" countries like the Netherlands, up to 75% of MMC pregnancies are terminated to prevent a life with handicaps and possible suffering, while on the other hand fetal surgery is applied to improve the outcome of patients with MMC.[7,25]

Fetal surgery as novel therapy

Based on the well documented outcome of a randomized controlled trial in the USA called the *MOMS-trial,* fetal surgery has become a treatment option for MMC. Fetal surgery is conducted while the fetus is still inside the womb and consists of the same surgical steps as postnatal surgery. The mainstay of fetal surgery is *open fetal surgery* via a laparotomy followed by a hysterotomy to gain access to the fetus.[7] More recently fetoscopic variants are being explored, mostly consisting of a laparotomy followed by a fetoscopic approach to the fetus.[26]

The impact caused by MMC is thought to come from the embryologic defect itself and by subsequent damage to the spinal cord during the pregnancy also known as the "the two-hit hypothesis". The second hit is caused by the impact of neurotoxic amniotic fluid and mechanical stress on the spinal cord that lies unprotected outside of the spinal column in case of a MMC. By freeing the *placode,* "re-tubulation" and covering it with multiple waterproof layers of dura, muscle, fascia and skin during pregnancy the spinal cord is protected against the secondary damage.

When compared to MMC patients with postnatal repair, MMC patients with fetal repair have better motor scores, less urological deficits and are more independent.[7] The rate of ventriculo-peritoneal shunts hydrocephalus drops from 84% to 40% . These benefits continue to exist over time.[27]

Fetal surgery, when successful, reduces the severity of MMC but the MMC itself is not cured. Fetal surgery is invasive not only to the fetus but it may also cause complications to the pregnant, healthy mother, such as damage to the womb causing premature delivery and complications in future pregnancies.

Both the choice between terminating pregnancy or continuing, as well as the choice between fetal or postnatal surgery need to be based on right information, stressing the role of proper, well informed prenatal counseling.

Aim of this thesis

This dissertation has 2 major subjects:

1. to provide data in order to improve counseling upcoming parents confronted with a MMC pregnancy and
2. to provide a training model to support implementation of fetal surgery for MMC.

In **Chapter 2** we analyse the outcome on a cohort of MMC patients in our institution. This cohort will also serve as a historical cohort for comparison with fetal surgery we hope to perform in the near future.

In **Chapter 3** we perform a long term follow-up study on different outcome parameters in the same cohort of MMC patients we published on 10 years ago with the aim to gain more insight in these patients wellbeing at older age.

Chapter 4 covers a worldwide survey we performed amongst neurosurgeons on diversity in the management of patients with MMC and on knowledge of the only RCT performed comparing fetal and postnatal surgery for MMC.

We conduct a meta-analysis and systematic review in **Chapter 5** on the cumulative incidence and relative risk of TSC in the prenatal closure group compared to the postnatal group in MMC patients.

Chapter 6 describes the position of fetoscopic surgery for MMC as opposed to open fetal surgery. Open fetal surgery for MMC has become a widespread treatment option and in pursuit of minimizing its maternal risks, fetoscopic techniques are being explored. This creates an expanding but fragmented field in which the optimal fetoscopic technique is yet to be determined. An RCT like the one for open fetal surgery is unlikely to ever take place and we discuss alternative ways of gathering strong data.

Chapter 7 shows the development of a realistic simulator for the training of fetoscopic MMC surgery to provide a training opportunity for centres that are starting a fetoscopic MMC repair program.

In **Chapter 8** we discuss the results of the afore mentioned papers and formulate future perspectives in order to further improve both the counselling of and fetal surgery for MMC.

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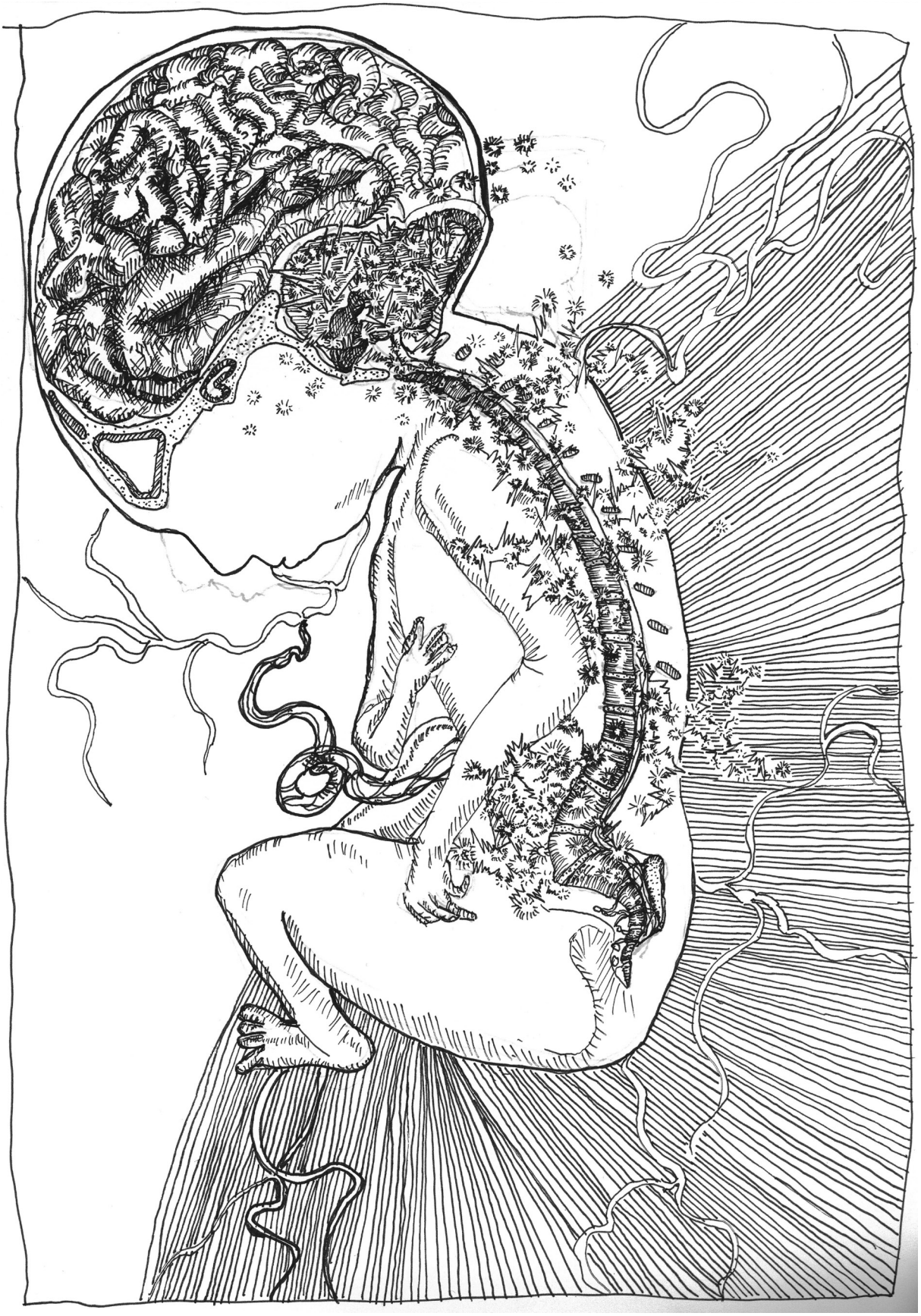

Chapter 2

Contemporary management and outcome of myelomeningocele: the Rotterdam experience

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Abstract

Objective

Myelomeningocele (MMC) is the most common form of spina bifida, with a lifelong impact on the quality of life for infants born with this condition. In recent decades, fetal surgery has evolved from an experimental therapy to standard of care for many centers in the world. In this study, the authors aimed to provide an overview of the current management and outcomes for infants with MMC managed at their institution. This then provides a center-specific historical cohort for comparison with future antenatal-treated MMC cases.

Methods

This is a retrospective, single-institution cohort study including all consecutive MMC cases between January 1, 2000, and June 1, 2018, at Erasmus MC. Outcome data included closure of the defect (location, timing, and surgical parameters), hydrocephalus management, Chiari malformation type II (CMTII) management, incidence of spinal cord tethering and outcome, motor outcomes, and continence.

Results

A total of 93 patients were included with predominantly lumbosacral lesions. Two patients died during follow-up. Hydrocephalus was present in 84%, with a 71% ventriculoperitoneal shunt reoperation rate. Surgery was performed in 12% for a tethered spinal cord at a mean age of 8 years. Decompression surgery was performed in 3 patients for CMTII. Special education in 63% was significantly associated with hydrocephalus ($p < 0.015$). Nineteen percent of patients were able to walk independently, and 47% were nonambulators. Social continence for urine was obtained in 75% of patients, 4% had fecal incontinence.

Conclusions

This study provides an overview of current MMC outcomes at the authors' center and will serve as a historical cohort for comparison with future fetal surgery cases operated on at the center in the coming years. Apart from a relatively low surgical untethering rate, the authors' outcome data are comparable to those in the literature. Hydrocephalus is highly prevalent in postnatally treated MMC patients; in this study as in much of the literature, hydrocephalus is correlated with a low cognitive function. Fetal surgery for MMC halves the need for shunt treatment in a select group of MMC pregnancies, constituting a major indication for us to undergo the transition to a fetal surgery center. The fetal benefits of open antenatal surgery for MMC are well established, yet long-term data on especially tethered spinal cord are eagerly awaited.

Introduction

Myelomeningocele (MMC) is the most common form of spina bifida. Patients with MMC face lifelong disabilities such as paralysis of the lower limbs; sensory loss; impaired cognition; and bladder, bowel, and sexual dysfunction. Most cases are identified during routine anomaly scanning around 20 weeks of gestation, and a large proportion of parents opt not to continue the pregnancy (termination of pregnancy).

This, in combination with the increased use of folic acid supplementation during pregnancy, has reduced the incidence of neural tube defects in the past decades.[31] For instance, in the US, the incidence of neural tube defects at birth decreased 19% following folic acid supplementation between 1990 and 1999.[9,16] However, more recent data showed that this dramatic decline in incidence has stabilized in later years, with approximately 3.39 per 10,000 children born with spina bifida in 2003–2004.[4]

Management of MMC is complex, and multidisciplinary treatment is warranted. Usually, shortly after birth, the MMC defect will be closed surgically to prevent further damage to the spinal cord and infection. MMC patients are at risk for developing other conditions. A highly prevalent one is the development of hydrocephalus.[14] Diversion of CSF is usually performed by shunting, alternatively by creating an endoscopic third ventriculostomy (ETV).

Another condition associated with MMC is Chiari malformation type II (CMTII).[2,20,23,24] Even though almost all patients with postnatal MMC repair have a CMTII on imaging, only a proportion present with clinical symptoms. Clinical symptoms may include neck pain, muscle weakness, central apnea, dysphagia, stridor, and opisthotonus. The first-line treatment of CMTII is also ventriculoperitoneal (VP) shunting, whereas foramen magnum decompression with or without duraplasty can be considered when shunting is not providing adequate relief of symptoms.

In addition to CMTII, the majority of patients with MMC have a tethered spinal cord (TSC) on imaging, but only a minority will also present with clinical symptoms. Tethering of the spinal cord can result in back or leg pain, syringomyelia, decline in motor function, progression of scoliosis, and bladder dysfunction. The goal of surgical treatment is to release the spinal cord.[19]

In 2011, the results of the Management of Myelomeningocele Study (MOMS) trial were published.[1] In this randomized controlled trial, 183 women before 26 weeks of gestation were randomized between prenatal surgery and conventional postnatal repair. Despite the more frequent occurrence of pregnancy-related complications such as preterm birth, the outcomes of the patients who underwent antenatal repair were favorable. For example, less than half of them required the placement of a shunt. Furthermore, the patients had a reduced rate of CMTII and better cognitive function and motor skills. Although clinically relevant, tethering of the spinal cord is often a late-occurring complication, and long-term

data are not available. Fetal closure of MMC seems to be associated with a higher TSC rate, even at a very young age as shown in the MOMS trial.

The purpose of the current study was to evaluate the contemporary management and long-term outcomes of patients with MMC managed at our institution, Sophia Children's Hospital, Rotterdam, the Netherlands. To this end, we assessed the rate of shunting, untethering procedures, and decompression interventions for CMTII in relation to clinical outcome. This series provides a contemporary cohort that could improve counseling parents about the long-term complications and risks of postnatal repair. This also allows comparison to much-awaited long-term outcomes of the MOMS trial, in particular to TSC rates. Furthermore, as our institution is currently transitioning toward the establishment of a fetal surgery center, the present study provides a center-specific historical cohort to compare with future antenatal-treated MMC cases.

Methods

Management of MMC at the Sophia Children's Hospital

Annually, approximately 15 patients are diagnosed with MMC at the Erasmus MC-Sophia Children's Hospital. The diagnosis is usually suspected at the routine 20-week anomaly ultrasound scan and confirmed with a more detailed scan at our center. The latter also aims to diagnose associated abnormalities and to evaluate the extent of the spinal abnormality (i.e., lesion level, presence of CMTII, hydrocephalus). All women carrying an MMC fetus are counseled by a maternal fetal medicine specialist as well as a pediatric neurosurgeon. Amniocentesis is offered to identify associated genetic abnormalities. If the decision is made to continue the pregnancy, the ensuing pregnancy care takes place at our institution.

Postnatal closure consists of microsurgical freeing of the placode, followed by neurulation of the tube. Next, the dura is dissected and closed around the newly constructed neural tube. A musculofascial flap is used to cover the defect, and the skin is closed. In large skin defects, the plastic surgeon is asked to perform a skin flap.

If the parents opt for fetal surgery, they are currently referred to University Hospitals Leuven, Belgium. Further follow-up and delivery by cesarean section in the current and future pregnancies take place at our institution.

After birth, MMC patients are followed regularly at the MMC outpatient clinic. During these specific consulting visits, patients are seen by a multidisciplinary team of specialists from departments such as neurosurgery, orthopedic surgery, rehabilitation medicine, urology, pediatrics, neurology, social work, and furthermore by dedicated nurses.

Patient Selection and Data Extraction

This is a retrospective, single-institution cohort study. Using a departmental database, a chart review was performed on all patients born between January 1, 2000, and June 1, 2018, who underwent closure of an MMC defect. All surgically treated MMC patients who are currently under treatment at the Sophia Children's Hospital were included. Patients were excluded if they had any other form of spina bifida (such as spina bifida occulta).

The following outcome data were collected: 1) type of surgical closure of the MMC defect, location of defect, timing of repair, and surgical parameters; 2) management of hydrocephalus: shunt procedures, ETVs, and reoperations; 3) management of CMTII and an indication for decompression; 4) management of spinal cord untethering; and 5) long-term quality of life: bowel and bladder function, level of functioning, and the ability to walk according to the Hoffer classification.[8]

Institutional review board approval was not needed since this was an anonymous retrospective study.

Statistical Analysis

IBM SPSS (version 21.0, IBM Corp.) was used for analysis of data; $p < 0.05$ was considered to be statistically significant. The p value and confidence intervals were both determined using the Pearson chi-square test. Categorical data are presented as valid percentages.

Results

Patient Characteristics and Closure of the Defect

A total of 93 patients were included in this study (47 females); 3 patients had been excluded because 2 of them had a meningocele and 1 had a spina bifida occulta. All patients were followed up for a mean duration of 11.8 years (range 1.0–18.2 years). No patients were lost to follow-up. No patients died after delivery or before surgical closure. Two patients died during follow-up, one due to an unrelated infection at the age of 10 months and the other at the age of 17 years who had a short history of deterioration, which ended in asystole. Although this patient had never shown any signs of a clinically relevant CMTII, the deterioration and subsequent death might at least be partly due to CMTII.

Fifty-nine (80.8%, 59/73) patients were born after 37 weeks of gestation, while 14 (19.2%, 14/73) were born between 33 and 37 weeks. Table 1 shows the level of the MMC lesions. Most were located in the lumbosacral area.

The two most recent patients underwent an antenatal repair abroad, while the remaining 91 underwent postnatal closure of the MMC. Postnatal repair was performed within 48 hours after birth in 17 patients (21%, 17/80) and in 63 (79%, 63/80) patients after 48 hours (between day 3 and day 8). In 58 patients (73%, 58/81), the plastic surgeon performed the

closure of the skin by the means of a flap. See Fig. 1 for an overview of surgical procedures performed on patients born with MMC at our center.

An overview of the number of patients who underwent surgical procedures related to MMC throughout the years.

Hydrocephalus

Hydrocephalus was present in 78 patients (84%), of whom 74 underwent VP shunt placement as initial treatment, 2 underwent ETV as primary treatment, and 2 patients were successfully treated conservatively. See Fig. 2 for a flowchart showing the management of hydrocephalus. Five (7.1%) patients were treated within a week after closure of the MMC, 59 (84.3%) between 1 week and 1 month after closure, and 6 (8.6%) between 1 month and 1 year after closure of the MMC. Of the 2 patients who underwent antenatal repair, 1 needed shunt placement due to hydrocephalus.

Flowchart depicting the treatment of hydrocephalus among MMC patients. VPS = VP shunt.

Fifty-five of 76 (72%) patients needed at least one revision during follow-up with a mean of 2.9 revisions (range 1–8 revisions). The main reasons were shunt malfunction in 65.5% and infection in 25.5% of cases. In 5 patients, an ETV was performed instead of a shunt revision (Table 2).

Hindbrain Herniation

Radiological evidence of CMTII on MRI was present in 79 patients (90%), which was clinically relevant in 5 patients. In 3 patients (4%), posterior fossa decompression was indicated for bulbar symptoms in 2 patients and because of loss of motor function in the remaining patient (Table 3). Two patients improved after surgery; the remaining patient had to undergo reoperation with no clear clinical improvement.

Tethering of the Spinal Cord

Similar to CMTII, almost all patients showed a TSC on MRI. In 11 patients (12%), an untethering procedure was deemed necessary. The mean age at surgery was 8 years (range 3–16 years). The indications for surgery were back and leg pain in 1 patient, progression of scoliosis in 2, bladder dysfunction in 2, and decline in lower-limb motor function in 4 patients.

Since 2009, surgery has been performed using intraoperative neuromonitoring (IONM), and in the majority of cases a widening nonresorbable dural patch was used.

Long-Term Quality of Life

Cognition

Thirty-two patients (37%, 32/86) attended regular schools, whereas 54 (63%, 54/86) go to special schools, and 4 patients did not reach school age at the time of this study. The

presence of radiological hydrocephalus was significantly associated with following special education ($p < 0.015$).

Ability to Walk

Table 4 shows the ability to walk according to the Hoffer scale (n = 86; data were missing in 3 patients, and 4 patients were still under the age of walking at the time of the study; 18.6% of patients were able to walk independently at the last time of follow-up and 46.5% were nonambulators.

Urine Continence

We defined social continence as having no involuntary loss of urine between the clean intermittent catheterizations (CICs). There are various definitions for social continence depending on the purpose of research, but, in general, this term refers to an acceptable situation for the patient without significant disturbance of daily activities.

Sixty-eight patients (75%, 68/91) had social continence. Twenty-one patients (23%, 21/91) reported some degree of involuntary loss of urine in between the CICs.

All patients started with CICs and anticholinergics shortly after birth. In total, 8 patients received a bladder augmentation with or without a continent catheterizable stoma. Nine patients received a continent catheterizable stoma alone. One patient needed a temporary vesicostomy at the age of 2 years in order to protect the upper urinary tract. None of the patients born in our hospital experienced a significant deterioration of renal function.

Bowel Function

Ten patients had undisturbed bowel emptying, whereas 4 patients reported some fecal incontinence. The vast majority of the patients (84%) had severe difficulties in emptying their bowels properly (Table 4).

Discussion

In this study, we describe a contemporary cohort of infants who underwent postnatal repair for MMC. Hydrocephalus remains the main condition requiring surgical intervention in the first month of life for the majority of cases. Despite radiological diagnoses of CMTII and TSC, these can most often be treated conservatively. Interestingly, the rate of untethering surgery in our series is relatively low. Motor function skills, cognitive capacity, and the occurrence of bladder/bowel dysfunction are comparable to other case series such as the National Spina Bifida Patient Registry (NSBPR) consisting of almost 8000 patients (age range 0–89 years). The NSBPR aims to identify variation between institutes and its impact on clinical outcomes, facilitate research, and improve health-related quality of life among patients with spina bifida.[28]

Hydrocephalus

Our rate of 84% is comparable to that of both the NSBPR and MOMS trial. Kim et al.[13,14] looked at shunting rates among NSBPR centers[8] and included 4448 patients with MMC. Eighty percent of patients had undergone at least one procedure for hydrocephalus. Among the 23 centers, the shunt rate varied from 72% to 96%. The shunt rate in the MOMS trial was 82% in the postnatal group and 40% in the prenatal group.[1] Tulipan et al. showed similar outcomes for the entire MOMS trial population in 2015.[30]

Seventy-one percent of our patients needed at least 1 revision, which is a very significant number but comparable to that reported in the literature, with rates ranging between 64% and 95%. We found a shunt infection rate of 25%, which is rather high compared with that of Bowman et al. (10%) but comparable to that of Tuli et al. (24%).[5,29] Overall, this demonstrates that hydrocephalus is a significant and very challenging condition in MMC patients, with a profound effect on cognitive function.

In recent years, the role of ETV as a treatment option for hydrocephalus has been reemerging. In a pediatric population of 501 patients with mixed etiologies of hydrocephalus (e.g., tumor, aqueductal stenosis) the success of ETV was 71%;[17] 41.5% of the ETVs failed during follow-up, and 24% of these patients underwent re-ETV and 76% required shunting. Patients 0–6 months old were more likely to have ETV failure, which is also the age category in which most patients in our series undergo a CSF-diverting procedure. Another study consisting of 18 pediatric patients with MMC treated with ETV or VP shunt showed a similar rate of ETV success (37.5%).[26] Because of the risk of infection as well as the high reoperation rate in VP shunting, we consider ETV the preferred approach whenever feasible; ETV also shows promising results in patients who underwent prenatal closure.[6]

The rate of shunt infection at our center may be deemed as relatively high (with 14 of the 74 shunts being infected). Throughout the years, multiple recommendations have been proposed to decrease the rate of shunt infections.[7,15,21,27] Having a specific shunt protocol can help decrease infection rates, as can the use of antimicrobial-impregnated and -coated shunt catheters. Intraoperative irrigation with saline or the use of antimicrobial sutures for wound closure also show positive effects on shunt infection rates.

In a retrospective study of 127 patients with MMC, the concurrent placement of a shunt with the repair of the MMC defect, versus a delayed insertion of the shunt after repair, did not lead to any significant rates of shunt complications.[25]

CMTII

At our institution, when patients with MMC present with complaints of hindbrain herniation, a thorough assessment including MRI and sleep and swallow studies is performed. If indeed clinically relevant CMTII is present, we first establish the functioning of the shunt. We only consider a surgical decompression if there is no doubt about shunt function and

the Chiari complaints are substantial. The rate of decompression surgery for CMTII in our center (4%) is rather low compared with that of 9.15% in the NSBPR.[13] Adzick et al.[1] found a 5% decompression surgery rate in the MOMS trial for the postnatal group and a 1% rate for the prenatal group at the 1st year after birth. In our cohort, 2 patients underwent decompression surgery for CMTII before the age of 12 months (at 4 and 8 months). The third patient was 3.5 years old at surgery. It is well known that CMTII can become manifest at older ages, emphasizing that a long follow-up is needed to determine the incidence of CMTII decompression surgery.

Among the 23 NSBPR centers enrolling more than 10 patients, the rate of decompressions varied from 1.28% to 23.57%. Reoperation was performed in 10.8% of the patients who underwent a CMTII decompression. In 2.7% of this group, even a second or third reoperation was needed. At our center, one patient underwent reoperation. Since only 3 patients underwent surgery for CMTII, this constitutes a 33% reoperation rate. Due to these small numbers, a proper comparison is limited.

TSC

The percentage of cases that required surgical intervention for TSC in our series is relatively low. Similar cohort series, however, have reported a long-term risk of surgery for TSC of up to 32%.[5] On the other hand, the oldest patient in our cohort was 18 years, and the majority are several years younger, which might in part explain our lower rate. Furthermore, the indication for TSC surgery at our institution is based on very stringent criteria; hence, this could also account for differences in surgery rates compared with other single-center series.

The treatment of clinically important TSC is challenging and often requires surgical interventions with not always successful outcomes. As such, an optimal closure technique at the initial surgery seems essential to prevent such long-term complications. With this in mind there is some concern about antenatal repairs. Despite clear benefits on motor skills and CMTII, the MOMS cohort also had a relatively higher need for TSC surgery in infants who underwent prenatal closure. Albeit not significantly different, in 8% of fetal surgery cases an untethering surgery was performed at the age of 12 months compared with only 1% in the postnatal group. This emphasizes the importance of long-term follow-up studies as are currently organized by the MOMS centers. On the other hand, the surgical technique to close the MMC during open fetal surgery is in principle similar to what is used in postnatal repair. Ongoing research on improvement of fetal surgery for MMC, especially of the fetoscopic technique, is therefore of the utmost importance.[22]

Ability to Walk

Of our patients, 19% were able to walk independently, which is comparable to the 21% in the postnatal group of the MOMS trial. It is less than half of the 42% of patients who were able to walk independently in the prenatal MOMS trial group, showing the clear benefit of fetal MMC closure on this socially important factor.

Cognition

In our cohort only one-third of patients attended regular schools, whereas the majority needed special education. The radiological presence of hydrocephalus was the most important risk factor for cognitive developmental delay. This is similar to what has been published by various groups.[3,18] Our relatively high rate of shunt infection might also play a role in this. Interestingly, a more recent cohort series consisting of 108 cases from the MOMS trial did not confirm this association. They observed no difference in cognitive function between patients without hydrocephalus, shunt-treated hydrocephalus, or untreated hydrocephalus.[10]

Before the MOMS trial, Johnson et al. showed that shunt-treated MMC patients who underwent antenatal MMC closure had lower neurodevelopmental outcome scores at the age of 2 years.[12] A systematic review by Inversetti et al. demonstrated no differences in the risk for neurodevelopmental impairment between antenatal- and postnatal-treated infants.[11]

Overall, the correlation between hydrocephalus and a higher need for special schools in our cohort of MMC patients represents only part of the literature and may represent the effects of shunt placement and high occurrence of revision surgery.

Strengths and Limitations

The main strength of this study is related to the unique standardized multidisciplinary follow-up clinic at our institution, which results in a low lost-to-follow-up rate. This provides a wealth of information about contemporary outcomes of infants with MMC. Our study is limited by its retrospective design and the inevitable loss of data.

Conclusions

This study provides an overview of current outcomes for infants born with an MMC managed at our center. The overall outcomes are similar to those reported in the literature. However, we did observe a relatively low incidence of surgery for TSC. This study will serve as a historical cohort for comparison with future fetal surgery cases operated on at our center in the coming years. Hydrocephalus is highly prevalent in postnatally treated MMC patients, as is the revision rate for VP shunts, in which infection is a major reason for revision. In our study as in much of the literature, hydrocephalus is significantly correlated with a low cognitive function. Fetal surgery for MMC has been shown to halve the need for shunt treatment in a select group of pregnancies, and this constitutes a major indication for our center to undergo the transition to a fetal surgery center. Since shunt malfunction and shunt infection are frequently seen in shunt-treated MMC patients, we strongly promote ETV to be considered in case the need for a shunt revision is anticipated. The fetal benefits of open fetal surgery for MMC are well established in a select group of MMC pregnancies, yet it is well known and also illustrated by our series that MMC-related complications such as clinically relevant CMTII and especially TSC often occur years after closure of the MMC.

Therefore, multicenter, long-term clinical data, especially regarding TSC in antenatally operated MMC patients compared with postnatally operated MMC patients, are eagerly awaited; an anticipated higher rate may stimulate ongoing research on further improvement of fetal closure techniques.

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TABLE 1. Baseline characteristics of patients and surgical closure of the MMC

	No. of Patients (%)
Total	93
Sex	
Male	46 (49.5)
Female	47 (50.5)
Gestational age in wks (n = 73)	
<37 wks	14 (19.2)
≥37 wks	59 (80.8)
Mean time of op after birth (n = 80)	
≤48 hrs	17 (21.3)
≥48 hrs	63 (78.8)
≤7 days	58 (92.1)
Defect location (n = 93)	
Thoracic	5 (5.4)
Thoracolumbar	13 (14.0)
Thoracolumbosacral	1 (1.1)
Lumbar	35 (37.6)
Lumbosacral	28 (30.1)
Sacral	11 (11.8)

TABLE 2. Management of hydrocephalus

	No. of Patients (%)
Presence of hydrocephalus (n = 93)	
Yes	78 (83.9)
No	15 (16.1)
Primary treatment w/ a shunt (n = 82)	
Yes	74 (90.2)
No	8 (9.8)
Mean duration until op for hydrocephalus (n = 70)	
<1 wk	5 (7.1)
>1 wk to <1 mo	59 (84.3)
>1 mo to <1 yr	6 (8.6)
Reop during follow-up (n = 78)	
Yes	55 (70.5)
No	23 (29.5)

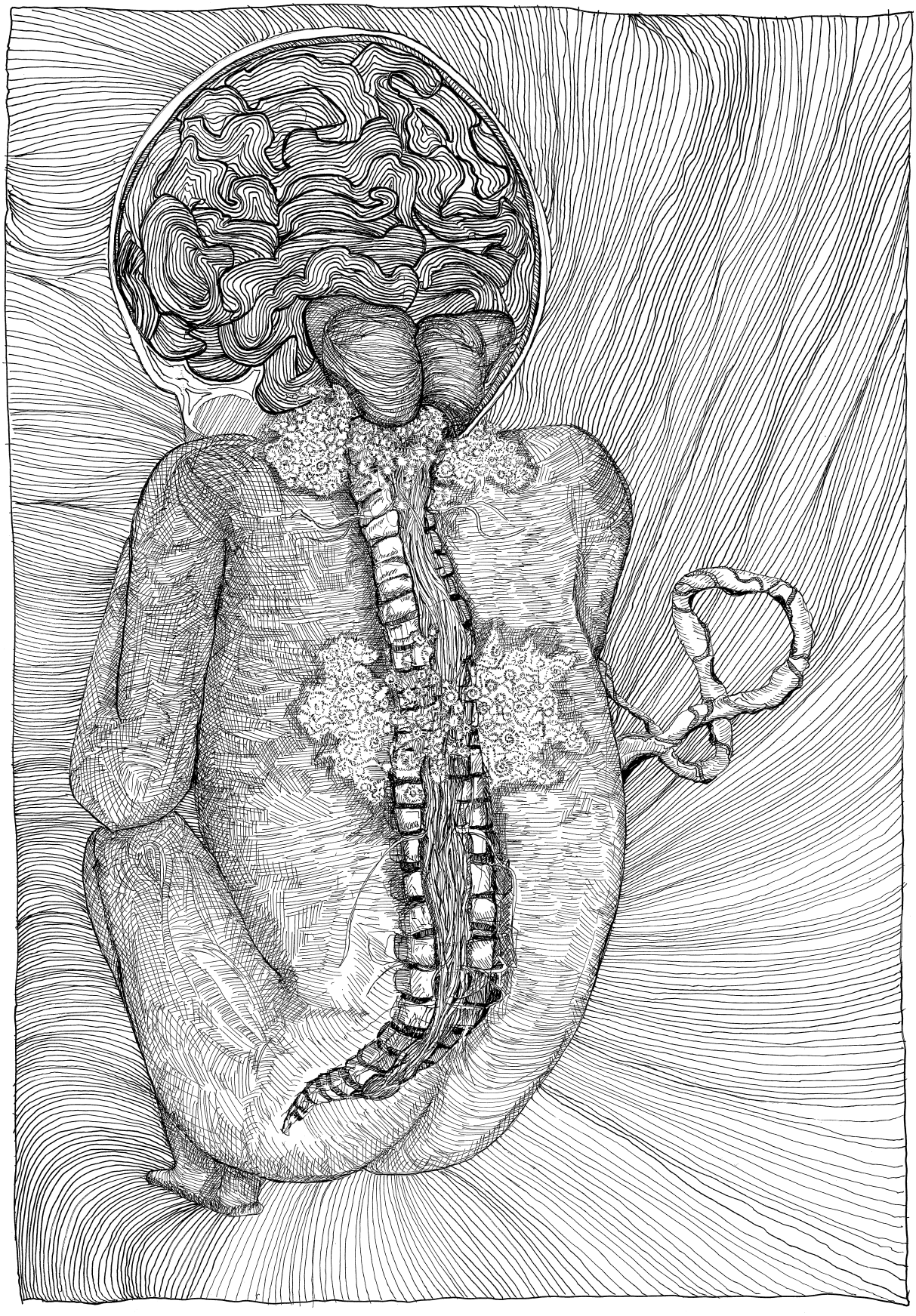
	No. of Patients (%)
Reasons for revision (n = 55)	
Overdrainage	2 (3.6)
Infection	14 (25.5)
Malfunction	36 (65.5)
Check & change	2 (3.6)
CSF leakage	1 (1.8)
Eventual reop	
VP shunt	50 (90.9)
ETV	5 (9.1)

TABLE 3. Management of hindbrain herniation

	No. of Patients (%)
CMTII on imaging (n = 88)	
Yes	79 (89.8)
No	9 (10.2)
Clinical symptoms of CMTII (n = 74)	
Yes	4 (5.4)
No	70 (94.6)
Indication for decompression (n = 4)	
Central apnea	3
Stridor	0
Neck pain	1
Syrinx	0
Swallowing disorders	0
Initial decompression for CMTII (n = 2)	
Bone only	1
Duraplasty	1
No. of reops for CMTII (n = 1)	
1	1
2	0
>2	0
Need for tracheostomy	2

TABLE 4. Quality of life at last follow-up

	No. of Patients (%)
Ambulation according to Hoffer (n = 86)	
Nonambulators	40 (46.5)
Nonfunctional ambulators	7 (8.1)
Household ambulators	9 (10.5)
Community ambulators	14 (16.3)
Independent ambulators	16 (18.6)
Level of education (n = 90)	
Special education	54 (60.0)
Regular education	32 (35.6)
Too young	4 (4.4)
Bowel function (n = 90)	
Constipation	76 (84.4)
Incontinence	4 (4.4)
Normal	10 (11.8)
Urinary continence (n = 91)	
Yes	68 (74.7)
No	23 (25.3)



Chapter 3

Newborns with myelomeningocele: their health-related quality of life and daily functioning 10 years later

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Abstract

Objective

Ten years ago, the authors reported on the outcome of their study investigating the degree of discomfort and pain in newborns with myelomeningocele (MMC), using the parameters of unbearable and hopeless suffering. In the current study, they investigated the quality of life, daily functioning, pain and fatigue, ability to communicate, and number of surgeries in the same cohort of patients. They subdivided their study population into severe (Lorber) and less severe (non-Lorber) cases and compared these cases with a healthy population (non-MMC group) and with each other.

Methods

The parents of 22 of 28 patients gave informed consent for this study. The KIDSCREEN-27 and PEDI-CAT (Pediatric Evaluation of Disability Inventory) were used to assess quality of life and daily functioning. Pain and fatigue were self-reported on a 10-point numeric rating scale. Communication and ambulation levels were determined using the Communication Function Classification System (CFCS) and the Hoffer ambulation scale. Using reference data from the KIDSCREEN-27 and PEDI-CAT, the authors created a healthy population comparison group.

Results

There was no significant difference in health-related quality-of-life (HRQOL) scores between Lorber and non-Lorber patients, except that school environment domain scores were lower in the Lorber group. When comparing the HRQOL of MMC patients with that of the non-MMC group, the physical well-being and parent relations and autonomy domains scored significantly lower. The daily functioning of MMC patients was lower on all domains of the PEDI-CAT compared with the non-MMC group. Lorber MMC patients scored lower on all domains of the PEDI-CAT when compared with non-Lorber patients. All patients were capable of communicating effectively; most patients (n = 18) were considered CFCS level I, and 4 patients were considered CFCS level II.

Conclusions

This study shows that MMC is a severe, lifelong condition that affects patients' lives in many domains. All the patients in this study are capable of effective communication, irrespective of severity of MMC. Overall, the data show that in newborn MMC patients, future unbearable suffering with respect to pain, mobility, cognition, and communication is hard to predict and may not always occur.

Introduction

The extended treatment of children with myelomeningocele (MMC) has been at the center of ethical debate because of the expected quality of life, related to the severity of the associated outcomes in both early and later life.[1] In the 1970s, this led to the development of the Lorber criteria to distinguish between severe and less severe cases of MMC.[2] If cases were considered too severe for active treatment, namely closure of the defect and in the vast majority subsequent shunt insertion, palliative care or active termination of life could be offered as an alternative to prevent unnecessary prolongation of suffering. In the Netherlands, every case of termination of life in newborns is assessed using guidelines from the Groningen Protocol. Its foundation is based on the concept of unbearable suffering, which is described for infants as «... not dependent on intensive medical treatment but for whom a very poor quality of life, associated with sustained suffering, is predicted.»[3]

Since the routine 20-week anomaly ultrasound scan during pregnancy was implemented in the Netherlands, MMC has mostly been detected before the time limit of legal termination of pregnancy. This warrants patient-centered counseling with a shared decision-making approach between the future parents and doctors regarding whether to continue or terminate a pregnancy. This decision greatly relies on adequate predictions of the child's quality of life, mobility, severity of pain, ability to communicate, and number of surgeries needed throughout life.

Predicting the future quality of life in MMC patients is extremely difficult and becomes more important with the introduction of fetal surgery. When choosing to continue a pregnancy, future parents are faced with the choice between fetal surgery, which shows clear benefits for the patient but comes with well-established maternal risks, and postnatal surgery, which has no maternal risks.[4]

We previously reported on the short-term conditions of newborns with MMC in our Rotterdam study on discomfort and pain in newborns with MMC.[5] Our findings showed that, in all cases, there were low levels of discomfort and pain. Adequate comfort levels could be achieved with a routine pain protocol (consisting of painkillers and physical therapy) in all newborns with MMC independent of the severity of the disease. Our current study assesses the long-term conditions of the same group of MMC patients based on their quality of life, functioning, and extent of pain and fatigue.

Methods

Patient Selection and Data Extraction

This study is a retrospective, single-institution, cohort study. We obtained approval from the Erasmus Medical Center Medical Ethical Review Board. The parents of the 28 included patients in our former study were sent a letter detailing the purpose and procedures of

this research project. Parents and patients who agreed to participate were invited for an interview at our outpatient clinic or were visited at home after the collection of written informed consent. The duration of the full interview session ranged from 2 to 3 hours. The order in which all questionnaires were administered was the same for all participants.

Patient Characteristics

For patient characteristics, we collected data on age, sex, education level, and MMC severity. We distinguished between primary, special primary, secondary, and special secondary education. MMC severity was based on the Lorber criteria, which include thoracolumbar lesions, severe paraplegia, gross enlargement of the head, kyphosis and other severe congenital defects, or birth injuries as adverse prognostic criteria.[2]

Health-Related Quality of Life and Functional Outcome

The primary outcome was health-related quality of life (HRQOL) measured with the Dutch version of the KIDSCREEN-27 questionnaire.[6] This questionnaire consists of several questions among 5 domains: physical well-being, psychological well-being, parent relations and autonomy, social support and peers, and school environment. Questions are answered on a 5-point scale (total score range 0–100) considering a time frame of 1 week and assess the frequency of behavior and feelings. Higher total scores indicate higher quality of life.

We used the Pediatric Evaluation of Disability Inventory (PEDI-CAT) to measure functional outcome.[7] The PEDI-CAT provides normative data on the child's functioning relative to that of his or her peers. The normative standardization sample was based on an extensive online panel. The domains tested are daily activities, mobility, social/cognitive items, and responsibility.

Ambulation and Communication

Ambulation was scored using the Hoffer ambulation scale.[8]
The level of communication was scored by parents using the Communication Function Classification System (CFCS).[9] The CFCS was initially designed to classify the daily communication of patients with cerebral palsy and consists of a 5-point scoring scale, looking at all forms of communication, verbal and nonverbal.

Pain and Fatigue

Pain and fatigue were scored based on the week prior to the interview using the numeric rating scale (NRS), in which pain and fatigue are represented on a scale where a score of 0 represents absolutely no pain and fatigue and a score of 10 represents the worst imaginable pain and fatigue (see Bolton[10] and Gladman et al.[11] for validation).

Non-MMC Group Data

To compare functioning and quality of life between MMC children and a healthy population, we created a healthy population comparison group (non-MMC group) based on the means of reference data from the KIDSCREEN-27 and its manual. We paired every child in our population with a healthy child of their age (based on obtaining a normal score).[7,12]

Statistical Analysis

We did not assess distribution for nominal or ordinal data. Statistical differences in age, sex, and education between severe (i.e., Lorber) and less severe (i.e., non-Lorber) MMC groups were determined using the Mann-Whitney U-test, Fisher exact test, and Fisher-Freeman-Halton exact test. A Shapiro-Wilk test was used to evaluate the distribution of all nonnormal group data. A box plot and Mahalanobis distance were checked to determine univariate or multivariate outliers. Assumptions of linearity were assessed using a scatterplot. Box's M-test was used to determine the homogeneity of variance-covariance matrices. Hotelling's T^2 was run to determine the effect of MMC and Lorber versus non-Lorber patients on KIDSCREEN-27 and PEDI-CAT scores. Subgroup analysis of KIDSCREEN-27 and PEDI-CAT domains was done using an independent t-test or Well's t-test when the assumption of equal variance could be met. A Bonferroni adjusted α level of 0.05 with a simultaneous 95% confidence level was used. A p value ≤ 0.05 was considered significant, and all analyses were performed using SPSS version 22.0 software (IBM Corp.).

Results

Patient Characteristics

Twenty-two subjects entered this follow-up study.[10] The mean age on the interview day was 11.0 years (95% CI 10.4–11.6), ranging from 8.0 to 12.9 years. Our patient population consisted of Lorber (n = 6) and non-Lorber (n = 16) subjects. Sex, age, and level of education showed no significant differences between both groups (Table 1). The reasons for not participating were lack of interest (n = 2), anxiety issues (n = 1), major surgery scheduled (n = 1), family-related circumstances (n = 1), and no response (n = 1).

HRQOL of Children Born With MMC

Five quality-of-life measures were assessed via the KIDSCREEN-27 questionnaire: physical well-being, psychological well-being, parent relations and autonomy, social support and peers, and school environment. Patients with MMC versus the non-MMC group had a significantly lower mean score in all subdomains, as shown in Table 2. The differences between the non-MMC group and the MMC group on the overall KIDSCREEN-27 scores were also statistically significant ($F[5, 38] = 41.049$, $p < 0.001$; Wilks' $\Lambda = 0.156$; partial $\eta^2 = 0.844$), as was the difference between the Lorber and non-Lorber groups ($F[5, 16] = 3.162$, $p < 0.05$; Wilks' $\Lambda = 0.503$; partial $\eta^2 = 0.497$). However, the only significant difference in subdomains when comparing the Lorber to the non-Lorber group was in the school environment (Table 2).

Functioning of Children Born With MMC

Four measures of daily functioning were assessed via the PEDI-CAT questionnaire: daily activity, mobility, cognition, and responsibility scores. The differences between the non-MMC and MMC groups on the overall PEDI-CAT scores were statistically significant ($F[4] = 35.485$, $p < 0.001$; Wilks' $\Lambda = 0.216$; partial $\eta^2 = 0.784$), with the scores in the MMC group being lower. Similar differences were seen between the non-Lorber and Lorber groups ($F[4, 17] = 7.182$, $p < 0.001$; Wilks' $\Lambda = 0.372$; partial $\eta^2 = 0.628$). The mean mobility scores were 15.3 points (95% CI 11.5–19.0; $p < 0.01$) higher in the non-MMC group than in the MMC group and 12.6 points (95% CI 7.0–18.1; $p = 0.573$) higher in the non-Lorber group than in the Lorber group. The MMC group also scored significantly lower regarding daily activity, cognitive, and responsibility scores than the non-MMC group. However, there was no significant difference between the Lorber and non-Lorber groups in these domains (Table 3).

Mobility

Nearly half of the patients (45.5%) are household or community ambulators, and the remaining patients are wheelchair-bound. The household/community ambulator group consists entirely of non-Lorber patients.

Communication

All patients (n = 22) reached level I (n = 18) or II (n = 4) on the CFCS, which means that they were able to communicate effectively, albeit slowly in 4 patients. There was no statistical difference between Lorber and non-Lorber patients regarding CFCS ($p > 0.05$). The 4 patients with CFCS level II did report self-evaluated slower communication compared with peers.

Pain and Fatigue

Almost three-quarters of the patients experienced some degree of pain in the week prior to the interview. Whereas most children (n = 12) reported low levels of pain (NRS scores of 1.0–3.0), 4 children reported moderate levels (NRS scores of 4.0–6.0). In total, 6 patients (27.3%) reported no pain in the week prior to the interview. Pain could be effectively treated with pain medication in all patients.

Four children (18.2%) reported no fatigue in the week prior to the interview. Eighteen children experienced some degree of fatigue on average, ranging from moderate fatigue (8 patients; NRS scores of 4.0–6.0) to severe fatigue (10 patients; NRS scores of 7.0–9.0).

There were no significant differences in pain or fatigue between Lorber (mean 1.8 ± 0.7) and non-Lorber (mean 1.9 ± 0.5) patients (95% CI –1.85 to 1.99; $t[20] = 0.079$; $p = 0.698$).

Number of Surgeries

Overall, patients had a mean number of 18 ± 5 (range 6–30) surgeries consisting of 5 ± 1 (range 0–14) neurosurgical procedures, 1.2 ± 0.6 (range 0–14) orthopedic procedures, and

11.8 ± 0.6 (range 6–23) urological procedures. The number of surgeries was the highest in the 1st year after birth (mean 1.3 ± 0.4). The Lorber group (16.7 ± 5.2) did not differ significantly from the non-Lorber group (16.4 ± 6.0) (95% CI 5.45–6.03; t[11] = 0.112; p = 0.913).

Discussion

Among the many factors affecting the quality of life and function in spina bifida patients, the level of mobility, sensory deficits, cognitive impairments, and incontinence seem to be major contributing factors.[5,13] This study shows that MMC patients score considerably lower regarding functioning and quality of life when compared with their peers without MMC, but this did not directly translate into a worse perception of physical well-being. Comparing Lorber and non-Lorber MMC patients, we found a significant difference only regarding perceived quality of life in the school environment and not in the other domains. Considering the effects of MMC on the quality of life and the number of surgeries, we conclude that MMC is a severe but manageable condition.

The primary motivation for conducting this study was to offer new insights into the long-term follow-up of MMC patients. No study before has reported on the same group of patients 10 years after the initial evaluation of discomfort and pain.[5] This study does not offer a direct cross-sectional comparison with our previous work on the same cohort 10 years ago. Changes in age are reflected in different and often more complex parameters of quality of life. Hence, a direct comparison would not be sufficient.

In the Netherlands, the active ending of life for newborns with severe MMC has been at the center of debate for many years.[14] This resulted in a broader discussion about the option of active termination of life for newborns with severe untreatable diseases in general. Eventually, the Groningen Protocol was developed in 2004 to aid clinicians when making these difficult decisions. Its unique perspective has sparked an international debate over the last 2 decades.[14–20] The protocol contains a specific set of criteria that are essential in evaluating clinical decisions. This process warrants careful discussions considering different viewpoints, but the active ending of a newborn's life is legal under Dutch law when the criteria are met. Infants born with a severe MMC will often have profound disabilities with a significant impact on their daily lives and hence could be considered to suffer unbearably and hopelessly according to the criteria mentioned in the Groningen Protocol. Active termination of life was reported in 22 cases of severe MMC between 1997 and 2004 using the criteria set within the Groningen Protocol.[20]

In their cohort, Verhagen et al. included 22 newborns with severe MMC.[20] Their lives were terminated because it was concluded that unbearable and hopeless suffering was present and that their future quality of life would be severely affected. This included potential hospital dependency, lifelong and untreatable discomfort and pain, an inability to communicate, and low self-sufficiency. Despite the undeniable severe impact on quality of life, we

argue that the prediction of future unbearable suffering in this group of patients remains challenging. We observed relatively low levels of pain, apart from 4 patients with moderate levels of pain in the week before the interview. More importantly, this pain could be adequately managed for all patients using low-impact analgesics. Fatigue ranged from moderate to severe. These scores are lower than self-reported pain and fatigue ratings in children with, for instance, chronic arthritis or cerebral palsy.[21,22] We understand the differences in methodological use between these studies and ours, but we think it is acceptable to state that these MMC children do not suffer unbearably. Also, this suffering also does not continue throughout their youth, which is regarded as another argument for eligibility according to the Groningen Protocol.

Because of their physical and cognitive impairments, MMC patients are thought to experience a significant dependency on parents and caretakers. Dependency on the medical circuit, which involves frequent hospital visits and surgeries, is seen as a factor that affects patients' quality of life.[5] In our cohort, children had indeed undergone a considerable number of surgeries in the first 10 years of their lives. Even though our results show a significant difference between PEDI-CAT (limitations in activity level) and KIDSCREEN-27 (HRQOL) scores between the MMC population and the non-MMC group, this difference was not significant in terms of physical and psychological well-being. Additionally, our findings also show that all children can communicate effectively, although some were considered slow.

This study has several limitations because of its retrospective nature and sample size, especially when comparing the Lorber group to the non-Lorber group. The sample size was dictated by reporting on the same cohort as 10 years ago. In the future, we recommend that a prospective cohort study with a larger sample size be conducted to overcome these limitations.

Conclusions

Our study shows that MMC is a severe lifelong condition that affects patients' lives in many domains and that all our patients are capable of effective communication, irrespective of the severity of MMC.

Overall, our data show that in newborn MMC patients, future unbearable suffering with respect to pain, mobility, cognition, and communication is hard to predict and may not always occur. The difficulty of defining and predicting unbearable suffering after birth as well as in future life underlines the extreme importance of adequate counseling based on the available literature for future parents confronted with a spina bifida pregnancy.

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TABLE 1. Patient characteristics

	Total Population	Non-Lorber Group	Lorber Group
Sex			
Male	10 (45.5)	8 (50)	2 (33.3)
Female	12 (54.5)	8 (50)	4 (66.7)
Mean age, yrs (SD)	11.0 (1.4)	11.13 (1.42)	10.64 (1.21)
Education			
Primary school	4 (18.2)	4 (25)	0
Secondary school	1 (4.5)	1 (6.3)	0
Special primary school	12 (54.5)	7 (43.8)	5 (83.3)
Special secondary school	5 (22.7)	4 (25)	1 (16.7)

Values are given as the number of patients (%) unless otherwise indicated.

TABLE 2. KIDSCREEN-27 subscores evaluated between the cohort versus the normal group and the non-Lorber versus the Lorber group

	Cohort vs Normal Group						Non-Lorber vs Lorber Group					
	Mean Difference	95% CI		df*	t	p Value	Mean Difference	95% CI		df*	t	p Value
		Lower Bound	Upper Bound					Lower Bound	Upper Bound			
Physical well-being	−13.90	−19.25	−8.56	31	−5.31	0.040	5.32	−7.38	18.02	8	0.96	0.364
Psychological well-being	−0.99	−5.28	3.31	29	−0.47	0.011	0.00	−10.54	−10.53	8	0.00	0.999
Parent relations & autonomy	13.55	10.08	17.03	25	8.03	<0.001	−0.45	−6.40	5.50	17	−0.16	0.876
Social support & peers	−3.17	−8.86	2.51	21	−1.16	<0.001	−2.86	−16.32	6.02	10	−0.48	0.645
School environment	4.77	−1.45	10.98	27	1.58	0.001	16.15	1.86	30.43	7	2.64	0.032

*Equal variance is not assumed.

TABLE 3. PEDI-CAT subscores evaluated between the cohort versus the normal group and the non-Lorber versus the Lorber group

	Cohort vs Normal Group						Non-Lorber vs Lorber Group					
	Mean Difference	95% CI		df*	t	p Value	Mean Difference	95% CI		df*	t	p Value
		Lower Bound	Upper Bound					Lower Bound	Upper Bound			
Daily activity score	−6.19	−9.26	−3.11	23	−4.16	<0.001	9.80	3.6	16.01	8	3.64	0.007
Mobility score	−15.29	−19.01	−11.57	21	−8.54	<0.001	12.58	7.03	18.13	13	4.91	<0.001
Cognitive score	−3.88	−5.58	−2.17	25	−4.69	<0.001	4.87	0.85	8.89	7	2.86	0.024
Responsibility score	−4.81	−7.3	−2.33	25	−3.99	0.001	9.35	4.21	14.49	6	4.41	0.004

*Equal variance is not assumed.

Chapter 4

Neurosurgeons' opinions on the prenatal management of myelomeningocele

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Abstract

Objective

Improvement in imaging and surgical technological innovations have led to the increasing implementation of fetal surgical techniques. Open fetal surgery has demonstrated more favorable clinical outcomes in children born with open myelomeningocele (MMC) than those following postnatal repair. However, primarily because of maternal risks but also because of fetal risks, fetal surgery for MMC remains controversial. Here the authors evaluated contemporary management of MMC in the hope of identifying barriers and facilitators for neurosurgeons in providing fetal surgery for MMC.

Methods

An online survey was emailed to members of the Congress of Neurological Surgeons (CNS) and International Society of Pediatric Neurosurgery (ISPN) in March 2019. The survey focused on: 1) characteristics of the respondents, 2) the practice of counseling on and management of prenatally diagnosed MMC and 3) barriers, facilitators and expectations of fetal surgery for MMC. Reminders were sent to improve the response rate.

Results

A total of 446 respondents filled in the survey, mostly (59.2%) of whom specialized in pediatric neurosurgery. The respondents repaired an average of 9.6 MMC defects per year, regardless of technique. Regardless of the departments in which the respondents were employed, 91.0% provided postnatal repair of MMC, 13.0% open fetal repair and 4.9% fetoscopic repair. According to the surgeons, the most important objections to performing open fetal surgery were lack of cases available to become proficient in the technique (33.8%), the risk of maternal complications(23.6%), and concern for fetal complications (15.2%). The most important facilitators considered by advocates of prenatal closure are the decreased rate of shunt dependency (37.8%), a decreased rate of hindbrain herniation (27.0%), and an improved rate of motor function (18.9%). Of the respondents, only 16.9% agreed that open fetal surgery should be the standard of care.

Conclusions

The survey results showed diversity in the management of patients with MMC. In addition, significant diversity remains regarding fetal surgery for MMC closure. Despite the apparent benefits of open fetal surgery in selected pregnancies, only a minority of centers and providers offer this technique. As a more technically demanding technique that requires a multidisciplinary effort with less well-established long-term outcomes, fetoscopic surgery may face similar limited implementation, although the surgery may pose fewer maternal risks than open fetal surgery. Centralization of prenatal treatment to tertiary care referral centers, as well as the use of sophisticated training models, may help to augment the most commonly cited objection to the implementation of prenatal closure, which is the overall limited caseload.

Introduction

Meningomyelocele (MMC) characterized by extrusion of the spinal cord together with the meningeal membranes,is the most severe and common form of spina bifida [11]. Standard treatment is closure of the MMC defect within 48 hours of birth to minimize infectious and traumatic risk to the tissue.[14,16] Since publication of the first case of surgical closure of an MMC defect in 1892, only limited progress has been made in surgical repair with the primary goals of creating a watertight closure over the open neural placode.[6] Patients born with MMC can face lifelong disabilities such as neurological deficits below the level of the defect, hydrocephalus, hindbrain herniation, scoliosis, tethering of the spinal cord, urinary and fecal incontinence, and sexual dysfunction.

Early in vivo studies suggested that prenatal intervention could prevent secondary insults to the neural placode and development of hindbrain herniation or hydrocephalus due to persistent intrauterine CSF leak. Further surgical innovations and improvement in instrumentations refined this technique and improved mortality and morbidity rates[1,25]. Initially, fetal surgery started as an option to treat potentially lethal conditions such as congenital diaphragmatic hernia, improving early mortality rates[19,28]. With increasing knowledge and experience, the indications of fetal surgery have broadened towards treating non-lethal diseases such as MMC[1,8]. Early case series of fetal MMC repair showed promising results at the end of the last century, and eventually lead to a randomized controlled trial published in 2011.

In the Management of Myelomeningocele Study (MOMS) women who were diagnosed with a fetus having MMC, were randomized to receive open fetal surgery before 26 weeks of gestation or conventional postnatal surgical repair[2]. This trial was stopped prematurely given the efficacy of prenatal surgery. Results showed that only 40% of the prenatal surgery group needed the placement of a shunt versus 82% in the postnatal surgery group at one year. In addition, children with MMC in the prenatal surgery group were also less likely to have hindbrain herniation, had a better level of motor functioning and were more likely to walk independently. However these promising fetal outcomes came at the expense of maternal morbidity with higher rates of preterm delivery and a higher risk of maternal complications such as placental abruption and chorioamniotic membrane separation. Fetal surgery also carries risks for the fetus such as pulmonary edema, requirement of transfusions and a lower birth weight. Furthermore, the MOMs had strict inclusion criteria reflected by the fact that 1087 women underwent preliminary screening after which 183 underwent randomization.

Fetoscopic techniques were developed in the hopes of lowering maternal morbidity both in the current MMC pregnancy as well as future pregnancies. Developments and refinements of fetoscopic procedures have further improved techniques [9,22]. Unlike open prenatal

repair, fetoscopic surgery was less well received by the neurosurgical community due to the complexity of the procedure and less established outcomes[12,13].

With the rise of fetal surgery and increasing evidence for its risks and benefits in treating selected pregnancies with MMC, neurosurgeons may increasingly face ethical dilemmas, such as weighing maternal risks against potential fetal benefits. An expected paradigm shift in the treatment of MMC since publication of the MOMS trial has led to interest in knowing the current management and application of fetal surgery of our colleagues. We aimed to identify the barriers and facilitators for fetal closure perceived by the neurosurgeons providing current techniques for MMC repair. Therefore, we conducted a survey on the management of MMC by neurosurgeons to evaluate the clinical practice worldwide.

Methods

Based on previous literature a first concept survey was developed[2-4,15,18,27]. This survey was reviewed by two pediatric neurosurgeons experienced in treating MMC, as well as a fetal-maternal-medicine specialist before being finalized. The survey consists of 17 questions and can be divided into three sections:

1) characteristics of the respondents such as sub-specialization, tenure and country of employment;
2) the practice of counseling on and management of MMC such as the items discussed during counseling of potential upcoming parents, amount of MMC defects closed yearly and the availability of prenatal surgery to treat MMC;
3) barriers, facilitators and expectations of fetal surgery for MMC.

The survey can be found in the supplementary material. Institutional Review Board waived the need for approval as this research does not involve patients.

Members of the Congress of Neurological Surgeons (CNS) and of the International Society for Pediatric Neurosurgery (ISPN) were approached by an email invitation containing a cover letter, to fill in a survey. The CNS was founded in 1951 and represents more than 9000 international members. Members include residents, neurosurgeons, medical students amongst others. The ISPN consists out of more than 350 pediatric neurosurgeons In March 2019 the survey was distributed by email, using SurveyMonkey (Palo Alto, CA, USA). To increase the response rate reminders were sent. By filling in a survey, respondents gave informed consent. Only responses from neurosurgeons and neurosurgery residents were included.

Data were analyzed using the IBM SPSS Statistics version 21.0 for Windows (IBM Corp.) Descriptive statistics were used to present data in frequencies and percentages. Categorical data were analyzed using chi-squared test. A p-value <0.05 was considered to be statistically significant.

Results

Characteristics of the respondents

A total of 448 respondents filled in the survey. Two responses were not from neurosurgeons or neurosurgery residents and were therefore excluded. Eighty-four percent of the respondents were from the CNS while the remaining 16% were from ISPN. Respondents were employed in a total of 58 countries with the USA (56.3%), Brazil (5.2%), and India (4.9%) having the most respondents (see figure 1 for a geographical overview). Africa was least represented (2.7%Table 1).

Respondents had a mean clinical experience of 21.6±12.9 years (mean ± standard deviation), with residents having a mean clinical experience of 5.5 years(Table 1). Most of the respondents had pediatric neurosurgery as their sub-specialization (59.2%). Spine (29.6%) and Neuro-oncology (28.3%) followed as the most frequent sub-specializations.

Among the respondents, 81.0% treated patients with MMC. Neurosurgeons sub-specialized in Pediatric Neurosurgery were more likely to treat patients with MMC ($p<0.001$). Among neurosurgeons not subspecialized in pediatric neurosurgery, 54.8% treated patients with MMC. Neurosurgeons performing closure of MMC defects, operated 9.6±17.9 patients annually.

Counseling and management of MMC

Three-quarters (74.5%) of the neurosurgeons and 50% of the residents deemed themselves sufficiently informed to counsel parents ($p = 0.008$), and 72.2% of the respondents actually counsel potential parents with children suspected to have MMC. Of those neurosurgeons who deemed themselves insufficiently informed to counsel, 37.2% still counsel potential parents. Table 2 gives an overview of several items discussed by respondents during the counseling of potential parents. All items differed statistically significantly between pediatric and non-pediatric neurosurgeons. Surgical closure of the MMC defect, the need for CSF shunting, and the expected level of motor function were always discussed by 83.1%, 75.3% and 69.4% of respondents, respectively. Termination of the pregnancy and the option of fetal surgery were never discussed by 35.6% and 23.7% of the neurosurgeons, respectively.

Ninety-one percent of the departments in which the neurosurgeons are employed provide conventional postnatal surgical closure of MMC defect. Open fetal and fetoscopic procedures are provided by 13.0% and 4.9% of the centers respectively. Four out of all centers provided fetal surgery, but did not perform conventional postnatal surgery. Performing more surgical closures annually, was not associated with providing fetal surgery ($p>0.05$).

Table 3 gives an overview of the disciplines involved in the treatment of (unborn) patients with MMC. As regards clinical management by the respondents, neurosurgery (78.0%), obstetrics (77.4%), and pediatrics (59.9%) were always involved in the care of MMC patients. Rehabilitation medicine, orthopedics, and neurology were never involved according

to 27.5%, 26.6%, and 23.4% of respondents, respectively. Pediatric neurosurgeons were less likely than non-pediatric neurosurgeons ($p = 0.002$) to involve pediatrics.

Barriers, facilitators and expectations of Fetal Surgery for MMC

When asked to rank the most important objections for providing open fetal surgery to treat MMC, 33.8% ranked 'too few cases available to become proficient in the technique' as number one.(Fig.2) The risk of maternal complications and the risk of fetal complications were ranked second and third respectively by 23.6% and 15.2%. Costs and ethical concerns were ranked last by 32.4% and 27.0% respectively.

The most important reason to provide open fetal surgery according to respondents was a decreased rate of shunt dependency (37.8% of respondents; Fig. 3), followed by a decreased rate of hindbrain herniation (27.0% of respondents) and an improved rate of motor function (18.9% of respondents). Ranked last was the motivation to give parents a treatment option during gestation (18.2% of respondents).

When comparing postnatal surgery with open fetal surgery and fetoscopic surgery, respondents expected the risk of maternal complications to be the highest for open fetal surgery (89.2% of respondents), closely followed by fetoscopic surgery (79.9% of respondents; Table 4). Conventional postnatal closure was expected to have the lowest risk (92.5% of respondents). Open fetal surgery (70.6% of respondents) and fetoscopic surgery (66.8% of respondents) were expected to have the highest risks for perioperative fetal complications. No significant differences could be identified in expectations between countries providing fetal surgery and countries that do not. Furthermore, no significant differences could be identified between residents and neurosurgeons regarding barriers, facilitators and expectations of fetal surgery. (Fig 3)

Table 5 gives an overview of respondent answers regarding the outcomes of open prenatal surgery. Among all respondents, 62.6% assumed that fetal surgery would lead to a higher risk of neonatal death, which contrasts with what the MOMS showed

Table 6 gives an overview of respondent opinions regarding the position of fetal and fetoscopic surgery in the management of MMC. More than half of the respondents (54.4%) disagreed or strongly disagreed that open fetal surgery should be the standard of care. Similarly, more than half of the respondents (58.1%) disagreed or strongly disagreed that potentially damaging women as a result of fetal surgery is acceptable. Pediatric neurosurgeons were more likely than no pediatric neurosurgeons to disagree on both of these items ($p < 0.001$ and $p = 0.003$, respectively). Reactions to the statement "denying potential improvement in the quality of life of MMC patients by not offering fetal surgery is acceptable" were more divided with almost a third (strongly) agreeing, a third being neutral, and almost a third (strongly) disagreeing. Slightly more than half (50.7%) of the respondents

strongly disagreed or disagreed with the statement that providing fetoscopic surgery without performing a randomized controlled trial is acceptable.

Discussion

This study gives an overview of the current management of MMC and opinions on fetal surgery by neurosurgeons worldwide. Open fetal surgery (13.0%) and especially fetoscopic surgery (4.9%) are provided by only a minority of the centers in which the respondents are employed. Despite the well-documented decreased rates of shunt dependency and hindbrain herniation and improved rate of motor function in strictly selected pregnancies, only 16.9% of respondents agreed that open fetal surgery should be the standard of care. The most important objections to the procedure are a limited caseload available to become proficient in the technique, the risk of maternal complications, and the risk of fetal complications. The bind in the trade-off between maternal health and the health and quality of life of patients with MMC is illustrated by the equally divided opinions regarding the statement that 'denying potential improvement in the quality of life of MMC patients by not offering fetal surgery is acceptable'.

Comparison with other studies

When the results of the MOMS were published in 2011, a paradigm shift was expected.[2] However, such a shift was not reflected in our results: 23.7% of respondents never discuss the option of fetal surgery during counseling, and only 16.9% agree that open fetal surgery should be standard care. Moreover, only 13.0% of respondents offer open fetal surgery, while 4.9% offer fetoscopic surgery. An explanation for these low rates may be the generalizability of the MOMS, which included pregnancies carrying fetuses with MMC based on strict inclusion criteria. Results of fetal surgery for other pregnancies are less well-documented and warrant prospective studies. Another explanation may be the maternal comorbidity and the risk for future pregnancies. In the literature, a maternal complication rate of 6.2% for fetoscopic surgery and a rate of 20.9% for open fetal surgery have been reported[29]. When taking into account only serious maternal complications such as those requiring ICU-care or surgical intervention, risk rates of 1.7% and 4.5% are reported for fetoscopic and open procedures respectively. Our results showed that 62.6% of the respondents assume that open fetal surgery carries a higher risk of neonatal death. Moreover, almost 40% wrongly assume a higher maternal mortality rate. These data may imply that a factor contributing to the nonoccurrence of the paradigm shift may be a lack of knowledge—on the one hand, a lack of knowledge because the outcomes reported in the literature may not be known among respondents, and on the other hand, because the results reported in the literature (e.g., MOMS) may not be generalizable to all pregnancies carrying fetuses with MMC.

Previous studies have shown that fetal surgery, especially fetoscopic surgery is technically demanding and requires dedicated training[12,13,20]. This may be reflected by the fact that

only 4.9% of the departments surveyed provided fetoscopic surgery. A number of studies have been conducted to assess the relationship between hospital and surgeon volume and surgical mortality and morbidity [7,24]. These studies have shown that a high surgeon volume results in superior outcomes for patients. Paradoxically, the majority of the respondents also agrees that performing one case of fetal surgery per month is acceptable, which mirrors the respondents current practice of approximately 9.6 MMC repairs per year.

In the light of high case volume the Maternal-Fetal Management Task Force released a position statement in which minimum criteria are recommended to ensure optimal maternal and fetal outcomes[10]. In this statement, an initial experience of 5 cases is required together with an adequate annual volume of cases to maintain proficiency. The exact amount of cases meant with "adequate" is subject to debate, however. A recent meta-analysis on the learning curves of fetal surgery estimated that competence for standard hysterotomy is reached after 35 cases and that competence for minimally invasive procedures is reached after 56 cases.[20]

In this context, a smaller number of centers dedicated to fetal surgery, in which surgeons perform larger volumes of cases, is more desirable than a more disseminated offering of fetal surgery. A remedy toward achieving and maintaining proficiency may be adequate training models.[26] Assisted nowadays by 3D-printed models, it is possible to create case-specific models to prepare for complex procedures such as fetoscopic surgery.

Another debatable subject is the position of fetoscopic surgery. In a recent meta-analysis, outcomes of fetoscopic and open repair of MMC defects, published after MOMS, were analyzed and compared.[21] A total of 11 studies were included, 4 retrospective and 7 prospective, comprising 436 patients. Fetoscopic MMC repair (percutaneous or laparotomy access combined) was associated with a lower rate of uterine dehiscence; however, this came with a higher rate of dehiscence or CSF leakage of the MMC defect, requiring postnatal revision. There were no between group differences regarding fetal and postnatal mortality, rate of shunt placement, reversal of hindbrain herniation, motor response, gestational age before birth, chorioamniotic membrane separation, or placental abruption. Expectations of our respondents were similar with 89.2% expecting open fetal surgery to have the highest risk for maternal complications. Authors of another meta-analysis concluded similarly, suggesting that before performing a randomized study, endoscopic techniques should be improved first.[5]

To date, no randomized controlled studies have compared the two techniques of fetoscopic and open postnatal repair. Only a minority of our respondents, 21.9% (strongly) believe it is acceptable to provide prenatal fetoscopic surgery without performing a randomized controlled trial. Fetoscopic surgery faces multiple barriers to implementation, as indicated by the reluctance of neurosurgeons to offer open fetal repair for MMC with only 13.0% of centers in our respondent pool offering the procedure.

Strengths and limitations

Some limitations of this study must be acknowledged. First, the response rate could be a limitation. The survey was mailed to 7671 functional email addresses of CNS members. Three hundred seventy-four responses were from CNS members leading to an estimated response rate of 4.9%. Of note, some of the email addresses may have belonged to medical students or other allied health professionals who may not have been eligible to fill out the survey. The importance of the response rate when judging the quality of cross-sectional research, however, is subject to debate.17,23 Given that 446 neurosurgeons with variable tenure and representing 58 countries responded to our survey, we expect a limited risk of nonresponse bias. However, we assume that MMC-dedicated centers, which also offer fetal surgery, may have been more inclined to respond. Another limitation may be the unfamiliarity of the respondents with either the care of patients with MMC or prenatal surgery. However, 81.0% stated that they treat patients with MMC and 91.0% worked at a department where either postnatal or prenatal surgery is provided

Conclusions

The survey results show the diversity in the management of patients with MMC. In addition, significant diversity remains regarding fetal surgery for MMC closure. Despite the apparent benefits of open fetal surgery in selected pregnancies, only a minority of centers and providers offer this technique. As a more technically demanding technique that requires multidisciplinary effort with less well-established long-term outcomes, fetoscopic surgery may face similar limited implementation, although the surgery may pose fewer maternal risks than open fetal surgery. Centralization of prenatal treatment to tertiary care referral centers, as well as the use of sophisticated training models, may help to augment the most commonly cited objection to the implementation of prenatal closure, which is the overall limited caseload

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Table 1: characteristics of the respondents

Function	446	**Years of clinical experience**	21.6 ±12.9
Neurosurgeon	394 (88.3%)		
Neurosurgeon in training	52 (11.7%)	**Continent of respondent**	446
		Africa	12 (2.7%)
Specialties		Asia and Oceania	67 (15.0%)
Epilepsy	39 (8.7%)	Europe	45 (10.1%)
Functional	28 (6.3%)	North America	280 (62.8%)
Peripheral nerve	25 (5.6%)	South America	42 (9.4%)
Pediatrics	264 (59.2%)		
Neuro-oncology	126 (28.3%)	**Department provides:**	
Neurovascular	83 (18.6%)	Postnatal surgical closure of MMC	406 (91.0%)
Neuro trauma	93 (20.9%)		
Spine	132 (29.6%)	Open fetal surgery	58 (13.0%)
Other	47 (10.5%)	Fetoscopic surgery	22 (4.9%)

TABLE 2. Items discussed during counseling by pediatric versus nonpediatric neurosurgeon respondents

Item	**Pediatric Neurosurgeons**	**Nonpediatric Neurosurgeons**	**p Value**
No. of respondents	265	181	
Termination of pregnancy			<0.001
Always	22.0%	12.2%	
Often	8.2%	3.8%	
Sometimes	17.1%	13.7%	
Rarely	25.7%	18.3%	
Never	26.9%	51.9%	
Repair of defect			<0.001
Always	92.7%	65.7%	
Often	4.1%	10.4%	
Sometimes	1.2%	4.5%	
Rarely	0.4%	3.0%	
Never	1.6%	16.4%	
Need for CSF shunting			<0.001
Always	85.4%	57.0%	
Often	11.4%	18.5%	
Sometimes	2.0%	6.7%	
Rarely	0	2.2%	
Never	1.2%	15.6%	

Item	Pediatric Neurosurgeons	Nonpediatric Neurosurgeons	p Value
Option of fetal surgery			<0.001
Always	43.4%	15.2%	
Often	13.1%	10.6%	
Sometimes	14.8%	17.4%	
Rarely	13.5%	17.4%	
Never	15.2%	39.4%	
Hindbrain herniation			<0.001
Always	66.9%	36.6%	
Often	18.4%	15.7%	
Sometimes	9.0%	17.2%	
Rarely	3.7%	11.9%	
Never	2.0%	18.7%	
Risk of spinal cord untethering			<0.001
Always	68.2%	44.8%	
Often	15.9%	20.1%	
Sometimes	10.2%	14.2%	
Rarely	4.1%	3.7%	
Never	1.6%	17.2%	
Expected level of motor function			<0.001
Always	76.8%	55.6%	
Often	15.9%	17.3%	
Sometimes	3.7%	7.5%	
Rarely	0.8%	2.3%	
Never	2.8%	17.3%	
Urological management			<0.001
Always	80.1%	48.9%	
Often	11.4%	16.5%	
Sometimes	4.5%	12.0%	
Rarely	1.2%	3.0%	
Never	2.8%	19.5%	
Orthopedic management			<0.001
Always	58.4%	31.6%	
Often	22.9%	18.0%	
Sometimes	11.4%	22.6%	
Rarely	4.5%	6.8%	
Never	2.9%	21.1%	

TABLE 3. Disciplines involved in the management of MMC

Discipline	Pediatric Neurosurgeons	Nonpediatric Neurosurgeons	p Value
Pediatrics			0.002
Always	55.6%	71.3%	
Often	12.5%	10.3%	
Sometimes	8.6%	6.9%	
Rarely	16.8%	1.1%	
Never	6.5%	10.3%	
Genetics			NS
Always	22.6%	25.3%	
Often	23.9%	26.6%	
Sometimes	27.4%	22.8%	
Rarely	16.1%	10.1%	
Never	10.0%	15.2%	
Neurosurgery			NS
Always	78.4%	77.0%	
Often	15.2%	8.0%	
Sometimes	4.0%	6.9%	
Rarely	1.6%	4.6%	
Never	0.8%	3.4%	
Orthopedics			NS
Always	21.7%	16.7%	
Often	14.7%	11.1%	
Sometimes	14.3%	25.0%	
Rarely	23.5%	18.1%	
Never	25.8%	29.2%	
Neurology			NS
Always	17.0%	9.6%	
Often	18.8%	17.8%	
Sometimes	20.6%	35.6%	
Rarely	20.6%	12.3%	
Never	22.9%	24.7%	
Obstetrics			NS
Always	78.5%	75.0%	
Often	9.8%	8.3%	
Sometimes	4.9%	9.5%	
Rarely	4.5%	3.6%	
Never	2.4%	3.6%	

Discipline	Pediatric Neurosurgeons	Nonpediatric Neurosurgeons	p Value
Rehabilitation medicine			0.001
Always	33.5%	31.6%	
Often	9.3%	18.4%	
Sometimes	8.4%	21.1%	
Rarely	19.5%	6.6%	
Never	29.3%	22.4%	
Social work			NS
Always	38.7%	46.2%	
Often	24.8%	17.9%	
Sometimes	12.2%	9.0%	
Rarely	12.2%	10.3%	
Never	12.2%	16.7%	
Urology			NS
Always	33.2%	32.9%	
Often	13.2%	16.5%	
Sometimes	12.3%	19.0%	
Rarely	20.5%	8.9%	
Never	20.9%	22.8%	

NS = not significant.

TABLE 4. Expectations regarding the risks of maternal and fetal complications of three techniques to close MMCs

	Level of Risk		
Complication & Procedure	Most	Moderate	Least
Maternal complication			
Postnatal surgery	2.7%	4.8%	92.5%
Open fetal surgery	89.2%	8.8%	2.0%
Fetoscopic surgery	79.9%	13.6%	9.5%
Fetal complication			
Postnatal surgery	16.3%	21.4%	62.2%
Open fetal surgery	70.6%	19.9%	9.5%
Fetoscopic surgery	66.8%	22.7%	10.5%

TABLE 5. Respondent knowledge about open prenatal surgery performed before 26 weeks of gestation

Statement	Respondent Answer	
	True	False
Fetal surgery leads to a higher risk of maternal death	39.4%	**60.6%**
Fetal surgery leads to a higher risk of maternal complications such as placental abruption	**90.6%**	9.4%
Fetal surgery leads to a higher risk of neonatal death	62.6%	**37.4%**
Fetal surgery halves the neonatal CSF shunt rate	**68.2%**	31.8%
Children who underwent prenatal surgery have a lower level of mental & motor function	11.5%	**88.5%**

Answers in boldface type indicate results of the MOMS.

TABLE 6. Overview of respondent opinions regarding the place of fetal surgery in the management of MMC

Statement	Pediatric Neurosurgeons	Nonpediatric Neurosurgeons	p Value
Providing prenatal fetoscopic surgery w/o performing an RCT is acceptable			NS
Strongly agree	5.5%	8.3%	
Agree	14.0%	18.8%	
Neutral	25.5%	31.3%	
Disagree	34.0%	28.1%	
Strongly disagree	21.0%	13.5%	
Potentially damaging women due to fetal surgery is acceptable			0.003
Strongly agree	2.5%	5.2%	
Agree	17.5%	11.5%	
Neutral	17.5%	34.4%	
Disagree	37.5%	36.5%	
Strongly disagree	25.0%	12.5%	
Open fetal surgery should be standard care			<0.001
Strongly agree	5.0%	4.2%	
Agree	12.0%	12.5%	
Neutral	21.5%	43.8%	
Disagree	36.0%	27.1%	
Strongly disagree	25.5%	12.5%	
A neurosurgeon performing only 1 fetal surgery case/mo is acceptable			0.006
Strongly agree	25.0%	10.5%	
Agree	43.0%	37.9%	
Neutral	13.5%	25.3%	
Disagree	10.0%	15.8%	
Strongly disagree	8.5%	10.5%	
Denying potential improvement in QOL of MMC patient by not offering fetal surgery is acceptable			NS
Strongly agree	9.5%	7.3%	
Agree	23.5%	14.6%	
Neutral	31.0%	41.7%	
Disagree	22.0%	27.1%	
Strongly disagree	14.0%	9.4%	

QOL = quality of life; RCT = randomized controlled trial.

Figure 1: a geographic overview of the working locations of the respondents.

Figure 2: the most important objections for not providing open fetal surgery for the treatment of MMC.

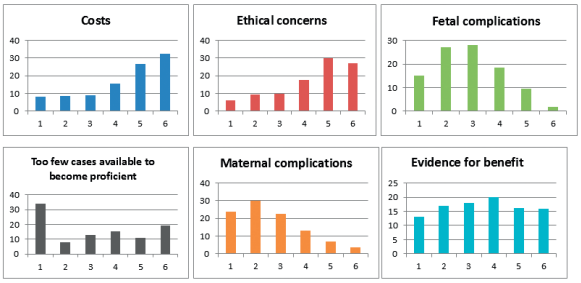
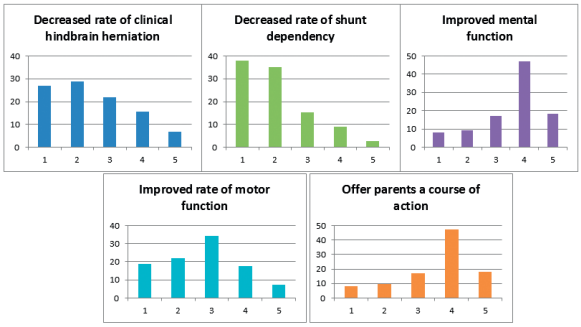
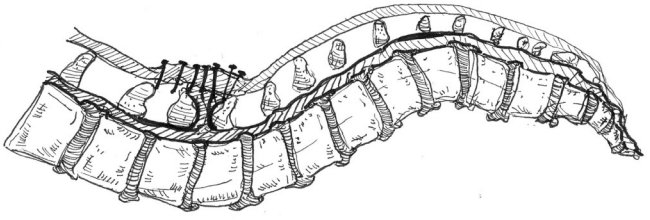
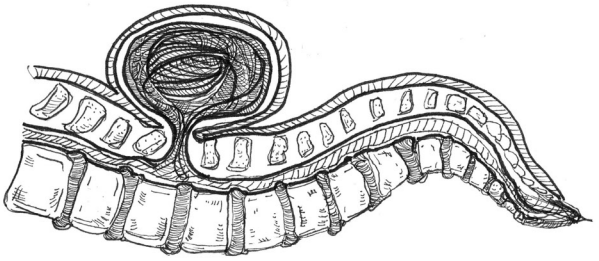
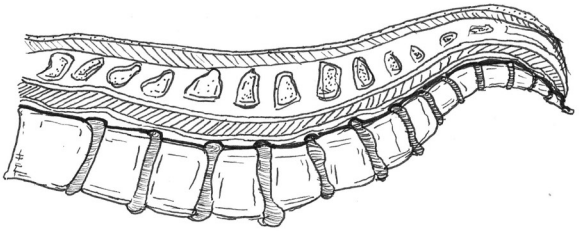


Figure 3: the most important reasons to provide open fetal surgery for MMC.









Chapter 5

Higher risk of tethered spinal cord in children after pre 1 natal surgery for myelomeningocele A systematic review and meta-analysis under peer review

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Abstract

Background

We performed a systematic review and meta-analysis on the incidence of secondary tethered spinal cord (TSC) between prenatal and postnatal closure in patients with MMC. The objectives was to understand the incidence of secondary TSC after prenatal surgery for MMC compared to postnatal surgery for MMC.

Methods

The systematic search was performed using the search terms "spina bifida", "spinal dysraphism", "tethered spinal cord", and synonyms in Medline, Embase, and the Cochrane Library on the 3rd of October, 2021. Primary studies reporting on type of repair, lesion level and TSC were included. Non-English or non-Dutch reports, case reports, conference abstracts, editorials, letters and comments, and animal studies were excluded. The included studies were critically appraised by two reviewers for risk of bias according to the PRISMA guidelines. The cumulative incidence of TSC among both MMC closure types was calculated, as well as the incidence of TSC. The association between the occurrence of TSC and surgical closure technique was evaluated by calculating the relative risk and 95% confident interval.

Results

Ten studies were included for quality assessment, including 2724 patients, of whom 2293 underwent postnatal closure and 431 prenatal closure.

In the prenatal closure group, the cumulative incidence of TSC was 32.7% (n = 141) and 20.7% (n = 621) in the postnatal group. Relative risk (RR) of TSC in patients with prenatal MMC closure compared to postnatal MMC closure was 1.83 (95%CI 1.466 to 2.300). Limitations include the follow-up periods for prenatal groups vs. postnatal groups, which differed dramatically. In the postnatal closure studies, tethering before the first year of life was very uncommon.

Discussion

This study shows an increased cumulative incidence and relative risk of TSC in the prenatal closure group compared to the postnatal group in MMC patients. In order to improve counselling on and outcome of MMC more long-term data on TSC after fetal closure for MMC is needed.

Introduction

Tethered spinal cord (TSC) describes a spectrum of clinical symptoms that accompany spinal cord traction, either due to its fixation at the site of spinal dysraphism or due to scaring at the site of its surgical repair[1, 2] Primary tethering of the spinal cord is seen at birth in all patients with myelomeningocele (MMC) [3-5], while secondary re-tethering complicates 2.8-32% of surgical MMC closures.[6-11] The latter is the combination of the fixed position of the spinal cord and its predefined length thereby interfering with the physiological ascent in the spinal canal during the early years of development. Consequently, the first signs of retethering often occur during the period of rapid longitudinal growth, usually between 5 and 9 years of age. [6, 11]

Tethered spinal cord can superimpose additional neurologic and structural handicaps on patients with MMC which can range from pain, lower limb weakness, gait disorders, neurogenic bowel and bladder to orthopedic abnormalities such as progressive scoliosis, leg-length discrepancy, foot asymmetry, and foot deformity. [12-14] [15-17] Accordingly, tethered spinal cord has the potential for an independent significant impact on a wide range of outcomes that affect functionality and quality of life in patients with MMC.

Prenatal MMC closure is a more recently introduced treatment that has been shown to improve hindbrain herniation, decrease the need for postnatal shunting for hydrocephalus as well as improving motor function and neurodevelopmental outcomes. On the other hand, despite these beneficial effects, there appeared to be an increased need for secondary spinal cord untethering surgery before the age of 12-months and a higher incidence of dermoid cysts in infants that underwent prenatal surgery.[18] A recent literature review and evidence-based guideline concluded the presence of class II and III evidence demonstrating an equal or higher incidence of TSC developing after prenatal MMC closure.[19] However, no meta-analysis has been performed to weigh the outcome of retethering between prenatal and postnatal closure groups. Given the importance of spinal cord tethering in determining outcome of patients with MMC we aimed to perform a systematic review and meta-analysis to evaluate the current literature on the incidence of retethering between prenatal and postnatal closure in patients with MMC.

Methods

Search strategy

This study was conducted in line with the PRISMA guidelines and registered in PROSPERO, (identification number 383940) .[20] We systematically searched the literature for primary intervention studies reporting on the incidence of symptomatic secondary TSC in the MMC population. The systematic search was performed using the search terms “spina bifida”, “spinal dysraphism”, “tethered spinal cord”, and synonyms in Pubmed, Medline, Embase, and the Cochrane Library on the 30th of January, 2023.

Study selection and eligibility criteria

Two investigators (C.C.K. and J.K.H.S.) independently assessed the titles and abstracts to identify randomized clinical trials (RCTs) or cohort studies on the incidence of secondary TSC between prenatal and postnatal myelomeningocele repair. Primary studies reporting on type of repair, lesion level and TSC were included. Non-English or non-Dutch reports, case reports, conference abstracts, editorials, letters and comments, and animal studies were excluded. Subsequently, full texts were independently evaluated for eligibility following inclusion and exclusion criteria. The two investigators reviewed the titles and abstracts for relevance and identified citations for full-text review using the online reviewing tool Rayyan.[21] (http://rayyan.qcri.org)

The occurrence of TSC was either defined by symptomatic TSC, which included neurologic or urological deterioration (i.e., new-onset upper urinary tract dilatation, decreased bladder compliance, incontinence, and gait deterioration) or by the necessity of surgical intervention for tethered cord release.

Data extraction

Two investigators extracted data with any disagreement resolved by consensus. For each relevant study, the following data were collected: first author, year of publication, country of conduct, study design, number of patients in the intervention group (prenatal repair), number of patients in the control group (postnatal repair), the mean age of TSC diagnosis, gender, anatomical level of the defect, the incidence of symptomatic tethered cord syndrome, incidence of surgical intervention of symptomatic tethered cord syndrome.

Quality assessment and publication bias

The included studies were critically appraised for risk of bias using the Cochrane tool of bias in Revman 5.4. This tool scores articles on the presence of bias on three levels ("low," "high," "unclear") on seven subdomains. The patient selection was considered at a "high" risk of bias if studies did not randomly assign patients to intervention (prenatal repair) or control group (postnatal repair) or if allocation was not concealed prior to the assignment, as is automatically the case in prospectively and retrospectively organized cohort studies. Performance bias was deemed at "high" risk if participants and personnel were not blinded for the allocation during the study. Detection bias was regarded to be a concern when the outcome assessor was not blinded. Attrition and reporting bias were considered "high" risk if studies provided incomplete outcome data or were selective in presenting their outcome data. Finally, problems encountered in trials that could not be assembled in any of the other categories are covered by "other bias". Publication bias was visually assessed using Deek's funnel plots.

Statistical analysis

Sample size calculations, based on a 25% incidence of TSC after postnatal MMC closure and a 45% incidence after prenatal MMC closure and a marginal error of estimates of 5% with

a 95% confidence interval, yielded a minimum of 270 patients in the prenatal group and 54 patients in the postnatal group to determine the relationship between closure technique and occurrence of TSC.[22]

The cumulative incidence of TSC among both MMC closure types was calculated, as well as the incidence of TSC in the prenatal and postnatal groups. The patients' baseline characteristics were presented either by frequency or by sample mean and standard deviation. In cases where only the sample median was given, the estimated mean was calculated via the quantile estimation method.[23] The association between the occurrence of TSC and surgical closure technique was evaluated by calculating the relative risk and 95% confident interval. Further subgroup analysis was performed to identify the difference in relative risk between study designs, follow-up periods and publication year. All analyses were performed using SPSS 27.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

Results

Study identification and selection

The systematic search yielded 4719 articles. After removal of duplicates, 4477 articles were screened by title and abstract for eligibility. 73 articles were retrieved for full-text assessment and evaluated for inclusion. Sixty-three articles were excluded due to various reasons as outlined in Figure 1. Twenty-six studies were excluded on the basis of their publication type (i.e. abstracts or case-report studies), 20 for reporting a different outcome than TSC, 8 were duplicates, 7 concerned a population different from MMC patients and 2 did not specify which closure technique was used. Finally, 10 studies were included for quality assessment. [7-11, 24-28]

Study characteristics

The included studies were published between 2006 and 2021 with a mean study period of 13.9 ± 7.7 years (Table 1). The largest share of included studies were multicentre retrospective cohort studies (40%).[7, 9, 11, 24] One randomized controlled trial and a retrospective cohort with a historical control were also included. [27, 28]

In total, the included studies reported on the outcomes of 2724 patients, of whom 2293 underwent postnatal closure and 431 prenatal closure of the MMC defect. Of the included patients, 49% was male (Table 2). Most patients had a MMC at the lumbar level (n = 1039) followed by sacral (n = 372), thoracic (n = 138) and cervical lesions (n = 2) , in 1173 patients the level was not specified. The prenatal closure group had 59.95% (n = 226) patients with lumbar MMC lesions, as compared to 69.3% of the postnatal closure group (n = 813) (Table 3). On average, patients presented with or were surgically treated for TCS at age 7.1 ± 1.7. The mean follow-up periods averaged between 4.0 and 11.8 years of age. Four postnatal studies (44.4 %) with a total number of 507 patients did not include patients with TSC under

the age of 2.5 years, while the majority of prenatal closure studies with a total number of 125 patients reported on patients with TSC before the first year of life. [7, 8, 10, 24, 25, 28]

Quality assessment

The quality assessment of the included studies is presented in Figure 2. Generally, studies were considered to be of moderate quality. Due to the nature of the study design of most included studies, selection bias was considered as an overall high risk. Similarly, we considered the studies at a high risk of performance bias due to the type of intervention (surgical). Very little concern was raised with regard to incomplete or selective reported data.

Tethered Spinal Cord

In the prenatal closure group, the cumulative incidence of TSC was 32.7% (n = 141), as compared to 20.7% (n = 621) in the postnatal closure group. The relative risk (RR) of TSC in patients with prenatal MMC closure compared to postnatal MMC closure was 1.83 (95%CI 1.466 to 2.300). A further subgroup analysis was done to evaluate the difference between study types, duration of follow-up, and study period. When comparing study types, the overall RR for TSC when evaluating the RCT & controlled cohort studies compared to the other studies was 0.559 (95%CI 0.475 to 0.658). The overall RR for TSC in studies with a follow-up period of 8 or more years was 2.016 (95%CI 1.724 to 2.359) compared to studies with a shorter follow-up.

Discussion

This study showed an increased cumulative incidence and relative risk of TSC in the prenatal closure group compared to the postnatal group. Since the fetus is supposed to heal with less scarring, this may seem remarkable.[29-32] Yet after 24 weeks of gestation, skin healing in the fetus is thought to be histologically identical to that in adults, and fetal surgery for MMC takes place around the 24th week of gestation.[18] If skin healing is identical in prenatal closure and postnatal closure, probably so is its effect on retethering. A potential explanation for the higher relative risk of rethetering in fetal closure for MMC may lie in the differences in surgical techniques between prenatal and postnatal closure, for instance, related to the re-tubulation of the placode, which is commonly done in postnatal surgery but not always possible in prenatal surgery.

In addition, the neurosurgical part of prenatal surgery is continuously evolving, largely driven by the development of a fetoscopic approach.[33, 34] Nevertheless, it is important to acknowledge the higher incidence of TSC, and we emphasize the necessity of further studies specifically focusing on this aspect of postnatal outcomes as it provides important information for preoperative counseling. However, it is also essential to guide future efforts in optimizing the prenatal closure technique.

There are several limitations of this study. First, the number of patients that underwent postnatal closure outweighed prenatal closure patients 5.5 to 1. The prenatal cohorts are small, and only one RCT has been conducted up to this point. Furthermore, there is a significant selection bias to be considered. Not all patients qualify for prenatal closure and might be excluded due to the severity or location of the defect or maternal morbidities. The limited availability of RCTs means that the majority of included studies are composed of retrospective cohorts. Although it is known that surgical cohort studies are not necessarily of a lesser methodological quality than surgical RCTs, there is a risk of performance bias. [35-37] Finally, follow-up periods for prenatal groups vs. postnatal groups differ dramatically. Where retrospective studies on postnatal closure have follow-up periods of over 20 years, prenatal closure generally only reports on the first 3 to 4 years of a patient's life, with one study reporting on a follow-up of up to 10 years. [28]

This shorter follow-up raises an interesting question regarding the incidence and risk of developing TSC. Previous studies on TSC following postnatal MMC closure have shown that most patients undergo tethered cord release between the age of 9 and 15.[7] The pathophysiology of increased strain on the spinal cord during a period of rapid growth results in an increase of symptomatic TSC.[1, 38-40] In postnatal closure studies, tethering before the first year of life is very uncommon. The first successful prenatal MMC closure was performed in 1997, and thus very few prenatal patients in that study have reached adulthood at this point in time.[41] Therefore, long-term results or complications remain unclear. It has been proposed that TSC occurs at a younger age in the prenatal closure group, while the absolute number of TSC remains equal to that of postnatal closure groups.[24] Yet, no data has been put forward to support these claims. As is shown in our systematic review, MMC patients who underwent prenatal closure seem to have a higher relative risk of developing TSC at a younger age. With puberty in foresight, these patients might be at risk of reoccurring tethering with the need for multiple surgical interventions, of which each carries a significant risk of further neurological deterioration.

In the end, there is a need for more follow-up data on the patients who have undergone prenatal MMC closure since the early beginning of this century. During prenatal MMC counseling, the direct functional outcomes and the possible need for future surgical interventions are important factors to consider when discussing the impact of MMC.

Conclusions

This meta-analysis and systematic review shows that the cumulative incidence and relative risk of TSC are increased in the prenatal closure group compared to the postnatal group in MMC patients. In order to improve counseling on and the outcome of MMC, more long-term data on TSC after fetal closure for MMC is needed.

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Tables

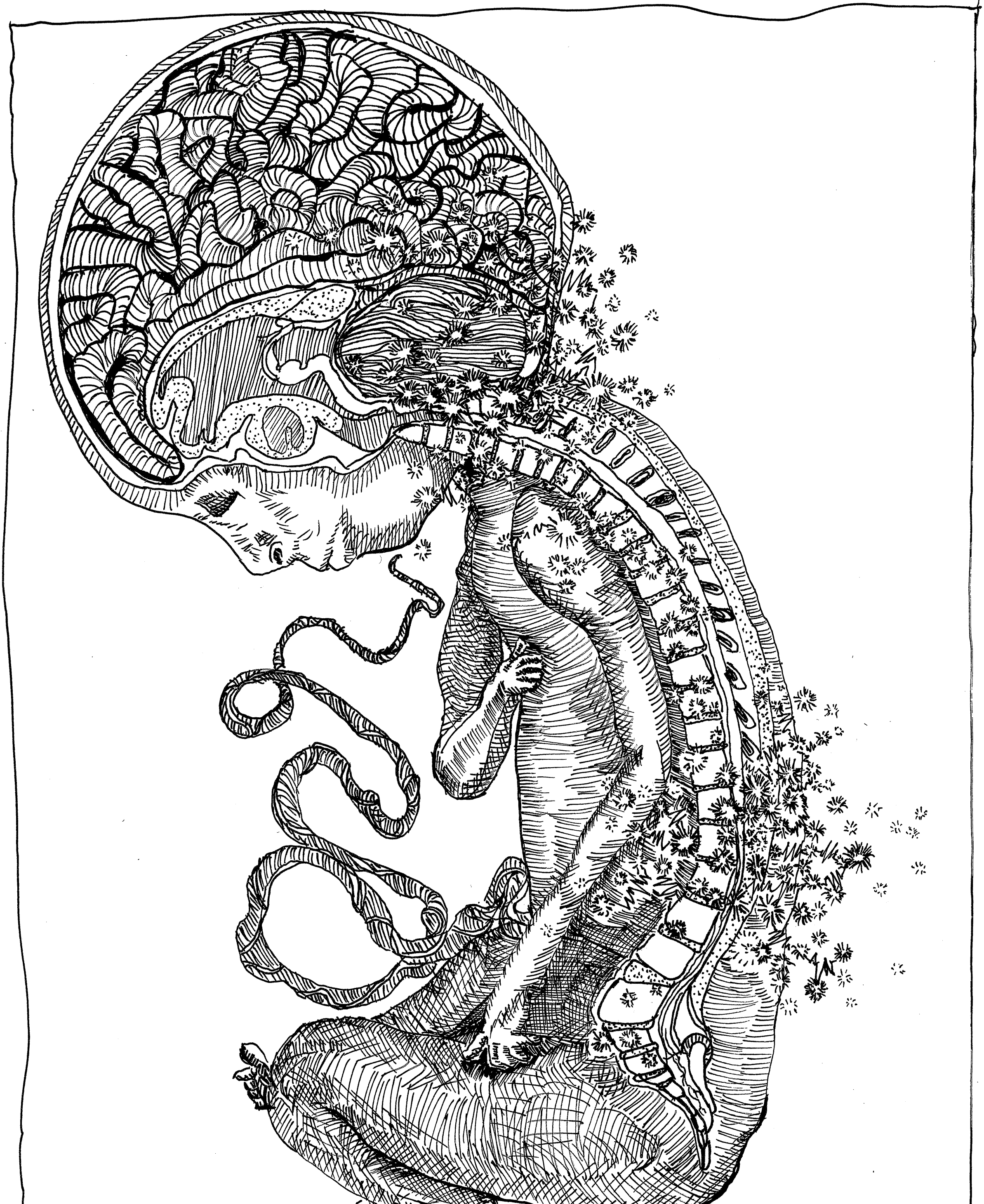
Table 1: Characteristics of the included studies.

Author	Publication Date	Location	Study type	Temporality	Study Period		Closure type	TCS definition
					From	Until		
Worley et al.	2021	Multicenter, USA	Cohort Study	Prospective with historic control	1997	2017	Prenatal and Postnatal	Surgical TCS release
Borgstedt et al.	2020	Multicenter, Denmark	Cohort Study	Retrospective	1996	2015	Postnatal	Surgical TCS release
Houtrow	2020	Multicenter, USA	Randomized Controlled Trial (Follow-Up)	Prospective	2011	2017	Prenatal and Postnatal	Surgical TCS release
Spoor et al.	2019	Rotterdam, The Netherlands	Cohort Study	Retrospective	2000	2018	Postnatal	Surgical TCS release
Kellogg et al.	2018	Multicenter, USA	Cohort Study	Retrospective	1995	2015	Postnatal	Surgical TCS release
Beuriat et al.	2018	Lyon, France	Cohort Study	Prospective	2015	2016	Postnatal	Surgical TCS release
Bowman et al.	2009	Multicenter, USA	Cohort Study	Retrospective	1975	2008	Postnatal	Symptomatic TCS
Danzer et al.	2008	Multicenter, USA	Cohort Study	Retrospective	1998	2003	Prenatal	Symptomatic TCS
Talamonti et al.	2007	Milan, Italy	Cohort Study	Retrospective	1980	2005	Postnatal	Symptomatic TCS
Tufan Tarca et al.	2006	Istanbul, Turkey	Cohort Study	Retrospective	1996	2005	Postnatal	Symptomatic TCS

Table 2: Patient characteristics

Author	Publication Date	No Patients postnatal	No. Patients prenatal	Gender		Follow-up period (in years)				No. Tethering		Age of TCS presentation (years)			
				Male	Female	Mean	Median	Minimum	Maximum	Postnatal	Prenatal	Mean	Median	Minimum	Maximum
Worley et al	2021	648	298	468	478	3.95	NA	1.42	11.5	54	102	NA	NA	NA	NA
Borgstedt	2020	166	0	82	84	NA	25	12	46	45	0	NA	12	5	15
Houtrow	2020	82	79	74	87	NA	NA	6	10	12	23	NA	NA	NA	NA
Spoor	2019	93	0	46	47	11.8	NA	1	18.2	93	0	8	NA	3	12
Kellogg	2018	153	0	64	69	9.9	NA	2	20	24	0	NA	NA	NA	NA
Beuriat	2018	46	0	22	24	8.1	NA	1	18	7	0	6.7	NA	2.8	13.6
Bowman	2009	502	0	56	58	12	NA	1.1	11	114	0	7	NA	0.84	21.8
Danzer	2008	0	54	NA	NA	NA	NA	NA	NA	0	16	3.1	2.3	0.3	7.8
Talamonti	2007	202	0	101	101	9.3	NA	1	25	75	0	7.5	NA	4	25
Tufan Tarca	2006	401	0	NA	NA	NA	NA	NA	NA	56	0	5.8	4.1	0.3	15

NA = Not Available



Chapter 6

Fetoscopic myelomeningocoele closure: Is the scientific evidence enough to challenge the gold standard for prenatal surgery?

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Abstract

Since the completion of the Management of Myelomeningocoele Study (MOMS), maternal-fetal surgery for spina bifida has become a valid option for expecting parents. More recently, multiple groups are exploring a minimally invasive approach and recent outcomes have addressed many of the initial concerns with this approach. Based on a previously published framework we attempt to delineate the developmental stage of the surgical techniques. Furthermore, we discuss the barriers of performing randomized controlled trials (RCTs) comparing two surgical interventions and suggest that data collection through registries is an alternative method to gather high-grade evidence.

Introduction

After its publication in 2011, the Management of Myelomeningocele study (MOMS) has led to a widespread expansion of centers offering prenatal surgery for fetuses with a spina bifida.[1,2] The benefits of prenatal surgery are a reduction in the need for ventriculo-peritoneal (VP) shunt placement, as well as improved mental development, motor and urological outcomes.[1,3] The downside of open maternal-fetal surgery is the high maternal morbidity and the risk of uterine rupture due to the large hysterotomy in current and subsequent pregnancies.[4] In addition, any fetal intervention results in an increased risk of preterm birth and complications of prematurity.

Because of these risks many groups have explored the possibility of a fetoscopic approach already since the 1990's.[5] One initial attempt included a maternal laparotomy but due to high maternal and fetal risks it was nearly immediately abandoned in favor of open maternal-fetal surgery.[6] Yet, several researchers continued to explore a percutaneous fetoscopic approach.[7–10] With ongoing experience more steady techniques were established, though the benefits of a minimally invasive approach were initially offset by longer surgery times, increased risk of preterm premature rupture of membranes (PPROM), preterm delivery and higher fetal and neonatal mortality.[7,8,10–12] These discouraging results temporized many centers in adopting an endoscopic approach.

In 2017, the first clinical series of an alternative fetoscopic technique was reported, combining maternal laparotomy with a two-port fetoscopic closure (open fetoscopy).[13] The technique is still evolving but recent results are promising, as they provided first, early evidence for a lower risk of PPROM and longer interval to delivery .[13–15] In addition, albeit not evaluated in a clinical trial, the rate of VP shunting and motor outcome appeared to be in the range of what was observed in the MOMS trial.

Improving performance as well as ongoing criticisms from others triggered the idea to set up a consortium studying the outcomes of fetoscopic spina bifida closure.[16] This raises the question on how exactly top-level evidence will be gathered and, for instance, whether it is justifiable not to do so in a randomized controlled trial (RCT) with head to head comparison of the investigational (fetoscopic) technique versus what is the standard of care (the open approach). Conversely, one may consider introducing the fetoscopic approach based on the available literature. In this paper we discuss the challenges of evidence-based medicine in maternal-fetal surgery and alternatives to performing an RCT. We also propose a framework that could be used as guidance to define the developmental stage of any novel treatment, provided a wide support, a spirit of collaboration, and honest registration can be established and techniques become more consistent.

Concerns about the fetoscopic approach

The use of fetoscopy for spina bifida closure has been controversial from the moment it was introduced. The main concerns were about the safety of using CO_2 for intra-amniotic insufflation, the high intraoperative complications and fetal mortality rates, the high PPROM and preterm birth rates, the use of patches to cover the defect instead of anatomical closure and the fragmented and incomplete reporting of neurological outcomes. In the last years many of these concerns are being addressed and more recent outcomes are encouraging (table 1). The safety of CO_2 insufflation was questioned because initial animal experiments observed the development of a normoxic fetal acidosis, particularly at higher pressures.[17–20] However, recent evidence has shown that this could be mitigated by reducing insufflation pressures and adjusting the humidity and temperature of the insufflated gas.[20] In addition, the effect of CO_2 in humans may be less prominent as was recently demonstrated in a clinical case series.[21] Nonetheless, the latter study analyzed *venous* samples which may not entirely reflect the fetal pH/pCO_2 and there was a considerable delay between cessation of insufflation and sampling.[21] As CO_2 is highly soluble any increased values could have resolved at the time of sampling. Reassuringly, there is currently no evidence of immediate adverse effects on cerebral development based on postnatal MRI.[22]

The initial high intraoperative complications and perinatal mortality observed with the percutaneous approach have improved in the latest experience published by the two most experienced groups in the world.[7–9,16,23] In the most recent series, *excluding* cases from learning curves, the procedure was technically feasible in almost all cases.[7,16] Likewise, fetal and neonatal deaths (4/131, 3%; two fetal and two neonatal deaths) were similar to what is reported for open spina bifida repair (2/91, 2%; one fetal and one neonatal death).[7,9,16,24] In the largest series of the exteriorised-uterus fetoscopic approach, even including the learning curve, the procedure was technically feasible in 90% of cases with one fetal demise (table 1).[13] On the other hand, technical success is determined by the surgeon at the end of surgery, but the true benefit can only be defined by comparing outcomes.

The next big game changer is that PPROM rates are going down, in experienced hands even below the level observed following hysterotomy, and as a consequence a more advanced median gestational age at delivery. This particularly seems consistent for the fetoscopic approach with exteriorized uterus.[13,16] The reason for this is not entirely clear. The use of heated and humidified CO_2 could partially explain this as a recent animal experiment indeed reported reduced inflammatory cell reaction in the fetal membranes compared to cold (room temperature) and dry CO_2.[20] The exteriorized uterus also enables the transuterine fixation of the membranes prior to port placement and closure at the end of the operation. A third explanation could be the difference in shear stress applied to the membranes when positioning the trocar through only one layer instead of multiple layers with a percutaneous technique.[25,26]

These changes add to the generic advantage of all fetoscopic approaches to not mandate a caesarean section and indeed vaginal births have been reported in up to 70% of cases.[16]

Nevertheless, despite these promising observations there are still a number of concerns remaining. One of the main criticisms is the lack of a unified technique for the neurosurgical part of the intervention, which seems rather 'eminence based'. This is however not only a privilege of fetoscopy. The neurosurgical techniques are rapidly evolving making it difficult to compare outcomes not only between centers, but also within the same center. A fetoscopic repair is technically more challenging and requires specific surgical skills necessitating extensive training and a longer learning curve, recently calculated to be at least 56 cases for the percutaneous approach compared to 35 for open surgery.[27] This has consequences in terms of volume load of centers considering fetoscopic repair. This also translates into longer surgery times at a time that the fetal brain is very sensitive to external factors: during mid gestation there is extensive synaptogenesis described as brain growth spurt.[28,29] It is unclear whether prolonged exposure to maternal anesthesia as well as CO_2 has consequences on developmental outcomes.[29]

The lack of standardization does not pertain for the surgical technique but also to the reporting of postnatal outcomes. The MOMS trial included an extensive evaluation of postnatal neurodevelopmental outcomes in a standardized blinded manner and to a contemporary cohort of infants that were operated postnatally. The majority of these infants were included in a long-term follow-up study up to ten years of age (MOMS 2).[30] Conversely, based on the current available evidence scattered in several publications and sometimes in absence of a control population it is difficult to determine whether the fetoscopic repair is not inferior to the open approach.[8,31,32] The percutaneous approach is associated with a higher need of postnatal corrections of CSF leaking, which may be related to the closure technique. On the other hand, the reported VP shunt rates in recent series of both fetoscopic approaches are similar to that in the prenatal surgery arm of the MOMS.[16] In general, there are also promising motor outcomes, but given the diversity in the used methodology it is hard to compare actual outcomes. Like in the MOMS-trial a blinded assessment of outcomes should be performed. An option is an independent panel of experts reviewing videos, charts or direct examinations of the child at a determined age.

As a result of the above encouraging observations, fetoscopic surgery for spina bifida repair has progressed from a controversial and highly experimental treatment to an acceptable alternative that several centers consider and/or implement. This is mainly driven by the need for attenuating the obstetric consequences (uterine incision) and maternal morbidity (percutaneous approach). The current questions therefore remain on what exact technique provides optimal neuroprotection, best obstetric outcomes and reduced maternal morbidity. This prompts the next question about how the highest-quality scientific data can be obtained and when one or more experimental surgical techniques will be sufficiently documented to be considered equivalent to the current gold standard of open fetal surgery?

Benefits of an RCT

Evidence-based medicine has become the cornerstone of modern healthcare. The effectiveness of any intervention is ideally determined using the highest-quality scientific data and in this respect RCTs are considered top level. In an RCT, patient subjects are randomly assigned to one of the compared treatments, mostly one 'standard' treatment and one 'experimental' treatment. The process of randomization eliminates the influence of selection bias and reduces confounding factors.[33] In maternal-fetal therapy there have been several landmark RCTs, including the Eurofoetus trial for twin-to-twin transfusion syndrome, the Solomon laser trial, the MOMS trial and the recently completed Tracheal Occlusion To Accelerate Lung growth (TOTAL) trial.[1,34–36] All of these have contributed to the acceptance of maternal-fetal therapy and formed the basis of ongoing collaborative consortia that strive to move this field of medicine forward. Conversely, they have taken long and often led to controversy. Also, some failed to recruit sufficient patients.[37]

Limitations of an RCT

Despite RCTs being often rated as the gold standard, this may not be applicable to every type of research.[38,39] First, there are some concerns when it comes to RCTs evaluating surgical interventions in general. For example, all surgical RCTs are complicated by the fact that for every case there is a countless number of confounders (such as pathological findings, surgeon's expertise and surgical approach as well as shift in the management for the condition over time) which may have its effect on standardizing the investigated treatment.[40] A second concern is the discrepancy between the time to gather evidence from an RCT and the pace of developing novel techniques. For all the RCTs in maternal-fetal surgery mentioned above, slow recruitment made it challenging to complete enrollment of sufficient patients. The MOMS trial took nearly ten years to complete and likewise the TOTAL trial evaluating the effect of fetoscopic tracheal occlusion for infants with a congenital diaphragmatic hernia has only recently finished recruitment after more than a decade. This could be explained partially by the rarity of these conditions but at least as much by the hesitancy of parents to undergo investigational procedures in pregnancy and physician's bias. On the other hand, most procedures will go through an experimental preclinical and clinical phase prior to the initiation of clinical trials, and this often inspires other centers to start clinical programs, who later on find it difficult to question that intervention. This so-called 'back-door' phenomenon, *i.e.* offering interventions outside of clinical trials, is common and weighs on recruitment rates. The powerful 'technological imperative' – the idea that if something can be done it should be done - is an important aspect for both physician and patient and increases the urge to offer a not always thoroughly studied treatment.[41] During the MOMS trial, a moratorium was imposed by the US maternal-fetal surgical centers except for the three trial centers, but repeating a study like this to objectively assess the benefit of a fetoscopic repair seems difficult. Fetal therapy in general often generates (social) media attention and not uncommonly this could be a driving factor.

Moreover, when for instance designing an RCT to study the benefits of a fetoscopic approach it may become difficult to identify the most relevant primary outcome and a single RCT may not answer all research questions. The main justification for a fetoscopic intervention is to improve or have at least comparable obstetric outcomes, however it should not be non-inferior concerning neurological outcomes. Therefore, two or more endpoints seem imperative.

Another reason why an RCT in maternal-fetal surgery is challenging is that it is *difficult to determine equipoise*.[42] Although there might theoretically be *equipoise*, clinical and patient *equipoise* might be difficult to achieve. The principle of *clinical equipoise* has been described by Freedman, arguing that in order to be able to enroll patients in RCTs, within the medical community there should be an overall state of uncertainty between the trial arms.[43] Yet on the other hand, every individual investigator is also influenced by personal biases, opinions and 'gut-feelings' and technical skills making true clinical equipoise difficult to achieve.[42–44] Moreover, often the results during the experimental stage of a novel intervention are promising and hyped, as such doctors (as well as patients) will unconsciously develop a positive bias towards one of the treatment arms. We expect that this well-known issue of 'dissemination first, evidence later' is one of the most challenging factors when designing a clinical trial for a fetoscopic closure. This inadvertently influences counselling and hinders an unbiased decision to participate in an RCT.

In addition, *patient equipoise* relies on the same degree of uncertainty about the two different treatments. A source of conflict lies in the fact that the only patient is the mother, yet it is the future child who will possibly benefit from the intervention. Though the mother benefit from a less invasive procedure, the fetus (future child) may potentially benefit more from an open procedure, as this technique has proven benefit. The potential psychological benefit for the mother related to doing everything possible for her unborn child out of altruism is a very difficult item to include in a risk benefit analysis as it is almost impossible to score. As the novel procedure aims to solve a limitation of the current standard treatment this translates in a positive bias towards the investigated treatment. It is important to note that her risks and benefits not only include the benefit for the fetus, but also the implications for other family members such as future siblings.

As was underlined by Rodrigues *et al*., when *patient equipoise* cannot be established independently of the existence of theoretical and *clinical equipoise,* consent to randomization might not be possible and therefore RCTs become difficult to organize. The concept of *total (theoretical, clinical and patient) equipoise* is therefore described as 'an overwhelmingly fragile concept' particularly for unblinded interventional studies.[43] Nevertheless, this should not be considered the only reason not to pursue randomization in maternal fetal surgery.

Another limitation is that most centers have invested in gaining expertise in one technique and thus it is challenging, maybe impossible, to find centers that can offer different treatments in an unbiased manner. This does not only apply to studies comparing open *vs.*

fetoscopic methods, but also studies that will compare the different fetoscopic techniques (percutaneous *vs.* open).

Taking all together, it seems that an RCT for the comparison of the different surgical methods for prenatal spina bifida closure will be very challenging, maybe impossible for several reasons. Hence, alternative options should also be explored on how to determine when an 'experimental' therapy becomes the gold standard.

The continuum of research

Most regulatory bodies depart from a dichotomous approach labelling treatments as either experimental or established. However, there is no clear consensus of the extent of this research phase and thus it remains unclear when available evidence is convincing enough to decide that a new technology or treatment is no longer to be labelled as 'experimental'.[45] To evaluate the implementation of new technologies in the field of reproductive medicine, a conceptual framework and a scoring tool were developed.[46] We propose that with some minor adaptations, this framework can be used as a general tool for evaluating new treatments in other medical specialties, such as maternal-fetal surgical interventions (table 2). This framework describes that the development of novel techniques ideally follows a continuum that distinguishes three categories: experimental, innovative and established treatments.[46] Experimental therapies should only be offered in a research setting, aiming at showing efficacy and safety in animals and case reports in humans ('proof of concept'), with approval of a medical research ethical committee. Innovative treatments have progressed from this initial phase and there is albeit limited evidence of efficacy and short-term safety in humans. The label 'innovative treatment' entails an intermediate phase of research in a novel treatment to provide generalizable knowledge, comparable to a phase III drug research study. Obviously, this should be done with continuous oversight of regulatory bodies. The scoring tool provides a means to determine the status of a novel treatment within this continuum rating the therapy in four criteria: efficacy, safety, procedural reliability and effectiveness. [46]

Within this framework, open fetal spina bifida closure is categorized as an established therapy (figure 1). Both fetoscopic approaches would rank as innovative treatments, however based on the most recent series effectiveness could be scored as acceptable and thus equivalent to an established treatment (Figure 1).[15,16,47]

The following recommendations were suggested for interventions that fall in the innovative treatment category: 1) treatment should only be offered by expert centers; 2) there should be a commitment to closely monitor their practice conducting thorough follow-up studies with the purpose of publishing the (positive and negative) results in peer-reviewed journals; 3) patients should be adequately informed about all relevant aspects of the procedure (including surgical expertise) and about the status of the treatment (lack of long-term outcomes should be emphasized) and 4) centers should always be prepared to stop treat-

ment when there are signs of serious concerns based on their own studies or on published reports.[46] This also implies that all patients should also be asked for their consent for any innovative treatment and also to be contacted in the future for follow-up studies. Therefore, requiring formal approval of a medical research ethics committee is essential.

The difficulty of maternal-fetal therapy is that the status of the treatment should be balanced between the benefits and risks for the fetus and the maternal risks, and this is evidently not incorporated in the framework of Provoost *et al*.[46]

International registries

A pragmatic alternative for evaluating the effect of surgical interventions is to generate large, prospective, cohort registries with standardized data collection for key outcomes. The data acquired within the MOMS trial were collected with a scientific rigor that is currently not present for fetoscopic interventions. There are important inconsistencies in selection criteria, operative methodology and data points differ, there is overlap between series and the postnatal outcomes are not reported uniformly.

Regardless, every center developing an innovative therapy has a moral obligation to monitor its own outcomes. Given the relative scarcity of these maternal-fetal interventions such registries need to be organized within (inter)national collaborations. Establishing collaborative networks stimulates transparency between competing centers and enabling generation of larger series assessing short- and long-term follow up. It also offers the opportunity to unify the technique based on the collective experience of the participants, thereby accelerating the innovation phase. With this goal, a consortium of 25 North American Fetal Therapy Network (NAFTNET) centers agreed to collect data of all fetal MMC interventions prospectively from 2012 onwards.[48] In parallel, the International Fetoscopic Myelomeningocoele Repair Consortium was founded in 2018 to advance knowledge on the fetoscopic technique by providing data into a common registry.[16] Such international collaborations are essential and all centers performing these interventions are strongly encouraged to participate. Moreover, every effort should be made to collate registries and in order to facilitate this a minimum data set should be agreed upon covering ***all*** aspects of the MMC repair including maternal views and experience. In addition, a continuous comparison to a contemporary cohort of infants with postnatal closure remains essential. But more importantly it is our responsibility as scientific community to determine the most optimal outcome measure to compare the fetoscopic versus the open approach. This consensus outcome could then be used to calculate the number of cases needed to generate the evidence to favor one of the treatments with sufficient power without performing an RCT.

Conclusion

Maternal-fetal surgery has become a widespread treatment option for fetuses with a spina bifida. In pursuit of minimizing maternal risks, fetoscopic techniques are being explored. We have discussed that these inventions have progressed from an experimental to an inno-

vative stage, albeit that the optimal fetoscopic approach has not been determined. Nevertheless, the promising results created an expansion of centers offering such interventions, resulting in fragmentation of surgical experience and the publication of outcomes. Although an RCT is generally considered the highest level of evidence to evaluate the effects of any treatment, we foresee major difficulties organizing such a study for this indication. We propose that gathering data from high quality international registries with standardized outcomes and long term follow up could be a valuable alternative. Yet, until we are able to establish superiority of a fetoscopic approach, we cannot entirely discard the necessity of an RCT. In the absence of high-quality evidence, we emphasize the importance of careful and balanced in-depth counselling taking in consideration individual risks and benefits for every patient.

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Table 1: Overview of procedural, pregnancy and neonatal outcomes.

	Postnatal repair	Open fetal surgery	Percutaneous fetoscopy		Open fetoscopy
Cases (N)	92[1,24,48,49]	91[1,24,48,49]	Germany: 71[8] (59)[7,9]*	Brasil: 60[16] (80)[#]	58 (40 /18) [15§]
GA at surgery (wks)	n.a.	19-25.9^	21.0-29.1^	24-28.9^	24.9 ± 0.7 / 25.0 ± 0.5
Surgery times (min)	Not reported	105 ± 23.2	140-315	83-450	261 ± 58 / 237 ± 47
PPROM	7.6%	44%	84.3%	67%	28% / 29%
Fetal demise (N)	0	1	0/71	1 (+1 TOP)/60	0/32 // 1/18
GA at delivery (wks)	37.3 ± 1.1	34.0 ± 3.0	32+2	32.5 [26.9-40.7]	36.5 ± 3.5 // 37.6 ± 3.1
Vaginal birth	Not reported	0%	0%	22%	50% // 47%
NND (N)	2/92	1/91	2/71	0/60	0/32 // 0/17
Dehiscence at repair site CSF leakage	n.a.	13/77 (13%)	28%	10%	25% // 0 %
Treated for hydrocephalus	84%	44%	45%	14/30 (47%)	47% // 33%[+]

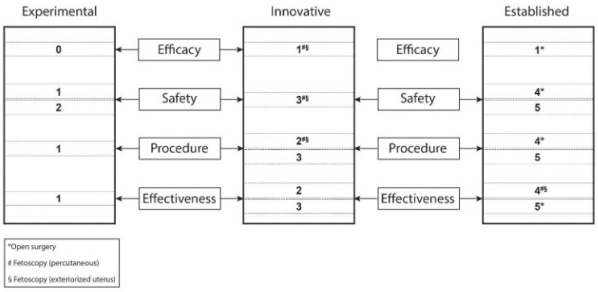
GA: gestational age; PPROM: preterm premature rupture of membranes; NND: neonatal death; VP shunt: ventriculo-peritoneal shunt; TOP: termination of pregnancy. Data are presented as mean ± standard deviation; median [interquartile range] or absolute numbers (N), depending on what is published in the respective papers. *data are from two papers with two overlapping study populations, data depicted are for total cohort (N=71) unless not available. [#] data from learning curve (N=20/80) not included. [§] 40 cases between 2014 and 2017, 8 cases where surgery was not successful and outcomes for 32 cases are reported; 18 cases from 2017 onwards with triple layer repair[15]. ^range; [+]only 12/17 cases were older than 12 months.

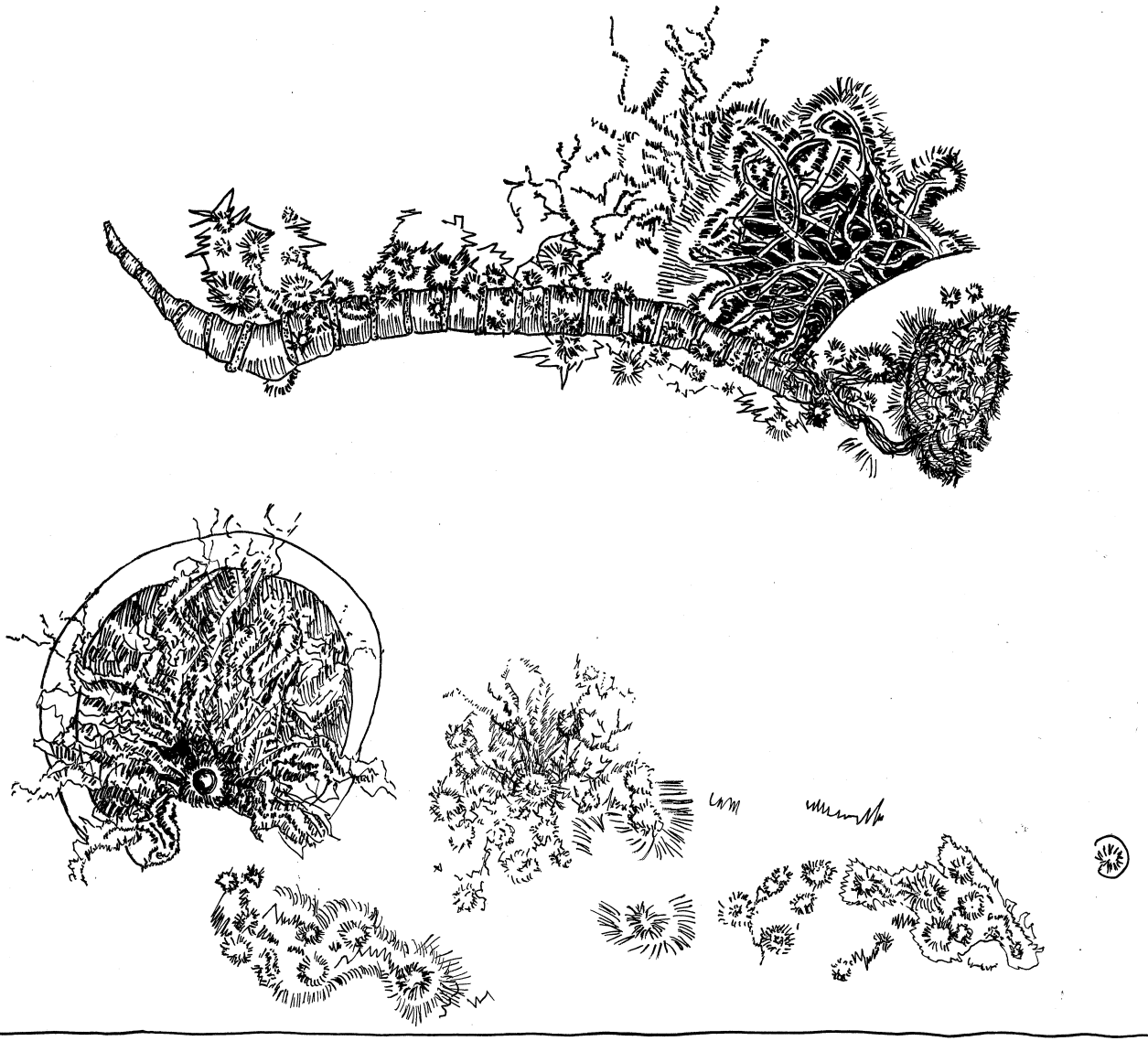
Table 2. Scoring tool for distinguishing between treatments (modified for maternal-fetal therapy, based on Provoost et al[46])

Criterion	Definition	Scoring
Efficacy	Proof of principle	no proof of principle has been demonstrated *proof of principle has been demonstrated *Efficacy' is an all-or-nothing criterion that only has one threshold*
Safety	Safety of the procedure, referring to: maternal outcomes fetal outcomes neonatal outcomes	Considered safe in animals Reassuring 'proof of concept' case-reports *Reassuring short-term data in humans (up to at least 3 months post-delivery) in peer-reviewed journals **Reassuring mid-term data in human (up to at least 5 years post-delivery and including fertility, subsequent pregnancy outcomes and data on psychological development) in peer-reviewed journals Reassuring long-term data in human (up to at least 25 years post-delivery, including data on psychological development and preferably on fertility of the operated fetus) in peer-reviewed journals
Procedure	Procedural reliability and transparency: the similarity or variability of the procedure in different centers and the potential for implementation by other centers	No procedure has been described yet, or the procedure varies enormously between centers *Technical performance of the procedure is highly variable between centers Technical performance of the procedure is relatively comparable between centers **Technical performance of the procedure is highly comparable between centers Throughout different centers, the procedure is considered a routine technique with common technical performance
Effectiveness	The likelihood of producing the desired outcome compared with outcome of conventional (postnatal), established therapies	Completely unknown, doubtful or extremely low *Low Reasonable Acceptable but not as high as established therapies **As high or higher than established therapies

*Threshold to move from experimental to innovative treatment
**Threshold to move from innovative treatment to an established treatment.

Figure 1: Adapted from Provoost et al[46]. Assessment tool for the transition from an experimental treatment to an innovative treatment and to an established treatment.





Chapter 7

Development of a simulator for training of fetoscopic myelomeningocele surgery

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Spina bifida aperta (SBa) is a severe condition, with significant neurological impairment due to local neural damage in combination with central brain abnormalities (Arnold-Chiari II malformation and hydrocephalus amongst others). Fetal surgery can ameliorate postnatal outcomes, but the current gold standard of an 'open' (*i.e.* requiring maternal laparo- and hysterotomy) procedure comes with substantial maternal risks.[1] The latter has prompted multiple centers to develop a fetoscopic approach. However, these are complex procedures and require a substantial learning curve.[2] Simulation training provides an excellent opportunity to gather sufficient exposure, and thus has become an essential part of training programs for junior surgeons.

Ideally, a simulation model combines both purposes of training and surgical preparation, and is realistic, case-specific, low cost, reusable and of non-animal origin. This study aimed to create such a training simulator, based on the laparotomy-assisted fetoscopic technique described by Belfort *et al.*[3]

The steps for surgical repair of the SBa defect are: 1) dissection of the placode with release into the spinal canal; 2) closure of the myofascial layer and 3) closure of the skin to create a watertight closure of the defect; for which the designed defect needed to have all of the relevant anatomical structures. For realistic simulation of the fluid-filled sac, fluid spill, a reduction in tension of the arachnoid and retraction of the placode into the spinal canal should be visible after incision. To allow future correlation with the defect's characteristics on ultrasound imaging, the defect had to be incorporated into a model part that could be inserted into a fetal model.

The fetus needed to have the appearance and size of a 25 weeks' fetus, with adequate flexibility to allow external version.

The uterine model was designed to have the following properties: a realistic appearance of a uterus of 25 weeks' gestation, the ability to stretch with insufflation, the possibility to train port placement using the Seldinger technique and provide an accurate representation of the intra-uterine space during fetoscopic surgery. Additionally, *external visualisation* and a case-specific location of the placenta should be possible to plan the position of the port insertion sites.

All components and casting moulds for silicon parts were designed in Fusion 360 (version 11.5.6, Autodesk, San Rafael, CA, USA). Moulds for silicone casting were printed using a thermoplastic polymer (Tough PLA, Ultimaker B.V., Utrecht, The Netherlands) on a 3D printer (Ultimaker S5, Ultimaker B.V.). For specific components, different materials were chosen based on their specific properties. Silicone pigments were used to dye silicone casts (Silc Pig® Smooth-On Inc., Macungie, PA, USA)

The defect was incorporated in a reusable flexible insert containing rigid vertebrae (red TPU 95A and white ABS, Ultimaker B.V). The placode with the spinal cord, arachnoid, myofascial and skin layers were made of silicone rubber (Dragonskin™ FX-Pro™, Smooth-On Inc). To allow suturing and to create homogeneous stretch properties of the skin layer, two layers of stretch mesh were incorporated in perpendicular directions. For a watertight connection to the polyurethane insert, the tissue layers were connected using cyanoacrylate glue (Super Glue Gel, Bison,). The defect was represented by a cavity at the SBa site, which was connected by a channel to a Luer lock connector. The channel holds the spinal cord and allows infusion of water using a two-way Luer lock valve.

To provide an appropriate reflection of the weight and flexibility, the reusable fetus was made of silicone rubber (Ecoflex 00-30, Smooth-On Inc.). On the posterior side of the fetus, there is an opening for the insert.

The uterus was made from pourable flexible polyurethane foam (FlexFoam-iT! V, Smooth-On Inc.) and the placenta was made of silicone foam (Soma Foama 15, Smooth-On Inc.). The design was based on MRI images. Insertion and removal of the fetal model, placenta and amniotic fluid is possible through a 75 mm diameter opening at the cervical end. Both the uterus and placenta were covered in pigmented silicone (Dragonskin Fx-Pro, Smooth-On Inc.). For training purposes, the placenta can be placed at any location on the uterine wall. After inserting the fetus and adding the amniotic fluid, the opening at the cervical end is closed. A plastic hinge connector (Tough PLA, Ultimaker B.V.) allows watertight closure of the uterus and connects it to a wooden support frame. The hinge mimics the exteriorised position and allows positioning of the uterus for port placement.

For evaluation, we used a simulator of which the fetus had a lumbar SBa and an anterior position of the placenta. Four obstetricians with experience with fetoscopic port placement evaluated this part of the procedure. The uterus was partially filled with saline to substitute amniotic fluid. The material of the uterus allows the external visualisation of the placenta with a light source. This feature avoids the need for an ultrasound device at each training session. A 12 French cannula (Performer Introducer, RCFW-12.0-38-J, Cook Medical, Bloomington, IN, USA) was inserted into the uterus, followed by insufflation. The correct position of the port with respect to the fetus was visually confirmed using a 0° 4 mm rod lens scope (27015A, Karl Storz, Tuttlingen, Germany) connected to a TELE PACK+ monitor (Karl Storz).

The neurological part of the surgery was evaluated by three pediatric neurosurgeons experienced in postnatal SBa repair, this was done directly on the fetus to allow for tactile feedback of the tissue layers. The insert containing the SBa defect was filled with water to simulate spinal fluid. The myofascial layer can be dissected and sutured, followed by interrupted sutures to close the skin layer. Sutures were performed using 5-0 Monocryl™ (Ethicon Inc., Raritan, NJ, USA). Once finished, the water tightness of the operated SBa was tested using the incorporated valve system.

After completion of the procedure, realism of appearance and handling were separately evaluated using a 4-point scale. For each component appearance was scored, while handling was assessed per procedural task. For all items the following score was applied: 1) unrealistic, 2) a bit realistic, 3) close to realistic and 4) realistic. Additionally, three yes-no questions evaluated the expert opinion on the usefulness of the simulator for training and for case-specific preparation.

The participants were able to perform all tasks on the simulator and all aspects of the simulator were rated between "close to realistic" and "realistic". The content validity was rated through the realism of the performed tasks, which were also rated between "close to realistic" and "realistic". The surgeons all agreed that the simulator is suitable for use as a training model for fetoscopic repair of SBa as well as for case-specific surgical preparation based on the tissues and tissue handlings. They agreed that the simulator can improve cooperation between obstetrician and neurosurgeon.

In this paper we describe the development and evaluation of a training simulator for fetoscopic SBa surgery. It is the first training model containing a realistic and modifiable representation of the uterus, placenta and fetus. The developed model provides an excellent opportunity for both training and case-specific surgical preparation. Moreover, the materials used are widely available and thus, provided the availability of a 3D printer, the model can be easily reproduced with minimal investment costs.

Most parts of the design are reusable, including the fetus and plastic base of the insert. The uterus can be used several times, depending on the leakage caused by trocar placement. The silicone components of the defect are single-use. The set-up time for training purposes using non case-specific pre-produced components is 30 minutes. The production costs for a set of silicone components are around 60 euros. For case-specific training the insert containing the defect needs to be printed and the silicone components of the insert have to be cast, requiring approximately 2 days of production time.

There are several training models available for fetoscopic SBa surgery. In one model the fetus consists of a doll on which a piece of raw chicken is attached to its back and is then placed in a kickball forming the uterus[4]. This model does represent the fetus within a restricted surgical space, however it does not account for the different tissue layers of the SBa and watertight suturing cannot be assessed. Likewise, the kickball does not provide the limitations with port placement that the anatomy of the uterus and location of the placenta impose. A more refined version of the fetus in this model was recently published[5]. Using 3D images of the fetal spine a case specific fetal defect can be generated that has proven to be very useful in rehearsal of the surgical procedure. The uterus was still represented by a kickball.

Another simulation model that is commercially available has a realistic appearance of the maternal abdomen and uterine wall, however the fetal model is basic and has no SBa[6].

Another important consideration is that this simulation model is relatively expensive, especially when compared to the model that we developed.

At the moment, there are two different animal models for fetoscopic SBa surgery. One was created to evaluate a running single suture technique using two-port access. This surgical model consisted of lambs with surgically created SBa defects[7]. The other was developed specifically for the purpose of training the fetoscopic approach. In this leporine model the abdominal cavity mimics the amniotic cavity and defect repair is practiced on the gastric fundus[8]. While both models are high in fidelity, these uterine analogues are either thinner (sheep) or of a different structure (rabbit abdominal wall) than a gravid uterus and thus less realistic. In addition, animal models are logistically difficult to use repeatedly, are expensive and come with ethical constraints. Our model can be used repeatedly without the logistical and ethical constraints associated with animal models.

There are several possible applications of our simulator in dedicated fetal surgery centers apart from it is possible role in shortening extensive learning curves[2]. For instance, as it is a desktop model with limited preparation time, this simulator provides an easily accessible opportunity for more experienced surgeons to maintain certain surgical skills, but also to rehearse or recreate unusual operative complications. In addition, because the simulator contains a uterus and a fetus, it also provides an opportunity for multidisciplinary practice. The simulator may also provide a standardized environment in which technical improvements and alterations can be evaluated. For example, a 2-port technique can be compared with a 3-port technique in identical settings. But also, adaptations such as the use of a dural patch, as well as instrument or entry port modifications could be tested using this simulation model. One could also recreate other neural tube defects on the insert, such as myeloschisis, but adaptations of the fetal model for other fetoscopic interventions such as gastroschisis are also relatively easy.

Case-specific modifications require processing of ultrasound imaging or MRI, this can thus far, not be done automatically. The materials used in this model negatively influenced the spatial resolution of the ultrasound imaging and thus it is currently not possible to fully practice the ultrasound guided parts of the procedure (*i.e.* determination of fetal position, trocar placement and fixation). Regarding the limitations of this study, the evaluation experiment was based on subjective feedback from a small group of participants. However, we feel that this was sufficient to demonstrate the realistic appearance of the model.

In summary, we describe the development of a low-cost, realistic training simulator for fetal surgery of SBa for which the fetal and maternal anatomy, the intended surgical procedure, design and production requirements were investigated. Future developments should focus on continuing refinement of its components, validation as a training device and evaluation of its role in surgical planning.

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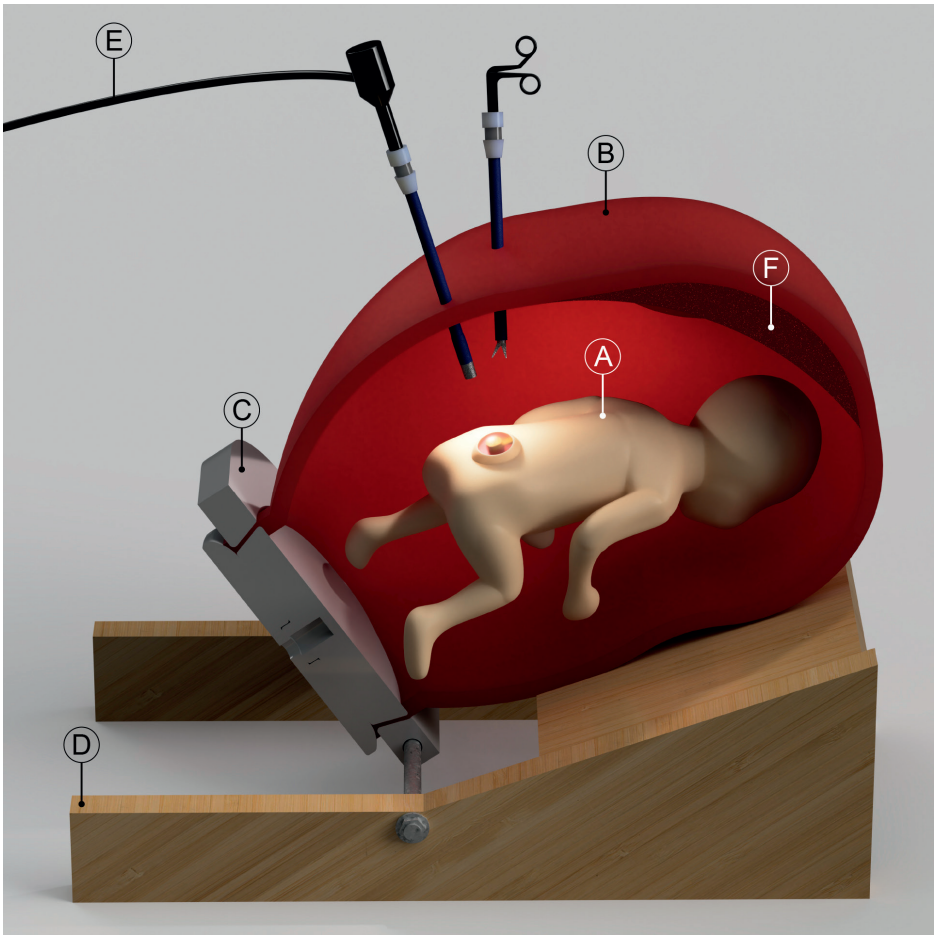
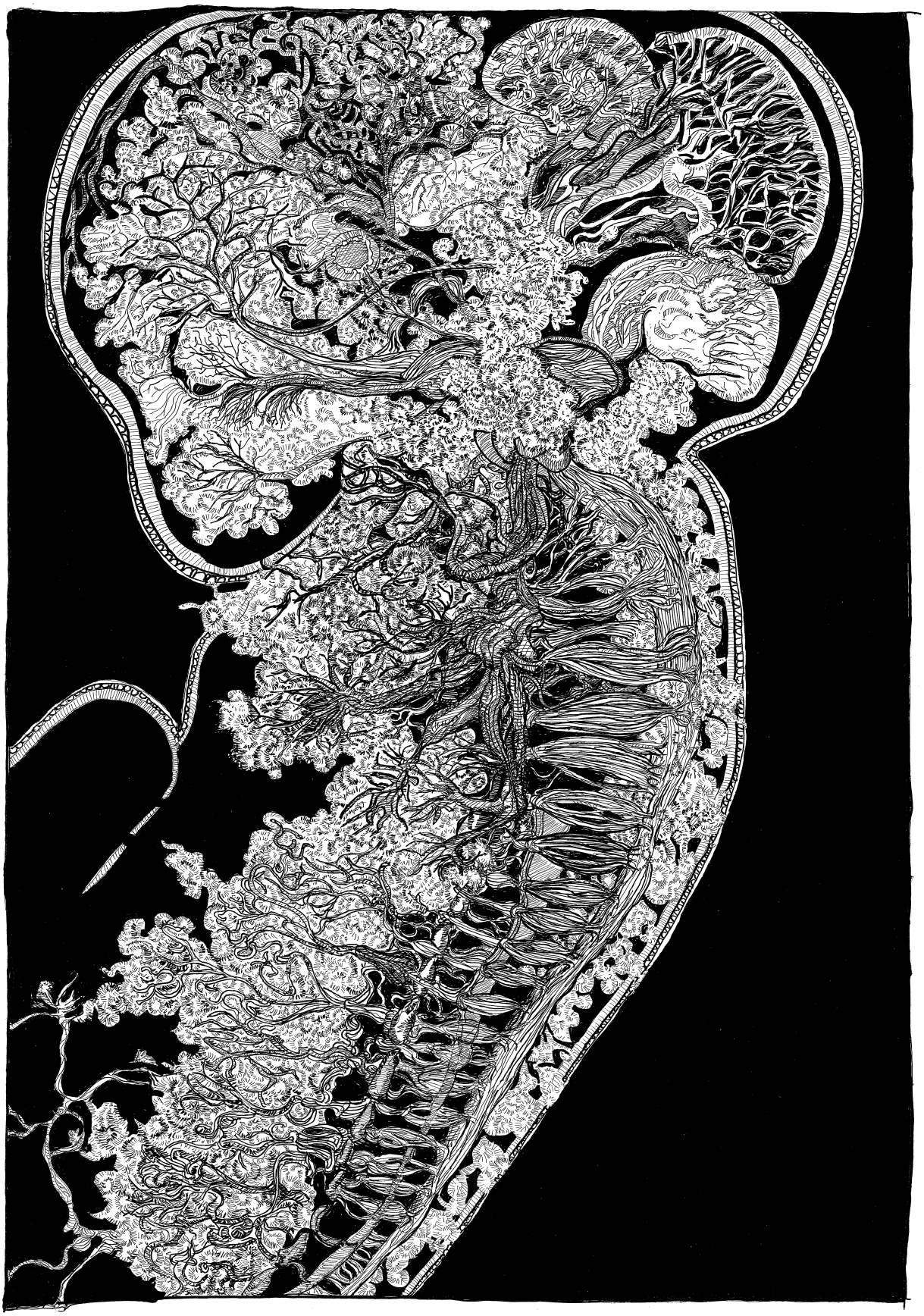
Figure 1 Graphic representation of the fetoscopy simulator. The fetal model (A) is placed inside the uterus (B) to recreate the surgical environment during fetoscopy. The uterus is closed off using a connector (C) that forms a hinge together with the wooden support structure (D). The ports with the fetoscope and trocars (E) can be inserted anywhere on the uterus at least 5 cm from the placenta (F).





Chapter 8

General discussion

General Discussion and future perspectives

In this thesis we aim to improve the prenatal counselling of upcoming parents confronted with a MMC pregnancy as well as to provide a realistic training model for fetoscopic MMC repair to gain surgical skills and to also improve the fetal treatment of MMC.

Counselling

Counselling needs to facilitate the choice between continuation or termination of the MMC pregnancy and between fetal or postnatal surgery. In order to improve counselling more solid data is required. In an effort to provide data for a better counselling and to be able to compare future results of fetal surgery in our centre we conducted a cohort study on MMC patients of the past 2 decennia in **Chapter 2**. The study shows, in line with the literature that MMC is a severe disease.[1,2,3] Postnatal surgery aims to prevent further deterioration due to extra damage to the spinal cord, hydrocephalus or infection of the central nervous system. It does not cure the disease or lessen the existing severity in any way.

This severity leads to a high rate of termination of the pregnancy in countries like the Netherlands where this possibility is legally embedded. On the other hand it also has driven the search for novel therapies such as fetal surgery in order to improve the outcome of patients with MMC.[4,5,6]

Data on long term outcome and quality of life of our own rather extensive cohort of MMC patients has already proven very helpful in informing upcoming parents confronted with a MMC pregnancy during our counselling.

Another form of therapy that physicians together with parents sometimes feel themselves forced to consider, is to actively end the live of a newborn with MMC. Verhagen reported on the active termination of 22 newborns with according to the Lorber criteria severe MMC.[7,8,9] This lead to worldwide and not seldom fierce discussions.[10,11,12,13] The legal basis for active life termination in these newborns is defined as unsustainable suffering and pain. The existence of severe pain was investigated in a cohort of newborns with MMC at our institution in 2012 and it was concluded that presence of severe untreatable pain could not be confirmed in these newborns with MMC.[14]

We analyzed the same group of MMC patients 10 years later (**Chapter 3** of this thesis); they are all severely impacted by the MMC, had undergone a large number of surgeries in their short lifespan, yet effective communication is possible in all of them and we did not find signs of unbearable suffering. Therefore, predicting future low quality of life and using this prediction as a foundation for the active termination of newborns suffering from MMC may not always be possible.

With the possibility of fetal corrective surgery for MMC , the role of counseling in early pregnancy becomes more important, enabling upcoming parents to decide better between very early treatment by fetal surgery or early termination of gestation. This may prevent the emotional struggle about ending a newborn's life based on future predictions. These predictions will contain the same amount of uncertainty yet the termination of a pregnancy may cause significantly less hurt than the active ending of a newborn's life, notwithstanding the impact of terminating a pregnancy.

Apart from severe cases where there is little doubt about the immense impact on the quality of life, counselling needs improvement. This includes informing upcoming parents on the outcome and risks of fetal surgery, which is important in both the choice between fetal and postnatal surgery and the choice between termination or continuation of the MMC pregnancy. For well-informed counseling extensive data is needed as well as knowledge of this data by the physicians involved in the counselling.

To date the only randomized controlled trial performed on comparing the outcome and risks of fetal surgery with postnatal surgery for MMC is the MOMS-trial where patients were randomized between open fetal surgery and post-natal surgery.[1] In order to know to what extend the option of fetal surgery is discussed in counselling around the world as well as to establish how well-informed physicians involved in MMC counselling are about the MOMS-trial, we conducted a worldwide survey in **Chapter 4.**

Taking into account that part of the responders came from countries where fetal surgery for MMC is not available we found that almost 24% of physicians did not mention fetal surgery in their counselling of upcoming parents confronted with a MMC pregnancy. Knowledge of the MOMS-trial data was considered to be rather poor; the majority of respondents assumed fetal surgery has a higher fetal mortality and 40% supposed a higher maternal mortality, both assumptions are not supported by the MOMS-trial.

Data on the outcome of both fetal and postnatal treatment of MMC and a widespread knowledge of this data amongst physicians involved in the counseling and care of MMC is critical as it improves both the counseling and the care of MMC.

Although the MOMS-trial provides high-quality data on both forms of treatment, so far strong data on occurrence of tethered spinal cord syndrome (TSC) is missing. TSC is a relatively late complication in which traction on the spinal cord that is adherent to the scar tissue from the closure of the MMC causes worsening of bladder and/or bowel dysfunction and/or more leg- and/or backpain. TSC can also worsen the often present spinal misalignment.

Next to worsening of existing complaints new deficits may appear due to the formation or worsening of a syrinx either caused by spinal cord tethering or the incomplete treatment of associated hydrocephalus, such as shunt disfunction.

The MOMS-trial reports TSC needing a surgical untethering in 11% of fetal surgery patients within 12 months after birth. This is rather high since the median age of untethering after postnatal surgery is 6-13years.[15,16,17,18]

A Secondary analysis of the MOMS-trial data published in 2021 does not actually report on TSC, it only states that despite a higher surgical untether-rate in their fetal surgery patients reported on by Houtrow in 2020, there was no higher rate of spasticity in the fetal group. Spasticity often is a sign of TSC.[19,20] Houtrow in 2020 indeed reports a higher rate of TSC in the fetal patients of the MOMS-trial.

Mazzola conducted a systemic review on the incidence of TSC in fetal versus postnatal repair, however no meta-analysis had so far been performed.[21] It is therefore that we conducted a systemic review and meta-analysis in **Chapter 5**, in order to weigh the outcome of retethering between fetal and postnatal closure groups.

Here we show that the cumulative incidence and relative risk of TSC are increased in the prenatal closure group compared to the postnatal group in MMC patients. As TSC can lead to an increase of existing complaints and deficits as it can lead to the appearance of new ones and the surgical treatment can be challenging we conclude that for well-informed counselling on and a better outcome of MMC more long-term data on TSC after fetal closure for MMC is needed.

Fetal surgery for MMC

Chapter 6 describes the position of fetoscopic surgery for MMC as opposed to open fetal surgery. Open fetal surgery for MMC has become a widespread treatment option and in pursuit of minimizing its maternal risks, fetoscopic techniques are being explored.[5,22] This created an expanding but fragmented field in which the optimal fetoscopic technique is yet to be determined. An RCT like the one for open fetal surgery is unlikely to ever take place and we suggest gathering data from high-quality international registries with standardized outcomes to be a valuable alternative. Working together in an international setting like we do with our international partners on the development of our fetal program leads to better care and research projects, both forming a firm base for setting up these international registries.

In the absence of high-quality evidence, we again emphasize the importance of careful and balanced in-depth counselling taking in consideration individual risks and benefits for every patient.

In **Chapter 7** we demonstrate a realistic simulator for the training of fetoscopic myelomeningocele surgery to provide a training opportunity for centres that are starting a fetoscopic MMC repair program as well as for more advanced centres to maintain their skills. It is the first simulation model with adjustable spinal defect and placental localisation. In order to stop CSF leakage during the remaining pregnancy and after birth the fetal closure needs to be watertight. Our model involves a valve system which can be filled with water

simulating the CSF filled cele and making post-surgery testing of water tightness possible. All steps of the procedure, both gynaecological and neurosurgical are integrated in our model and neurosurgeons and gynaecologists can practise working together using the model as they do in the real situation.

There are several models available for fetoscopic MMC closure.[5,23,24,25,26] Compared to the more low fidelity ones ours is more realistic as is has different layers of tissue that can be prepared and sutured, it incorporates both a real size fetus and uterus as well as a placenta that can be case-specifically positioned within the uterus. The existing high fidelity models are either expensive or animal based models making them less attractive.

Even though further objective validation of our model is required, the potential for using this model in preoperative planning and in obtaining surgical skill is promising as is its use in developing new techniques for further improvement of fetoscopic closure of MMC.

Future perspectives

Prevention

Daily folic acid intake for women who aim to get pregnant and fortification of daily used foods have decreased the prevalence of MMC pregnancies dramatically. Although data remains somewhat unclear, there is a raising concern that higher intake of folid acid may be related to an increase seen in craniosynosthosis.[27,28]

Where MMC, also called "spina bifida"(Latin for non-fused spinal bone) is a late (i.e. non-) fusion of bone, craniosynosthosis is a too early fusion of the bones of the skull. This would mean that treating one end of the spectrum, namely non-fusion leads to an increase on the other side of the spectrum: too early fusion. Data is far from conclusive yet but we as one of the major cranio-facial centres in the world could invest in better understanding this trend.

Research may focus on differentiating future mothers on their personal need for folic acid, either based on dietary habits or metabolic predisposition.

Philosophy

The treatment of MMC is advancing in a technical manner adding to the debate that has always accompanied this severe congenital disease. Familiar questions on quality of life, suffering and how both are affected by handicaps and impairments along with more recent questions on the status of a fetus as a patient and its mother as a healthy part of the invasive treatment made us start a study together with our Department of Philosophy. We aim to address these questions in order to embed our counselling and treatment in a strong philosophical foundation.

Counselling

We have tried to improve the counselling on MMC and its fetal and postnatal treatment by providing data as well as by showing the lack of knowledge about the MOMS-trial amongst physicians involved in the counselling as well as the significant number amongst them who do not discuss the option of fetal surgery with upcoming parents confronted with a MMC pregnancy. Here lies an important role for the field to expand the awareness of fetal options for MMC and its outcome. The European Reference Networks (ERN) like Ithaca form the right platform for this.[29]

In order to further establish well-informed counselling we would like to create a digital tool to be used in counselling on MMC pregnancy. Treating physicians can upload characteristics of the fetus concerning the ventricular size, Chiari II presence, the level and extent of the MMC, the presence of clubfeet, outcome on amniotic fluid tests and other relevant data.

Based on the literature such a digital tool would construct the most likely outcome on mobility, continence, hydrocephalus, future independence and other relevant future functional outcome parameters. By doing so for both fetal treatment and postnatal treatment and by incorporating the maternal risks related to fetal surgery in this equation upcoming parents can, based on these gathered data, better decide between termination and continuation of the pregnancy as they can between fetal and postnatal treatment in case of continuation. With more research being conducted and uploaded in the system the predictions and comparisons become more accurate. One could consider creating a tool available to the public as well in order for upcoming parents to be more well prepared for the counselling and the often hard choices that lie ahead.

Next to Chiari II many other brain anomalies are highly present in patients with MMC, some thought to be epileptogenic. Epilepsy is thought to be rather prevalent in MMC patients ranging around 20%. Future research should analyse the prevalence of all the different anomalies and the frequency of epilepsy and try to access their correlation. A way for us would be to establish the epilepsy rate amongst the cohort of MMC patients we reported about in Chapter 2 and to screen all of their MRI's for brain anomalies.

Fetal treatment

Open fetal treatment of MMC has proven its benefits for the MMC patient. Fetoscopic techniques are being explored and applied in order to generate at least the same fetal benefits with less maternal morbidity. In this pursuit a lot is still to decide upon and to improve. Kabagambe performed a review and meta-analysis on the outcome comparing percutaneous fetoscopic, fetoscopic via maternal laparotomy and open fetal surgery.[30] The rate of uterine dehiscence was higher after open repair while dehiscence and leakage form the MMC repair site were more seen after both fetoscopic approaches. Percutaneous repair showed the highest rate of premature rupture of membranes and preterm birth, where fetoscopic repair via laparotomy had the lowest preterm birth rate.

The open technique changed since the data of the MOMS-trial came out mainly concerning the size of the hysterotomy which over the past years decreased to the size of just the MMC defect, creating a smaller incision in the uterus. This incision however, is still larger than those of the two ports in the fetoscopic approach combined, yet the difference is less than it was in the MOMS-technique. A question to answer on the short term is whether we will see less premature births from the current open fetal approach than we did from the open approach performed in the MOMS trial.

Will a vaginal delivery become possible after this smaller form of open fetal surgery? In a time where fetoscopic approaches are tried and refined but also the open approach is becoming less invasive it is important to understand the goals and endpoints of fetal treatment for MMC.

Further improvement of fetal surgery techniques will accomplish our most important goal; achieving the best possible outcome for both the fetus and the mother.

Using a technique that does not require a maternal laparotomy is clearly very interesting in achieving the best possible outcome for the mother, however the current percutaneous technique shows poor results with regards to premature rupture of membranes, preterm birth and MMC repair site dehiscence and leakage. Our model can be used for assessing the feasibility of instruments combined with portals that would allow for a small straight passage through the uterus wall and for the motions and the angles of the instruments to all take place deep to this portal in the uterus causing less stress on the wall of the uterus.

Following the two-hit hypothesis the best possible outcome comes from the earliest intervention possible; protecting the spinal cord from further secondary damage at the earliest stage. From that perspective the less invasive the technique, the sooner it can be performed and the more fetal benefit can be achieved. An interesting phenomenon we learned from fetal surgery for MMC is that Chiari II can be cured by performing surgery to the spinal defect during the fetal period. Chiari II is considered to be a malformation as opposed to Chiari I which is deemed to be a deformation. In Chiari I the brainstem and cerebellum are formed in a normal manner and only the cerebellar tonsils herniate through the foramen magnum. Successful surgery for Chiari I does result in relief of complaints and in a the reappearance of a normal anatomical situation. In Chiari II however the brainstem and cerebellum are malformed and surgery may relief the complaints but a normal anatomical situation will not occur: malformed tissue will stay malformed. However fetal surgery results in a significant reduction of Chiari II, this leads to the conclusion that a malformation in the making may still be reversible. We hypothesise that the earlier one intervenes in the development of a malformation the more it may still be reversible. Performing fetal surgery at an earlier stage may translate into a smaller percentage of MMC patients with Chiari and subsequent hydrocephalus.

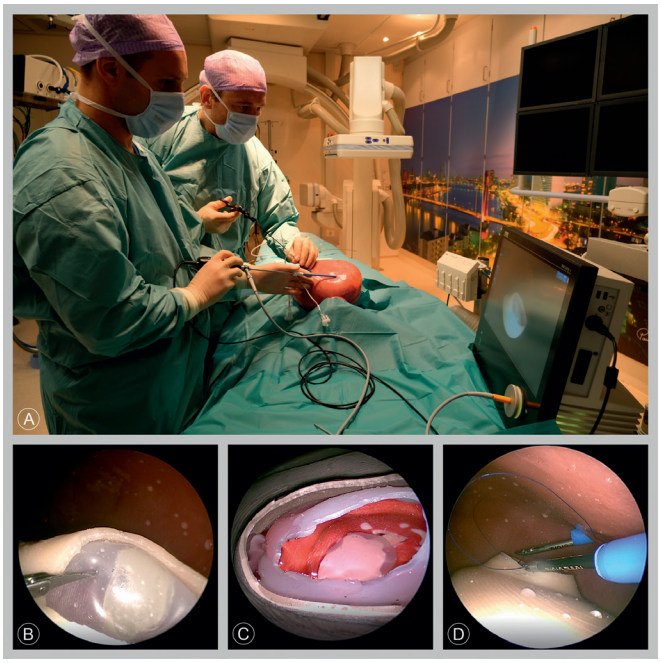
Fetoscopic techniques are more minimally invasive than the open technique. Yet surgery time is longer. Does this make the three port fetoscopic technique practised in some fetal centres less likely to be the future since it is a bit less minimally invasive than the more common two-port technique? Or is the reduction in surgery time due to the extra working channel more important?

Our current model doesn't allow for assessment of stress on the uterus walls yet. We can however compare surgery time of the two- and the three-portal technique after completing the learning curve for both.

We are also setting up research lines in which we test smaller instruments, to the nanoscale as well as transcutaneous imaging techniques both reducing the need for access to the uterus as to further minimize the impact on the uterus and the fetus.

All the above suggestions may very well make it possible to perform surgery a few weeks earlier, with less maternal risks and better fetal results. However performing fetal surgery at a much earlier stage will require a far more drastic rethinking of the process. The two key components of the treatment of MMC are freeing of the neural placode and watertight closure of the defect.

Freeing of the placode is not the most difficult or invasive part, in comparison with closure of the defect. Undermining the respective tissue layers and suturing them watertight together is not possible in a fetus of for example 16 weeks. Creating a patch that can adhere to the tissue surrounding the defect could solve this. Our close collaboration with the technical university of Delft forms the ideal ground for the development and testing of such a patch.



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Chapter 9

Summary

Summary

Myelomeningocele (MMC) is a complex open neural tube defect of the spinal cord caused by failure to fuse of the neural tube early in gestation. Leakage of cerebrospinal fluid (CSF) through the defect is thought to cause the brainstem and cerebellum to descend through the foramen magnum known as Chiari II or Arnold Chiari Malformation (ACM). This descend of brainstem and cerebellum causes obstruction for the CSF flow resulting in ventriculomegaly or hydrocephalus. A more late complication seen in children born with MMC is tethering of the spinal cord at the site of surgical repair known as a form of secondary tethered spinal cord syndrome (TSC).

MMC can be diagnosed by ultrasound which in the Netherlands is routinely performed in the 13th and 20th week of gestation. MMC is a severe lifelong condition negatively affecting many domains such as mobility, continence, cognition, sexual function and independence.

Mainstay of treatment still is postnatal closure of the defect usually followed by insertion of a lifelong ventriculo-peritoneal shunt to address the hydrocephalus.

An RCT in the USA showed that in a select group of MMC pregnancies, the need for a CSF diverting shunt halves by performing fetal surgery. This constitutes a major reason for us to undergo the transition to a fetal surgery centre.

Even though the benefits of open fetal in MMC for the foetus are well-established, long-term data on especially tethered spinal cord are eagerly awaited.

Survival rates in children with MMC changed only in the second halve of the 20st century with advances in surgery and mainly in the treatment of hydrocephalus. Survival increased but so did the number of severely impacted MMC patients. In the two most recent decades two important developments took place in MMC, following the introduction of prenatal diagnosis; an increase in active termination of pregnancy of the majority of MMC-pregnancies in countries like the Netherlands to prevent the often severe prognosis on the one hand and fetal surgery to close the defect during pregnancy in order to improve postnatal outcome on the other.

This dissertation is on the impact of MMC, the importance of well-informed counseling, the role of fetal surgery, and finally on simulation models to improve the technique of fetal surgery for MMC.

Chapter 1 provides an introduction on MMC followed by an overview of the current outcome in a cohort of MMC patients at/from our institution which will hopefully also serve as a historical cohort for comparison with fetal surgery cases in the near future in **Chapter 2.** The outcome is comparable with the literature apart from a relatively low rate of surgical untethering. Hydrocephalus is highly prevalent in postnatal treated MMC patients. In this study as in much of the literature, it is correlated with a low cognitive function.

Chapter 3 shows the results of a study performed on the same cohort of MMC patients, 10 years after we first published on that cohort 10 years ago when they were newborns. The study showed that the patients' lives were affected in many domains. All patients were capable of effective communication, irrespective of severity of MMC. Overall, our data show that in newborn MMC patients future unbearable suffering with respect to pain, mobility, cognition and communication is hard to predict and may not always occur.

Chapter 4 covers a worldwide survey we performed amongst neurosurgeons showing diversity in the management of patients with MMC. In addition, significant diversity remains regarding fetal surgery for MMC closure. We feel that centralization of prenatal treatment to dedicated tertiary centres, as well as the use of sophisticated training models, may help overcome the most commonly cited objection to the implementation of prenatal closure, namely the overall limited caseload.

The meta-analysis and systematic review in **Chapter 5** shows that the cumulative incidence and relative risk of TSC are increased in the prenatal closure group compared to the postnatal group in MMC patients. We conclude that in order to improve counselling on and outcome of MMC more long-term data on TSC after fetal closure for MMC is needed.

Chapter 6 describes the position of fetoscopic surgery for MMC as opposed to open fetal surgery. Open fetal surgery for MMC has become a widespread treatment option and in pursuit of minimizing its maternal risks, fetoscopic techniques are being explored. This creates an expanding but fragmented field in which the optimal fetoscopic technique is yet to be determined. An RCT like the one for open fetal surgery is unlikely to ever take place and we suggest gathering data from high-quality international registries with standardized outcomes to be a valuable alternative. In the absence of high-quality evidence, we emphasize the importance of careful and balanced in-depth counselling taking in consideration individual risks and benefits for every patient.

In **Chapter 7 we** demonstrate a realistic simulator for the training of fetoscopic myelomeningocele surgery to provide a training opportunity for centres that are starting a fetoscopic MMC repair program as well as for more advanced centres to maintain and improve their surgical skills. It is the first simulation model with adjustable spinal defect and placental localisation. Further objective validation is required, but the potential for using this model in preoperative planning and in obtaining surgical skill is promising.

In the general discussion in **Chapter 8,** we elaborate on the important role of well-informed counselling in order to be able to decide upon terminating or continuing a MMC pregnancy and to be able to choose between fetal or postnatal surgery. More solid data will improve counselling. Digital tools may form an useful adjuvant in counselling. Using realistic simulation models may improve technical skills and offer opportunities to develop new surgical techniques for fetal closure of the MMC defect and facilitate innovations to enable closure of the defect at an even earlier gestational age.

Chapter 10

Nederlandse samenvatting

Myelomeningocele (MMC) is een complex open neuraalbuisdefect van het ruggenmerg veroorzaakt door een onvolledige sluiting van de neuraalbuis vroeg in de zwangerschap. Lekkage van hersenvocht door het defect wordt geacht de hersenstam en het cerbellum te doen verzakken door het achterhoofdsgat, dit wordt Chiari II of Arnold Chiari Malformation (ACM) genoemd. Dit verzakken van de hersenstam en cerebellum veroorzaakt een obstructie waardoor de hersenvochtcirculatie verstoord raakt hetgeen resulteert in ventriculomegalie of hydrocephalus. Een latere complicatie van MMC wordt gezien in kinderen met MMC waarbij het ruggenmerg onder spanning komt te staan op de plek van de chirurgische correctie, genaamd secundaire tethering van het ruggenmerg (TSC).

MMC kan worden gediagnosticeerd middels echo welke in Nederland routinematig worden verricht in de 13e en 20e week van de zwangerschap. MMC betreft een levenslange heftige aandoening met een negatieve impact op vele domeinen als mobiliteit, continentie, cognitie, zelfstandigheid en seksuele functies.

De standaard behandeling is nog altijd het operatief sluiten van het defect kort na de geboorte, meestal gevolgd door het aanbrengen van een levenslange ventriculo-peritoneale drain (VPD).

Een RCT in Amerika liet zien dat in een geselecteerde groep MMC zwangerschappen de noodzaak tot een VPD halveert door foetale chirurgie. Dit vormt een hoofdreden voor ons om de transitie naar een foetaal therapie centrum te ondergaan.

Ook al zijn de voordelen van open foetale chirurgie goed bekend; lange termijn data over TSC zijn schaars en zeer gewenst.

De overleving van kinderen met MMC verbeterde pas in de 2e helft van de 20ste eeuw door ontwikkelingen in de chirurgie en met name door de behandeling van hydrocephalus. De overleving nam toe maar zo ook het aantal hevig aangedane patiënten.

In de twee meest recente decennia deed zich een tweetal belangrijke ontwikkelingen voor met betrekking tot MMC; de vaak somber prognose leidde tot actieve zwangerschapsbeëindiging in landen als Nederland, maar ook tot foetale chirurgie van de aangedane foetus om deze sombere prognose te verbeteren.

Deze thesis handelt over de impact van MMC, de rol van foetale chirurgie, het belang van goed geïnformeerde counseling en tot slot over oefenmodellen om de veelbelovende maar invasieve foetale chirurgie voor MMC te verbeteren.

Hoofdstuk 1 betreft een inleiding over MMC. Gevolgd door een overzicht van de uitkomsten van een cohort van MMC patiënten in ons ziekenhuis dat tevens zal dienen als een historisch cohort ter vergelijking met foetale chirurgie patiënten in de hopelijk nabije toekomst in **Hoofdstuk 2**.

De uitkomsten zijn vergelijkbaar met die in de literatuur behoudens een relatief laag percentage chirurgische *untethering* van het ruggenmerg. Hydrocephalus kent een hoge prevalentie in postnataal geopereerde MMC patiënten, in onze studie zoals ook in veel van de literatuur is hydrocephalus gecorreleerd aan een lagere cognitieve functie.

Hoofdstuk 3 toont de resultaten van een studie betreffende hetzelfde cohort MMC patiënten waarover wij 10 jaar geleden publiceerden, toen als pasgeborenen. De levens van allen zijn in vele domeinen aangedaan, evenwel waren zij allen in staat tot effectieve communicatie, ongeacht de ernst van de MMC. Samenvattend laat onze data zien dat toekomstig ondraaglijk lijden met betrekking tot pijn, mobiliteit, cognitie en communicatie zich lastig laat voorspellen voor pasgeborenen met MMC en dat dit zich niet altijd voor doet.

Hoofdstuk 4 behelst een wereldwijde survey welke wij uitvoerden onder neurochirurgen. Deze toont een ruime diversiteit in de behandeling van patiënten met MMC, dit geldt eveneens voor de rol van foetale chirurgie hierin. Wij achten centralisatie van de prenatale behandeling in toegewijde tertiaire centra van eminent belang als ook het gebruik van realistische trainingsmodellen, beide om het meest geuite bezwaar tegen de implementatie van foetale chirurgie voor MMC te adresseren; een lage case load.

De meta-analyse en systematic review in **Hoofdstuk 5** laat zien dat de cumulatieve incidentie en het relatieve risico van TSC verhoogd zijn in de foetale chirurgie groep vergeleken met de postnataal geopereerde MMC patiënten. In dit hoofdstuk concluderen wij dat meer lange termijn data met betrekking tot TSC na foetale chirurgie zeer gewenst is.

Hoofdstuk 6 beschrijft de positie van foetoscopische chirurgie voor MMC ten opzichte van open foetale chirurgie voor MMC. Open foetale chirurgie voor MMC is een breed geaccepteerde behandelmogelijkheid geworden, foetoscopische opties worden uitgeprobeerd om maternale risico's te verkleinen. Hierdoor is een groeiend maar ook een gefragmenteerd veld ontstaan waarin de optimale foetoscopische benadering zich nog moet tonen. EEN RCT zoals die voor open foetale chirurgie is niet waarschijnlijk en in dit hoofdstuk stellen wij voor om data van hoogstaande internationale databases met gestandaardiseerde uitkomstmaten te verzamelen als bruikbaar alternatief. In de afwezigheid van high-quality bewijs benadrukken wij graag het belang van de zorgvuldig gebalanceerde counseling toegespitst op de individuele risico's en voordelen per patiënt.

Tot slot behandelt **Hoofdstuk 7** een realistische simulator voor de training van foetoscopische MMC sluiting voor beginnende foetale centra, alsook voor het onderhouden en verbeteren van chirurgische vaardigheden in meer ervaren centra.. Dit is het eerste simulatiemodel met een aanpasbaar spinaal defect alsook een variabele lokalisatie van de placenta. Verdere objectieve validatie is geïndiceerd maar het gebruik ten behoeve van de ontwikkeling van chirurgische vaardigheden is veelbelovend.

Hoofdstuk 8 betreft de algemene discussie waarin we de belangrijke rol van goed geïnformeerde counseling benadrukken om zo een weloverwogen keuze mogelijk te maken tussen beëindigen en voortzetten van de zwangerschap als ook tussen foetale en postnatale chirurgie. Door een toename aan solide data zal de counseling verbeteren. De invoering van "digital tools" zou een belangrijk adjuvans kunnen zijn in deze.

Het gebruik van realistische trainingmodellen kan helpen de chirurgische vaardigheden te verbeteren en kan mogelijkheden bieden om het MMC defect op een nog eerder moment te kunnen sluiten en zo de uitkomsten verder verbeteren.

List of abbreviations

CFCS = communication function classification system;
CI = confidence interval
CIC = clean intermittent catheterization;
CMTII = chiari malformation type II;
CNS = Congress of Neurological Surgeons
CSF = cerebro spinal fluid
ETV = endoscopic third ventriculostomy;
HRQOL = health-related quality of life;
ISPN = International Society for Pediatric Neurosurgery
MMC = myelomeningocele;
MOMS = Management of Myelomeningocele Study;
MRI = magnetic resonance imaging
NAFTNET = North American Fetal Therapy Network
NRS = numeric rating scale;
NSBPR = National Spina Bifida Patient Registry;
PEDI-CAT = pediatric evaluation of disability inventory
PPROM = preterm premature rupture of membranes
PRISMA = preferred reporting items for systematic reviews and meta-analyses
RCT = randomized controlled trial
RR = relative risk
SBa = spina bifida aperta
TOTAL = tracheal occlusion to accelerate lung growth trial
TSC = tethered spinal cord;
VP = ventriculo peritoneal
VPS= ventricular peritoneal shunt

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About the author

Jochem Spoor was born in Almelo on the 14th of January 1980. Suffering from meningitis aged 7 and being fed interesting books on the brain by his uncle Frans Zitman who was a professor in Psychiatry first in Nijmegen and later in Leiden created an early and profound interest in the central nervous system. Growing up in an inspiring family where free thought, reading, music and travel were all encouraged from a young age on created the right circumstances to make this interest run like a thread through life.

After finishing Gymnasium at the **Openbare Scholen Gemeenschap Erasmus** (what's in the name?) he started studying Law (finished in 2006), Philosophy (unfinished business so far) at the **Rijksuniversiteit Groningen** and two years later Medicine, which was finished at **Universiteit Leiden** in 2009 after internships in different hospitals in Leiden and The Hague.

The mysterious central nervous system along with the practical development of very basic surgical skills by being part of a student-team that was responsible for the surgical removal of eyes of donors for their corneas and their hearts for heart valve donation made neurosurgery very appealing.

Spending substantial time at the department of neurosurgery at **Leids Universitair Medisch Centrum** (LUMC) for his senior internship and during a month of free time in between internships at the department of Neurosurgery at **Universitair Medisch Centrum Groningen** (UMCG) confirmed this. And while the summer of 2006 spent in Ghana at the **Korlebu Teaching Hospital Accra** further deepened his other medical interest: medicine around the globe, the choice to pursue a neurosurgical career had been made.

Neurosurgical training took place at the **Erasmus MC** where pretty soon a special interest for pediatric neurosurgery sparked because of the intense full size pediatric neurosurgical department; its people, the patients and the way it was run.

After finishing his training in June 2016 a fellowship pediatric neurosurgery at **Great Ormond street Hospital** in London UK followed where he and his family lived in Dalston Hackney and had a year of less busy agenda's and intense family time.

The fellowship focused on cranio-synosthosis, neuro-oncology and spinal dyshraphisms, the fields that still interest him most.
Research is felt to be highly appealing as it allows for the mind to wonder, while it demands clear concepts to prove or disprove ones hypotheses in order to benefit patients.

Since May 2017 Jochem works as a pediatric neurosurgeon at **Erasmus MC Sophia Children's Hospital** where one of his main focuses is the treatment of *spinal dyrhaphisms*, in that he chairs the *Erasmus MC center of expertise for spina bifida and other spinal dysrhaphisms*, is part of the new Sophia's Fetal Therapy Center and wrote this Thesis.

PhD Portfolio

Name	Jochem Karel Hendrik Spoor
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PhD period	January 2019-April 2023
Promotor	Prof. Dr. C. Dirven
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Year	workload (ECTS)	
PhD training		
2017	0.3	Integrity in scientific research (London UK)
Specific courses		
2017-2019	6.0	Yearly European Society of Paediatric Neurosurgeons course (ESPN).
2018	1.0	Ultrasound course Birmingham UK
Presentations		
2019	0.7	NVNA (Nederlandse vereniging assistenten Neurochirurgie) Amsterdam: presentatie over fetal surgery voor MMC en begeleiding die dag
2019	0.6	2 presentations International Society of Pediatric Neurosurgeons (ISPN) Birmingham
2020	0.3	Prenatale Geneeskunde voor de specialist Rotterdam
2020	0.3	BEN (Beroepsvereniging Echoscopisten Nederland) Amsterdam
2021	0.3	Landelijke werkgroep Neonatale Neurologie
2022	0.3	Landelijke vereniging operatie–assistenten Hilversum
2022	0.2	Farewell symposium Dr de Laat Erasmus
2023	0.3	International Society of Pediatric Neurosurgeons (ISPN) Singapore
Conferences		
2019	1.0	International Society of Pediatric Neurosurgeons (ISPN) Birmingham UK
2022	1.0	International Society of Pediatric Neurosurgeons (ISPN) Singapore
Teaching		
2018-	3.0	Annually Multiple Lectures Pediatric Neurology Minor on MMC
2018-	2.0	Annually multiple lectures to neurology/neurosurgery nurses on MMC and:
2018-	2.0	on hydrocephalus
2019-	1.5	Annual lecture Erasmus Summerschool on MMC

2021-	1,5	Lecture on fetal surgery for MMC, NEURV Erasmus
2022	2.0	6 lecture-course on fetal surgery for MMC, IFMS Netherlands and co-organizing it
2022	0.3	lecture on fetal surgery for MMC for VCMS Nederland
2023	0.3	podcast on neurosurgery and fetal surgery for MMC, VCMS Rotterdam
2023	0.5	patient presentation and lecture on MMC for Medical students 3rd year Erasmus MC
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Other

2017-	1.0	Honorary Fellow Paediatric Neurosurgery Great Ormond Street Hospital, London UK
2019-	2.0	Editor for *Tijdschrift voor Neurologie en Neurochirurgie (TNN):* Dutch&Belgian Journal on Neurology and Neurosurgery.
2019-	2.0	Coordinator of Erasmus MC Spinal Disraphism Center of Excellence Erasmus MC/Sophia Children's Hospital Rotterdam, the Netherlands
2020-	0.3	Member of the Workgroup Spina bifida of the ERN Ithaca
2020-	0.3	Member ERN Ithaca

Publications

- **The Bcl-2 inhibitor Obatoclax overcomes resistance to histone deacetylase inhibitors in patient-derived glioblastoma cells.** Berghauser Pont, **Spoor** et al. Genes and Cancer November 2014
- **Out of body experience during awake craniotomy, case report and review of the literature.** Bos, **Spoor** et al. World Neurosurgery August 2016
- **Letter to the editor: Progressive neurology in a young woman with a known Currarino's triad.** Hoefnagel, **Spoor**, et al. Eur Spine J August 2016
- **TP53 mutated glioblastoma stem-like cell cultures are sensitive to dual mTORC1/2 inhibition while resistance in TP53 wild type cultures can be overcome by combined inhibition of mTORC1/2 and Bcl-2.** Venkatesan, Hoogstraat, Caljouw, Pierson, **Spoor**, et al. Oncotarget September 2016
- **Extensive calcification of the ligamentum flavum causing cervical myelopathy in a Caucasian woman.** Roet, **Spoor**, et al. Springer Plus November 2016
- **Delayed ischaemia due to vasospasm after fenestration of a large arachnoid cyst**. **Spoor**, et al. Br J Neurosurg, June 2017
- **Haemorrhage into a cavernoma after traumatic head injury in a child.** Ogborne, **Spoor**, James Childs Nevr Syst. July 2017
- **A novel non-instrumented surgical approach for isthmic spondylolisthesis in patients with radiculopathy. Spoor,** et al. Neurosurgical Focus January 2018
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- **Neurosurgeons' opinions on the prenatal management of myelomeningocele.** Gadjradj, **Spoor**, et al. Neurosurg Focus. 2019
- **Secondary vault reconstruction after open or minimal invasive correction for unisutural, multisutural or syndromic craniosynostosis: the impact of diagnosis and type of initial surgical technique.** Mathijssen,…**Spoor**, van Veelen. Plastic and Reconstructive Surgery 2019: accepted.
- **Dural sinus volume in children with syndromic craniosynostosis and intracranial hypertension.** de Goederen ¨ **Spoor** .. J Neurosurg Pediatr 2020
- **Sudden death in epilepsy: There is room for intracranial pressure.** DibuÉ, **Spoor,..** Brain Behaviour 2020
- **Spontaneous externalization of a ventriculoperitoneal shunt tip through the navel.** Gadjradj,.. **Spoor** BrJ Neurosurg 2020
- **Disciplinary law and neurosurgery: a 10-year analysis of cases in the Netherlands.** Dronkers,.. **Spoor.** Neurosurg Focus 2020
- **Disappointing results of spring-assisted cranial vault expansion in patients with Crouzon syndrome presenting with sagittal synostosis.** Wilson,**... Spoor,..** Neurosurg Focus 2021

- **Vagus nerve stimulation in patients with Lennox-Gastaut syndrome: A meta-analysis.** DibuÉ,.. **Spoor**,.. Acta Neurlog, Scand 2021
- **Presympotomatic treatment of classic late-infantile neuronal ceroid lipofuscinosis with cerliponase alfa.** Schaefers,...**Spoor**,.. Orphanet J Rare Dis. 2021
- **Does conus morphology have implications for outcome in lumbosacral lipoma?** Thompson, **Spoor,...** CNS 2021
- **Proposed definition of competencies for surgical neuro-oncology training.** Kamp..**Spoor,**.. J Neurooncol 2021
- **Secondary vault reconstruction after open or minimal invasive correction for unisutural, multisutural or syndromic craniosynostosis: A cohort study on the impact of diagnosis and type of initial surgical technique.** Mathijssen,.., **Spoor,..** J Plast.Recon.Esth. Surgery 2021
- **Fetoscopic myelomeningocoele closure: Is the scientific evidence enough to challenge the gold standard for prenatal surgery**? Verweij.., **Spoor,...** Prenat Diagn. 2021
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- **Development of a simulator for training of fetoscopic myelomeningocele surgery. Spoor**,... Prenatal Diagnosis 2023
- **Brain stem encephalitis is a rare complication of COVID-19.**Shamier, **Spoor,...** J of Neuroimmunology 2023

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Bookchapters

Leerboek Acute Geneeskunde, hoofdstuk Neurochirurgie currently 5th edition. **Spoor,** Haitsma

Awknowledgements/Dankwoord

Na eerst te werken aan een proefschrift in basaal onderzoek binnen de neuro-oncologie is door de focus op spinale dysraphismen en de betrokkenheid bij het opzetten van een foetaal therapie centrum de switch gemaakt naar de behandeling van myelomeningocele (MMC). Wat een andere pathologie, wat een ander type onderzoek, maar wat even fascinerend. Onderzoek doen terwijl je neurochirurg bent en probeert een goede vader te zijn is voor mij bijzonder pittig. Het kan evengoed ook heerlijk zijn, als je denkend aan de drie liefste apen van de wereld eind 2018 voor het eerst meekijkt naar foetale chirurgie in Johns Hopkins USA en aan alles merkt dat je hier meer van wilt weten en aan bij wil dragen.
Dit proefschrift vormt slechts een kleine bijdrage en onze foetale stappen worden vooralsnog voorzichtig gezet maar ik weet mij gesterkt door familie, vrienden en collegae waarvoor ik bijzonder dankbaar ben.

Clemens Dirven, mijn promotor, opleider en afdelingshoofd. Ik ben buitengewoon dankbaar voor hoe je deze drie bepalende functies vervult en hebt vervuld, bepalend in mijn vorming tot neurochirurg en onderzoeker. Dankbaar op iedere dag dat het allemaal wel reilt en zeilt, maar in het bijzonder dankbaar op dagen die minder gaan, om wat voor reden ook. Zoals toen je vorige zomer onverwacht langskwam in Voorburg en we een tijd buiten zaten te praten, het deed me denken aan je bezoek aan ons huis in London, beide keren "was je toch in de buurt", London vanwege je zoon die daar toen studeerde.

Alex Eggink, mijn co-promoter. Veel dank voor je begeleiding, je goede gevoel voor formulering en je inspirerende ideeën. Maar vooral voor het samenwerken; ik prijs mij gelukkig met jou samen te mogen knallen voor de behandeling van MMC-patienten. Ik hoop dat we nog veel mooi werk zullen verzetten samen.

Marie-Lise van Veelen, co-promotor maar bovenal zéér gewaardeerd collega. Ik schrijf collega maar er staat eigenlijk; voorbeeld, opleider, vraagbaak, top-kinderneurochirurg. Het voelt nog steeds als een groot voorrecht om met jou op onze mooie maar ook kwetsbare afdeling te mogen werken. Dat we dat nog een flink aantal jaren samen mogen doen.

Philip DeKoninck, "my Gyno". Dank voor je hulp, je samenwerking, je scherpe wetenschappelijke blik, je vriendschap. Burgers&beer onder de snelweg @ Bubba's Burgers in Houston, samen met René en Alex voor het eerst naar Johns Hopkins, onze eerste keren mee-opereren in Leuven; ik vind het super dit alles samen met jou te doen en zie zeer uit naar alles wat we hopelijk nog gaan doen.

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Ahmet Baschat, thank you so much for taking part in the commitee and today's symposium. The visits to your department of fetal surgery at Johns Hopkins and your visiting professorship here with us form a great inspiration.

Dominic Thompson thank you so much for being willing to take part in today's committee and symposium. My time at Great Ormond Street formed me as a junior paediatric neurosurgeon, for which I continue to be extremely grateful.
Your profound knowledge of spinal dysrhaphisms both surgical and conceptual are unmet and I can't thank you enough for allowing me to steal your brain every now and then when confronted with a very challenging case.

Irene Mathijssen, dank voor vandaag en dank voor dat prachtige cranio-faciale centrum van ons, het is me een voorrecht er deel van te mogen uitmaken, wat een prachtig team. Ik vind onze samenwerking erg fijn en hoop wat meer tijd te gaan vinden nu voor cranio-onderzoek.

René Wijnen, niet lang na ons eerste bezoek aan Johns Hopkins stond er ineens een 3D-printer, de basis van ons simulatie model: je doortastendheid, pragmatisme en actie-gedreven manier van aanpak vind ik geweldig. Dank, ook voor vandaag.

Ard Struijs, paranymf en knappe kop. Je kennis en ideeën zijn een inspiratie. Ik geniet van onze gesprekken en de stappen die we zetten; laten we onze plannen tot een succes maken.

Martijn Nooijen, paranymf en zwagermans, dank voor vandaag. Pa was paranymf bij zijn zwager en het is me een eer dat jij dit vandaag bij mij bent. Veel meer dank natuurlijk voor al je hulp, voor de super-oom die je voor m'n kinderen bent, dank voor m'n prachtneven en prachtnicht. Ik kan me geen betere zwager wensen.

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Frank en Willem, knappe dwarse koppen, heel veel dank voor jullie onmisbare kennis en hulp bij de ontwikkeling van het simulatie model en de begeleiding van Amanda, Lis en Fatima; zonder jullie was dit niet gelukt. Ik hoop dat we zullen blijven samenwerken aan de verbetering van de foetale behandeling van MMC.

M'n studenten, ik heb van jullie allen geleerd. Ik hoop dat het wederzijds was.
In het bijzonder:

Lis en Fatima, wat een prachtig model hebben we gemaakt. Succes in jullie carrières.

Wouter, slimme vent. Onze samenwerking ontstond op de poli en de OK in het Maasstad en ik denk dat we op het punt staan een aantal fraaie juridische papers te publiceren ikv je PhD. Dank voor een prachtige samenwerking.

Charlotte: ik ben onder de indruk van je schrijven, je statistische kennis je goeie ideeën. Wat prachtig dat je fetal PhD is begonnen, laten we er iets heel moois van maken.

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OK, 1Noord, Cranioteam, Kinderneurologen, Ortho, IC, Neo, Radiologen, allen: wat werken we in een prachtig ziekenhuis en wat is het een voorrecht om dat samen met jullie te mogen doen.

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Staf; veel dank voor het onderdeel mogen zijn van een groep gedreven toegewijde neurochirurgen die de zorg garanderen voor een fors achterland, dag en nacht. Ik denk dat we een prachtgroep zijn.

AIOS; toppers, wat hebben jullie pittige tijden gehad rond Corona met alle extra taken en diensten die dat met zich bracht en ook nu nog. De 5540 is een eikel, maar jullie kunnen

‘m allemaal de baas. Het is mooi te zien hoe jullie je ontwikkelen en daar een beetje aan bij te mogen dragen.

Lieve familie, lieve vrienden;
Het is heel fijn om keihard te werken in een vak dat ingrijpend en veeleisend is, maar alleen als het privé en met je dierbaren goed gaat.
Het is heel fijn om je omringd te weten door lieve familie en vrienden, vooral als het privé of met je dierbaren even niet zo goed gaat.
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Martje, onze allerliefste kinderen; ik ben je veel verschuldigd

Mam, wat woonden we heerlijk aan de Dennenlaan 8 met z’n viertjes; jij, pa, Anne en ik. Pa en jij hebben me altijd overal in gesteund en gestimuleerd, wat de basis is voor alles. Tegenwoordig ben je al even onmisbaar voor de volgende generatie. Dank voor alles lieve moe.

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Lieve Maxine, DibüÉ of mine, let’s make it work.

MAH DiBüÉ