Fetoscopy for meningomyelocele repair: past, present and future

Cirurgia fetal endoscópica para correção de mielomeningocele: passado, presente e futuro

Nicole Silva Bevilacqua[1], Denise Araujo Lapa Pedreira[1,2]

ABSTRACT

Meningomyelocele is a malformation with high prevalence, and one of its main comorbidities is Arnold-Chiari malformation type II. The intrauterine repair of this defect has been studied to reduce the progressive spinal cord damage during gestation. The purpose of the present review was to describe the evolution of fetal surgery for meningomyelocele repair. Searches on PubMed database were conducted including articles published in the last 10 years. Twenty-seven articles were selected, 16 experimental studies and 11 studies in humans. A recent study demonstrated that the fetal correction results in better prognosis of neurological and psychomotor development, but open surgery, which has being used widely, has considerable maternal risks. Studies in animal and human models show that the endoscopic approach is feasible and leads to lower maternal morbidity rates. Two endoscopic techniques are currently under assessment - one in Germany and another in Brazil, and we believe that the endoscopic approach will be the future technique for prenatal repair of this defect.

Keywords: Meningomyelocele/surgery; Spina dysraphism; Fetus/ surgery; Fetoscopy

RESUMO

A meningomielocele é uma malformação de alta incidência e, dentre suas principais comorbidades, está a malformação de Arnold-Chiari tipo II. A fim de reduzir os danos progressivos durante a gestação, tanto a nível medular, quanto sobre a fossa posterior, a correção intrauterina desse defeito vem sendo estudada. A presente revisão teve por objetivo descrever a evolução da cirurgia fetal para a correção da meningomielocele. Foi realizada uma pesquisa na base de dados PubMed, incluindo artigos publicados nos últimos 10 anos. Foram selecionados 27 artigos, sendo 16 de estudos experimentais e 11 sobre pesquisa em humanos. Um estudo recente demonstrou que a correção pré-natal resulta em melhor prognóstico neuropsicomotor, porém a abordagem a céu aberto, que vem sendo amplamente utilizada, possui um risco materno considerável. Estudos, tanto em modelo animal, quanto em humanos, mostram que a abordagem endoscópica é factível e apresenta menor morbidade materna. No momento, duas técnicas de abordagem endoscópica estão sendo estudadas, uma na Alemanha, e outra no Brasil, e acreditamos que a via endoscópica será o futuro da correção pré-natal desse defeito.

Descritores: Meningomielocele/cirurgia; Disrafismo espinal; Feto/cirurgia; Fetoscopia

INTRODUCTION

Myelomeningocele (MMC) is one of the most common types of open neural tube defect, leading to exposure of the spinal cord to the external environment. This is a malformation with high incidence worldwide, affecting about 1.9 per 10,000 live births in Brazil[1] and between 0.5 and 1.0 per 10,000 in the United States.[2]

Individuals affected by this disease may have varying degrees of motor deficit, fecal and urinary incontinence, and central nervous system changes due to the herniation of the elements of the posterior fossa into the spinal canal. This group of central nervous system malformations known as Arnold-Chiari type II malformation can lead to progressive dilation of cerebral ventricles, requiring ventriculo-peritoneal shunting (VPS) for the treatment of hydrocephalus.

[1] Universidade de São Paulo, São Paulo, SP, Brazil.

[2] Hospital Israelita Albert Einstein, São Paulo, SP, Brazil.

Corresponding author: Denise Araujo Lapa Pedreira – Fetal Therapy Program, Hospital Israelita Albert Einstein – Avenida Albert Einstein, 627/900 – Morumbi – Zip code: 05651-900 – São Paulo, SP, Brazil Phone: (55 11) 2151-9040 – E-mail: denise.pedreira@gmail.com

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VPS is performed by implanting a permanent valve system, which can lead to secondary complications that could potentially affect neurological and psychomotor development, such as infection, malfunction and obstruction.

Until recently, treatment of the disease was only possible after birth, and consisted of surgical repair of the spinal defect by suturing in layers. This closure eventually leads to anchoring of the cord into the surgical site and, as the child grows, there may be neurological changes associated with stretching of the cord and nerve roots. The set of clinical symptoms associated with this anchoring is known as tethered cord syndrome. It occurs in 20-30% of affected individuals and may lead to delayed neurological and psychomotor development, sometimes requiring reoperation to release the cord.

It is estimated that approximately 70% of MMC cases can be prevented by increasing the levels of folic acid available in the preconceptional period up to the seventh week of gestation, when the closing of the neural tube is completed. That is why some food products have been "fortified" in the United States; in Brazil, since 2004, folic acid has been added to flours for periconceptional supplementation. However, this fortification had a lower-than-expected impact – approximately 40% – in reducing the incidence of the defect. Therefore, in October 2012, the Brazilian Federation of Gynecology and Obstetrics started a campaign promoting preconceptional supplementation with folic acid for all women of childbearing age. The recommended daily dose is 400 micrograms in oral tablets, starting at least 3 months prior to conception.[3,4]

Until recently, posnatal treatment of MMC was the only alternative available, without encouraging results. A few years ago, clinical evidence and studies in animal models suggested that correcting the defect before birth could favor neurological development and fetal surgery became an treatment alternative. However, antenatal surgery poses risks to maternal health, and such risks do not exist in neonatal surgery. Therefore, it was only in 2011 that it became universally accepted, when a prospective randomized clinical trial comparing antenatal and postnatal repair was published, demonstrating a significantly better prognosis in the group treated before birth.

This important study used an open approach to fetal surgery, which is associated with higher risks for the mother, when compared to minimally invasive techniques of endoscopic fetal surgery (fetoscopy). Although the first attempts to perform antenatal repair of the defect in humans were endoscopic,[5] the failure due to technical difficulties inherent to this approach led to its abandonment, and the open approach soon became widely used. Our goal was to review the literature on antenatal repair of MMC, with emphasis on the study of minimally invasive techniques, using fetoscopy, to establish its current state of use and future prospects.

METHODS

This is a descriptive review study. We searched the articles published in the PubMed database and Cochrane library over a 10-year period (June 2003 to June 2013). The search was conducted in June 2013. The descriptor used was "myelomeningocele", and we searched the following keywords and their combinations: "myelomeningocele", "prenatal", "fetal repair", "fetal surgery", "in utero surgery", "in utero repair" and "intrauterine repair". The search included only articles in English or Portuguese. The studies found were divided into four basic categories: experimental studies, human studies, studies related to the Management of Myelomeningocele Study (MOMS) and studies on ethical and legal aspects.

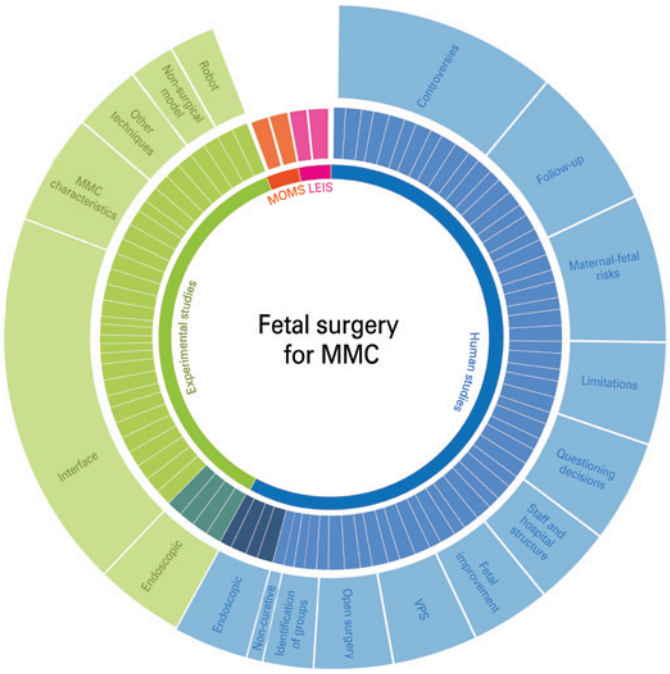
The studies selected for review were human studies using endoscopic and open techniques, conducted after the study MOMS, including the latter. Articles cited by the selected articles but published before 2003 were added when deemed highly relevant from the historical perspective.

We excluded all experimental studies performed in animal models other than sheep, because they were the most similar model and the most widely used before the start of clinical trials to test new fetal surgery techniques. Studies that addressed only the ethical-legal aspects were also excluded as well as review and opinion studies (only original articles were included). We also excluded studies in humans conducted before the MOMS study because their main limitations and questions were solved by the MOMS study, which has the highest level of scientific evidence to date.

Search results

The results were obtained using the following combinations: myelomeningocele prenatal repair (43), myelomeningocele fetal repair (74), myelomeningocele fetal surgery (172), myelomeningocele fetal (233), myelomeningocele in-

utero surgery (44), myelomeningocele in-utero repair (29), myelomeningocele intrauterine repair (23). The 78 articles primarily selected were arranged in a concentric diagram (Figure 1) representing the general categories in proportional sectors. The predominant articles referred to human studies conducted before the MOMS study (approximately 57.6%), followed by experimental studies (37.2%) and articles on ethical and legal aspects (2.6%).



MMC: myelomeningocele; VPS: ventriculoperitoneal shunting; MOMS: Management of Myelomeningocele Study.

Figure 1. Concentric diagram of the 78 articles primarily selected. The majority were non-randomized human studies (approximately 58.6%) and experimental studies (36%), with few articles related to legal aspects and the randomized study Management of myelomeningocele Study. Most articles covered the endoscopic approach

After applying the exclusion criteria, 27 studies were selected, 16 experimental and 11 in humans.

DISCUSSION

Endoscopic repair *versus* open fetal surgery

In 1999, the first attempt to repair MMC in human fetuses was carried out by Bruner et al.[5] using an endoscopic technique for prenatal repair of the defect. However, due to the high rate of complications such as prematurity and high fetal mortality (50%), the endoscopic technique was abandoned by this group, and replaced by open repair.

In the open technique, the uterus is exposed by laparotomy, and the myometrium and amniotic membranes are opened and the fetus is directly exposed. The classical neurosurgical technique is used to repair the defect (three layers suture repair: duramater, aponeurosis and skin). However, there are significant maternal risks associated with this procedure, and new minimally invasive alternatives have been investigated using animal models.

Animal models

Aiming at a minimally invasive repair, several techniques have been developed to simplify the correction of the defect itself. Different materials have been studied with the aim to create an interface to "cover" the defect, protecting the cord from exposure to the amniotic fluid.

Among these materials, of which many are dura substitutes, special note should be given to the use of biosynthetic cellulose film (BioFill®, Fibrocel, Paraná, Brazil, and Bionext®, Bionext, Paraná, Brazil), in national experimental studies.[6] The cellulose stimulated the formation of a fibroblast layer around the film in anatomical continuity with the duramater, resulting in the formation of a neoduramater. This material prevented adhesions between the cord and the scar tissue with the advantage, at least in theory, of preventing the tethered cord syndrome. This new technique was then successfully applied endoscopically for the repair in sheep fetuses.[7]

Later on, this simplified technique was compared with neurosurgical correction of the defect in three layers - the same used in the MOMS study. The study showed that the new technique was faster, with increased capacity to preserve the spinal cytoarchitecture, in addition to the fact that cellulose induces the formation of a neodura, which was not observed in the group subjected to the classical technique.[8] Although the long-term effects of this new technique are not yet know, it has the potential to prevent the neurological damage inherent to the neurosurgical repair technique, demonstrated for the first time in this study.[9]

Other authors studied other materials to be used as an interface. Kohl et al.[10] tested nonabsorbable polytetrafluoroethylene and collagen films; Yoshizawa et al.[11] used a dermal matrix (Alloderm®, USA) and a synthetic film (GORE-TEX®, United States), which proved to be as effective as the classical neurosurgical technique for neurological preservation in a sheep model. Fauza et al.[12] associated the injection of neural

stem cells with the surgical repair, showing better prognosis in the group receiving the stem cells.

Eggink et al.[13] tested collagen matrices, showing that sheep fetuses undergoing repair had minimal neurological damage, with the advantage of this matrix allowing molded according to surgical needs.

Von Koch et al.[14] tested a dura substitute (Duragen®, United States) sutured to the skin or fixated with biological glue (BioGlue®, United States), demonstrating a better prognosis in treated fetuses without any clear conclusions on the differences among the tested materials. Fontecha et al.[15] successfully used an interface (Silastic®, Spain) fixated with bioadhesive gel (Coseal®, USA). This same combination was subsequently tested using an endoscopic technique for its application,[16] proving to be efficient in protecting the spinal cord, as well as preventing cerebellar herniation. These authors then further developed the technique using one single port for the endoscopic correction in sheep.[17]

Recently, Saadai et al.[18] tested biodegradable scaffold nanofibers to cover the defect in sheep, theorizing that this structure could stimulate remodeling of the neuronal tissue and thus restore its function. The authors observed a good integration with adjacent tissues and suggested that the addition of growth factors could accelerate regeneration and possibly yield better results. Chart 1 summarizes the main articles with their surgical techniques and materials.

Chart 1. Articles published between 2003 and 2013 on techniques for repair of myelomeningocele-like defects in sheep fetuses

N	Authors	Year of publication	Title	Repair method	Interface used	Number of cases
1	Herrera et al.[8]	2012	Comparison between two surgical techniques for prenatal correction of meningomyelocele in sheep	Classical neurosurgical repair Approximation of skin edges and suture on the interface	NU Bionext® Integra®	3 3
2	Kohl et al.[10]	2003	Percutaneous fetoscopic patch coverage of experimental lumbosacral full-thickness skin lesions in sheep	Approximation of skin edges and suture on the interface	Nonabsorbable PTFE Collagen	5 5
3	Yoshizawa et al.[11]	2004	Fetal surgery for repair of myelomeningocele allows normal development of anal sphincter muscles in sheep	Classical neurosurgical repair Coverage with the interface, sutureless	NU AlloDerm® or GORE-TEX®	4 4
4	Fauza et al.[12]	2008	Neural stem cell delivery to the spinal cord in an ovine model of fetal surgery for spina bifida	Coverage with the interface sutured to the skin Coverage with the interface sutured to the skin with delivery of neural stem cells	AlloDerm®	7 9
5	Eggink et al.[13]	2005	In utero repair of an experimental neural tube defect in a chronic sheep model using biomatrices	Coverage with the interface sutured to the skin Only skin suture Coverage with the interface sutured to the skin	Collagen UMC Biomatrix® NU SIS Biomatrix®	 4 3 5
6	von Koch et al.[14]	2005	Myelomeningocele: characterization of a surgically induced sheep model and its central nervous system similarities and differences to the human disease	Direct application of BioGlue® BioGlue® + interface with corner stitches Classical neurosurgical repair	NU DuraGen® NU	2 1 1
7	Fontecha et al.[15]	2009	Inert patch with bioadhesive for gentle fetal surgery of myelomeningocele in a sheep model	Coverage with an interface closed with bioadhesive	Silastic® Silastic® + Marlex Mesh®	8 6
8	Fontecha et al.[16]	2011	Fetoscopic coverage of experimental myelomeningocele in sheep using a patch with surgical sealant	Coverage with an interface closed with bioadhesive	Silastic®	9
9	Saadai et al.[18]	2011	Prenatal repair of myelomeningocele with aligned nanofibrous scaffolds-a pilot study in sheep	Approximation of skin edges and suture on the interface	Scaffolds	2

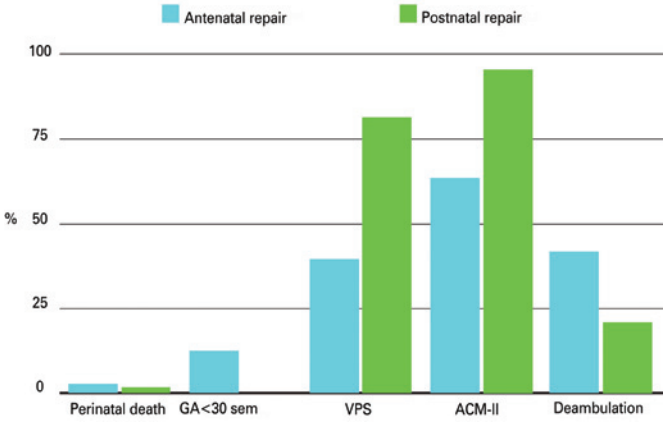
PTFE: polytetrafluoroethylene; NU: not used; UMC: biodegradable matrix; SIS: small intestinal submucosa.

Clinical trials: the MOMS study

In 2011, the results of the randomized prospective study MOMS were published.[7] This study looked into primary effects, such as fetal or neonatal death, or the need for VPS within 12 months, and detrimental effects, including surgical and pregnancy complications, neonatal morbidity

and mortality, Arnold-Chiari tipe II malformation components, need for VPS, locomotion, psychomotor development, and degree of functional concordance between the injury anatomic and funcional levels. The study inclusion criteria were lesions between T1 and S1; evidence of hindbrain herniation; gestational age between 19 and 25.9 weeks at the time of randomization; normal karyotype; resident in the United States; and maternal age of 18 years and over.

The study found that the group subjected to prenatal surgery showed better results, such as a two-fold increase in the possibility of ambulation, despite prematurity (13% of infants subjected to fetal surgery were born before 30 weeks). According to the authors, the positive effects were related to the time of surgery, avoiding progression of the injury and allowing for a near-normal nervous development. Furthermore, the correction reduced the rate of hindbrain herniation, enhancing the CSF flow and thus resulting in less need for VPS, *i.e.* 40% in the prenatal group *versus* 80% in the postnatal correction group (Figure 2). On the other hand, the open technique resulted in high maternal morbidity, with high rates of premature labor, need for maternal blood transfusion at delivery, placental abruption, maternal acute lung edema after fetal surgery due to effects of the tocolytics required, dehiscence or thinning of the uterine wall in nearly 25% of cases. The presence of the an uterine scar outside the uterine active segment required they also found dehiscense required all births to be C-sections.



GA<30 sem: gestational age at birth; MOMS: Management of Myelomeningocele Study; VPS: ventriculoperitoneal shunting; ACM: Arnold-Chiari malformation.

Figure 2. Side effects studies MOMS
This chart based on data from the study[7] shows significant reduction of cases with Arnold-Chiari II malformation, as well as lower frequency of ventriculoperitoneal shunting in children subjected to fetal correction of myelomeningocele (64% and 40%, respectively) when compared to postnatal surgery (96% and 82%, respectively). This same group was twice as likely to ambulate (42%) compared to newborns corrected after birth (21%). In contrast, higher prematurity rates were observed in the fetal surgery group.

The authors emphasize the importance of surgeries being performed in properly equipped centers by trained staff, in order to produce similar results. According to the authors of this study, it is important to note that not all patients benefited from fetal surgery, and only the longer-term follow-up of these children can establish whether the positive results are long lasting.

After publication of the MOMS, at least two centers in Europe started to offer fetal surgery using the open approach, one in Switzerland[19] and one in Belgium (L. Lewi, personal communication, August 2013). In Brazil, this technique has been applied since 2002.[20] Brazil is currently the country in the world with the second largest case series with the use of open surgery for MMC correction, according to Leal da Cruz et al.[21]

The Cochrane Library has an ongoing protocol with about the subject, but the results have not been published yet.[22]

Endoscopic fetal surgery

Endoscopic MMC correction was studied by two independent American groups. In 1998, Bruner et al.[5] published the results of repairs in four human fetuses, but only two fetuses survived and both required neurosurgical correction immediately after birth. In 2003, Farmer et al.[23] described attempted corrections in three human cases, where only one of the fetuses survived. The third case of this series was converted to a classical neurosurgical correction via open surgery. It is worth mentioning that, after 1995, to the safety of open surgery for fetal correction was rather questioned the risk of neurological damage associated with the technique *per se.* Bealer et al.[24] found about 20% of neurological damage in infants undergoing surgery for fetal diseases that did not affect neurological development.

It was only in 2006 that Kohl et al.[25] achieved survival of all three fetuses operated using the endoscopic approach. Dissection of the defect was not performed, and postnatal neurosurgical correction was necessary in all cases. Subsequently, the correction technique was modified allowing for definitive correction without the need for surgery after birth.[26] In their most recently published case series, successful correction was achieved in 16 of a total of 19 cases.[27] The post-natal follow-up of the 13 surviving fetuses showed the same fetal benefit found in the MOMS study, but without the serious maternal morbidities reported in that study.[27]

In Brazil, Pedreira et al. performed four fetal endoscopic surgeries to date, to correct the defect in human Fetuses,[28] using the technique illustrated in figure 3. There were no perinatal deaths and, in two of

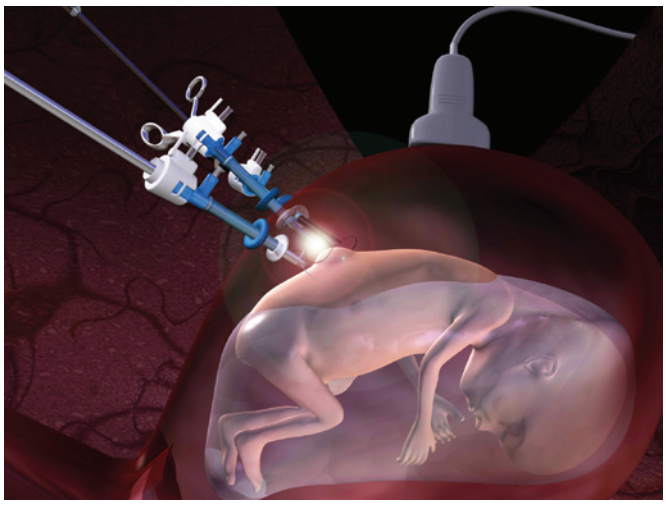


Figure 3. Illustration of the endoscopic technique for myelomeningocele repair, developed by Pedreira et al.[28]

the successful cases, the skin was completely closed and no additional correction was required after delivery. In addition, these two cases had not required VPS by the time this study was completed. This shows that this new technique can achieve definitive correction in one single surgical step, without the need for two-stage surgery.[9]

The Brazilian approach differs from the German for its simpler technical application, which uses only one single continuous suture layer and cellulose to facilitate repair by the fetus itself. Besides being cheaper, this technique also has the potential for greater neuronal preservation at the spinal cord level, and may potentially reduce the occurrence of cord tethering due to the presence of cellulose between the cord and the and the scar tissue. This experience, although initial, can lead to a paradigm shift in intrauterine correction of this defect in the coming years.

CONCLUSION

There is strong evidence that prenatal myelomeningocele correction improves neurological and psychomotor prognosis after birth, reducing the need for ventriculoperitoneal shunting, as well as the severity and incidence of cerebellar herniation, and doubling the chance of ambulation in fetuses subjected to intrauterine surgery.

Historically, endoscopy was the first approach to be used for prenatal repair of this defect. However, after the initial failure of endoscopic corrections at the turn of the 21st century, open surgery became widely used. However, the high maternal morbidity associated with this approach has been encouraging the ressurgence of the minimally invasive approach. Animal studies have led to the development of alternative techniques and the testing of new interfaces for minimally invasive repair. These new fetoscopic repair techniques are currently at different stages of clinical application. The first technique, developed in 2009 in Germany, resulted in the same neonatal benefits found in the MOMS study, associated with lower maternal morbidity. The initial results obtained in the Brazilian study seem promising. A larger number of cases over time as well as longer-term follow-up should demonstrate the validity and benefits of this new technique.

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