Chapter

Open Fetal Surgery and Fetoscopic Repair in Spina Bifida and Myelomeningocele in Romania

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Abstract

Spina bifida and myelomeningocele, although frequent, present difficulties when it comes to diagnosis and clinical management. The recent developments in ultrasound and MRI technologies and software, allow for an easier and more precise diagnosis. As such, in the first part of our chapter we will present general information, such as etiology, pathophysiology and methods of diagnosis. Fetal surgery, open or fetoscopic, represents a cure in most cases of spina bifida and in other cases reduces the chances of major developmental issues in babies born with this affliction. In the second part of our chapter, we will present the surgical protocols for both procedures, the indications, and the statistics that we have acquired in the cases we have diagnosed and operated on in the Regina Maria Maternity Hospital, Bucharest, the only center in Romania where these procedures are available.

Keywords: Spina bifida, Myelomeningocele, Open fetal surgery, Fetoscopic surgery, Fetal prognosis

1. Introduction

Spinal cord defects appear because of failure in the closure of the neural folds. These defects usually appear during the third and fourth weeks of gestation. Neural tube defects (NTD) can affect the meninges, vertebrae, muscles, and the skin. ([1]—Langman's). Meningocele and myelomeningocele are the most frequently encountered spinal dysraphisms.

Closed spinal defects include spina bifida occulta, lipomyelomeingocele and a multitude of other conditions.

Open spinal dysraphisms are mostly compatible with survival but usually the quality of life of the patient will be affected, depending on the level of the aperture. Symptoms are comprised of inability to walk, incontinence, scoliosis, digestive disorders, and hydrocephalus. [1, 2]

2. Embryology

Spinal dysraphisms appear from a failure of either: gastrulation, primary neurulation, disjunction or secondary neurulation.

Gastrulation is the process where the bilaminar embryonic disc becomes trilaminar. When this process happens, the neuroenteric canal forms and creates a temporary connection between the dorsal and ventral surface of the trilamiar disc. It is thought that split cord malformations and neuroenteric cysts arise from the persistence of this canal.

Neurulation begins when the formation of the central nervous system by signaling the ectoderm to differentiate and form the neural plate. This plate folds inwards, it's edges connecting to one another, completing the process known as primary neurulation.

After the primary neurulation, the neural tube separates form the ectodermic tissue, this process is known as disjunction. During this process, the mesoderm moves between the ectoderm and the neural tube, creating the meninges, skull, vertebrae and the paraspinal muscles. If this process starts prematurely or it is incomplete, a lypomeningocele or a dermal sinus may form. [1]

The secondary neurulation is the formation of the spinal cord above the midsacrum.

Open spinal defects appear from the delay or cessation of the primary neurulation.

Defects during the second neurulation are believed to be the cause for closed spinal dysraphisms.

Signaling pathways and cellular functions are also included in the formation of neural tube defects; planar cell polarity signaling, sonic hedgehog signaling, retinoid signaling and many others are though to be factors.

Some genetic factors, as well as environment factors are also included as rick factors of developing spinal dysraphisms, such as: valproic acid, fungal products (fumonisin), carbamazepine, trimethoprim, and folate and vitamin B12 deficiency, inositol, and maternal diabetes mellitus (environmental factors), the genetic factors include C67TT and a1298C polymorphisms of the methylenetetrahydrofolate reductase, this results in a 1.8-fold increase in risk of NTDs. [2, 3]

3. Clinical diagnosis

All pregnancies are at risk for neural tube defects, as such all women of fertile age as well as all pregnant women are encouraged to take folic acid supplements. It is paramount to take a full maternal history, as women with a history of anticonvulsant medication, diabetes or obesity are at higher risk for neural tube defects.

Prenatal clinical diagnosis relies on maternal elevated alpha-fetoprotein levels and amniocentesis, usually performed after 15–16 weeks of gestation. Although an early amniocentesis can be performed between 10 and 14 weeks of gestation, the low quantity amniotic fluid at this gestational age forces the practitioner to withdraw a smaller quantity which may not provide enough cells for analysis.

In the case of neural tube defects, an elevated alpha-fetoprotein and acetylcholinesterase level in the amniotic fluid and maternal blood usually prompts further investigations, such as high-resolution fetal ultrasonography and MRI. [3, 4]

4. Imaging

4.1 Ultrasound

Identifying spinal anomalies during a routine ultrasound screening usually varies depending on the skill and expertise of the operator.

A very detailed protocol should be followed for a correct diagnosis, both axial and longitudinal views of the spine have to be obtained. It is important to know the precise timing of ossification for each segment of spine. At 16 weeks ossification is complete up to L5, by 19 weeks it reaches S1 and by 22 weeks the process is complete. The best plane for the visualization of everted pedicles is the transverse one, as for an overlying sac, both transverse and longitudinal planes should be used as well as a high frequency transducer that would show cord tethering or placode content (**Figures 1** and **2**).

Chiari II malformations are very often encountered in fetuses with neural tube defects so, it is paramount that the fetal brain is scanned initially. Findings such as a small cisterna magna along with a rounded cerebellum (banana sign), concaved frontal bones (lemon sign) and ventriculomegaly are suggestive for Chiari II malformation. The banana sign has a 99% sensitivity in the diagnostic, the lemon sign has a lower sensitivity rate and can be present in normal fetuses. [5]

4.2 MRI

The MRI has become an invaluable addition in the diagnosis and preoperative preparation of spinal dysraphisms. 1.5 Tesla magnets are usually used although a 3 Tesla magnet can be useful in maximizing image quality. Orthogonal planes can also be used, adjusted to the preceding image set if the fetal position changes (**Figure 3**).

In order to pinpoint the fetal position a localizer sequence has to be used to guide the initial imaging plane which is aligned with the fetal anatomy that has to be examined. Ultrafast sequencing can also be used to minimize image degradation by fetal movements (**Figure 3**).

Single shot fast spin echo or half-Fourier acquisition single-shot fast spin echo sequences at 2 to 4 mm slice thickness are used to provide most of the diagnostic information (**Figure 4**) [6].

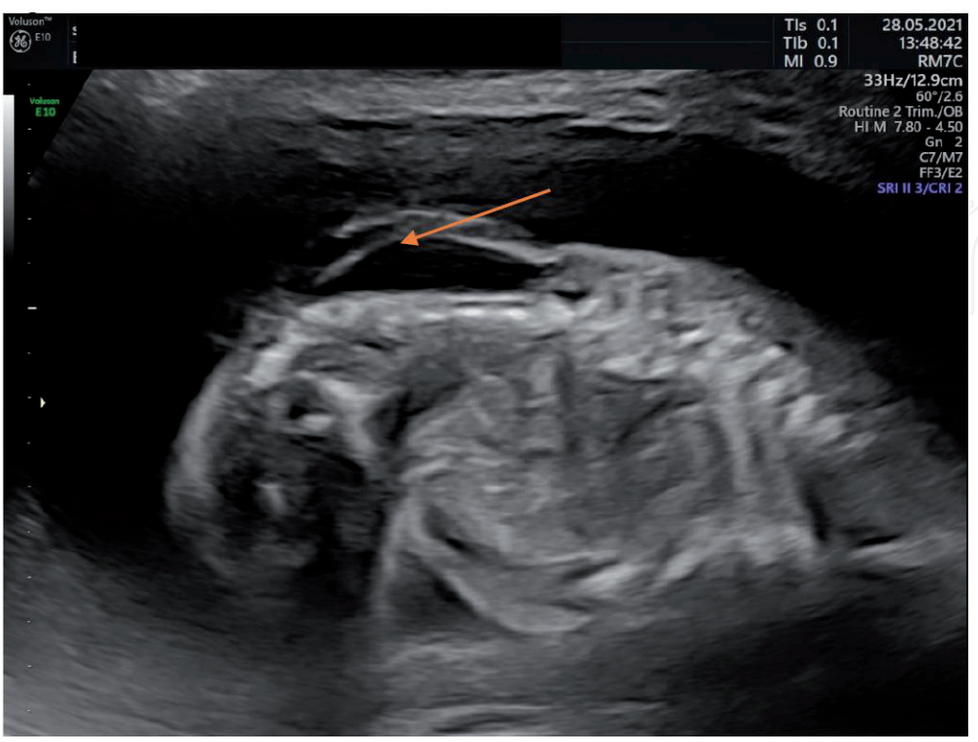

Figure 1.
Ultrasound depiction of a spinal dysraphism (arrow) during a routine 2nd trimester examination.

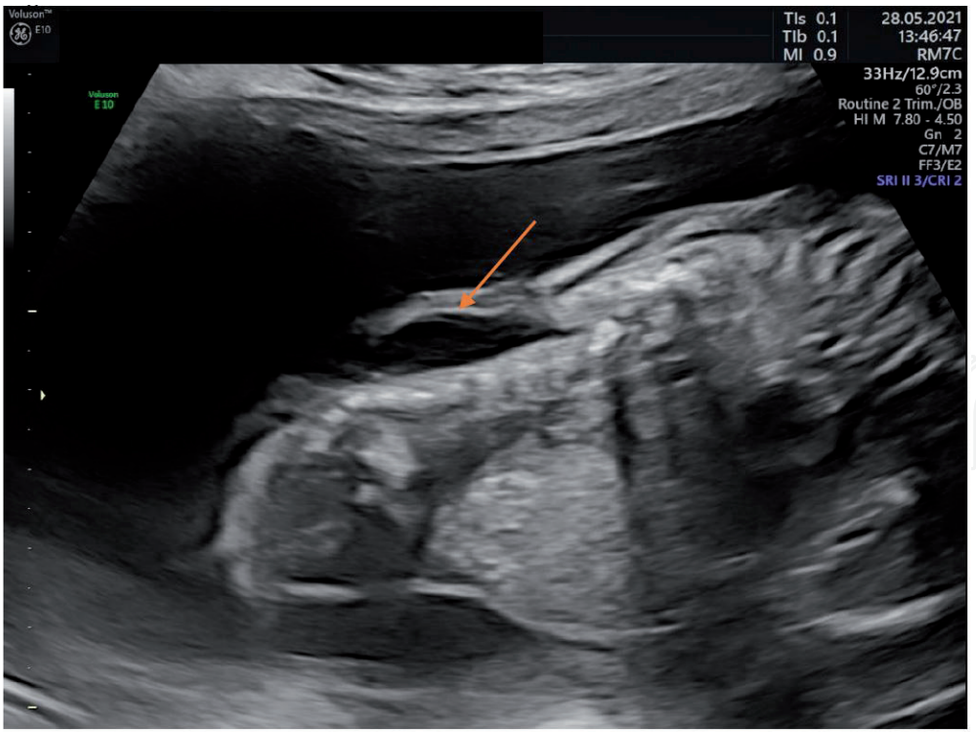

Figure 2.
Ultrasound picture (same case as **Figure 1***) in a different position where it is shown that there is no cord tethering (arrow).*

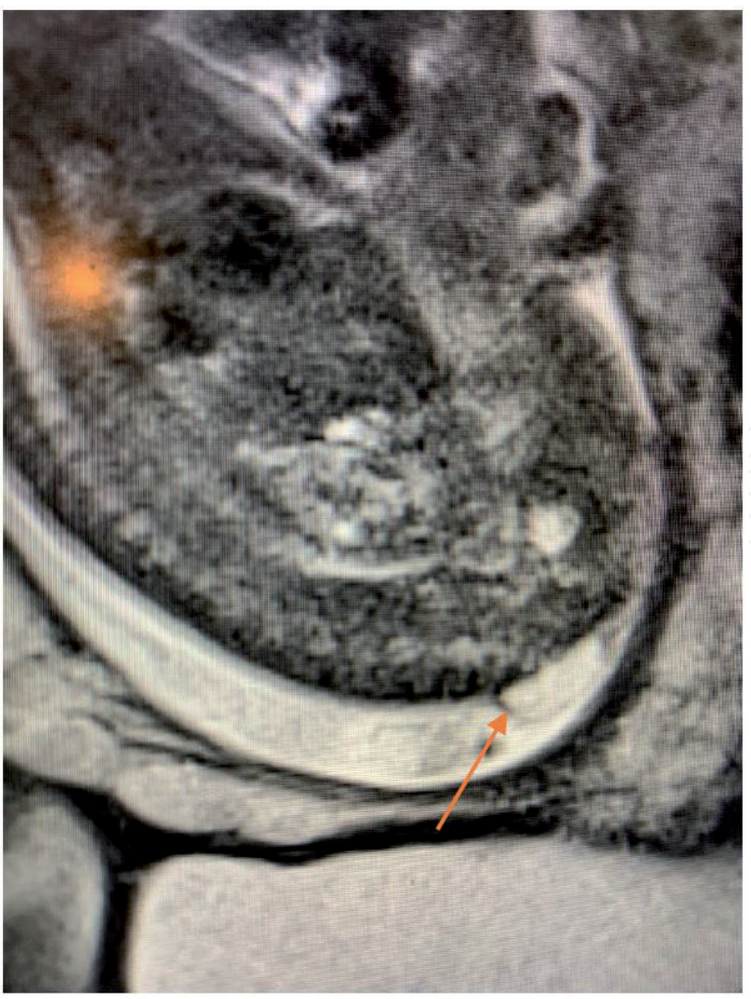

Figure 3.
MRI imaging of large, closed spina bifida defect (arrow).

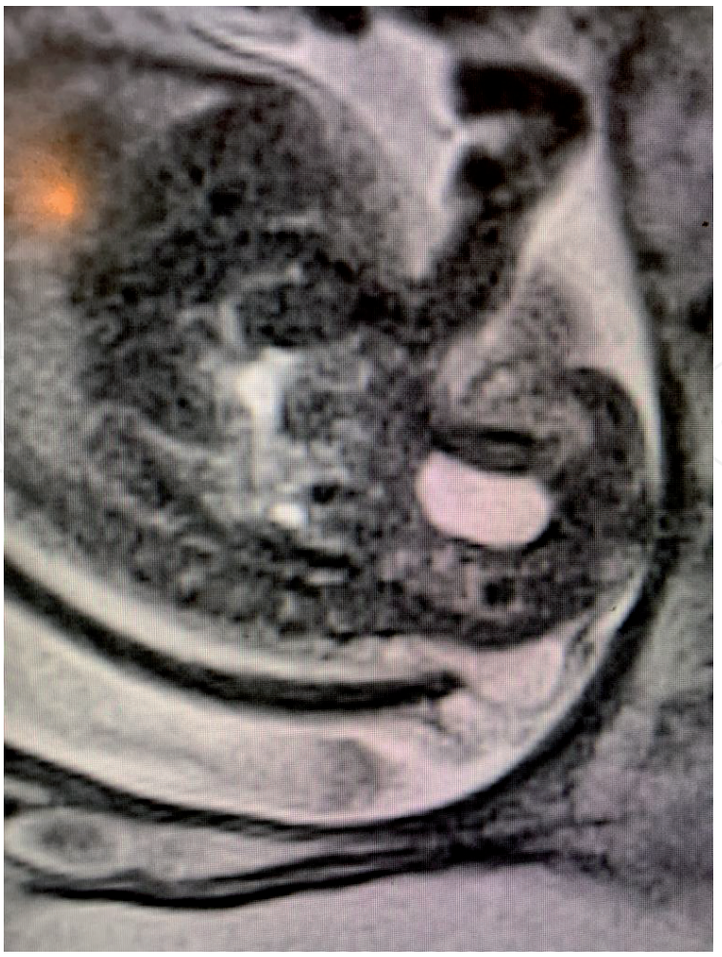

Figure 4.
MRI imaging showing closed neural tube defect (arrow).

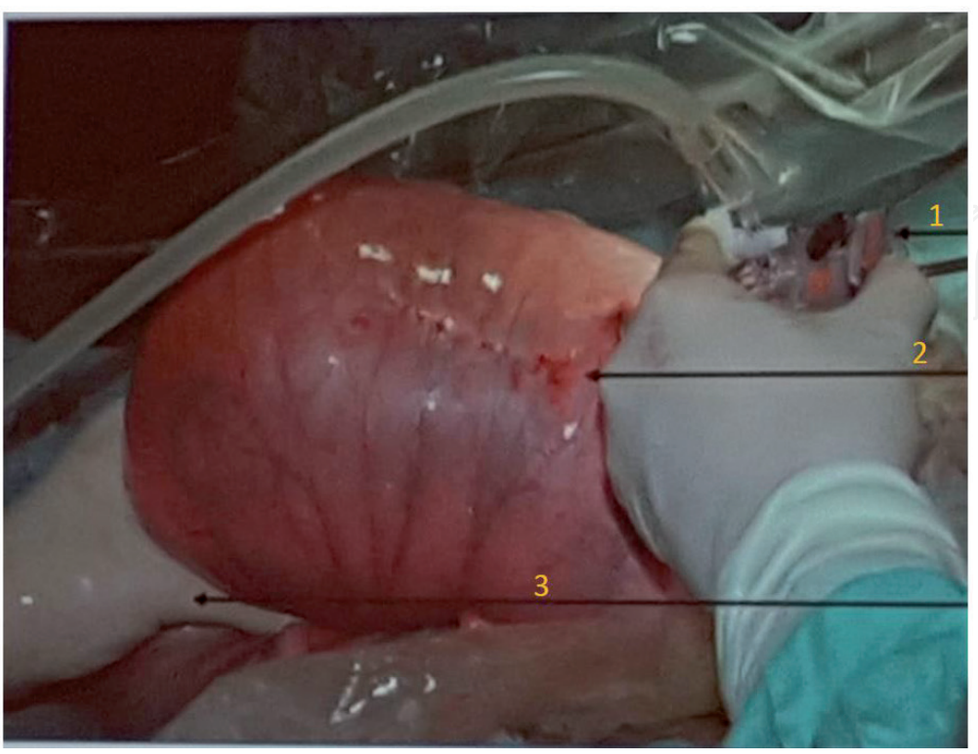

Figure 5.
1. Placement of fetoscopic trocars 2. Uterine wall 3. One hand is holding the fetus in order to create the pocket of gas in front of the operating field.

5. Treatment

5.1 Fetal surgery

5.1.1 History of spina bifida surgeries

The first time a spina bifida repair was performed was in 1994 using an endoscopic technique. In 1997 the first open(hysterotomy) in-utero spina bifida repair was performed at Vanderbilt University and at The Children's Hospital of Philadelphia.

The experience of these institutions suggested that babies treated in utero had a decreased incidence of hindbrain herniation and that after three weeks post-intervention, the hindbrain structures would ascent. Chiari II malformations were improved whereas other Chiari modifications were not (such as thinning of the corpus callosum), however it was shortly proven that the placement of fetal shunts is unnecessary in most cases.

The follow up also showed that after fetal surgery was performed the number of patients needing shut placement after birth has decreased significantly. Although most infants did not require shunting in the newborn period, some required it within the first year of life. A comparison between patients that underwent the fetal procedure prior to 26 weeks of gestation and those after 25 weeks of gestation showed that early fetal closure eliminates the leakage of spinal fluid and creates a back-pressure, reducing the herniation of the hindbrain.

Because of the selection and short follow-up processes in these cases, it was difficult to demonstrate the benefit to lower extremity function and sphincter continence, as well as cognitive function. However, findings showed an improved healing and scar formation, resulting in a more esthetic result. [7, 8]

5.1.2 Surgical technique

The decision to perform fetal surgery for spina bifida relies on the inclusion and exclusion criteria established in the world renown MOMS study (**Table 1**). To make a correct and informed decision, a high-resolution fetal ultrasonography, a fetal MRI scan as well as maternal and fetal serology are necessary in order to assess the extent of the defect. In any fetal operation maternal safety comes first, after which the next major goal is avoiding preterm labor. Spinal dysraphism repairs should be performed between 18 and 27 weeks of gestation, prior to this interval the fetal size would be too small and the tissues too fragile to accommodate the intervention and after 27 weeks of gestation there would be no shown benefit to the surgery compared to post-natal repair (**Table 1**).

This surgery requires a team that includes maternal-fetal specialists, neurosurgeons, pediatric surgeons, neonatologists, radiologists, anesthesiologists, and geneticists. The mother should always receive counseling and all the team members should explain their roles in detail before the procedure. [7]

Drug therapy to decrease the chances of preterm labor should be administered as follows: magnesium sulfate preoperatively and for the first 18–48 hours following surgery, indomethacin preoperatively and continued for 48 hours, oral nifedipine preoperatively and continued until delivery and terbutaline sulfate administered subcutaneously continuously by a pump if the other medication fails.

Anesthesia in neural dysraphism repairs is particularly complex as it affects both mother and fetus and it must take in consideration the uteroplacental factor. An epidural catheter is placed for postoperative analgesia before the rapid sequence

Inclusion Criteria:
Myelomeningocele at level T1-S1 with hindbrain herniation
Maternal age > 18 years
Gestational age between 18 and 25 weeks of gestation usually measured according to the first ultrasound and not patient's last menstrual period
Normal karyotype with written confirmation of culture results
Exclusion criteria:
Multifetal pregnancy
Abnormal foetal echocardiogram
Other related/unrelated foetal anomalies
Documented history of incompetent cervix
Cervix <20 mm measured by ultrasound
Preterm labour in current pregnancy
History of recurrent preterm labour
Maternal-foetal Rh isoimmunisation, Kell sensitisation, history of neonatal alloimmune thrombocytopenia
Maternal HIV or hepatitis B status positive or unknown
Uterine anomalies
Maternal medical conditions that are a contraindication to surgery or anesthesia
Maternal obesity
Placenta praevia
Fetal kyphosis >30°

Table 1.
Inclusion and exclusion criteria according to MOMS (Management of Myelomeningocele study) [7].

induction and the intubation are performed. Desflurane is usually used for maintaining the anesthesia, but nitrous oxide can also be a choice. Tice the amount of alveolar concentration is usually used to achieve uterine relaxation. In order to keep the arterial blood pressure close to the pre-induction base-line, ephedrine or phenylephrine is used. Vecuronium is administered for neuromuscular blockade.

The fetus also must be anesthetized before incision, usually with a narcotic and a muscle blocker delivered intramuscularly. [9]

There are three possible methods of performing spina bifida fetal interventions: open surgery, fetoscopy procedure and endoscopically (abandoned as it presented a high risk of membrane rupture and was proved unsatisfactory compared to the other two methods).

For open surgery, the uterus is exposed though a low transverse abdominal incision, using ultrasonography the fetal and placental positions are determined and the uterus is placed to have proper exposure. Hemostatic sutures are applied where the future incision will be, then with a monopolar cautery the hysterotomy is performed between these sutures. The incision is enlarged using a stapler that simultaneously cuts the uterine wall as well as applies hemostatic absorbable clips that will hold the amniotic membranes (**Figures 6** and **7**). Because the incision is in the upper portion of the uterine segment, it is important to relate to the mother that this and any future pregnancies will have to be delivered by C-section.

Maintaining uterine volume is paramount as it prevents placental separation, contractions, and fetal expulsion. For this reason, warm Ringer lactate solution is continuously pumped into the uterine cavity and the fetus is not completely

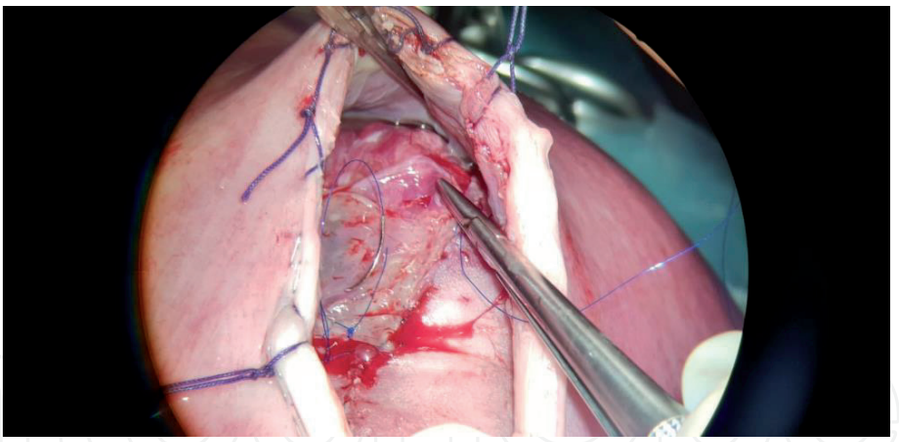

Figure 6.
Microscopic view of open spina bifida surgery. The amniotic membranes are sutured to the uterine wall. The defect is visible (arow) and our neurosurgeon started the repair.

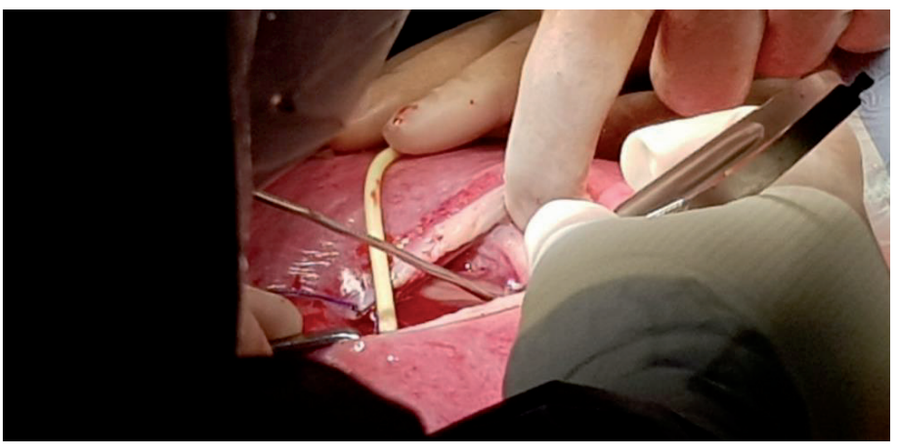

Figure 7.
Open spina bifida surgery. The Folley catheter is used to insert warm saline solution in the uterine cavity to replenish the lost amniotic fluid.

removed from the cavity, only being moved as much as needed to get optimal access to the operating area (**Figure 8**).

The myelomeningocele is closed rapidly and with as little blood loss as possible, the technique being similar to the standard post-natal variant. The full-thickness skin is incised circumferentially with a 15-blade knife until it reaches the fascia,

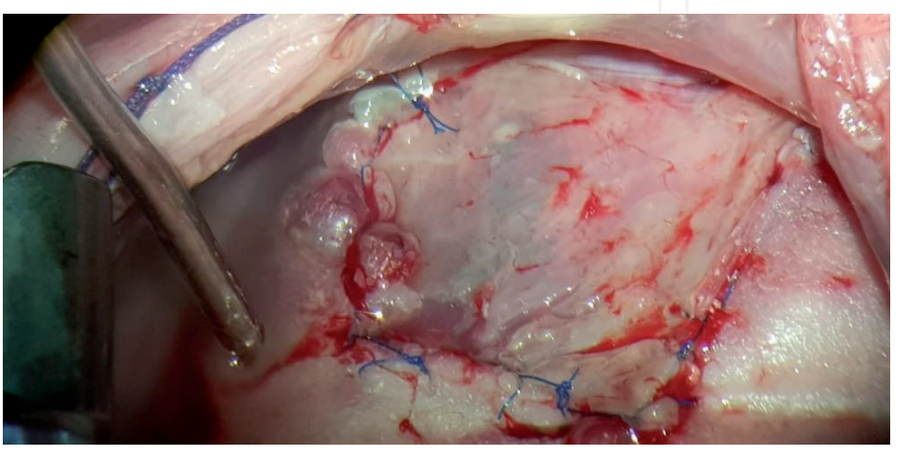

Figure 8.
Open spina bifida surgery. Final aspect of the repaired site (arrow).

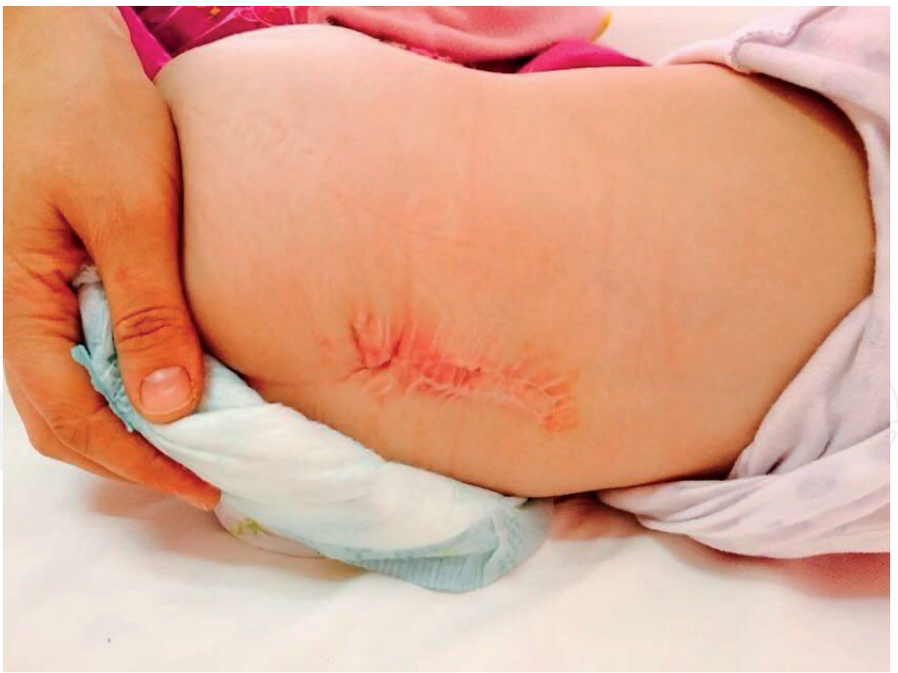

Figure 9.
Open spina bifida surgery. 1 month post-natal aspect of the surgery site.

the sac is mobilized to the facial defect, it is excised from the placode, removing all epithelial tissue in order to prevent future epidermoid inclusion cyst formation. The re-neurulation of the placode is not attempted as at this gestational age the tissues are extremely friable. It is preferred that the closure be done with dura and undermined fascia but either dura or fascia alone can lead to a successful result (**Figure 9**). The skin is closed with a 4–0 absorbable PDA suture, if the defect is too large acellular human graft material can be used.

The uterus is closed with a tight two-layer closure and transparent dressing must be used in order to perform future ultrasonographic examinations. [7]

The fetoscopic procedure begins as well with a transverse abdominal incision but this time the uterus is taken out of the abdominal cavity. Two or three ports are inserted in the uterine cavity through small incisions, under ultrasonographic guidance (**Figure 5**). A small quantity of amniotic fluid is taken out and replaced with CO2 to have a better visualization. It is very important that before the repair is commenced that a narcotic injection is administered to the fetus in order to have analgesia. The myelomeningocele sac is reduced by the neurosurgeon and the defect is then sutured. In the case of fetoscopic surgery, grafting is not possible as the trocar size does not permit it's passing so the extent of the defect must be meticulously asserted before the procedure (**Figure 10**).

Recent studies have shown that the fetoscopic procedure leads to equal success rates and better post-operative results when it comes to scarring compared to the open surgery. Also, future pregnancies can be delivered vaginally as the uterine scarring is minimal. Fetal short term neurosurgical results are similar to the open fetal surgery, 70% hindbrain herniation ascent and 45% of the patients did not need future treatment for hydrocephaly. The fetoscopic approach minimizes the risk of membrane ruptures and preterm delivery.

5.2 Statistics in our materno-fetal surgical center

In our materno-fetal center Regina Maria Maternity Hospital Baneasa we had a total of 37 patients whose fetuses were diagnosed with spina bifida between 2011

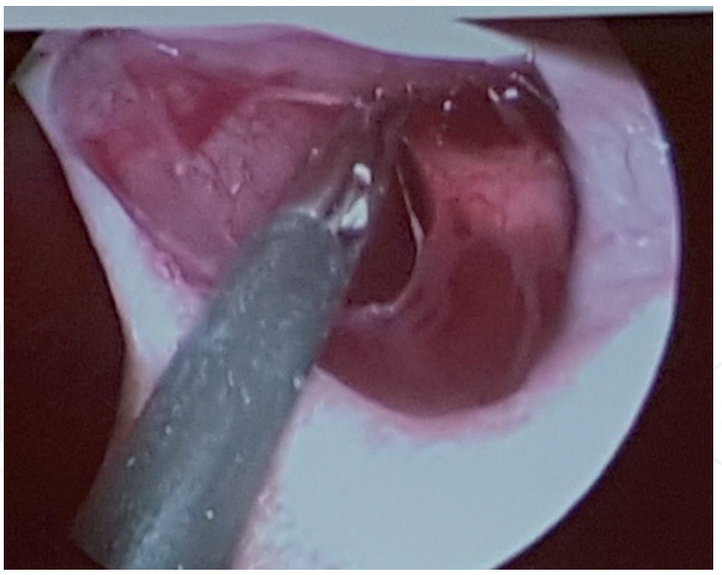

Figure 10.
Fetoscopic view of myelomeningocele defect before repair.

and 2021. Out of these 8 did not have the necessary inclusion criteria and 4 refused the intervention.

At the beginnings we started performing exclusively open surgeries. In total we have performed 18 open surgeries for spina bifida defects, out of these 6 gave birth before 30 weeks of gestation, 5 after 30 weeks of gestation and 7 after 34 weeks of gestation.

As the technology evolved and we have become more proficient in solving these cases, we have decided to perform fetoscopic interventions for spina bifida aswell. As such, from 2011 until 2021 we have performed 8 fetoscopic surgeries. In these cases, 1 patient gave birth before 30 weeks of gestation, 2 after 30 weeks of gestation and 5 after 35 weeks of gestation.

We did not have to perform any emergency hysterectomies during or after the spina bifida defect intervention, but we did have 2 cases that had membrane decollation. The decollation was minor (under 1 cm) in both cases so no treatment was needed.

At the one-year follow-up, we have observed that 6 of the babies had motor function impairment and 3 presented with urinary incontinence. Only 6 out of the 26 patients needed surgery for ventriculomegaly performed after birth.

According to our statistics we had a better outcome using the fetoscopic surgical method for spina bifida as the cases of birth under 30 weeks of gestation were significantly lower compared to open surgery. The results for after 30 weeks of gestation and after 34 weeks of gestation are comparable between the open and the fetosopic spina bifida repairment methods (**Table 2**).

Compared to the 2019 Zurich Center for Fetal Diagnosis and Therapy and the MOMS trial, our center delivers comparable results as seen in **Tables 3** and **4**. Even

	Open fetal surgery	Fetoscopic surgery	Total number of cases
No. of cases	18	8	26
<30 weeks of gestation	33.33%	12.50%	26.92%
>30 weeks of gestation	27.77%	25%	26.92%
>34 weeks of gestation	46.15%	46.15%	46.15%

Table 2.
Percentages of births according to weeks of gestation and surgical method.

	MOMS	Zurich	Regina Maria Maternity Hospital Bucharest
Components of the primary outcome, n (%)			
Death before shunt placement	2 (3)	1 (5)	0 (0)
Shunt criteria met	51 (65)	11 (55)	15 (60)
Shunt placed without meeting criteria	0	0	0
Degree of hindbrain herniation			
None	25/70 (36)	17/18 (94)	7/26 (26)
Mild	28/70 (40)	1/18 (6)	10/26 (40)
Moderate	13/70 (36)	0/18 (0)	9/26 (34)
Severe	0 (0)	0 (0)	0 (0)

Table 3.
Infant outcome at 12 months (table modified from Zurich Center data).

	MOMS (n = 78)	Zurich (n = 20)	Regina Maria Maternity Bucharest (n = 26)
Maternal outcome			
Chorioamniotic membrane separation, n (%)	20 (26)	5 (25)	2 (7)
Pulmonary edema, n (%)	5 (6)	0 (0)	0 (0)
Oligohydramnios, n (%)	16 (21)	4 (20)	0 (0)
Placental abruption, n (%)	5 (6)	0 (0)	0 (0)
Gestational diabetes, n (%)	4 (5)	3 (15)	0 (0)
Chorioamniotitis, n (%)	2 (3)	0 (0)	0 (0)
Preeclampsia or gestational hypertension, n (%)	3 (4)	0 (0)	0 (0)
Spontaneous labour, n (%)	30 (38)	13 (65)	0 (0)
Blood transfusion at delivery, n (%)	7 (9)	0 (0)	0 (0)
Status of hysterotomy site at delivery, n/total n (%)			
Intact, well-healed	46/76 (64)	8/20 (40)	20/26 (77)
Very thin	19/76 (25)	10/20 (50)	5/26 (20)
Area of dehiscence	7/76 (9)	2/20 (10)	0/26 (0)
Complete dehiscence	1/76 (1)	0/20 (0)	1/26 (3)
Fetal or neonatal outcome			
Bradycardia during fetal repair, n (%)	8 (10)	1 (5)	4 (15)
Perinatal death, n (%)	2 (3)	1 (5)	0 (0)
Apnea, n/total n (%)	28/77 (36)	1/20 (5)	5/26 (20)

	MOMS (n = 78)	Zurich (n = 20)	Regina Maria Maternity Bucharest (n = 26)
Pneumothorax, n/total n (%)	1/77 (1)	1/20 (5)	0/26 (0)
Respiratory distress syndrome, n/total n (%)	16/77 (21)	7/20 (35)	5/26 (20)
Patent ductus arteriosus, n/total n (%)	3/77 (4)	0/20 (0)	0 (0)
Sepsis, n/total n (%)	4/77 (5)	1/19 (5)	0 (0)
Necrotizing enterocolitis, n/total n (%)	1/77 (1)	0/19 (0)	0 (0)
Periventricular leukomalacia, n/total n (%)	4/77 (5)	0/20 (0)	1/26 (1)
Foot deformity, n/total n (%)	39/78 (50)	5/20 (25)	10/26 (40)

Table 4.
Maternal outcome and fetal or neonatal outcome (table modified from Zurich data Center).

though the number of patients is not an exact match to the MOMS trial, it is comparable to the Zurich study (**Table 3**) [10].

Our values show a diminished rate of maternal complications compared to the MOMS trial, the only prenatal complication encountered was chorioamniotic membrane separation. The hysterotomy site at delivery was intact in 77% of the cases, 20% very thin, 0% had an area of dehiscence and 3% complete dehiscence. Compared to the Zurich study, we showed a higher rate of well-healed hysterotomy site (77% vs. 40%) but a higher rate of complete dehiscence (3% vs. 0%) (**Table 4**).

Our fetal and neonatal outcomes show that compared to the Zurich trial the percentage of apnea and foot deformity is much higher, however when compared to the MOMS trial we show a much lower rate for these complications.

6. Conclusions

Spina bifida is a spinal dysraphism that has a higher incidence compared to other fetal malformations. Fetal surgery for this defect can restore some if not all the sequelae from hindbrain herniation to incontinence giving back the quality of life to the fetus, thus performing the intervention when the criteria are met is necessary especially since the statistic results are positive.

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