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Case Report

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Repair of spina bifida aperta with percutaneous minimal invasive fetoscopic method: First two cases in Turkey

İbrahim Alataş[1], Hüseyin Canaz[1], Kerem Özel[2], Ali Gedikbaşı[3], Thomas Kohl[4]

[1]*Department of Neurosurgery, Spina Bifida Research and Application Institute, Istanbul Bilim University, Istanbul, Turkey*
[2]*Department of Pediatric Surgery, Spina Bifida Research and Application Institute, Istanbul Bilim University, Istanbul, Turkey*
[3]*Maternal, Fetal Medicine and Perinatology Unit, Gynecology and Obstetrics Clinic, Ministry of Health Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey*
[4]*German Fetal Surgery Center, Giessen University, Giessen, Germany*

Abstract

Objective: To present with various experimental and clinical studies that the prenatal repair of spina bifida aperta by performing open fetal surgery provides better neurological results than postnatal repair. By starting to report clinical series after experimental studies on the repair of spina bifida aperta by endoscopic fetal surgery gives hope for the decrease of maternal complications.

Case: We aimed to discuss, in the light of literature, the early period neurological results of fetuses and our experience on two cases who were diagnosed at 21 weeks of gestation and undergone the repair of intrauterine spina bifida aperta by endoscopic method at 26 weeks of gestation.

Conclusion: We believe that maintaining experimental studies and sharing clinical experience on fetal surgery, which began to be an option in standard treatment algorithms for selected cases in the USA and Europe in the last decade, are of vital importance in terms of obtaining lower complication rates and better results.

Keywords: Fetal surgery, fetoscopy, spina bifida aperta.

Özet: Perkütan minimal invaziv fetoskopik yöntem ile spina bifida aperta onarımı: Türkiye'nin ilk iki olgusu

Amaç: Spina bifida apertanın, açık fetal cerrahi uygulanarak prenatal tamirinin, postnatal tamire göre daha iyi nörolojik sonuçlar sağladığı çeşitli deneysel ve klinik çalışmalarla gösterilmiştir. Endoskopik fetal cerrahi ile spina bifida aperta tamirine ait deneysel çalışmaların ardından klinik serilerin bildirilmeye başlanması, maternal komplikasyonların azaltılması yönünde umut vermektedir.

Olgu: Amacımız 21. gestasyon haftasında tanı alan ve 26. gestasyon haftasında endoskopik yöntem ile intrauterin spina bifida aperta onarımı uygulanan iki olguya ait tecrübemizin ve fetüslerin erken dönem nörolojik sonuçlarının literatür eşliğinde tartışılmasıdır.

Sonuç: Amerika ve Avrupa'da son on yılda, seçilmiş olgular için standart tedavi algoritmalarında yerini alan fetal cerrahi konusunda klinik tecrübelerin paylaşılması ve deneysel çalışmaların devam etmesinin daha düşük komplikasyon oranları ile daha iyi sonuçlar alınması noktasında büyük önem taşıdığına inanmaktayız.

Anahtar sözcükler: Fetal cerrahi, fetoskopi, spina bifida aperta.

Introduction

First intrauterine surgery in human was performed in 1981 by Michael R. Harrison in San Francisco, United States of America. In this procedure, open vesicostomy was applied to a fetus with posterior urethral valves.[1] Although a great advancement has been seen in fetal surgery in the last three decades, there are a limited number of indications requiring prenatal surgical procedure. Among classical indications, there are open spina bifida, congenital pulmonary airway malformations, sacrococcygeal teratoma, and congenital diaphragmatic hernia.[2]

Correspondence: Hüseyin Canaz. İstanbul Bilim Üniversitesi Spina Bifida Araştırma ve Uyg. Enstitüsü, Nöroşirurji Anabilim Dalı, İstanbul, Turkey. e-mail: drcanaz@gmail.com
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Spina bifida is the most common congenital anomaly after cardiac diseases, and it is a general term for neural tube defects which has a wide range and affects spine and spinal cord. Spina bifida aperta (SBA) is the most common form of open neural tube defects which causes spinal cord exposing external environment. Today, up to 95% of neural tube defects can be diagnosed before 20 weeks of gestation by ultrasonography alone or when it is used in combination with maternal serum alpha fetoprotein.[3] Its mean incidence is 1–2/1000 births in the world.[4] Terminations which are estimated to be about 25–50% are not included in this incidence rate.[5] Families who decide to maintain pregnancy should prepare themselves for a child who will need advanced care and require great medical expenses. Despite the aggressive treatment, about 14% of newborns with spina bifida cannot reach five years old.[5] When brain stem dysfunction symptoms associated with Chiari malformation accompany to the event, mortality increases up to 35%. Although IQ score of 70% of the patients is over 80, hardly half of them can live independently as an adult even under the best circumstances. While there is no newer data in Turkey, it was reported in 1994 that the annual cost for the care of children with spina bifida was $500 million in the USA.[6]

It was shown with various experimental and clinical studies that the prenatal repair of SBA by performing open fetal surgery provides better neurological results than postnatal repair.[4,7] On the other hand, the maternal complications of open fetal surgery requiring laparotomy and hysterectomy and their impact on following pregnancies cause anxiety.[8] Endoscopic fetal surgery is used in the treatment of various congenital anomalies. Although the results of the first clinical study on myelomeningocele repair with endoscopic fetal surgery was disappointing, experimental studies continued on this matter.[9–11] These studies were followed by the successful clinical studies performed by Kohl first, and then Pedreira et al.[12–14] These clinical studies showed that there were significant regression in cerebellar herniation, decrease in shunt need and better neurological functions of lower extremity after endoscopic fetal surgery like after open fetal surgery. The purpose of this paper is to present in Turkey the preliminary study of our clinical experience on performing myelomeningocele repair with endoscopic method.

Case Report

These surgeries, which have never been performed in Turkey before, were initiated with the approval of the Ministry of Health upon the decision taken in the workshop held by ministry on August 12, 2014 (No. 23642684/010.99). The inclusion criteria were neural tube defects between the levels T1 and S1, being between 19+0 and 27+6 weeks of gestation, presence of cerebellar herniation, lack of additional major fetal anomaly not associated with spina bifida and the presence of normal karyotype (**Table 1**). Maternal assessment included consultations for cardiology and pulmonary diseases and the measurement of transvaginal cervical length as well as routine preoperative assessments and examinations. Fetal evaluation was performed via detailed ultrasonographic examination, fetal echocardiography and fetal MR imaging. Consultancy services were provided to the patients by perinatology specialist, neurosurgery specialist and pediatric surgery specialist. Informed consent forms were obtained from the patients. The mother was administered corticosteroid for the induction of fetal pulmonary maturation 24 hours before the operation.

Case 1

There was no folic acid use before pregnancy according to the obstetric history, which was G2P1, of 32-year-old

Table 1. Inclusion criteria and contraindications.

Inclusion criteria	Contraindications
Open neural tube defect between T1 and S1 levels	Anterior located placenta
Being between 19+0 and 27+6 weeks of gestation	Multiple pregnancy
Presence of cerebellar herniation	Presence of kyphosis above 30 degree
Lack of additional major fetal anomaly not associated with spina bifida	Cervical length being less than 2 cm
Presence of normal karyotype	Body mass index being higher than 35
Maternal age being older than 18	Maternal diabetes, presence of hypertension
	Placenta with lower location

patient. At the 21 week of gestation, L4-L5 level myelomeningocele diagnosis was established. Additionally, the measurements of banana sign, cerebellar herniation and lateral ventricle were found as 7–8 mm in the detailed ultrasonographic evaluation, and pes equinovarus deformity was observed in the left foot. Leg movements were confirmed in the ultrasonography. No pathology was found in the fetal echocardiography. Karyotype was normal in the amniocentesis. With fetal MR imaging carried out at the 22 weeks of gestation, SBA and cerebellar herniation were confirmed (**Fig. 1a**).

The patient was taken to the operation at 25+2 weeks of gestation. Before the operation, 1 mg single dose cefazolin (Sefazol®, Mustafa Nevzat, Istanbul, Turkey) and 3 mg single dose betamethazone (Celestone®, Schering Plough, Istanbul, Turkey) were administered before the operation for prophylaxis purpose. After sPO_2 (oxygen saturation), ECG, noninvasive blood pressure, BIS (bispectral index), $EtCO_2$ (end-tidal carbon dioxide pressure) and TOF (train of four) neuromuscular monitorization were performed to the patients in supine position, rapid series anesthesia induction was completed by administering tiyopental sodyum 5–6 mg/kg, fentanyl 1–2 mcg/kg and rocuronium bromide 0.6 mg/kg intravenously. The patients were implanted arterial catheterization for invasive blood pressure and central venous catheter for central venous pressure measurement through internal jugular vein. Urination was followed up by attaching 14 F Foley catheter. Hemodynamic measurements of patients were carried out by PICCO device using femoral artery catheterization. Anesthesia was maintained with the infusions of sevoflurane 1–1.5%, remifentanil 0.1–0.2 mcg/kg/min, cisatracurium 0.1 mg/kg/h. Three trocars (12Fr) were applied percutanously with the ultrasound guidance by using Seldinger technique. After amniotic fluid was emptied partially, uterine cavity was filled with CO_2 by using a technique defined by Kohl et al.[12] For imaging intrauterine region, 2.7 mm 30 degrees endoscope (Karl Storz, Tuttlingen, Germany) was used. Standard 3.0 mm laparoscopic tools were used in positioning fetus, neural tissue dissection and patch saturation. The lesion was dissected by using needle electrode and the neural tissue was released from surrounding tissues. Absorbable dura graft (Lyoplant-Braun, Aesculap, Tuttlingen, Germany) made of bovine collagen was

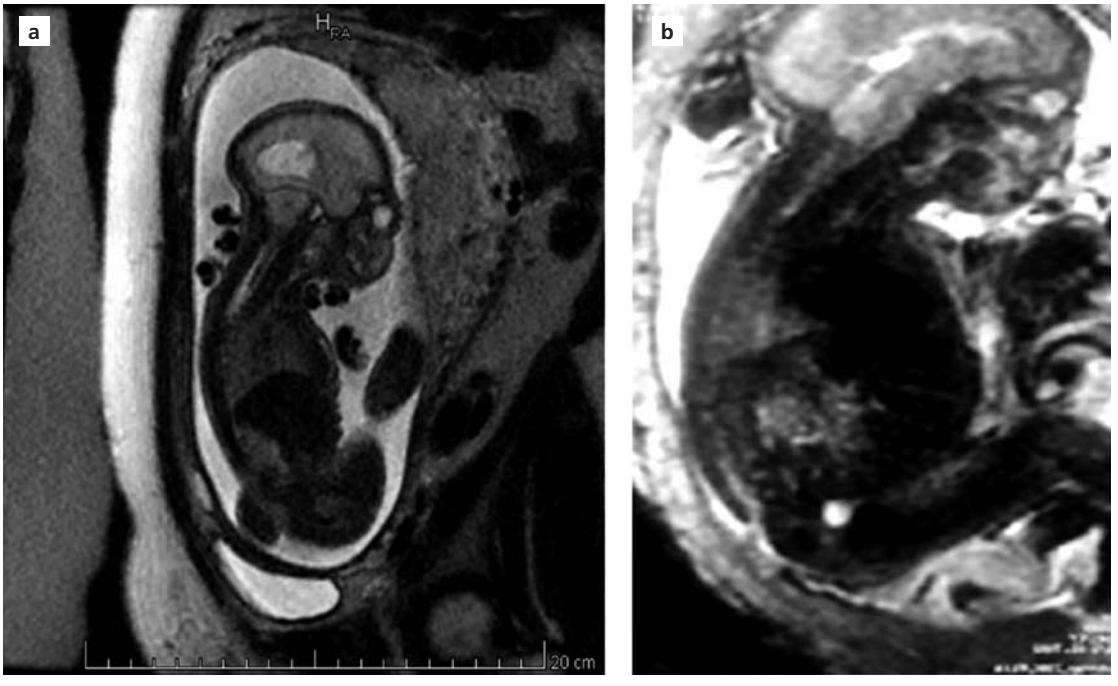

Fig. 1. In the fetal MR evaluation of Case 1 (**a**) and Case 2 (**b**) at 22 weeks of gestation, cerebellar herniation and L5-S1 level SBA lesion were evaluated at L5-S1 level.

used as patch. The patch was buried under dissected wound lips and the wound site was closed with nitinol sutures. After the lesion was closed, CO_2 in uterus cavity was emptied and in the meantime, cavity was filled with warm Ringer solution. After trocars were removed, trocar sites on abdominal wall were sutured with 4-0 prolene.

The patient was monitored in the intense care unit for postoperative 12 hours. During this period, no uterine contraction was observed in the patient. The patient taking nifedipine for tocolysis during postoperative period was discharged on 5th day under appropriate conditions. During the intrauterine postoperative period, it was seen that cerebellar herniation regressed partially and no enlargement was found in the ventricles during the following gestational period.

For tocolysis purpose, nifedipine (Nidilat® 10 mg or Adalat crono® 30 mg) was administered in the dose of 80–90 mg/day for the first 5 days and 60 mg/day as maintenance dose. As the second tocolytic agent, indomethacin (Endol® 100mg) was used as once before the operation and once postoperatively. Later on, the planning was done as required when contraction was detected in NST according to 34 weeks of gestation. However, it was only used on the day that contractions occurred.

Premature rupture of membrane (PROM) developed at 31+1 weeks of gestation. For pulmonary maturation, second dose steroid treatment was applied in accordance with the (antenatal corticosteroid therapy for fetal maturation) "rescue" dose definition of ACOG Committee Opinion No. 475. However, only the first dose could be applied since the deliveries were occurred. The contractions started at 4th hour during follow-up. Due to the contractions which could not be stopped despite the tocolysis, the pregnant woman was delivered via cesarean section on the same day. The weight of premature newborn was 1450, the height was 40 cm and head circumference was measured as 22.5 cm. 1-minute and 5-minute Apgar scores were 9 and 10, respectively. Together with the delivery, it was observed that the operation site on lumbar region was partially covered with the skin. Intubation and surfactant were not needed. Pes equinovarus deformity was observed in the left foot. No finding indicating intracranial pressure increase was seen during the hospitalization. Wound site care was done with hydrocolloid wound dressing. It was observed in the brain MR that cerebellar herniation regressed at postnatal third week (**Fig. 2a**). No complication associated with prematurity was observed in the patient who was monitored in the newborn intense care unit for 36 days.

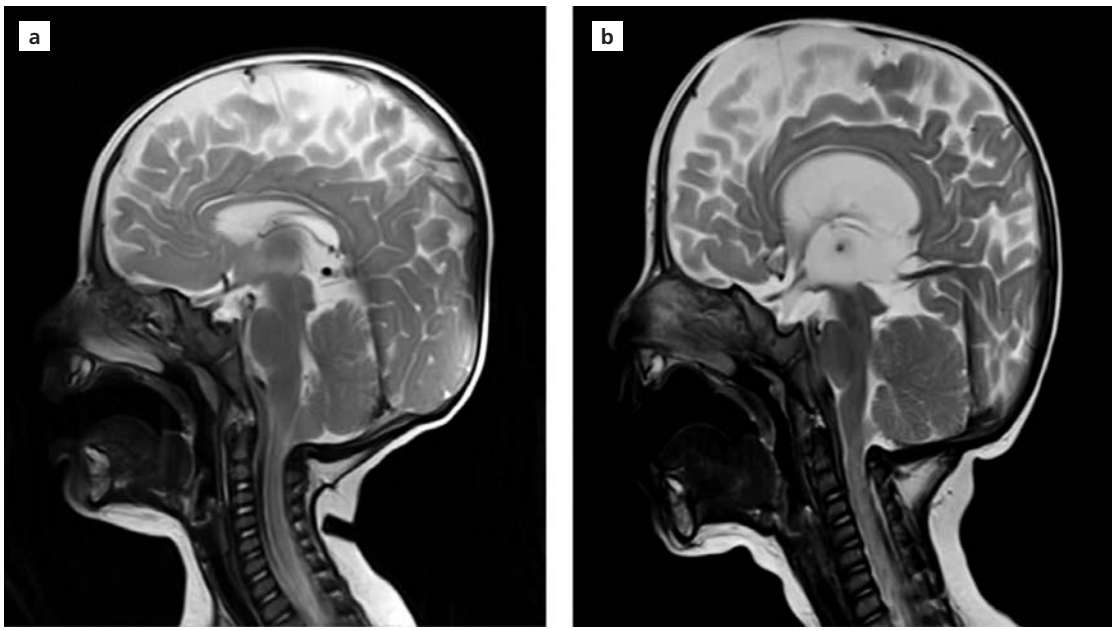

Fig. 2. Regression of cerebellar herniation is seen in the cranial MR imaging during postnatal 3rd week in Case 1 (**a**) and Case 2 (**b**).

Case 2

It was the first pregnancy of the 28-year-old pregnant woman, and there was no folic acid use in her history. Detailed banana sign and cerebellar herniation were detected in the pregnant woman who was established with L5-S1 level myelomeningocele diagnosis at 20 weeks of gestation. Leg movements were confirmed in the ultrasonography. No additional pathology was found in the fetal echocardiography. It was seen that lateral ventricle diameter of the pregnant woman, whose amniocentesis result was normal, expanded from 8 mm to 12 mm until 25 weeks of gestation during the follow-up. With fetal MR imaging carried out at the 22 weeks of gestation, SBA and cerebellar herniation were confirmed (**Fig. 1b**).

Fetoscopic surgical repair in the patient who underwent the operation at 25+4 weeks of gestation was carried out according to the technique defined above. The case was monitored in the intense care unit for postoperative 12 hours and no uterine activity was observed during this period. Nifedipine was used for tocolysis. The patient mobilized on the postoperative 1st day was discharged on the 4th day. Postnatal follow-ups showed no problem and it was seen that fetal ventricle diameters regressed to 9–10 mm and cerebellar herniation was also regressed.

The pregnant woman was hospitalized with the complaint of preterm labor at 31+3 weeks of gestation and intense tocolytic treatment was initiated by administering re-dose of steroid. However, since the case did not response to the agents at the end of 6-hour treatment, she was delivered by cesarean section. The weight of premature newborn was 1945 g, the height was 42 cm and head circumference was measured as 30cm. 1-minute, 5-minute and 10-minute Apgar scores were 5, 6 and 8, respectively. The patient was intubated when the newborn developed respiratory distress syndrome, and single dose of surfactant was administered. The premature responding to the treatment was extubated 36 hours later and followed-up. In the meantime, it was seen via the transcranial ultrasonography performed in the incubator at postnatal 6th hour that ventricle diameter was 9 cm. No finding of intracranial pressure increase was observed. First neurological examination of the newborn was free of problems, and it was seen that the operation site on lumbar area was almost completely covered by the skin.

In the cranial MR imaging performed on postnatal 3rd week, the findings for the regression of cerebellar herniation were confirmed postnatally (**Fig. 2b**). The newborn was discharges on postanatal 34th day upon the regression of prematurity-related problems and the recovery of wound site.

Discussion

Until the end of the last century, it was thought that SBA was developed as a result of neurulation defect occurring at the end of first month of gestation and Chiari II malformation, hydrocephaly, paraparesis or paraplegia, neuro-urologic and gastrointestinal problems, orthopedic, endocrine, mental and psychosocial problems developed primarily associated with this malformation. At SBA, histologic definitions of mechanical trauma signs, neural tissue degeneration and massive inflammation during postnatal period were done by Patten and Cameron 60 years ago.[15,16] Patten and Cameron stated that these changes in spinal cord were caused by the trauma occurring in neural tissue exposed to external environment during delivery. On the other hand, it was not said that this secondary effect occurring during late period of pregnancy may have a role in the etiology of neurological deficits. Additionally, nothing was asserted about the possibility that there may be a period where spinal cord functions are better and even close to normal despite the neurulation defect during the prenatal development of SBA.[2] After first fetal surgery was carried out by Harrison, an understanding was developed referring that congenital malformations may have a negative prenatal progress.

"Two hit hypothesis" was developed in the light of the evidences obtained from the experimental studies which were carried out to understand the prenatal natural progress of SBA since mid-1980s. Accordingly, while first strike is neurulation defect, second strike is the secondary destruction created in spinal cord by intrauterine environment. It was shown in the morphological studies performed on human fetuses that although all fetuses with SBA at the early weeks of gestation had neurulation defect, sensori-motor pathways were hystologically intact and progressive damage developed in neural tissue in the following weeks. Bouchard and Paek reported in their experimental studies that Chiari II malformation and hydrocephaly development were induced when cerebrospinal fluid leakage was created from lumbar SBA lesion, and they

provided a significant contribution to understand pathophysiology by showing the regression of cerebellar herniation and hydrocephaly when lesion was repaired during intrauterine period.[17,18]

Experimental studies for the intrauterine repair of SBA have begun in the first half of 80s.[4,7] Upon achieving positive results in animal models, the procedures of human intrauterine spina bifida repairs began in selected centers in the USA during the second half of 90s. In order to determine the benefits and risks of these initiatives, Management of Myelomeningocele Study (MOMS) was initiated in three selected centers in 2003. When the study, which was planned to include 200 patients, reached 187 patients in 2010, it was ended prematurely by the committee of information and safety follow-up. The reason to end the study was the fact that the results of fetal therapy group were found statistically significant prematurely and it was unethical to maintain the study.[4] Prenatal and postnatal surgery groups were compared in terms of primary results such as both fetus and newborn mortality rates, shunt need within first 12 months and motor and mental developments at 30th month as well as secondary results such as regression in cerebellar herniation, lower extremity motor functions and chance of walking freely. The results of fetal surgery group were found to be significantly better. On the other hand, premature rupture of membrane, oligohydramnios and preterm labor risks were significantly higher in prenatal surgery group.[4] When benefits to fetus and fetal and maternal risks were compared, MOMS study has made open fetal surgery a new standard treatment.[2]

Endoscopic myelomeningocele repair was first done by two separate independent groups in the USA. In 1998, Brunner et al. published their series including 4 cases.[9] In this study, pregnancy was continuing in two cases, but we reported that postnatal additional neurosurgical correction operation was necessary. In 2003, Farmer et al. reported in their series including 3 cases that single fetus survived and this case required postnatal additional neurosurgical correction.[19]

Kohl et al. published the results of 3 fetuses which underwent their operations via endoscopic method in 2006.[20] It was reported that all these three cases required postnatal neurosurgical correction. In these first cases, the defect was not dissected but only the lesion site was closed with patch, but the surgical technique was modified in the following cases and intrauterine dissection of pathological site was added to the protocol in order to eliminate/decrease the need for postnatal neurosurgical correction.[21]

Kohl et al. found similar results with MOMS study in terms of postnatal neurological findings of fetuses and possible maternal complications.[12] On the other hand, Verbeek et al. compared 13 cases which underwent postnatal neurosurgical repair with 13 cases repaired with fetoscopic method of Kohl group and reported that the neurological findings were better in the group which underwent fetoscopic SBA repair and the need for ventriculoperitoneal shunt requirement associated with hydrocephaly decreased significantly.[22]

These studies were followed by the series including 10 cases reported by Pedreira et al. from Brazil in 2015.[23] In this series reported, although endoscopic surgical technique was very similar to the technique reported by Kohl on basic lines of surgical technique, there are some small surgical technique differences during the repair of lesion. In the literature, there is no similar study published in Turkey.

We applied the technique defined by Kohl in 2 cases that we carried out endoscopic intrauterine repair. However, due to sociocultural reasons, we used bovine pericardium-made watertight dura graft instead of patch material obtained from swine pericardium and used in Germany.

Another difference than Kohl protocol is the tocolytic agents used and we referred to nifedipine and indomethacine instead of atosiban since it cannot be procured.

We observed that the fetal results of both cases were consistent with the fetal results. The regression of cerebellar herniation found by ultrasound and confirmed by fetal MR was shown with cranial MR at postnatal 3rd week. It was seen that both fetuses maintained leg movements. The patients followed up by neurosurgery team did not require ventriculo-peritoneal shunt associated with hydrocephaly at postnatal 6th month.

Premature rupture of membrane and preterm labor which were among the maternal complications reported in other series which underwent both open fetal surgery and fetoscopic procedure were also seen in our patients, and both fetuses were delivered at 31+ weeks of gestation via cesarean section. On the other hand, there were severe complications associated with prematurity in the infants.

Conclusion

There are strong evidences showing that intrauterine SBA repair decreases shunt requirement and cerebellar herniation incidence and increases the possibility to move independently two times, and as a result, neurological and psychomotor prognosis of patients improved. While endoscopic approach was used in the first intrauterine SBA repair tests, the complications encountered in these first cases lead to the wide use of open fetal surgery. On the other hand, high rate of maternal complications during and after open fetal surgery led to the continuation of animal studies to develop minimal invasive approach and to develop new techniques. While basic steps of fetoscopic repair techniques developed recently are similar, they have some differences. The technique we used in our cases was developed in Germany in 2009 and it was consistent with MOMS study when evaluated in terms of newborn prognosis. Promising results are coming from Brazil about the fetoscopic SBA repair. We believe that bigger population and longer follow-up periods would help fetal surgery techniques to develop and idealize.

Conflicts of Interest: No conflicts declared.

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