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Introduction

Open spina bifida (OSB) occurs is 0.5 to 1 per 1000 live births (Mathews, Honein et al. 2002). Antenatal correction of OSB via open fetal surgery has been shown to provide neonatal benefit relative to postnatal treatment (Adzick, Thom et al. 2011). However, the rate of maternal complications associated with the open fetal surgical approach, which requires maternal laparotomy and hysterotomy, is considerable. Furthermore, the legacy of open fetal surgery to subsequent pregnancies is also of major concern (Wilson, Lemerand et al. 2010). Endoscopic fetal surgery has become the acceptable form of treatment for many fetal conditions (Quintero 2002), and is associated with less maternal morbidity than open fetal surgery. As such, the fetoscopic approach has replaced the open fetal surgical technique for most fetal conditions that are amenable to in utero treatment. Therefore, a fetoscopic approach for the in utero treatment of OSB would be preferable, provided it can achieve at least the same clinical results as the open fetal surgery approach with less maternal morbidity.

Kohl et al. (Kohl, Hering et al. 2006, Kohl, Tchatcheva et al. 2009, Verbeek, Heep et al. 2012) have reported preliminary successful clinical data on an endoscopic approach for the in utero repair of OSB. Their initial experience involved partial CO2 insufflation of the amniotic cavity and the use of a patch to cover the medulla in three fetuses (Kohl, Tchatcheva et al. 2009). This technique was subsequently replaced by the dissection of the placode and closure of the defect in two-layers, in two other cases (Kohl, Tchatcheva et al. 2010). In their latest series of 19 patients, in 3 cases surgeries could not be completed (15%) and 3 fetal deaths occurred. However, no major maternal morbidity was reported and no neurosurgical repair was needed after birth, in the
remaining 13 cases. The postnatal results of these cases showed improvement in neurodevelopmental outcome, as well as reversal of the hindbrain herniation, comparable to the results of the MOMS trial (Verbeek, Heep et al. 2012).

Our teams have worked on an animal model of OSB to develop an endoscopic technique that could correct the condition avoiding the known limitations of open fetal surgery. We have worked to solve the technical issues characteristic of the minimally-invasive approach, simplifying the surgical technique to achieve a watertight closure, and taking advantage of the unique fetal healing characteristics (Pedreira, Valente et al. 2002, Pedreira, Valente et al. 2003, Oliveira, Valente et al. 2007, Pedreira, Oliveira et al. 2008, Abou-Jamra, Valente et al. 2009, Pedreira 2010, Pedreira, Quintero et al. 2011, Herrera, Leme et al. 2012). The purpose of this paper is to report our preliminary clinical experience with the fetoscopic correction of OSB using a cellulose patch and a single-layer closure technique.

Cases:

The research protocol was approved by the Brazilian National Ethics Committee (CONEP), and also by the Institutional Review Board of Samaritano Hospital, as a compassionate procedure in this initial series. Inclusion criteria were: open fetal spina bifida from T1 to S1, 19 ± 0 to 27 ± 6 weeks of gestation, presence of hindbrain herniation, no other major fetal anomalies detected by ultrasound, and normal karyotype. Maternal physical and laboratorial evaluation included an electrocardiogram (ECG), a cardiological evaluation, and transvaginal cervical length assessment. Fetal evaluation included a complete sonographic anatomical survey, fetal echocardiography,
and fetal MRI. In the absence of maternal or fetal exclusion criteria and after maternal counseling by an interdisciplinary team (fetal therapy specialist, pediatric neurosurgeon, neonatologist and obstetrician), patients were offered expectant management with postnatal repair, referral to another center for antenatal correction of OSB via open fetal surgery, or an attempt of antenatal endoscopic repair as per our protocol. All patients gave written informed consent. Antenatal corticosteroids for fetal lung/organ maturation were always given 72h prior to surgery.

**Case 1**: The patient was a 35-year old, primigravida with a family history of spina bifida. She had not taken preconceptional folic acid supplementation. A myelomeningocele from L5 to S4 with Chiari II malformation and bilateral talipes was diagnosed at 21 weeks’ gestation. A small ventricular septal defect was noted on fetal echocardiography. However, no other gross structural abnormalities were detected. The placenta was anterior. Amniocentesis revealed normal 46, XY karyotype and no chromosome 22q11.2 deletion. The patient was taken to the operating room at 25 weeks. Under general anesthesia using propofol remifentanil, sevoflurane and rocuronium, three vascular introducers (12Fr and 16Fr) were used as trocars and were placed percutaneously under ultrasound guidance, using a Seldinger technique. After partial amniotic fluid removal, CO2 insufflation of the uterine cavity, using the technique described by Kohl et al. (Kohl, Tchatcheva et al. 2010), a 2.7 mm 30 degree endoscope (Karl Storz, Tuttlingen, Germany) was used to observe the intrauterine environment. Standard 3.0 mm laparoscopic instruments were used for fetal positioning, and to circumferentially incise the transition between the skin and the arachnoid, releasing the neural placode. A cellulose patch (Bionext®, Bionext, Paraná – Brazil) was positioned
over the placode and no stiches were used to secure it to the adjacent tissues (Herrera, Leme et al. 2012). The skin was closed over the patch using a 2-0 monofilament single running stitch (Quill™ SRS, Angiotech, PA, USA) (Figure 1).

After aspirating the CO2, the amniotic fluid volume was replaced with warmed 0.90% w/v NaCl solution. Three ASD closure devices (Hellex® Gore, USA) were placed to close the membrane’s puncture sites. The deployment of the distal helix within the amniotic cavity was monitored using ultrasound guidance, while the placement of the proximal helix against the uterine serosa was confirmed under direct visualization via a 2.0 cm abdominal wall incision at the trocar entry sites.

Post-operatively, the patient did not require intensive care and had no uterine contractions. Atosiban® (Ferring – Sweden) (6,75mg IV bolus followed by 300 mcg/min for 3 hours and 100 mcg/min for 21 hours) was used prophylactically to avoid uterine activity for 24 hours. Normal ambulation was allowed from the first postoperative day onwards. Unfortunately, preterm premature rupture of membranes (PPROM) occurred immediately after surgery. Oral ampicillin was started and the patient was monitored closely for signs or symptoms of intraamniotic infection. Weekly ultrasounds were performed to monitor the fetal anatomy/well-being and the amniotic fluid volume. Three weeks after surgery, routine fetal MRI showed upward displacement of fetal cerebellum, and normal CSF in the posterior fossa (Figure 2A). At 32 weeks, the patient was delivered by cesarean section, for laboratorial suspicion of intraamniotic infection, steroids to improve fetal lung maturity where given. A 1500g male was born with Apgar’s of 9/10. The fetal skin was noted to be completely closed at the repair site (Figure 3A) and no further neurosurgical correction was necessary.
At delivery, the helix devices were visible from outside the uterus but 2 of them were partially dislodged. The three trocar holes in the membranes were visible and had increased in size to approximately 2.0 to 3.0 cm each.

The mother was discharged after uneventful recovery 4 days after delivery. The Baby was admitted to the NICU and also had an uneventful neonatal outcome. On the 9th day of life, postnatal MRI showed the cerebellum to be further above the foramen magnum and the medullar cone was observed inside the medullar canal, with the cellulose patch being visible separating the neural elements from the skin (Figure 2A). The baby was discharged after 34 days, and no prematurity related complications were noted. Neonatal echocardiogram showed the VSD defect had closed. At six months of age, there is no evidence of hydrocephalus and a ventriculoperitoneal (VP) shunt has not been required.

Case 2: The patient was a 33-year old primigravida with a positive family history of OSB. She had not used preconceptional folic acid supplementation. After obtaining written informed consent, the patient underwent fetoscopy at 27 weeks to correct a level L3-4 to S1 defect. The placenta was anterior and the same surgical technique described above was used, but trocar sizes were two of 11Fr and one of 14Fr. Due to technical difficulties, a two millimeter area of the fetal skin, at the rostral part of the defect, could not be completely approximated. No membrane closure devices were used in this case. Post-operatively, Atosiban® was also used prophylactically for 24 hours. The patient was discharged home on post-op day 4 and bed rest was not recommended. Weekly ultrasound showed normal amniotic fluid levels. The patient was admitted 6 weeks later
with PPROM. Antenatal corticosteroids for fetal lung maturity enhancement and antibiotics were initiated. A follow up fetal MRI showed upward displacement of the cerebellum, and normal fluid in the posterior fossa (Figure 2B). The patient went into labor 5 days later at 33 weeks, and a 1990g male newborn was delivered by c-section. A 2-cm skin dehiscence (the entire scar measured 5.0 cm) that contained neural elements was noted. The baby underwent immediate neurosurgical repair.

At delivery, the uterine puncture sites had healed and the three trocar holes in the fetal membranes were visible. These membrane defects also appeared to have increased in size, each measuring approximately 2.0 to 3.0 cm (very similar to the findings in case 1). The mother had an uneventful recovery. Routine neonatal brain scan showed scant amount of blood inside the ventricles, a finding deemed to be related to migration of blood from the neurosurgical repair site to the brain, since babies are kept in Trendelenburg position for 24 hours after surgery. Routine neonatal blood culture was positive for E. coli, but cerebral spinal fluid culture was negative, and this finding had no clinical significance. The baby was discharged on day 28 of life, without any prematurity related complications. VP shunting was required on day 53 of life due to increasing cephalic circumference (crossing centiles). The baby has had an otherwise uneventful course in the first 3 months of life.

**Case 3:** The patient was a 27-year-old, primigravida with a family history of spina bifida. She had not taken preconceptional folic acid supplementation. A myelomeningocele from L4 to S2 with hindbrain associated to bilateral talipes was diagnosed by US. The
placenta was anterior and the karyotype was normal 46, XY. After obtaining written informed consent, the patient was operated on the 25th week. The same technique described was used, but the neural placode could not be entirely incised, because of membrane detachment around the trocar's entry points. This was caused by the insufflated gas penetrating that space, and prevented any further repair. Thus, no patch was placed, and the skin was not closed.

Post-operatively, maternal intensive care was not needed and no uterine contractions occurred. Atosiban® was used prophylactically as previously described for 24h. The mother was discharged after 3 days and no bed rest was recommended. Weekly ultrasound showed normal amniotic fluid, and routine fetal MRI showed no upward displacement of fetal cerebellum. Preterm premature rupture of membranes (PPROM) occurred after 6 weeks and spontaneous labor started after 48h. The patient received antenatal corticosteroids, and was delivered by cesarean section at 31 weeks. A 1625g male was born and was immediately submitted to neurosurgical repair.

At delivery, two trocar holes in the membranes were visible and had increased in size, measuring approximately 3.0 cm each.

The mother had an uneventful recovery and was discharged 5 days after delivery. The baby was admitted to the NICU and had an uneventful neonatal outcome. VP shunt was placed on the 18th day of life due to increasing hydrocephalus and the baby was discharged after 28 days of birth. No prematurity related complications were noted. The baby is at present two months-old and doing well.
**Case 4:** The patient was a 31-year old primigravida with no familial history of OSB. She had not used preconceptional folic acid supplementation. After obtaining written informed consent, the patient underwent fetoscopy at 27 weeks to correct a level L3-S3 defect. The placenta was anterior and the same surgical technique described above was used. A 5mm balloon trocar was used, instead of the 14Fr, to help prevent membrane separation. No devices to close the membranes were used. Post-operatively, Atosiban® was also used prophylactically for 24 hours. The patient was discharged home on post-op day 3. Weekly ultrasound showed amnio-chorial detachment, but normal amniotic fluid levels and no bed rest was recommended. The patient was admitted 4 weeks later with PPROM. A second dose of corticosteroids for fetal lung maturity enhancement and antibiotics were initiated. A follow up fetal MRI showed the cerebellum to be above the foramen magnum, and normal fluid in the posterior fossa (Figure 2C). A cesarean section was performed at 33 weeks due to persistent elevation of the C-reactive protein and leukocytosis, and a 2380g male was delivered. A 1-cm skin gap was noted, but no neural elements were protruding, and one single stich was used to close it (Figure 3B). No neurosurgical repair was needed.

At delivery, two holes of 4.0 cm and one of 10.0 cm in membranes were present. The mother had an uneventful recovery. The baby was discharged on day 17 of life without any prematurity related complications. VP shunting has not been required.

**Discussion**

Our preliminary clinical experience suggests that definitive endoscopic repair of OSB may be performed using our simplified surgical approach. Although technical issues
remain, hindbrain herniation improved in the three cases in which the in utero surgery was successfully concluded, and only one of these babies has required ventriculoperitoneal shunt. Furthermore, in both cases (case 1 and 4) where the dissection of the neural placode was optimal and the skin closure was completed, a definitive defect repair was obtained and no attachment of the spinal cord to the skin was noted after birth.

Our minimally-invasive surgical approach for the correction of OSB stems from over a decade of animal research performed in our laboratory. (Pedreira, Valente et al. 2003, Oliveira, Valente et al. 2007, Pedreira, Oliveira et al. 2008, Abou-Jamra, Valente et al. 2009, Pedreira 2010). The animal work has addressed different challenges, including correction of hindbrain herniation, optimal preservation of the neural elements and avoidance of post-operative neural adhesion (Herrera, Leme et al. 2012). Our simplified technique uses a single-layer closure, and a biosynthetic cellulose patch that preserves the medulla and induces the formation of a neoduramater, without significant scarring (Oliveira, Valente et al. 2007). This is in contrast to the classical neurosurgical technique which, in our experiments, was associated with destruction of the normal medullar cytoarchitecture, and to meningoneural and skin adhesions. (Herrera, Leme et al. 2012)

Endoscopic attempts for the antenatal correction of OSB have been previously reported. In 1998, Bruner et al. reported the use of a maternal split-thickness skin graft placed over the exposed spinal cord or neural elements. The skin graft was attached to the fetal skin with fibrin glue prepared from autologous cryoprecipitate. The approach required performing a laparotomy to expose the uterus and the use CO2 exchange. A
total of 4 patients had been operated with this technique, only 2 fetuses had survived and both were submitted to postnatal neurosurgical repair (Bruner, Richards et al. 1999). In 2003, Farmer et al. described 3 cases where an endoscopic approach was attempted. In this series, the repair technique was shifted from a simple patch placement, to a two-layer, than a three-layer suture closure. The third case was converted to an open surgical procedure, and the endoscopic approach was abandoned after the survival of only one out of the three fetuses (Farmer, von Koch et al. 2003). In 2005, Kohl et al. (Kohl, Hering et al. 2006) reported 3 cases in which an endoscopic approach was used. Access to the fetus was percutaneous and included partial CO2 exchange. The defect was not dissected, it was only covered with a non-absorbable polytetrafluoroethylene patch, and neurosurgical repair was needed in all cases after birth. The surgical correction was subsequently changed to a definitive repair technique: the placode was dissected and a two-layer closure was used, including an absorbable patch (Durasis, COOK, Mönchengladbach, Germany) sutured onto the paraspinal muscle and a non-absorbable polytetrafluoroethylene patch (Gore MVP, Flagstaff, AR, USA) sutured to the adjacent skin (Kohl, Tchatcheva et al. 2009). In their latest series, 13 out of 19 cases were successfully repaired. In 3 cases the endoscopic procedure was abandoned due to placental hemorrhage, but all of these fetuses survived and underwent postnatal repair. In 3 other cases, the fetuses died due to placental hemorrhage, anesthetic and oligohydramnios complications. Our technique differs from that of Kohl et al. in that it involves a simple release of the placode from the skin, followed by placement of a cellulose patch over the placode, and the use of a continuous running suture to close the skin primarily. This technique allows the cellulose
patch to remain secured in place (over the placode) without the need for multiple interrupted stitches, but achieving a watertight skin closure. Using this technique in animals, we additionally found that the cellulose patch induced the formation of a new fibroblast layer over the medulla that was in anatomical continuity with the original dura mater (neo-dura mater) (Oliveira, Valente et al. 2007). The new dura mater formed may have an additional effect of protecting the medulla, preventing its adherence to the scar, and probably providing a secondary natural watertight dural closure.

Fetoscopic closure of OSB in this preliminary series was not possible in only one out of the four cases, despite the placenta was anterior in all of them. This was due to membrane detachment, while other series have reported placental abruption, bleeding from the port sites, and fetal bradycardia, as the reasons for unsuccessful completion of fetoscopic closure of OSB. Such complications have not occurred in our cases, and no fetal or neonatal deaths have occurred in this initial series.

The PPROM occurred in all our four cases, but pregnancies continued for at least 6 weeks and beyond after surgery (Table 1). Considering we are in the beginning of our learning curve, this interval maybe even further increased. In the MOMS trial, PPROM occurred in 46% of patients, and in 11 out of 13 cases in Kohl’s experience (Adzick, Thom et al. 2011, Verbeek, Heep et al. 2012). Despite PPROM shortly after surgery in case 1, the patient delivered 7 weeks later and optimal surgical results were achieved. Further research on membrane closure devices may minimize this risk in the upcoming future.

Aside from PPROM, there were no other maternal morbidities. No patient had uterine contractions immediately after surgery and uterine entry sites were healed at the time of
delivery. All patients were allowed to ambulate from the first postoperative days onwards and preterm labor occurred only after PPROM in two out of the four cases (Table 1). In the MOMs trial, even keeping modified bed rest after postoperative discharge, the complications reported included preterm labor (38%), abruption (6%), uterine scar thinning or dehiscence (36%), maternal transfusion (9%) and pulmonary edema (6%); all risks we hope our endoscopic approach should minimize.

We believe our technique will compare favorably to the technique currently in use (Kohl, Tchatcheva et al. 2009, Verbeek, Heep et al. 2012), because the single continuous running suture will be easier and faster to accomplish, and because definitive skin closure can be primarily achieved. The biosynthetic cellulose is a lower cost product than the patches currently used, but has the potential of using the fetal healing in its favor, by inducing a neoduramater formation.

Our preliminary experience suggests that our innovative endoscopic approach to fetal OBS definitive repair is feasible and scientifically sound. A Phase I trial has begun to assess the risks and benefits of the endoscopic repair of OSB using our fetoscopic approach and our new closure technique.
Acknowledgments

We wish to acknowledge Dr. Paulo H. Saldiva, Dr. Silvia Herrera, Dr. Marcus Vinícius Bittencourt and Dr. Patrícia de Oliveira for their significant contribution to the experimental research, clinical application and radiological analyses, respectively. We also would like to thank Dr. Thomas Kohl for his incentive and support during our initial clinical application.
References


Figure 1. Surgical steps in the fetoscopic treatment of meningomyelocele in human, using biosynthetic cellulose and a single-layer suture.

(A) Intact defect, lateral view: normal skin (S), transition zone (TZ) and meninges (M). Frontal view, in the detail.

(B) The cellulose (arrow) is protecting the dissected placode underneath.
(C) Beginning of the suture, the needle is including the transition zone of the skin. The cellulose (arrow) is entirely covering the placode.

(D) Final aspect of the completed running suture, note the suture (SU) itself is visible in one of the ends, and the skin is closed in the midline (arrow heads).
Figure 2. Fetal pre-operative and pos-operative MRI showing the upward cerebellar displacement, reappearance of the fluid around the brain and of the 4th ventricle after surgery in all cases (arrow heads).

(A) Case 1. Upper left, posterior fossa pre-surgery at 25 weeks. Upper right, pos-surgery at 29 weeks. Bottom left, near normal posterior fossa on the 11th day of life. Bottom right, spinal aspect at the repair site showing the cellulose (arrows) separating the skin from the neural elements.
(B) Case 2. Left, posterior fossa pre-surgery at 27 weeks. Right, pos-surgery at 33 weeks. Note the partial upward displacement of the cerebellum, the distance of the herniated cerebellum to the foramen magnum reduced from 9 to 5 mm.
(C) Case 4. Left, posterior fossa pre-surgery at 27 weeks. Right, pos-surgery at 32 weeks. Note the complete return of the cerebellum to above the foramen magnum.
Figure 3. (A) Immediately after birth, the skin is completely closed, in case 1. The suture (arrow heads) can be seen in both ends of the scar.

(B) Case 4 – immediate neonatal aspect of the repair site.

(C) Skin closure during sheep experiments. Note the resemblance of the closure aspect.
Table 1. Detailed description of the four cases submitted to endoscopic correction of spina bifida in the prenatal period.

<table>
<thead>
<tr>
<th>Case</th>
<th>MRI Level</th>
<th>GA surgery (weeks)</th>
<th>In utero successful closure</th>
<th>GA PROM</th>
<th>Reversal hindbrain herniation</th>
<th>GA delivery (weeks)</th>
<th>In Utero after surgery (weeks)</th>
<th>Indication delivery</th>
<th>Fetal weight (grams)</th>
<th>Defect at birth</th>
<th>NICU (days)</th>
<th>Neurosurgical repair</th>
<th>VP shunt</th>
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<tr>
<td>1</td>
<td>L5 - S4</td>
<td>25</td>
<td>yes</td>
<td>29</td>
<td>yes</td>
<td>32</td>
<td>7</td>
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<td>1500</td>
<td>closed</td>
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<tr>
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<td>L3/4 - S1</td>
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<td>yes</td>
<td>25</td>
<td>yes/partial</td>
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<td>6</td>
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<td>1990</td>
<td>3/5 closed</td>
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<td>yes</td>
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<tr>
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<td>L4 - S2</td>
<td>25</td>
<td>no</td>
<td>33</td>
<td>no*</td>
<td>31</td>
<td>6</td>
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<td>-</td>
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<tr>
<td>4</td>
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<td>yes</td>
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<td>yes</td>
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<td>PCR elevation</td>
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<td>17</td>
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</tbody>
</table>

MRI=magnetic resonance imaging. GA=gestational age, PROM=premature rupture of membranes, NICU=neonatal intensive care unit, PCR=protein C reactive, VP=ventriculoperitoneal

*after postnatal closure using the prenatal proposed technique + glue, there was reversal of hindbrain herniation