Editorial

Fetoscopic repair of spina bifida: safer and better?

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Introduction

Open spina bifida (OSB) is one of the most common birth defects, and often results in significant, lifelong motor and neurodevelopmental impairment. A recent randomized clinical trial, the Management of Myelomeningocele Study (MOMS), showed that prenatal compared with postnatal repair of OSB resulted in a reduced need for ventriculoperitoneal (VP) shunt placement and a decrease by one third in the rate of hindbrain herniation at 12 months of age, as well as doubling of the ability to ambulate without the assistance of orthotics and better level of motor function at 30 months. However, open in-utero repair was associated with higher rates of preterm birth, oligohydramnios, placental abruption, pulmonary edema and maternal transfusion at delivery, and a 35% risk of uterine thinning or dehiscence. Minimally invasive surgery with postnatal repair showed that, except for the incidence of tethered cord syndrome, prenatal correction of OSB is associated with improved neurological outcome. Early clinical reports also suggest that prenatal repair could result in reversal of the hindbrain herniation and improve Chiari-II malformation. These additional observations have generated great enthusiasm about the potential role of prenatal surgery in the treatment of OSB.

Rationale for prenatal treatment

Extensive animal work and observation of human fetuses terminated at different gestational ages suggest that the exposed medulla undergoes progressive damage in utero. Prenatal repair could thus prevent or ameliorate damage to the medulla and improve neurological outcome. Early clinical reports also suggest that prenatal repair could result in reversal of the hindbrain herniation and improve Chiari-II malformation. These additional observations have generated great enthusiasm about the potential role of prenatal surgery in the treatment of OSB.

Management of Myelomeningocele Study (MOMS)

The results of a randomized clinical trial (the MOMS trial) comparing prenatal repair of OSB via open fetal surgery with postnatal repair showed that, except for the incidence of tethered cord syndrome, prenatal correction of OSB is associated with improved neurological outcome. The trial enrolled 183 patients, referred to one of three treatment centers in the USA, and reported the results of 158 patients. The primary composite outcome (fetal or neonatal death, or need for VP shunting before 1 year of age) occurred in 68% of the prenatal repair group vs 98% of the postnatal repair group (P = 0.001) and the rate of VP shunt placement was 40% vs 82% (P = 0.001). The number of infants in the prenatal repair group who could walk without orthotics or devices was twice as high

OSB affects 3.5:10 000 live births in the USA and 1.4:10 000 live births in Brazil. It is characterized by non-closure of the elements that protect the medulla, leaving it exposed to amniotic fluid throughout pregnancy. The primary postnatal consequences of OSB are related to lifelong impairment of the control of sphincters and motor function at or below the level of the lesion, sometimes including paralysis. The lesion is associated with Chiari-II malformation, characterized by herniation of the cerebellum through the foramen magnum into the spinal canal.

Postnatal treatment of open spina bifida

The primary goal of postnatal treatment of OSB is to stop leakage of cerebrospinal fluid (CSF) from the lesion and to prevent infection of the exposed nervous tissue. To accomplish this, the neural placode is released and reshaped, the dura mater is closed in a watertight fashion, the paravertebral muscles are approximated, and the skin is closed. Approximately 52–91% of babies will require a VP shunt to treat ensuing hydrocephalus. Two types of complication can arise from postnatal surgical repair and VP shunting: problems with the VP shunt itself (e.g. obstruction or infection) and tethered cord syndrome. Both complications require subsequent neurosurgery, which can cause further loss of neurological function.

Impact of open spina bifida

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as that in the postnatal repair group (42% vs 21%). The composite score for mental development at 30 months was also better in the prenatal treatment group. By 1 year of age, 36% of infants in the prenatal repair group had no evidence of hindbrain herniation compared with only 4% of those in the postnatal repair group.

Maternal risks of open fetal surgery and uterine legacy

The MOMS trial was a very important step in demonstrating that prenatal correction is beneficial to the neurological outcome of affected individuals. However, the trial also showed that, compared with postnatal correction, prenatal correction via open fetal surgery was associated with statistically significantly higher maternal risks. These included an increased risk for preterm birth (79% delivering < 37 weeks in the prenatal repair group vs 15% in the postnatal repair group ($P < 0.001$) and 46% vs 5% delivering < 35 weeks ($P < 0.001$)), maternal pulmonary edema and placental abruption (6% vs 0%, $P < 0.01$), requirement for blood transfusion at delivery (9% vs 1%, $P < 0.05$) and uterine scar thinning or dehiscence in the index pregnancy (36% vs 0%, $P < 0.001$). Furthermore, open fetal surgery, which requires maternal laparotomy and hysterotomy, can have detrimental consequences to subsequent pregnancies. Wilson et al. reported uterine dehiscence in 14% and rupture of the uterus in 14% of subsequent pregnancies in patients submitted to open fetal surgery in the index pregnancy. While fetal outcome may be maintained or improved by open fetal surgery, it is vital to preserve concomitantly maternal outcome and future reproductive health. Both goals are achievable using an endoscopic approach to prenatal fetal surgery.

Fetoscopic repair of open spina bifida

A fetoscopic approach for the in-utero correction of OSB was first reported in 1997 by Bruner et al., who used a complex technique involving endoscopic placement of a maternal split-thickness skin graft over the fetal neural placode to close the defect. This approach was abandoned after results that were less than satisfactory in four cases, with only half of these fetuses surviving and both survivors requiring a VP shunt.

Development of a fetoscopic technique in animal models

The main goal of our research effort was to develop a surgical technique to repair OSB in utero that could be performed endoscopically. From the outset, we understood that such a technique would need to differ substantially from the classic postnatal multilayer closure to be clinically applicable, reliable and reproducible. Thus, the characteristics of the new surgical technique would need to allow covering of the spinal defect without requiring a multiple-layer closure. In addition to using a single-layer closure, fetoscopic repair of OSB should:

(a) be watertight and result in reversal of hindbrain herniation; and
(b) address risk factors associated with cord tethering to decrease the likelihood of such a complication.

Interestingly, while the intrauterine location of the fetus represents a technical challenge, it also represents a paradoxical benefit, because fetoscopic surgery is performed in an entirely different milieu, one which is aseptic and more conducive to healing than is the postnatal environment. We took these factors into account when developing our unique approach to repairing OSB, first in animal models and then in a phase-I clinical trial.

Bacterial cellulose (biocellulose) as a dura mater substitute

Our initial experiments focused on developing a practical way to protect the medulla. Through an extensive literature review (Table S1), we assessed several different materials that could be used as dural substitutes for the prenatal closure of meningo(myelo)cele-like defects. Based on this review, we chose to use a sterile biosynthetic cellulose patch, produced by a bacterium (Acetobacter xiluim), which had been tested successfully as a dura mater substitute after craniotomy in an animal model. This craniotomy study showed that the biocellulose elicited a low fibrotic reaction, and that a thin internal and a thick external connective tissue layer, formed by fibroblasts, enveloped the biocellulose implant without adhering to the cerebral cortex. This material has also been used clinically as a dura mater substitute in patients who had undergone craniotomy for various indications (i.e. tumor, trauma and cerebral edema).

To test the use of this biocellulose for correction of OSB, we used a fetal rabbit model, inducing and repairing a spinal defect at 23 days’ gestation (term = 30 days). We dissected the skin around the spinal lesion, placed the biocellulose underneath the skin edges, and approximated the edges using a single stitch. At 30 days’ gestation, the skin had healed completely, the biocellulose remained in place and no foreign body reaction was observed.

The next step was to test the biocellulose in a larger animal model, with a more prolonged gestation, to check for any long-term effects of the biocellulose patch. A larger animal would also help us to work out technical issues that would be critical for clinical application of the surgical technique in humans. In an ovine model of OSB, the patch was in place for a median of 28 days. We closed the skin using a continuous running suture and observed that the fetal skin was healed at birth. Microscopically, the inner fibroblast layer surrounding the biocellulose was found in anatomical continuity with the original dura mater, which led to the formation of a neodura mater. This observation suggested that direct closure of the dura mater during surgery may not be necessary.
finding represents a paradigm shift, because it indicates that a primary watertight closure of the dura mater was not essential for correction of OSB at the time of antenatal surgery, as it appeared that the fetus was able to repair the dura mater by itself subsequently.

We compared the biosynthetic cellulose with an acellular dermal matrix, a patch that has been used to correct OSB in humans. The biocellulose performed better, because it kept the medulla separate from the skin, thereby potentially avoiding spinal cord tethering, whereas the dermal matrix adhered extensively to the medulla (Figure 1).

Fetoscopic closure of ‘large defects’

In approximately 20–30% of fetuses undergoing prenatal correction of OSB using open fetal surgery, the skin defect is too large to allow primary skin closure. To address this potential problem, we tested placement of a bilaminar skin substitute (silicone and acellular dermal matrix) over our biocellulose graft. We hypothesized that the artificial skin would keep the biocellulose in place when approximation of the skin edges was not possible. We conducted a study which showed that the artificial skin induces the formation of neoskin above the biocellulose such that the dermal matrix becomes a scaffold for neodermis formation, allowing a new epidermal layer to be formed above the repopulated dermal matrix.

Definitive correction in a ‘single step’

We hypothesized initially that fetoscopic correction of OSB would require two steps: a palliative in-utero endoscopic step that would involve protection of the medulla, followed by definitive postnatal correction. However, after noting the development of a neodura mater and of a neoskin in our animal experiments, we surmised that we could achieve definitive OSB closure using prenatal endoscopic surgery alone (a one-step approach). This was subsequently shown to be the case in our preliminary clinical trial.

Comparison of repair techniques

Before conducting a clinical trial, we felt it was necessary to compare our innovative repair technique with the standard postnatal multilayer neurosurgical technique, which has been applied mostly as a translation from the postnatal treatment standard and has never been tested adequately in a fetal animal model. Therefore, using our ovine OSB model, we compared our skin-over-biocellulose repair to the standard multilayer closure technique that was used in the MOMS trial. Our data showed that the standard neurosurgical technique resulted in significant damage to the medulla, prevented the formation of a neodura mater and created a fibrous scar that caused adherence of the medulla to the skin. Conversely, our skin-over-biocellulose technique did not cause damage to the medulla, induced formation of a neodura mater (in anatomical continuity with the original dura mater) and created a natural separation between the medulla and the skin by the presence of the biocellulose (Figure 2). These findings suggest that the in-utero endoscopic approach is associated with better preservation of the posterior horns than is the

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standard technique, and that, potentially, it could be associated with a decreased likelihood of postoperative cord tethering.

Clinical experience with fetoscopic treatment: the German experience

In 2006, Kohl et al. reported the prenatal treatment of OSB in three patients between 23 and 26 weeks of gestation, using fetoscopy and partial carbon dioxide (CO2) insufflation of the uterine cavity. Surgery consisted of simply covering the defect with a polytetrafluoroethylene material, and all cases required postnatal neurosurgical repair. In 2009, the technique was further modified by the same group, providing definitive correction in utero and obviating the need for postnatal repair.

By 2012, the same group had operated on another 19 fetuses with OSB using an entirely percutaneous fetoscopic technique. Surgery consisted of circumcising the placode and removing the junctional zone tissue close to the normal skin. The spinal cord was then covered with an insoluble patch that was sutured onto the paraspinal musculature with interrupted stitches, aiming to achieve a watertight closure of the dura mater. Among these 19 cases, there were three fetal and three neonatal deaths. The remaining 13 patients were compared in terms of segmental neurological function and leg muscle ultrasound density (MUD) with age-matched controls who had undergone postnatal repair. The prenatal repair group was born at a statistically significantly lower gestational age compared with the postnatal repair group (median, 32 vs 39 weeks) and experienced more complications (chorioamnionitis, premature rupture of the amniotic membranes, oligohydramnios and infant respiratory distress syndrome necessitating intermittent positive-pressure ventilation). However, neurological function was better preserved in the prenatal compared with the postnatal repair group, with a median
motor and sensory gain of two segments and better knee-jerk \((P = 0.006)\) and anal \((P = 0.032)\) reflexes. The difference between the MUD caudal and cranial to the myelomeningocele was smaller in the prenatal than in the postnatal group, and this was associated with better preservation of segmental muscle function\(^{40}\). None of the mothers experienced uterine dehiscence or rupture and none required postoperative blood transfusion.

The same group subsequently reported 51 cases undergoing a slightly different technique, in which a porcine small-bowel submucosa patch was used over an inert Teflon patch if needed. In this series, amniotic fluid leakage occurred in 43 patients, and the mean gestational age at delivery was 33 (range, 24.6–38.1) weeks. All abdominal and uterine trocar insertion sites were healed and the majority of women delivered beyond 32 weeks of gestation\(^{41,42}\).

The first fetoscopic spina bifida repair performed in Brazil used the technique described by Thomas Kohl in direct collaboration with his group, while we awaited authorization from our National Ethics Committee to approve the use of our novel technique.

**Fetoscopic repair in humans: the CECAM trial**

After addressing in animal models several of the challenges mentioned above (i.e. the need to develop an endoscopically applicable watertight technique and the need to reduce the likelihood of cord tethering\(^{22–25,28,29,32,35}\)), our group conducted a phase-I trial of the fetoscopic repair of OSB, using our skin-over-biocellulose technique: the CECAM (Cirurgia Endoscópica para Correção Antenatal da Meningomielocele em humanos) trial. Patient inclusion and exclusion criteria were very similar to those of the MOMS trial. Surgery was performed under general anesthesia and with partial \(CO_2\) exchange. Two 11-Fr trocars and one 14-Fr, or 5.0-mm, trocar were used. Once the fetus was positioned adequately, the skin around the placode was circumcised. A biocellulose patch was placed over the lesion and the skin was reapproximated using a continuous running suture over the patch, without dissecting or suturing the dura mater.

We reported the results of the first four human fetuses from the CECAM trial in 2014\(^{44}\), and recently published the results of all 10 cases which underwent surgery in Brazil\(^2\). Surgery was completed in eight of the 10 cases. There was one fetal and one neonatal demise, and one case of unsuccessful prenatal repair underwent postnatal repair. No tocolysis was needed during surgery, and atosiban was used prophylactically for 24 h postoperatively.

The mean gestational age at birth was 32.4 weeks and delivery occurred at a mean of 5.6 weeks after surgery. Among the seven infants available for postnatal analysis, no CSF leakage was present at birth and, in six, there was complete reversal of the hindbrain herniation, indicating that a watertight closure of the dura had been achieved successfully.

A comparison between the anatomical lesion level and the motor/neurological segmental level can better express neurological improvement, since the motor level represents the lowest nerve roots that are preserved, i.e. the most distal active muscles present. The lower the motor level, the higher the chance the infant will be able to walk. Short-term observations showed that six of the seven (86%) infants had the same or better-than-expected (ranging from one to three levels better) motor vs anatomical level (assessed using neonatal magnetic resonance imaging), at a mean follow-up of 6.6 months. In the MOMS trial, 67\% (43/64) of cases treated prenatally showed the same or better motor than anatomical level compared with only 46\% (46/70) of cases in the postnatal surgery group. This suggests that the short-term motor outcomes with our technique are at least the same, if not better, than those reported in the MOMS trial.

In our series, there were neither maternal deaths nor significant maternal morbidity, except for preterm pre-labor rupture of membranes (PPROM), which occurred in all cases, but which did not affect our fetal outcomes significantly.

These results, although preliminary, indicate that our innovative technique is associated with less maternal morbidity than is open fetal surgery, and with as good or better neurological outcome of infants.

**Tethered cord syndrome and postnatal neurosurgical intervention**

One of the major postoperative complications of surgical repair of OSB is tethered cord syndrome. In the two available long-term follow-up case series published comparing prenatal with postnatal repair, there was a trend towards a higher incidence of tethered cord syndrome in the prenatal group\(^1,40\). Verbeek and colleagues\(^{40}\) reported tethered cord syndrome as a complication in 38\% (5/13 cases) of infants operated on prenatally vs 15\% (2/13 cases) of age-matched controls operated on postnatally \((P = 0.37)\). A similar trend for this complication was found in the MOMS trial\(^{43}\), with 8\% (6/77 cases) of babies needing surgery in the prenatal group, and 1\% (1/80 cases) of babies in the postnatal group needing surgery \((P = 0.06)\).

All antenatal techniques used to repair OSB may result in the need for postnatal neurosurgical intervention. Kohl’s group recently published the results of a 1-year follow-up of more than 70 cases treated fetoscopically\(^{44}\). Maternal and fetal benefits were largely sustained, but 28\% of the patients required early postnatal local neurosurgical intervention. In the MOMS trial, dehiscence of the repair site occurred in 13\% of cases from the prenatal group vs 6\% of cases from the postnatal group\(^44\). We expect the need for postnatal neurosurgical intervention in our patients to be lower because our goal is primary skin closure\(^2\). In our recent series of 10 cases, early postnatal intervention was required in only one of the eight cases treated successfully *in utero*.  

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Non-percutaneous fetoscopic closure

Another group in the USA recently reported the result in a case of fetoscopic closure of OSB.54 The procedure was not performed percutaneously, requiring a laparotomy and exteriorization of the uterus. The dura mater was included in the skin suture. At birth, the investigators observed CSF leakage and treated it successfully with steristrips. However, we believe that this may potentially lead to CSF leakage and may increase the risk of tethered cord syndrome.

We believe that any new closure technique should first be tested in an animal model, or be compared to the approaches currently in use in humans or, at least, to the classical neurosurgical technique. For instance, in our animal models, we showed that the suture itself may cause further damage to the nervous tissue (Figure 2).35 and some patches (i.e. acellular dermal matrix) can cause meningoneural adhesions (Figure 1)29. Such adhesions may result in tethered cord syndrome, which can compromise previously improved motor function, and which may be missed in early outcome evaluations, as this is usually a long-term complication.

Fetal acidosis and other central nervous system injuries

Another major concern is iatrogenic central nervous system (CNS) injury subsequent to the fetal surgical treatment itself. Bealer et al.46 found that among human newborns who had undergone open fetal surgery, 21% had CNS injuries and, in almost 50% of these cases, this finding could not be attributed to prematurity or fetal distress. The authors postulated that these injuries could have been caused by sudden changes in fetal cerebral blood flow during the operative and postoperative course, attributable mainly to the aggressive tocolysis needed for the acidoisis. Although a direct cause could not be determined (e.g. maternal-fetal hypoxia, fetal bradycardia, use of tocolytic drugs), periventricular leukomalacia or periventricular hemorrhage leading to hydrocephalus were attributed to disturbances during the open fetal surgery approach itself.

An issue that has raised concern extensively is the possible occurrence of fetal acidosis during fetoscopic surgery using partial CO₂ insufflation of the amniotic cavity.47 Kohl and colleagues have addressed this issue in sheep and did not find evidence of histological damage in the fetal brain after CO₂ insufflation during fetoscopy.38 Furthermore, in neither Kohl’s37 nor in our clinical series48 did imaging studies performed routinely after birth reveal evidence of adverse effects on the human fetal CNS from the use of partial CO₂ insufflation.

Future perspectives

The success of the MOMS trial underpins the rationale for treatment of OSB in utero. However, it also underscores the fact that fetal gains were obtained at the expense of the mother. Thus, there is a need to improve fetal outcome while decreasing maternal morbidity in the context of fetal surgery. From the fetal point of view, a significant proportion of fetuses still require a postnatal VP shunt and many suffer from cord tethering after antenatal open fetal surgery.43 From the maternal point of view, PPROM is an important complication in almost 50% of cases of open fetal surgery, and the incidence of uterine thinning or dehiscence of nearly 36% is a major issue1,25.

The fetoscopic approach is undoubtedly more challenging from a technical point of view, but has the potential to address all of the fetal and maternal shortcomings of the open fetal surgical approach. However, PPROM remains an important issue with which we still need to contend. Our skin-over-biocellulose closure technique overcomes the technical challenges associated with an entirely percutaneous approach while taking advantage of the unique healing properties of the fetus and of the intra-amniotic environment.

Concluding remarks

Prenatal compared with postnatal correction of OSB has proven to be of benefit to infants, but the open surgical approach is associated with significant maternal risks and long-term uterine injury. Our percutaneous fetoscopic repair technique is feasible and reliable, and is associated with infant outcomes as good as or better than those reported with open fetal surgery, without many of the associated maternal complications of the latter approach. Our technique is an improvement over previous OSB repair procedures and can be duplicated by others, thereby with the potential to become a new standard of care. Further research will be aimed at reducing the incidence of PPROM and reducing the operating time. Hopefully, such goals will not be unsurmountable and will allow the fetoscopic approach to become the surgical method of choice in the antenatal repair of OSB.

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